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Abstracts
The 21st Annual Meeting of the Israel Society for Neuroscience & The First Binational Australian-Israeli Meeting in Neuroscience
Hilton Queen of Sheba
Eilat, December 15–18, 2012

Journal of Molecular Neuroscience

All abstracts appear in alphabetic order based on the last name of the presenting author (underlined name)

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Cannabinoids ameliorate impairments induced by chronic stress to synaptic plasticity and short-term memory

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Background: Repeated stress is one of the environmental factors that precipitates and exacerbates mental illnesses like depression and anxiety. We have previously shown that cannabinoids prevent the impairment of learning and memory induced by acute stress. Here we aimed to find whether chronic cannabinoid treatment would alleviate the long-term effects of exposure to chronic restraint stress on synaptic plasticity and short-term memory. Since glucocorticoids have potent modulatory effects on emotional memory, we also measured glucocorticoid receptors (GRs) expression levels in the amygdala, hippocampus, prefrontal cortex (PFC) and nucleus accumbens (NAc).
Results: Late adolescence rats were exposed to 1 hr chronic restraint stress for two weeks followed by i.p. treatment with vehicle or with the CB1/CB2 receptor agonist WIN55,212-2 (WIN; 1.2 mg/kg). Thirty days after the last exposure to stress, rats demonstrated impaired long-term potentiation (LTP) in the ventral subiculum (vSub)- NAc pathway, impaired performance in the PFC-dependent object recognition task and the hippocampal-dependent spatial version of this task. Stressed rats also demonstrated significantly reduced expression of GRs in the amygdala, hippocampus, PFC and NAc one month after stress terminated. Chronic WIN administration has prevented the stress-induced impairment in synaptic plasticity in the vSub-NAc pathway and in recognition and spatial memory tasks with no effect on GRs levels.
Conclusion: Our findings suggest that cannabinoid activation could represent a novel approach to the treatment of cognitive deficits that accompany a variety of anxiety-related neuropsychiatric disorders.

How a taste memory is waiting hours for visceral information to form conditioned taste aversion?

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The innate reluctance to eat novel taste, gustatory neophobia, is one of the most important behaviors that prevent animals from ingesting large quantity of a new and possibly toxic food. The consumption of a novel taste that is not associated with negative visceral consequences leads to the formation of a non-associative form of sensory memory, known as incidental taste memory. Conditioned taste aversion (CTA) is an associative learning in which animals learn to avoid a novel taste (CS) associated with delayed poisoning (US). In contrast to other forms of associative learning, CTA can be established with CS-US intervals measured in hours. It is unknown how a memory of given taste is waiting the visceral consequence for such long delay. We hypothesized that kinase activity or kinases activity loops underlie this form of lingering memory. In order to test our hypothesis we first examined carefully the temporal limitation of the association. Our behavioral results in rats show that CTA can be established with the CS-US intervals of up to 8 hours. In addition, there is a negative correlation of aversive taste memory with the CS-US interval: the greater the CS-US interval, the weaker the CTA conditioning. Immunoblotting analysis following novel taste learning in gustatory cortex and basolateral amygdala reveals clear and transient phosphorylation of ERK I/II, GluA1-AMPARs and GluN2B-NMDARs. However, the activity of other receptors and kinases are correlated with delayed time of association. We now try to identify causality between these molecular pathways and remote associative time.

Functional imaging of local networks in the mouse olfactory bulb

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Sensory inputs to the mammalian olfactory bulb (OB) are organized in spatially segregated and functionally discrete units called glomeruli. These inputs are then processed by local neurons that shape odor representations in the OB. Local networks in the OB include different types of neurons like inhibitory periglomerular neurons (PGNs) and excitatory external tufted cells (ETs). Here, we used in-vivo two-photon calcium imaging to characterize the odor response profiles of these local populations in the mouse OB.
We expressed the genetically encoded calcium indicator GCaMP3.0 in ETs and PGNs using lentivirus and AAV1, respectively. Mice were implanted with a chronic window which allowed us to densely map odor responses from dozens of neurons per animal (n=~1100 PGNs, n=~500 ETs, n=9 mice). The two populations showed distinct response profiles. PGN maps were sparse, whereas single neurons responded to only few odors. In contrast, ETs maps were dense, whereas single neurons responded to a variety of odors. The differences between the populations were also manifested by high pairwise signal correlations between ETs, even for pairs located hundreds of microns away. In contrast, PGNs responses were usually uncorrelated. These results imply that PGNs are involved in local processing while ETs process inputs from larger regions.
We then compared how PGNs and ET's code 1 sec vs 15 sec odor stimuli. Long stimuli invoked dense responses in both populations, suggesting that most PGNs are recruited only during persistent odor stimuli. Interestingly, the temporal dynamics of ETs and PGNs were very different. ETs showed

fast adaptation while PGNs showed continuous or increased responses as long as the odor was present. These results suggest that ETs contribute to adaptive processing across odors. This adaptation may be regulated by persistent inhibition conveyed by PGNs. Our work provides a first comprehensive functional dissection of local networks in the mammalian OB.

The role of the ventromedial prefrontal cortex in first and second order embarrassment

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Embarrassment is a complex and self-conscious emotion which requires the presence of a real or imagined person in order to achieve (Miller, 1996). It has been suggested that embarrassment is caused by a person's feeling that they're committing an overt disruption of social performance, indicating that it requires intact social abilities and emotion regulation.In order to examine the neural basis of embarrassment we designed a task that assesses the feeling of embarrassment while performing a potentially embarrassing assignment (e.g. sing or dance) while being videotaped ("first order embarrassment") and the ability to feel embarrassment after viewing one's performance on film ("second order embarrassment"). Given the role of the ventromedial prefrontal cortex (VM) in social behavior and emotion regulation, it was hypothesized that it would have a key role in first order embarrassment.
A group of seven patients with localized VM lesions was compared to a group of non- VM lesions (n=4) and matched healthy controls (n=11).
The results indicate that, as compared to the two control groups, VM patients report lower embarrassment while being videotaped while showing normal levels of embarrassment when watching themselves on film.
These results suggest that the VM is important for the online feeling of embarrassment (first order embarrassment) which requires emotion regulation but not for the second order embarrassment.
This study was conducted with the support of the Israel Foundation Trustees (PhD grant 59/29).

The effect of lithium on brain inositol turnover

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Background The mechanism of lithium (Li)'s action is not yet resolved. Among numerous findings Li inhibits inositol-monophosphatase (IMPase) and reduces brain intracellular inositol. Li also down-regulates the expression of the sodium myo-inositol co-transporter (SMIT)1 responsible for inositol uptake from the extracellular fluid. The inositol depletion hypothesis suggests that Li's mood-stabilizing action is mediated through an effect on inositol metabolism. In agreement, both IMPA1 (encoding for IMPase1) and SMIT1 homozygote knockout mice exhibit Li-like behaviors. Since inositol signaling is cyclic, requiring continuous incorporation of inositol into the phosphatidylinositol pool to produce its second messengers, better understanding of brain inositol's turnover and how Li affects it is crucial for understanding the consequences of inositol depletion. We hypothesized that Li and bi-allelic IMPA1 knockout dampen brain inositol turnover.
Methods We used intracerebroventricular (icv) injection of 3H-inositol to determine inositol turnover into phosphoinositols (cytosolic) and phosphoinositides (membranal).
Results Frontal cortex: acute Li treatment of wildtype mice did not affect radiolabeled phosphoinositols levels while a significant two and 3.5 fold increase was obtained following chronic Li treatment and in IMPA1 HO KO mice, respectively. Hippocampus: acute and chronic Li treatment resulted in a trend of 3.5 fold increase in radiolabeled phosphoinositols; a significant seven fold increase was found in HO KO of IMPA1. No differences were found in the radiolabeled phosphoinositides levels. We then studied the effect of IP3 (vs. aCSF) trapped in liposomes administered 45 min prior the analysis. IP3 administration resulted in decreased immobility time in the forced-swim test and in an attenuated response to amphetamine, similarly to the effect of chronic Li treatment.
Conclusions The results corroborate the inositol depletion hypothesis.

Mechanisms of neurotoxicity in prion diseases

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Prion diseases are a group of neurodegenerative diseases involving the conversion of the cellular prion protein, PrPC, into a disease-associated form termed PrPSc. We have established a model of prion infection in organotypic cerebellar slice cultures that allows us to study prion replication in a complex cellular model. Prion replication within the tissue induces an innate immune response and causes a subtotal loss of cerebellar interneurons within 5-7 weeks.
Progressive accumulation of PrPSc can only occur when conversion of PrPC into PrPSc is faster than PrPSc clearance. Microglial cells are the brain's phagocytes and were therefore a plausible candidate for effecting PrPSc clearance. We studied this question in slice cultures from CD11b-HSVTK transgenic mice, from which microglia can be rapidly and completely ablated through exposure to ganciclovir. Depletion of microglia from non-infected cultures had no effect on the viability of non-microglial cells in brain slices. In infected tissue, however, microglia depletion led to a 15-fold increase in prion titers and the deposition of

PrPSc. These results suggest that microglia functions as a scavenger of prions.

We then asked which factors may control the priolytic activity of microglia. Engulfment of apoptotic bodies by phagocytes is mediated by milk fat globule EGF factor 8 (Mfge8) which, in the brain, is primarily produced by astrocytes. We found that Mfge8 ablation produced accelerated disease and reduced clearance of apoptotic bodies in vivo, as well as excessive PrPSc accumulation and increased prion titers in prion-infected C57BL/6x129Sv mice and organotypic cerebellar slices derived therefrom. Notably, these phenotypes correlated with the presence of 129Sv genomic markers in hybrid mice and were not observed in inbred C57BL/6 Mfge8-/- mice, suggesting that additional, hitherto unidentified genetic modifiers may exist. Because Mfge8 receptors are expressed by microglia, and microglial ablation increases PrPSc accumulation in organotypic cerebellar slices, we conclude that engulfment of apoptotic bodies by microglia is an important pathway of prion clearance and is controlled by astrocyte-borne Mfge8. Surprisingly, antibodies - and also F(ab)1 fragments thereof - binding to certain PrP epitopes induced a complete loss of NeuN-positive neurons within 14 days of treatment in a PrP-dependent manner. These results seriously question the safety of experimental therapies based on anti-PrP antibodies. As prion-mediated toxicity depends on the expression and conversion/aggregation of membrane bound PrPC it is appealing to speculate that antibody treatment induces converging neurotoxic signaling events as prion infections. Indeed, we have found a number of compounds that uncouple prion replication in slices from prion neurotoxicity; most of these compounds also suppress the toxicity of anti-PrP antibodies.

Comparing N-way decomposition methods, PARAFAC and Tucker, for the purpose of differentiating alpha and mu suppression during observation of motor acts using PARAFAC and Tucker methods

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EEG oscillations between 8-12 Hz are desynchronized and their amplitude reduced in humans while observing biological movement. This EEG modulation, commonly labeled mu-suppression, is recorded primarily over the sensory-motor cortex and reflects motor activity. The specific sensitivity to motor activity and a presumed source in the sensory-motor cortex distinguish mu rhythms from the parieto-occipital alpha waves. Nevertheless, since both rhythms share the same frequency range and, at rest, this frequency dominates the EEG across most scalp sites, disentangling mu rhythms from alpha is not trivial. This endeavor is further complicated by the evident sensitivity of alpha to the level of visual attention allocated to processing. This factor might be easily confounded with the perceptual aspects of motor manipulation. Indeed, although mu suppression is expected primarily at fronto central sites, similar (and sometime even larger) EEG modulation can be recorded from traditional alpha-dominated locations at parieto-occipital sites while observing motor acts. In order to separate mu from alpha EEG manifestations, I applied three analytic algorithms. Parallel Analysis of Factors (PARAFAC) and the Tucker model where used on a 3 and 4 dimensional representation of the data, and Principal Component Analysis (PCA) was used on a 2 dimensional representation of the data as a simple control model. The success of these methods at separating mu from alpha EEG manifestations was compared. The algorithms were applied to data recorded while 18 observers either grasp an object repeatedly or watch a video of a hand grasping the same objects. A video of a rolling ball was used as baseline. All three methods had low to moderate success in separating the different suppressions, although the 3 and 4-dimensional implementation of the Tucker model yielded a slightly better result. Future investigation of the optimal parameters required to use these methods efficiently is still required.

Improving the attention system: the benefits of practicing automatic inhibition

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Background: People often encounter situations in which mental processes contradict each other. In the current case, one mental process must be controlled and restricted so that one'sbehavior will fit one's intentions - this involves cognitive inhibition. Performing mental inhibition is a mental resource consuming task and it is thought to involve several brain mechanisms, such as the Anterior Cingulate Cortex (ACC) and the Pre Fontal Cortex (PFC). The current study examines techniques aimed at improving cognitive inhibition. Here we examine the notion that one is sometimes able to perform a task to perfection when it is done automatically but an attempt to do it intentionally end in failure. Using this notion we examine whether cognitive inhibition gains indirect improvement by exercising one's well-functioning automatic inhibition ability.Recently, we (Goldfarb et al., 2010) have shown that social priming may trigger automatic inhibition. For example, social priming of "dyslexia" can help inhibit the reading process in the Stroop task. Here we investigate this notion further and examine whether extended training of automatic inhibition affects the non automatic inhibition channel, and to what extent it can aid general mental inhibition abilities.

Results: We compared between three experiments, with three phases: baseline, inhibition practice, and test. The three experiments differed in their inhibition practice phase. In Exp.1 this practice phase involved automatic inhibition (social priming of "dyslexia"), in Exp.2 it involved non-automatic inhibition, and in Exp.3 it involved a control-non inhibition task.The results revealed that practicing automatic inhibition leads to the most improvement in the mental inhibition mechanism.
Conclusions: The results suggest that automatic and non automatic inhibition are based on common brain mechanisms and that automatic operation of the inhibition mechanism has a better behavioral outcome than intentional operation.

Long-lasting increase of corticosterone after fear memory reactivation: anxiolytic effects and network activity modulation in the ventral hippocampus

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Pathological fear and anxiety can be studied, in rodents, with fear conditioning and exposure to reminder cues. These paradigms are thought to critically involve the ventral hippocampus, which also serves as key site of glucocorticoid action in the brain. Here we demonstrate a long-lasting reduction of kainate-induced gamma oscillations in slice preparations of the ventral hippocampal area CA3, 30d after a single fear conditioning training. Reduction of gamma power was sensitive to corticosterone application and associated with a decrease of glucocorticoid and mineralocorticoid receptor mRNA expression across strata of the ventral hippocampal CA3. A fear reactivation session 24 h after the initial conditioning normalized receptor expression levels and attenuated the corticosterone-mediated recovery of gamma oscillations. It moreover increased both baseline and stimulus-induced corticosterone plasma levels and evoked a generalization of fear memory to the background context. Reduced ventral hippocampal gamma oscillation in both fear reactivated and non-reactivated mice were associated with a decrease of anxiety-like behavior in an elevated plus maze. Taking advantage of the circadian fluctuation in corticosterone, we demonstrated the association of high endogenous basal corticosterone plasma concentrations during morning hours with reduced anxiety-like behavior in fear reactivated mice. The anxiolytic effect of the hormone was verified with local applications to the ventral hippocampus. Our data suggest that corticosterone acting on ventral hippocampal network activity has anxiolytic-like effects following fear exposure, highlighting its potential therapeutic value for anxiety disorders.

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Seeking causative genes for human congenital general anosmia in multiply-affected Israeli families

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Background: General anosmia has negative effects on life quality, including impaired food and beverage enjoyment, social interactions and avoidance of poison and fire. An estimated 2.5-5 % of the general population suffers from acquired general anosmia or hyposmia. In contrast, congenital general anosmia (CGA) affects merely <0.1 %, and appears in isolated or syndromic forms. In specific cases, family members of patients with syndromic anosmia have been found to suffer from the isolated form of CGA. While for an appreciable number of syndromic CGA types a causative gene has been identified, none of the isolated CGA instances have been genetically deciphered. Most of the reported isolated CGA cases are sporadic, and family-based studies are relatively rare, primarily because samples are difficult to ascertain. In our previous report we have recruited 66 families of Jewish origin and performed whole-genome linkage analysis for selected families with multiple affected individuals with suspected founder variation. This study did not reveal significant linkage, probably due to small family size.
Results: We now report whole-exome next-generation sequencing in selected individuals from four of these families. Each family was separately analyzed under the appropriate mode of inheritance. We focused on family-shared variants present at minor allele frequency <0.05 in the 1000 Genomes Project, in 5000 exomes of the NHLBI database and in our own 50 exomes of Jewish individuals. These variants involved functionally reasonable genes, including such appearing in our recently constructed database of CGA candidate genes.
Conclusions: All implicated variants are now being further validated, examined for co-segregation in additional family members, and screened for low frequency in ethnically matched healthy controls. The identification of specific pathogenic functional CGA variants will help elucidate the molecular basis of general olfactory sensitivity.

Substrates coated with silver nanoparticles promote neuronal growth

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Manipulation of neuronal growth has important applications in regenerative biomedicine and bioengineering. Neurons grow and function while sensing and responding to a wide range of chemical and physical environmental cues through the tips of their developing neurites. It has been recognized that cells are highly influenced by the physical properties of substrates, including topography at the micro- and nano-scale. We examine the combination of physical and chemical stimulations by using active materials as the nanotopographic platform to promote neuronal regenerative response.

In this study we investigate the effect of silver nanoparticles, which are known for their excellent antibacterial activity, on neuronal growth. We grow neuroblastoma cells on surfaces coated with silver nanoparticles. The substrates are fabricated by using the sonochemical method, a simple, effective and non-toxic technique. We study and quantify the effect of the nanoparticles on the development and morphology of the neurites. We find that the silver nanoparticles function as favorable anchoring sites and the growth on silver nanoparticles coated substrates leads to a significantly enhanced neurites outgrowth. A comparison with other materials demonstrates a clear silver material-driven promoting role in addition to the nanotopographic effect. Our results, combined with the antibacterial effect of silver nanoparticles, propose silver nanoparticles as an attractive nanomaterial with a dual activity for the design of therapeutic platforms for neuronal repair.

Zebra finch - a novel natural GSK-3alpha knockout model to study the role of GSK-3beta in neural plasticity

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Neuron death and replacement are considered fundamental components of adult brain plasticity and critical factors in neurodegenerative diseases. However, we still do not fully understand all the mechanisms that regulate neurogenesis. Glycogen synthase kinase-3 (GSK-3) is a highly conserved kinase which serves as a critical regulator in cellular signaling, survival, differentiation and proliferation. GSK-3 has two known isozymes, alpha and beta. However, their distinct biological functions are not fully understood. We previously showed that unlike other vertebrates that harbor both GSK-3 genes, the GSK-3alpha gene is missing in birds. In addition, whereas in mammalian adult brain neurogenesis is restricted to few regions, it is robust in the avian brain. We use nasal procedure with a specific GSK-3 competitive inhibitor, L803-mts, to treat adult male zebra finches, and to examine its effects on behavior and neurogenesis. First we examined the effect of the inhibitor on downstream targets of GSK-3 in the brain. Indeed, treatment with L803-mts, increased levels of beta-catenin, cyclin-D and phosphorylated eukaryotic elongation factor-2 (eEF2) in the bird's brain, and provided proof of concept for the in vivo GSK-3 inhibition. These results could also hint for changes in neurogenesis as these targets are involved in cell proliferation. Then we investigated whether the inhibitor affects birds' singing behavior and motor activity. We measured a five-fold decrease in undirected songs which are used for communication between flock members, in treated birds. However, no changes occurred in motor activity, indicating that decrease in singing was not a result of nonspecific inhibitor effects. We currently study whether L803-mts affects cell proliferation in the ventricular zone of treated birds' brain. Our study suggests that GSK-3beta regulates singing behavior in birds and introduces birds as a natural alpha knockout model to study the distinct functions of GSK-3 isozymes.

Anterior cingulate dysfunction in OCD measured by EEG response to erroneous content

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OCD patients, compared to healthy participants, are known to demonstrate an enhanced Error Related Negativity after making mistakes (Gehring, Himle, & Nisenson, 2000). Nevertheless, it is not clear whether this hyperactive ERN reflects the activity of an action monitoring system that is over sensitive to punishment cues (Olvet & Hajcak, 2008) or a dysfunction of more general and less affective monitoring system that continuously seeks for erroneous information in the inner or outer environment. The latter option do not obligate the execution of an actual mistake but merely the identification of erroneous content (Tzur & Berger, 2007). We investigated this issue using an arithmetic task (Tzur & Berger, 2007) that was delivered to 9 OCD patients and 9 healthy controls. Participants were requested to indicate whether a solution of a simple equation is either correct or wrong. A non phase locked wavelet analysis revealed that OCD patients demonstrated enhancement of power compared to healthy participants in low frequency bands (delta, theta and alpha) after merely identifying wrong solutions. In contrast, no differences were found when correct

solutions were presented. Activity had a midline frontal locus, similar to previous findings, suggesting ACC as a possible source. These findings contribute to our understanding of the etiology of OCD, and perhaps to a more specific model regarding the cognitive deficits in OCD patients.

New reactive amall molecule scavengers of nerve agents

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The development of medical scavengers toward toxic organophosphorus (OP) nerve agents have primarily been based on stoichiometric or catalytic enzymes e.g. acetylcholinesterase (AChE) or paraoxonase 1 (PON1). However, enzyme scavengers may cause immunogenic response, have limited stability and create excessive payload due to large molecular size (MW 40-80KD). Therefore, we have embarked on designing new small molecules scavengers (SMS) that will rapidly detoxify OP nerve agents in vivo. The SMS are expected to be non-toxic, stable, highly soluble and non-discriminative toward optical isomers of OP nerve agents. Their multiple administration routes and pharmacokinetics could be controlled by adaptable formulations. The molecular design of novel SMS was based on combining two functions in one molecule: direct degradation of OPs and in parallel reactivation of OP-inhibited AChE. The direct attack on OPs was achieved by substituted benzohydroxamic (BHA) and pyridinehydroxmic acid (PHA) derivatives. Some BHAs and PHAs were then coupled via spacers to pyridine oximes providing hybrid compounds with both detoxification and reactivation potencies. Thus, 24 new compounds were synthesized of which 3 compounds were bifunctional hybrids. The new compounds were tested for detoxification rate towards sarin, cylsosarin and soman under physiological conditions (pH= 7.4, 37 °C). The fastest SMS toward OP agents were methoxy, dimethoxy and trimehtoxy BHA with $t_{1/2}$=1-2 min (1 mM SMS and 1 μM OP). The hybrid compounds 2-PAM-$(CH_2)_3$-4PHA and 2-PAM-Benz-4PHA displayed rapid detoxification as well as reactivation potency toward OP-AChE. 2-PAM-$(CH_2)_3$ 4PHA also displayed 30-fold faster kinetics than 2-PAM toward cyclosarin-inhibited AChE. The latter hybrid compound exhibited high decontamination activity (>98 %) toward cyclosarin on pig-ear skin in vitro using Franz diffusion cells. Our results indicate that the new hybrid compounds are promising scavengers of OP nerve agents.

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ApoE4 impairs synaptic activity and function in young naïve mice retinas

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Background: ApoE4 is the most prevalent genetic risk factor of Alzheimer's disease. Synaptic pathology which is the leading pathological hallmarks of the disease is accentuated by ApoE4. The extent, to which the synaptic effects are neuronal specific, remains to be determined. The retina, which is well organized in specific layers of cell types and synapses, provides a unique model system to study the neuronal and synaptic specificity of the effects of ApoE4.
We examined these questions by investigating the retinas of young naïve ApoE3 and ApoE4 targeted replacement mouse, utilizing immunohistochemistry, western blots and electroretinography (ERG).
Results: ApoE4 had no effect on the either the width of the different retinal layers, nor the levels of the different cell types. In contrast, ApoE4 had isoform specific effect on retinal synapses. Accordingly the levels of total synapses (monitored by synaptophysin) were lower in both the inner and outer plaexiform layers in ApoE4 retinas. Examination of synaptic specificity of this effect revealed decreased excitatory marker Vglut with parallel increase in the level of the inhibitory marker Vgat in ApoE4 retinas. Examination of the ratio of excitatory / inhibitory synapses, revealed a decreased ratio levels in the retinas of ApoE4 mice. This findings show that apoE4 has a synapse specific effect. ERG measurement revealed decreased amplitudes of the a- and b-waves ApoE4 compared to ApoE3, while no effect was observed in the response time. This suggests that the synaptic effect of ApoE4 has functional implications. Measurements of the ApoE levels showed lower levels in ApoE4 retinas compared to ApoE3, correlative with the observation in the brain. It is still to be determined whether these effects in the ApoE4 mice are due to loss of function or gain of toxic function.
Conclusions: These findings show that ApoE4 has specific synaptic effects in the retina, and that these affect lead to retinal dysfunction.

'Juvenile stress' exacerbates the impact of an exposure to an odor reminder of a stressful experience in adulthood

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While most individuals are able to cope with trauma, a minority fail to recover and exhibit prolonged and

maladaptive behavioral and physiological responses to the traumatic experience. Many times, these are manifested as symptoms of PTSD. Among the many proposed risk factors, early-life stress is predominantly associated with higher prevalence of both mood and anxiety disorders, particularly depression and PTSD (Heim & Nemeroff, 2001). Dealing with PTSD, a core symptom is the intrusive recollections of the traumatic experience. These episodes of re-experiencing are often triggered by reminders (e.g. places, sights, sounds and other sensations) of the traumatic event (Kardiner, 1941; Marx and Soler-Baillo, 2005). Therefore, the study was aimed to examine the long term ability of an odor reminder to act as an effective reminder of a stressful experience in adulthood. In addition, we evaluated the impact of an exposure to 'juvenile stress' as a predisposing factor that will exacerbate the impact of an exposure to odor reminder in adulthood.

The results suggest that an exposure to stress in juvenility and to an exposure to an odor reminder exacerbates the behavioral effects even one month following the exposure to stressful experience in adulthood.

Generation of spatial codes relies on the intact function of the oculomotor system: a study of Duane retraction syndrome

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The Simon effect (SE) shows that response times (RTs) are faster when stimulus location corresponds with response location, even when stimulus location is task-irrelevant—spatial codes even though irrelevant, affect response choices. It is still under debate how spatial codes are formed and why they cannot be ignored. Attentional accounts for the SE follow the premotor theory of attention, suggesting spatial attention is tied with the intention to perform a goal-directed spatial movement. That is, spatial attention and motor programming occur together and operate on the basis of the same spatial maps. We tested the attentional account for the SE by studying a visual Simon task in a patient (AR) who suffers from Duane syndrome (DS). DS is a congenital eye movement disorder characterized by inability of the patient to perform horizontal eye movements. AR's RTs were analysed as a function of visual field and contrasted with RTs from control participants. Results showed no SE (stimulus-response interference) when the targets appeared in the visual field to which AR could not perform eye movements. These results show that generation of spatial codes relies on intact function of the oculomotor system, supporting the role of spatial attention in stimulus-response interference.

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Does the olfactory epithelium sleep?

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Sleep is a rapidly reversible state characterized by loss of consciousness and reduced responsiveness to external stimuli. There is compelling evidence, however, that the sleeping brain is by no means incapable of processing sensory information. For example, odor pleasantness is processed during sleep. The sniff-response, an odorant-specific change in nasal airflow whereby pleasant odors drive stronger sniffs and unpleasant odors drive weaker sniffs, is evident in sleep. Nonetheless, the brain mechanisms underlying sensory processing during sleep remain unclear. The olfactory system provides an unusual framework to elucidate the brain substrates of sleep processing by presenting a unique opportunity to directly record neural activity in humans. Olfactory receptor neurons, a form of PNS-CNS transition neurons outside the skull, located in the olfactory epithelium, enable in vivo recording of olfactory responses (EolfG's) from behaving humans. Using this technique we set out to ask whether the EolfG's are influenced by the wake-sleep cycle. EEG, EOG, EMG, EKG and EolfG's were recorded at 1 kHz from 8 healthy subjects. EolfG's were recorded using Ag/AgCl electrode coated with Teflon tubing (0.8 mm OD) filled with Ringer-agar. Using a computer-controlled olfactometer we delivered odorants (Vanillin and Dimethyl Sulfide, duration=3 s, 15 repetition each, ISI ~25 s) into the recorded nostril via Teflon tubing, maintaining steady mechanical and thermal conditions (5.5 SLPM, 37 °C, 80 % RH) during both wake and sleep. EolfG responses were evident in 5 out of 8 subjects, and EolfG amplitude and EEG spectral power were calculated for each trial in each subject. Preliminary results show a significant correlation between EolfG amplitude and delta (0.5-4 Hz)/alpha (8-12 Hz) power (r=-0.41, p=0.048) in one subject. This correlation reflected higher EolfG amplitudes as sleep deepened, which suggests that the olfactory epithelium wakes up when we go to sleep.

Exposure to stress differentially affects behavior and expression of Kappa Opioid Receptor and GABA-A receptor in male rats

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Childhood trauma may predispose to the development of stress-related affective disorders. Acute exposure of rats to adult stress following previous exposure to juvenile stress resulted in altered behaviors reminiscent of affective disorders-like symptoms. These, were linked to activation of positive and negative affect brain areas. We compared expression of GABA-ARα1/α2 subunits, and of Kappa Opioid Receptor (KOR), as mediators of positive or negative affect, respectively, in correlation to behavior tests that were taken before and after the adult stress.

Results revealed that juvenile stressed rats spent more time and had more distance covered in open field center compared to control. In plus maze, juvenile stress group spent less time but had more distance in open arms. Surprisingly, in social interaction test, juvenile stress resulted in less time exploring familiar object than control group. After adult stress, juvenile +adult animals spent more time and had more distance in the center of an octagon field than control group. In zero maze, both juvenile and juvenile+adult groups spent less time and had less distance in open quadrants than control group and adult group. These behaviors were followed by changes in GABA-ARα1 and KOR. Adult and juvenile+adult stresses resulted in elevation of GABA-ARα1 level, in ventral PAG. In the same area, adult stress increased KOR level only in juvenile+adult group. Adult stress also elevated GABA-ARα1 level in dorsal PAG. In juvenile+adult the receptor protein level was much lower. KOR in dorsal PAG was higher in all groups compare to control. An additive erasing on KOR effect in juvenile+adult group was evident in BLA. An opposite effect on KOR was found in central amygdala.

Results indicate that while it is tempting to view the juvenile +adult group as an added result of both stressors, each stress group is in fact a unique condition, with characteristic profile of effects.

Transient interference with the ubiquitous transcription factor Sp1 leads to disparate behavioral response to sub-chronic and chronic stress

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Background: It is currently accepted that complex behavior and mental disorder results from a combination of biological susceptibility and exposure to environmental stimuli. However, most of the gene-environment interaction models focus on the interaction between environmental stimuli and a single candidate gene. We suggest that an alternative approach is interference with the expression of multiple genes followed by exposure to environmental insults, which better reflects real life.

Methods: Early interference with gene transcription was performed by treatment of 7 days old Wistar male rats for 4 days with the Sp1/DNA binding inhibitor, mithramycin. Environmental insult was mimicked by exposing these rats during adulthood (34 days) to sub-chronic (12 days, n=30) or chronic stress (28 days, n=48). The effects of mithramycin and stress treatment on behavioral response and serum corticosterone levels were assessed.

Results: Exposure of mithramycin treated rats to sub-chronic stress led to anxious behavior in the open field test, high startle response, low sucrose preference, indifference to novel objects and high serum corticosterone levels. However, exposure to chronic stress resulted in normal sucrose preference, startle response and serum corticosterone, novelty seeking behavior and reduced anxiety. In saline treated rats the extension of stress duration led to behavioral and hormonal adaptation to stress.

Conclusion: Our study suggests that postnatal temporal interference with multiple gene expression can lead to hyper-responsiveness to environmental stimuli, the features of which affects the phenotypic outcomes. Such a paradigm may be used to model gene -environmental interaction in the etiology of behavioral disorders.

Involvement of cAMP signaling pathway in inhibition of brain NO synthesis by BK

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Background: Bradykinin (BK) is a potent inflammatory mediator in the periphery. In Alzheimer's disease, where brain inflammation occurs, BK release is upregulated relatively early during the course of the pathology. Hence, BK was believed to promote neuroinflammation in several ways, including activation of microglial cells, that is responsible for the overproduction of pro-inflammatory mediators, such as nitric oxide (NO) which in turn lead to neuronal injury. However, BK was recently reported to have anti-inflammatory role. We found that BK reduce NO synthesis in microglia cells, but the mechanism is still unknown. As already known, cyclic adenosine monophosphate (cAMP) is an important regulator of inflammatory reactions. Increased cAMP levels results in activation of protein kinase A (PKA) and subsequently in the phosphorylation of cAMP response element binding protein (CREB) and increased transcription of inflammation-related genes. In this study we examined the involvement of cAMP pathway in inhibition of microglial NO synthesis by BK.

Results: Exposure of BV2 microglial cells to BK resulted in a significant decrease in basal NO production which was measured by the griess assay, while adding db cAMP

(cAMP analog) resulted in a significant increase in NO production. Similar results were obtained for lipopolysaccharide (LPS)-stimulated BV2 cells. In addition, H-89 (PKA inhibitor) mimics BK in reducing NO production in resting and LPS-stimulated cells. Also, Western blot analysis was performed using protein of nuclear extracts and antibodies directed against CREB, phosphorylated at Ser133 (p-CREB), revealed that BK inhibits CREB phosphorylation in resting and LPS-stimulated BV2 cells.

Conclusion: These results suggest that cAMP signaling pathway is involved in BK's anti-inflamatory effect in microglial cells, and may play an important role in neuroprotection during brain inflammation.

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Mechanisms underlying the contribution of GSK-3 to amyloid-beta pathogenesis

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Inhibition of Glycogen Synthase Kinase-3 (GSK-3) is a therapeutic strategy for neurodegenerative disorders, such as Alzheimer's disease (AD). However, the contribution of GSK-3 to amyloid pathogenesis has been under debate. To study this, we used '5XFAD' mice co-expressing mutated amyloid precursor protein (APP) and presenilin-1 (PS1) that develop massive cerebral Amyloid-Beta loads. Nasal treatment with a substrate-competitive GSK-3 inhibitor, L803-mts, reduced Amyloid-Beta deposits and ameliorated cognitive deficits in the 5XFAD mice. Analysis of hemi-brain samples indicated that L803-mts restored the activity of mammalian target of rapamycin (mTOR) and inhibited autophagy. Lysosomal acidification was impaired in the 5XFAD brains as indicated by reduced cathepsin D (CatD) activity and decreased N-glycoyslation of the v-ATPase subunit V0a1, a modification required for lysosomal acidification. Treatment with L803-mts enhanced lysosomal acidification in 5XFAD brains. Studies in SHSY-5Y cells and presenilin-deficient mouse embryonic fibroblasts further demonstrated that both GSK-3 isozymes, GSK-3 alpha and GSK-3 beta, impair lysosomal acidification and treatment with GSK-3 inhibitor restores this deficit. Taken together, our data implicate GSK-3/mTOR/lysosome axis in AD pathogenesis. We suggest that Inhibition of GSK-3 restores lysosomal acidification that in turn, enables clearance of Amyloid-Beta burdens and re-activation of mTOR. This work further highlights the therapeutic potential of GSK-3 inhibition in treating AD.

The role of nucleus accumbens MAPK signaling pathway in the expression of cocaine psychomotor sensitization

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Repeated administration of psychostimulant drugs such as cocaine induces psychomotor sensitization, which is thought to contribute to the development of drug craving by enhancing the incentive motivational value of these drugs. Among the enduring neuronal changes responsible for the expression of cocaine psychomotor sensitization, alterations in glutamate induced signaling and plasticity within the VTA and NAc play a critical role.

Previously we have shown that repeated cocaine injections increased NAc NMDA receptor subunits expression and distribution 21 days but not 1 day after withdrawal from cocaine. These changes were associated with an increase in the GluR1 subunit. We also found a time-dependent increase in ERK activity which was responsible for the increase in synaptic GluR1 levels in the NAc. In the same line, other studies have shown that following withdrawal from repeated cocaine injections the ratio of AMPAR/NMDAR evoked currents, an indicator of LTP in vivo or an increase in synaptic strength, is increased in the NAc.Together these results raised the hypothesis that MAPK signaling pathway is critically involved in the increase in synaptic strength in the NAc which ultimately leads the expression of psychomotor sensitization. We found that inhibiting the activity of ERK by the MEK inhibitor U0126, 1 day but not 7 days after sensitization in the NAc (core or shell), decreased the locomotor activity of rats that were challenged with cocaine to the levels seen in rats that were exposed to cocaine for the first time. Further, we found that AMPAR/NMDAR currents ratio that was recorded in the NAc (core and shell) slices following microinjection of U0126 10 days after withdrawal, was reduced to the level of the saline group. We therefore conclude that MAPK signaling plays a central role in the expression of cocaine psychomotor sensitization by increasing the synaptic strength at this region thereby leads to hyperactivity when re-expose to the drug.

Israel Science Foundation (ISF); David R. Bloom and Brettler Centers; School of Pharmacy

Mitotic motor proteins co-regulate microtubule organization in axons and dendrites

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In the axon, the microtubules (MTs) are nearly uniformly oriented with their plus ends distal to the cell body, while in the dendrite, MTs are non-uniformly oriented. We have proposed that these patterns are established and maintained by molecular motor proteins that transport MTs into these neurites with either the plus or the minus end of the MT leading. Our general hypothesis has been that cytoplasmic dynein is the principal workhorse for transporting MTs with their plus ends leading, and that the remainder of the work is performed by a small number of kinesins usually considered to be mitotic kinesins, namely kinesins 5, 6, and 12. The results of our recent studies on these motors indicate that, in fact, they do not fuel microtubule transport in the axon, but rather they somehow suppress it. We now think of these motors as "brakes" on axonal microtubule transport. We will discuss the evidence for this conclusion, as well as potential mechanisms by which these motors might behave as brakes. A potentially exciting hypothesis is that these motors act, at least in part, at the level of the cell body to restrain the transport of MTs into the axon while simultaneously promoting the transport of MTs of the opposite orientation into the dendrites. We posit that it is by this mechanism that the neuron co-regulates the polarity orientation of MTs in the axon and the dendritic arbor.

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A cognitive neuroscience hypothesis of mood and depression

Bar M

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The hypothesis presented here links cognitive processing with mood. Specifically, I propose that there is a direct and reciprocal relation between the cortical activation of associations and mood regulation, whereby positive mood promotes associative processing, and associative processing promotes positive mood. Previous research has identified a network of brain regions that mediate cognitive-associative processing in healthy humans. A critical insight that links those findings to studies of mood and depression is that depression is associated with both structural and functional abnormalities in these same brain regions. The proposed framework has many implications, most notably for diagnosing and treating mood disorders such as depression, for contextualizing adult hippocampal neurogenesis, for elucidating the role of cortical inhibition and foresight in the regulation of mood, and for a general non-invasive improvement of well being. Several key predictions are derived from this theory, and testing them has already provided supportive evidence.

NIH and NSF

Inhibition of TGF-beta signaling as a new anti-epileptogenic strategy in the blood-brain barrier dysfunction model for epilepsy

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Epilepsy is one of the most common brain disorders and is often preceded by traumatic or ischemic insult and associated with blood-brain barrier (BBB) dysfunction. We have previously demonstrated that BBB dysfunction underlies the induction of a transcriptional program mediated by serum albumin-induced transforming growth factor β (TGF-β) signaling. We thus tested losartan, an angiotensin II type 1 receptor blocker, which has been shown to block TGF-β signaling, as a potential anti-epileptogenic treatment. Epileptogenesis was induced by BBB opening using a focal application of the bile salt sodium deoxycholate (DOC, 2 mM) or bovine serum albumin (BSA, 0.2 mM). Rats were then treated with losartan; either locally (10 μM) in albumin-treated, or systemically (single dose of 100 mg/kgi.p. followed by 2gr/L in the drinking water for 21 days) in DOC-treated rats. Sham operated animals served as control. Epileptogenesis was monitored using telemetric electrocorticographic (ECoG) and analyzed with "in house" seizure detection algorithm. Brains were collected for molecular analysis. We show that losartan prevents albumin-induced smad2 phosphorylation (p=0.03) and upregulation of the astrocytic marker GFAP (p=0.035). Spontaneous seizure-like events (SLEs) were detected in 82 % of albumin- and 100 % of DOC-treated rats, compared to 29 % of controls (p=0.013), 25 % of albumin/losartan- and 40 % of DOC/losartan-treated. Importantly, in rats developing epilepsy, losartan significantly decreased the number of recorded seizures; 5.02 vs. 0.29 seizures/week in albumin and albumin/losartan-treated rats, respectively (p=0.002) and 8 vs. 0.9 in the DOC and DOC/losartan groups, respectively (p=0.042). We highlight the potential of a commonly used, well tolerated anti-hypertensive drug in the prevention of injury-related epilepsy, probably through a TGF-β-dependant signaling blockade.

An examination of the effect of type of script read on brain activity in regular and dyslexic readers – an ERP study

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Background: Brain-imaging studies indicate that reading orthographies varying in phonological transparency elicit

distinct brain activity in regular readers. Behavioral studies have also suggested that regular readers adjust reading-routine to the orthography read. Dyslexia is a neurobiological disorder, manifested in difficulties in word recognition. The purpose of this study was to examine whether dyslexics would also exhibit distinct brain activity when reading different orthographies. ERP's of dyslexic and regular readers were compared while performing a word recognition task in the two forms of Hebrew script (the phonologically transparent pointed script and the phonologically opaque unpointed script). A visual non-orthographic task controlled for the visual difference between the scripts.

Results: Behavior. A main effect of form of script on response-times was obtained ($F(1,46)=15.26$, $p<.001$, $\eta p2=.25$), and it was larger in dyslexics than in regular reader. Electrophysiology. The form of script affected amplitudes associated with early visual-orthographic processing in both groups (regular readers: $F(1,23)=34.03$, $p<.001$, $\eta p2=.60$; dyslexics: $F(1,23)=6.37$, $p<.05$, $\eta p2=.22$) at occipital-temporal sites. The results suggested that this effect was not visual per-se. At later orthographic-linguistic stages of processing, an effect of form of script on central-parietal amplitudes appeared earlier in regular readers (350 ms: $F(1,23)=10.25$, $p<.01$, $\eta p2=.31$) than in dyslexics (450 ms: $F(1,23)=4.77$, $p<.05$, $\eta p2=.17$). Both early and late effects of form of script were larger in regular readers than in dyslexics.

Conclusion: The effect of form of script on behavioral measures was larger in dyslexics than in regular readers. In contrast, the same effect on brain activity was larger in regular readers than in dyslexics. This suggests that dyslexics lack cognitive flexibility of adjusting processing to the constraints imposed by different orthographies.

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Computational prediction of novel protein–protein interactions in the post synaptic density

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Background: The post synaptic density (PSD) is a specialization of the cytoskeleton at the synaptic junction, containing hundreds of different proteins. Its function is to detect and respond to neurotransmitter that is released from presynaptic terminals. It is widely believed that characterizing the protein components of the PSD and their interactions can help elucidate the mechanism of long-term changes in synaptic plasticity, which underlie learning and memory. Unfortunately, proteomic and interactomic measurements provide an incomplete (false negatives) and noisy (false positives) picture of the PSD composition and the interactions between its protein compounds. Interactomic data for example, are obtained from small-scale experiments, which are highly trustworthy but suffer from low coverage, or from high throughput experiments, which produce more false interactions.

Results: In this study we propose a computational framework to improve the reconstruction of the PSD network. The approach is based on learning the characteristics of PSD protein interactions from a set of high confidence interactions, and predicting new interactions between candidate proteins. For this we created a "seed" network of trusted proteins and interactions by merging data from papers reporting interactions between proteins localized to the PSD, and expand it with data collected from large scale repositories. We then predicted how proteins that are suspected to reside in the PSD interact with proteins in the network. This method yielded a set of predicted interactions, half of which had supporting evidence in the literature. We found connections of particular interest between proteins of the LRRTM family and PSD-95, possibly connecting disease related regulators with intracellular signaling pathways.

Embracing disorder: making sense of complex population codes

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Background: Cognitive tasks require the joint activity of a large population of neurons. Hence there is no a priori reason to find single neurons with easily interpretable activity profiles. Yet when we record from single neurons, we look for and bias our models by precisely these neurons. Here, we use data from the delayed vibrotactile discrimination task from the Romo laboratory to highlight the "not easily interpretable" neurons[1,2].

Results: We compare three different models to data recorded from the prefrontal cortex of monkeys performing this task. The first model is a highly organized linear attractor model, where the internal connectivity is dictated by the neurons' tuning curves. The second model is a randomly connected network with chaotic activity, where the only

training is done on the readout. The third model is an intermediate obtained by training the internal and external connectivity of an initially random network. We show that the data most resemble neurons from the intermediate model, but that some "orderly" features of the data are present in the chaotic model as well.

Conclusions: Initially random networks are able to perform a working memory and decision making task after training. Our results suggest that prefrontal networks may begin in a random state relative to the task, and initially rely on modified readout for task performance. As training proceeds, more tuned neurons with less time-varying responses should emerge as the networks become more structured. Furthermore, our results provide a cautionary note about interpretation of seemingly ordered features of the data as hinting on specific network structures.

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mTORC1 inhibition disrupts reconsolidation of alcohol-associated memories and prevents relapse

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Background: Relapse to alcohol abuse is caused by retrieval of alcohol-associated memories. Memory reconsolidation is a process in which memories are temporarily destabilized upon their retrieval (reactivation), and then undergo restabilization in order to persist. During this process, the reactivated memory becomes labile to manipulations, offering an opportunity to interfere with unwanted memories. Activation of the kinase mammalian target of rapamycin complex 1 (mTORC1) is required for synaptic proteins translation, and is implicated in synaptic plasticity, learning and memory. Here, we tested whether reconsolidation of alcohol-related memories upon their retrieval activates the mTORC1 signaling pathway, and whether these memories can be disrupted by inhibiting this pathway, with the goal of preventing relapse to alcohol seeking and intake.

Results: Reactivation of alcohol-related memories increased the phosphorylation of the mTORC1 substrates 4E-BP and S6 kinase, and the S6K substrate S6, in the prefrontal cortex and amygdala, indicating activation of this pathway. To test whether mTORC1 inhibition during memory reconsolidation interferes with subsequent alcohol seeking, we administered the mTORC1 inhibitor rapamycin (20 mg/kg, i.p., or 50 μg/side, intra-amygdala) immediately after memory reactivation, and observed reduced alcohol seeking and intake 24 hrs and even 2 weeks later. Importantly, alcohol seeking was not affected by rapamycin when the memory reactivation session was omitted, or when rapamycin was administered 5 hrs after memory reactivation, suggesting that the memory retrieval initiates a time-limited vulnerability window, during which memories are destabilized and can be disrupted.

Conclusions: Our findings suggest that reactivation of alcohol-associated memories activates the mTORC1 pathway in specific brain regions, and that inhibition of this pathway can be used to disrupt the memories and reduce relapse.

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Inactivation properties of Na+ channels in the axonal spike trigger zone of cortical pyramidal neurons

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Background: In cortical pyramidal cells, as in many CNS neurons, spikes generally initiate in the axon initial segment (AIS) - the proximal part of the axon where the neuronal membrane is not covered with a myelin sheath and which possesses a distinctive, specialized assembly of voltage gated channels and associated proteins. Preferable AIS spike initiation is explained, at least partially, by lower activation voltage of local Na^+ channels. To what extent the inactivation properties of these channels differ from those in soma and dendrites? Molecular studies suggest that Na^+ channel inactivation is voltage independent process that derives all of its apparent voltage-dependence from activation. If inactivation rate indeed depends only on the rate of activation, low-threshold axonal channels are expected to be more prone to inactivation and therefore less available at functionally critical subthreshold voltages.

Results: We probed the voltage dependence of the axonal Na^+ channel inactivation by measuring changes in fluorescence of Na^+ -sensitive indicator, SBFI, elicited by single action potentials in layer 5 pyramidal neurons in neocortical slices. As with conventional Na^+ current recordings, we assumed that the amplitude of Na^+ flux could provide us with an estimate of Na^+ channel

availability before an action potential was fired. We found that axonal Na^+ channel availability was nearly maximal at resting potential, as stepping the membrane even to very negative potentials caused no significant increase in Na^+ influx. By applying slow depolarizing current ramps to the soma, we found that the availability of the AIS Na^+ channels changes very little.

Conclusion: Voltage dependence of inactivation of the AIS Na^+ channels is rightward shifted as compared with somatic channels, making the formers fully available even at very depolarizing voltages.

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Neurons grpwing atop topographic nano-cues mimic neuron-neuron interactions

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Understanding the influence of the neuronal chemical and physical environment on the neuronal growth has great implications for both neuronal repair and for neuro-engineering. Previous studies have identified processes that take place along neuronal growth and influence the geometry of the neuronal dendrites and axons, which show extremely diverse complex structures. A key mechanism is the ability of the motile growth cones at the tips of growing processes to measure environmental cues. According to previous studies, the substrate topography has an important role in neuronal growth. We study the effect of topographic nano-cues on the neuronal growth and morphology. We use photolithography to fabricate substrates with repeatable pattern ridges of nano-scale heights between 10 nm to 150 nm. We plate leech neurons atop the substrates and analyze the response of the entire neuronal branching tree to the patterned substrates and find significant effect compared to non-patterned substrates. Moreover, we show that the interactions with the nano-cues trigger a growth strategy similarly to interactions with other neighbor neuronal cells, as reflected in their morphometric parameters. The number of branches and the number of neurites originating from the soma decrease following the interaction demonstrating a tendency to a more simplified neuronal branching tree. According to common paradigms neuronal connections that are functional tend to stabilize the structure. It is interesting to analyze gap junctions and synapse formation along the neuronal growth in order to investigate whether neurons identify the interactions with the nano-ridges as functional. Further investigation will strengthen our understanding of the interplay between neuronal function and form.

Thalidomide analog, 3'6,dithiothalidomide, as a neuroprotective treatment for minimal traumatic brain injury - possible mechanisms

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Background: Traumatic brain injury (TBI) is a leading cause of death and lifelong disability in individuals under the age of 50. TBI occurs when an external force is applied to the head. In contrast to TBI in which a brain morphological alteration is detectable, mild traumatic brain injury (mTBI) lacks visible objective structural brain damage. mTBI patients frequently suffer from long-lasting cognitive, behavioral and emotional difficulties that include biochemical changes such as apoptosis and inflammation. Till today there is no effective treatment or cure for patients with mTBI. Tumor necrosis factor-alpha (TNF-a) is a cytokine that is fundamental in the systemic inflammatory process. TNF-a levels are increased post TBI and can lead to secondary damage in the brain tissue and instigate an apoptotic cascade in susceptible neurons leading to dysfunction or death. Thio analog 3,6'-dithiothalidomide have been synthesized of N-a-phthalimidoglutarimide, the backbone of the well-known drug, thalidomide in order to reduce the initial rate of synthesis of TNF-a.

Results: In the current study, we evaluated the efficacy of the potent drug, 3,6'-dithiothalidomide on the recovery from mTBI in a closed head weight-drop model in mice. Mice were assessed for spatial learning using the Y-maze test 30 days post injury. We found improvement in cognitive performance in mice that received the analog 12 hr after injury compared with the mTBI group. Moreover, administration of the analog 1 hr post injury prevented the elevation of TNF-a 12 hr post mTBI. Immunflouresence of NeuN showed decreased number of neurons in the brain 72 hours post injury. This neuronal loss was prevented after the analog treatment.

Conclusion: These results imply a potential novel neuroprotective effect of 3,6'-dithiothalidomide. However, it is still unclear whether the mechanism involves neurogenesis or prevents apoptosis, further investigation needs to be done.

Frontal lobe segmentation based on inversion recovery layers imaging

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Background: The cortex laminar arrangement of neuronal structures is the basis of brain parcellation (Brodmann areas,

BAs). The ability to image the cortical sub-structures in-vivo, in 3D and for the whole brain is one of the holy-grails of neuroscience. In this work we utilized inversion-recovery magnetic resonance imaging (IR-MRI) to detect and characterize cortical sub-structures via T1 contrast.
Results: We show that T1 distribution along the cortex has a Gaussian mixture that may allow its segmentation into 5-6 clusters. Clustering analysis of high contrast IR images of the cortex appeared to have laminar arrangement (i.e., IR layers). Previous work (Barazany, 2009) showed that there is a correlation between the IR layers and its histological cytoarchitectonic characteristics. The purpose of this work was to examine the IR layers characteristics at different cortical BAs, focusing on BAs of the frontal lobe. We show that the width of the IR layers changes significantly between different cortical regions. This observation indicates that the IR layers has a morphological meaning and can be used for regional cortical architecture studies both in healthy and diseased human brains. The cellular interpretation of the IR layers still needs to be investigated.
Conclusions: The results of this work indicate that IR could become a powerful tool for in vivo assessment of cortical layers. The proposed methodology can advance our understanding of the relationship between regional variability in the cortical lamination and function in developing and adult healthy brains as well as in various neurological and psychiatric diseases.

Astrocyte inflammation: possible role for kinins
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Background: The nine amino-acid kinin, Bradykinin (BK) is a powerful mediator of peripheral inflammation. However, the role of bradykinin in the regulation of brain inflammation is not clear. Elevated levels of bradykinin were found under pathophysiological conditions such as brain inflammation. Brain inflammation includes activation of glial cells, elevated expression of pro inflammatory enzymes such as cyclooxygenase and release of inflammatory mediators such as prostaglandins. The aim of this study was to investigate long term effects of BK and Lys-Des-Arg10-BK (B1 receptor agonist) on prostaglandin E2 (PGE2) synthesis in primary astrocytes. Protein and mRNA levels of cyclooxygenase species (COX-1 and COX-2), key enzymes in PGE2 synthesis, were also measured following treatment with BK and B1 receptor agonist.
Results: In basal and lipopolysaccharide (LPS) - stimulated cells BK increased PGE2 release as well as COX-2 protein levels by 30 %-40 %. By contrast, B1 receptor agonist decreased PGE2 release and COX-2 protein levels to control levels. Both kinins had no effect on COX-1 protein levels. COX-2 mRNA levels were also affected in an opposite manner by BK and B1 receptor agonist treatments. Several lines of evidence have demonstrated that MAPK may be involved in regulation of expression of PGE2 by kinins in various cell types. Specific MAPK inhibitors (U0126 for, ERK1/2 SB203580 and SB220025 for p38- MAPK and SP600125 for JNK) completely abrogated BK and B1R agonist effects on PGE2 synthesis in basal and LPS stimulated astrocytes. Western blot analysis revealed a significant increase in phosphorylation of ERK1/2 but not of JNK and p38, after treatment with BK. No change in kinases' phosphorylation was observed upon B1 agonist treatment.
Conclusion: Our results imply, for the first time a dual and long-term regulatory role of kinins in astrocyte inflammation.
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The morphology of microglia is altered in aging and in a mouse model of Alzheimer's disease
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Objective: Microglia are derived from monocyte lineages which reside within the central nervous system (CNS) already during development once the vasculature is formed. The cells integrate within the neural tissue exhibiting a unique ramified morphology which allow them to constantly scan their territory and contribute to neuronal network function and repair. Since microglia cells are long-lived they are subjected to senescence processes. Although studies have shown that microglia senescence can be reflected by morphological changes, detailed quantification of such changes are not suficiently established.
Methods: We developed a digitized tool that allowed us to quantitatively characterize the fine microglia structure in the brain's cortex of adult mice and the morphological changes the cells undergo with aging and the progression of Alzheimer's-like disease. In addition we established quantitative methods to evaluate the coverage of the neural tissue by resident microglia.
Results: We found that compared with microglia in young mice, microglia in mice aged 21 months labeled either by GFP expression under the CX3CR1 promoter or immunostained with anti-Iba-1, are less ramified, have decreased amount of branches and lower amount of fine processes. Notably, the morphological aberrations of microglia appeared in a mouse model of AD already at 9 months of age associated with the deposition of amyloid plaques. Overall, we demonstrate a significant reduction of the volume coverage by individual microglia with age, a process that is expedited in a mouse model of AD.

Conclusions: Our results indicate that microglia are subjected to age- and disease-related changes that may indicate their state of activation along with a compromised ability to support neuronal function and repair.

A two-signal model for non-pathological activation of the choroid plexus epithelium for trafficking to the central nervous system

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The healthy brain is an immune privileged site, shielded by barriers from circulating immune cells. Nevertheless, numerous studies have suggested that a continuing dialogue between the brain and circulating immune cells is needed to maintain life-long brain plasticity, including neurogenesis, cognitive ability, and resilience to stress. Since the blood-cerebrospinal fluid barrier (BCSFB), at the brain's borders, is constantly exposed to circulating immune cells, we hypothesized that at this junction, the choroid plexus (CP) epithelium can sense signals coming from the central nervous system (CNS) parenchyma via the cerebrospinal fluid (CSF) and through dialogue with circulating immune cells, translate them into a reparative or protective mechanism. Here we found that different T cell populations, with distinct cytokine polarities, accumulate at the CP of healthy animals and affect the immunomodulatory properties of the CP epithelium and its ability to facilitate trafficking of leukocytes. We further show that activation of the CP for expression of trafficking molecules is tightly regulated by two signals; with the first signal coming from the CNS parenchyma, and the second from outside the CNS. Taken together, our findings demonstrate that the CP epithelium is endowed with immunological plasticity allowing it to serve not only as a filter for CSF nutrients, but also as an active interface for selection of circulating immune cells, regulating immune cells trafficking into the CNS.
The first two authors contributed equally to this study.

Active vision of barn owls: a kinematic analysis

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Background: Most animals use their vision as an active process. The combination of vision with the motion of sensory organs generally enhances the quality and quantity of the acquired visual information. In this study, we have investigated head movements of barn owls (tyto alba) with advanced kinematic tools from screw theory, with focus on side-to-side peering head motions. Screw theory allows a kinematic study with emphasis on the linear / rotational components of the examined movements. Experiments were conducted on two freely viewing perching barn owls in a motion-capture system providing kinematic recordings with very high precision.
Results: Peering motions were compared to other motions with regard to the screw parameters describing the motion. For both owls, the screw parameters were almost constant along peering motions when compared to the reference motions ($p<1e\text{-}5$). Furthermore, the screw intensity (denoting the similarity of the motion with a screw motion) was found to be smaller in peering motions for both owls ($p=0.04$ and $p=0.002$, respectively).
Conclusions: Screw analysis of the peering head motions of barn owl provided a characterization of those peculiar peering movements, supposedly used to improve depth estimation. The insights provided by this study will be implemented on a robotic agent in order to to build a Microsoft's Kinect–mounted mobile robotic platform that would replicate head movements of barn owls to improve robotic visual acquisition and scene reconstruction.

T-type calcium channel CaV3.2 upregulation in epileptogenesis: underlying mechanisms and functional consequences

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Background: Temporal lobe epilepsy (TLE) is one of the most common seizure disorders in adults. However, the underlying mechanisms during its pathogenesis, collectively referred to as epileptogenesis, are poorly understood. Using the pilocarpine model of TLE, we have recently found that the pore-forming T-type calcium channel subunit $Ca_V3.2$ is upregulated early in epileptogenesis. Moreover, deleting *$Ca_V3.2$*impeded the development of TLE in this model. Therefore, we attempted to identify the molecular signaling cascades involved in *$Ca_V3.2$* transcriptional regulation.
Results: First, we determined the promoter region *in silico* and observed stimulatory and inhibitory clusters. Furthermore, we found binding sites for the transcription factor early growth response 1 (Egr1/Zif268/Krox-24) and the zinc sensor metal-regulatory transcription factor-1 (MTF1) to be highly overrepresented within the *$Ca_V3.2$* promoter region. mRNA expression analyses and dual-luciferase promoter assays revealed that the *$Ca_V3.2$* promoter was strongly

activated by the two transcription factors. Congruently, whole-cell T-type calcium currents were significantly larger after Egr1 and MTF1 overexpression. Furthermore, rAAV-mediated overexpression of these factors in mice hippocampi *in vivo* also caused $Ca_V3.2$ upregulation.
Conclusions: The transcription factors Egr1 and MTF1 regulate *$Ca_V3.2$* promoter activity and mRNA expression and hence, the size of T-type calcium currents. These findings may provide new possibilities for pharmacological intervention aimed at preventing the process of epileptogenesis.
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Optogenetic in-vitro activation of hippocampal mossy fiber synapses reveals major role for tomosyn in short-term plasticity
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Background: Tomosyn is an evolutionary conserved, syntaxin-binding protein that inhibits vesicle release in several invertebrate models, as well as in mammalian chromaffin cells. The role of Tomosyn in regulating neurotransmitter release in the mammalian CNS, however, remains poorly understood. Interestingly, Tomosyn is highly expressed at hippocampal mossy fibers (MFs), the axons of dentate granule cells that synapse onto CA3 pyramidal neurons. In this study, we sought to determine the role of tomosyn in setting the characteristically low initial release probability (P_r) observed at the MF synapse. To this end, we injected into the dentate gyrus lentiviral particles containing both a tomosyn RNAi sequence and ChIEF - a channelrhodopsin2 variant with improved activation kinetics. Acute hippocampal slices were prepared 1-2 weeks following injection and extracellular MF responses in the CA3 area were elicited both optically, enabling activation of RNAi-expressing cells only, and electrically by bulk stimulation of MFs. Tomosyn knock-down effects on short-term plasticity were assessed by measuring the change in response to various stimulation paradigms.
Results: When stimulated optically, tomosyn RNAi-expressing synapses exhibited a significant reduction in various forms of activity-dependent facilitation, compared to a control group, consistent with an increase in basal P_r. However, this effect was hardly observed when the same slices were stimulated electrically and uninfected neurons were inevitably recruited along with the infected ones.
Conclusions: These data strongly suggest that Tomosyn levels at MF terminals regulate short-term synaptic plasticity, consistent with Tomosyn's acting role as a negative controller of the vesicle release mechanism. Our findings also highlight both the feasibility and the potential power of combining optogenetics and gene targeting approaches in order to investigate molecular mechanisms of presynaptic release at central synapses.

Evaluation of the CerS2 null mice brain pathology
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Sphingolipids (SLs) are highly enriched in the CNS, especially in myelin where they account for more than half of the total lipid content. The lipid composition of different brain areas and brain components was studied in detail in the 1960s and it has been documented that different lipids are found in specific cells and regions of the CNS. There are exciting clues that levels of ceramides and SLs with defined acyl chains lengths change in a number of neurological conditions. The discovery of the six ceramide synthases (CerS) conveyed new information implying that the acyl chain length is of great importance in both physiology and in pathophysiology. Recently, our laboratory has generated a CerS2 null mouse. CerS2 is the most ubiquitously expressed CerS and has the broadest tissue distribution. This mouse showed abnormal bilateral and symmetrical vacuolization and gliosis in specific brain areas. Myelin degeneration and detachment was also observed, probably due to reduced levels of galactosylceramide, a major component of myelin. Additional abnormalities included convulsions originating from a sub-cortical region and striking alterations in their circadian rhythms, in the middle of the night their activity drops down dramatically. Moreover, young CerS2 null mice present higher levels of anxiety measured in a bright open field arena and showed longer reaction times in acoustic startle response measurements. In the Pre Pulse Inhibitory (PPI) paradigm CerS2 null mice do not respond in reducing their reaction time, as expected. These results show that ceramides play a critical key role in brain function and they might be involved in the pathogenesis of psychiatric disorders. Through the analysis of the CerS2 null mouse brain and the distribution of the different CerS in different cell types of the CNS we will try to shed some light on the relation between known neuronal conditions and psychiatric disorders, and SLs composition.

Time limited functional properties of transplanted neural stem cells
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Neural stem cells (NSC) possess powerful immunomodulatory and neurotrophic properties. NSCs effectively attenuate

neuroinflammation, protect the brain from immune-mediated injury and facilitate its self repair capacity. However, the therapeutic value of NSC therapy in chronic diseases is critically dependent on their long term functions. We therefore examined whether transplanted NSCs maintain their immunomodulatory and trophic properties over time.
Transplanted NSCs could not support their own long term survival, becoming highly dependent on environmental cues. Damaging versus induction of a local neurogenic environment significantly compromised or improved graft survival, respectively. In accordance, long term cultured NSC spheres exhibited dramatic decline in proliferative activity, increased apoptosis and reduced neurotrophic factor secretion.
Then, in two experimental paradigms, intracerebroventricular transplanted syngeneic NSCs attenuated an early relapse of experimental autoimmune encephalomyelitis, but failed to inhibit delayed relapses, albeit good survival of transplant. Moreover, following allogeneic transplantation, NSC grafts failed to inhibit the allogeneic immune reaction and were rejected from the host brain. In correlation, long term cultured NSCs lost their capacity to inhibit immune cell proliferation in vitro. In conclusion, long-term functional changes in transplanted NSCs lead to loss of their therapeutic immunomodulatory and neurotrophic properties.
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Sexually dimorphic processing of social cues in the medial amygdala: functional and developmental aspects
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Different individuals display varied responses to given stimuli. A consistent and dramatic example involves the distinct behavioral and physiological responses of males and females to socially relevant cues. The reproducibility of these sex specific behaviors implies the existence of sex-specific differences in the neuronal circuits that process such information. However, how differences in neuronal function lead to such behavioral differences remains poorly understood, particularly in mammals. To understand the mechanisms that account for these differential behaviors, we measured neuronal responses to social stimuli in male and female mice in the first two brain relays along the vomeronasal pathway. Our recordings revealed that striking changes in neuronal response properties emerge at the level of the vomeronasal (medial) amygdala, but not in the previous processing stage (the accessory olfactory bulb). Experiments with juveniles and with hormonally challenged mice indicate that this dimorphism is not present at birth, but rather appears around the time of puberty. Our results thus provide a striking example of a sexually dimorphic neuronal circuit with direct relevance for reproductive behavior.

Conditioned sexual aversion
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To ensure survival and reproduction, animals recognize their conspecifics via detection of pheromones, and engage in innate, gender-specific social behaviors. Sexual preference is defined as the attraction male mice have for female conspecific odors, versus male odors. This preference is innate, and thought to be 'hard-wired' and genetically programmed in the nervous system. This study was set to test the influence of negative environmental stimuli on pheromone-mediated innate responses, such as sexual olfactory preference, sexual behavior and aggressive behavior.
We applied the conditioned olfactory aversion (COA) paradigm on adult wild-type (wt) male mice. Mice learned to associate soiled bedding embedded with female odors with delayed lithium-chloride (LiCl) toxicosis, and were tested for their olfactory preference and sexual behavior towards a female intruder. In addition, in order to examine the lasting period of this unique association we applied an extinction protocol at the end of the experiment.
Results show that following LiCl injections, wt male mice learned the aversion to female odors and as a consequence their initial sexual olfactory preference disappeared. Furthermore, the olfactory conditioned male mice were tested for their behavioral responses toward intruder female mouse. Surprisingly, the manipulated males presented avoidance behavior from the female and engaged in significantly less sexual behavior (mounting and pelvic thrusts) in compared to the control male mice. In the extinction assay, we found that the preference to female over male odors was regained after two weeks, however the behavioral course persisted. These results indicate that negative past experience can alter male innate sexual preference and affect its evolutionary reserved behavioral sequence towards a female conspecific. The neuronal circuits and processes which are involved in this behavioral change remain to be elucidated.

Decreased "Default-Mode" activity in trained meditators
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Background: A growing body of brain imaging research has focused on "task-negative" brain responses - in which performing an extrinsically oriented task leads to reduced brain activation compared to baseline, "resting-state" condition. The source of this task-negative response is still debated; however we have proposed that it reflects a spontaneous

tendency to shift attentional resoruces intrinsically during rest (Preminger et al., 2010). An interesting question concerns the manifestation of such default responses in individuals that were trained over extended periods in meditation methods. Here, we investigated this issue by comparing the magnitude of default responses in untrained individuals and individuals trained for 16.5 y years (avg.) in Mindfulness meditation (MM).

Methods: fMRI data was collected from 15 proficient MM and 23 control participants during a DMN visual localizer, and a "thoughtless" instructed condition.

Results: Comparing the controls with the MM revealed a significantly higher "Default" activation in the controls compared to the meditators. Similarly, the "thoughtless" condition showed a weaker level of inhibition in the meditators compared to the controls.

Conclusion: Our results show a reduced level of "rebound" signals during rest in long term meditators. A likely source of this effect may be a better ability of the meditators to prevent a spontaneous lapse into intrinsic processing and "mind wandering" during rest.

Preminger, S., Harmelech, T., & Malach, R. (2010). Stimulus-free thoughts induce differential activation in the human default network. NeuroImage, 54, 1692–1702.

Proinflammatory cytokines a potential targets for therapeutic intervention in central nervous system disorders

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Background: Cytokines of the TNF superfamily sustain inflammation and eventually cell death, by activation of downstream apoptosis pathways set into motion after binding with specific death receptors. The expression of proinflammatory/proapoptotic cytokines is inducible by noxae, such as proteins, trauma, and ischemia. Tumor necrosis factor related apoptosis inducing ligand (TRAIL) is a member of the TNF family which induces death of both tumor and normal cells.

Results: Human neurons exposed to the Alzheimer's disease-related neurotoxic protein amyloid-beta (AB), display increased expression of TRAIL and its death receptors. On the other hand, a TRAIL neutralizing antiserum rescues numerous AB-challenged neurons from apoptotic death. Similarly, the exceeding apoptotic rate associated with mechanical spinal cord injury is also sustained by TRAIL, which, in addition, recruits other cytokines, such as FasL and IL-1, that sinergistically contribute to enlargement of damage. Either spinal neuron apoptosis rate and consequent functional deficit are significantly attenuated by administration of anti-TRAIL serum in the mouse. Moreover, middle cerebral artery occlusion in the rat, results either in overexpression of TRAIL in the corresponding ischemic areas, and in attenuated expression of its neutralizing decoy receptors. Preconditioning, a mild, transient subocclusion of the middle cerebral artery, is a neuroprotective modality that prevents extensive ischemic damage and is associated with significantly attenuated expression of TRAIL and its death receptors in the neurons of the ischemic area.

Conclusions: The bulk of these data clearly shows that TRAIL is a potent mediator of cell death associated with neuroinflammatory processes, and that neutralization of its detrimental effects results in restraint of neural damage. It is thus plausible to hypothesize that the TRAIL system represents a relevant target for innovative treatment of central nervous system disorders.

The effect of grouping on neural competition in object-category selective cortex

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Background: Single-cell electrophysiology studies have shown that multiple stimuli presented simultaneously in the cell's receptive field compete for representation by mutually suppressing neural responses. Suppressive interactions among multiple stimuli have been also reported in fMRI studies that showed lower fMRI signal to simultaneously presented stimuli than to the same stimuli presented sequentially. These fMRI studies have so far examined such competition effect only for low-level stimuli (e.g. gabor patches). In the present study we aimed in examining whether such effect of neural competition also exists for preferred and non-preferred stimuli in object category selective brain areas. In addition, we asked whether grouping of two simultaneously presented stimuli would reduce this competition effect. We presented pairs of faces and headless bodies above and below fixation simultaneously or sequentially.

Results: Our results show significant competition effect between two faces presented simultaneously in the face-selective areas, and between two bodies presented simultaneously in the body-selective areas. Competition was also found when a body was presented above a face, but was reduced when a face was presented above a body, generating the perception of a person.

Conclusions: Our findings show neural competition between multiple object stimuli in object category selective cortex. They also show that competition in object-selective areas occurs between objects, and not between features within an object, therefore, once stimuli are grouped together by perceptual organization processes, they are perceived as a unit rather than two competing stimuli, and neural competition is reduced.

Implementing novel methods for evaluating consciousness in chronic vegetative subjects

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Background: The clinical evaluation of consciousness in coma patients based on their exhibited behavior is difficult and remains erroneous in many cases. Coleman et al (2009) demonstrated different levels of hierarchical auditory processing in patients suffering from disorders of consciousness. Moreover a few patients were able to perform willful modulation of their brain activity (Monti, 2010) and this method was used to communicate with one of the patients. These promising results were used to implement a clinical service for consciousness evaluation done by the fMRI unit in Hadassah.
Results: 10 subjects were scanned so far. Patients (ages 11-67) were all diagnosed as vegetative state or minimal conscious. Patients suffered from traumatic brain injury (6) or anoxic brain damage (4). The main challenges in translating this test to clinical diagnosis are the uncontrolled motion of many patients and the severe brain damage that creates extreme difficulties in recognition of brain structures. In some patients accuracy of results is questionable due to the significant artifacts. Functional tests included a hierarchical auditory test (patients heard noises, language like non words, words (in familiar and non-familiar voices), their name), an imagery task, and a visual task. While in 8 patients auditory related activation was found, only in 4 differential activation was found for language. 5 of the patients showed differential response to their own name. In three patients a response to visual stimuli was identified. In one patient the auditory and linguistic systems were clearly activated in a hierarchical pattern, and moreover willful modulation of brain activity was identified in the imagery test.
Conclusion: FMRI can reveal the existence of awareness without open channels of communication. Our results show the possibility of using fMRI as a clinical tool to assess consciousness and thus improve diagnosis and supply a good marker of prognosis.

Can we train the dyslexic's brain to read better?

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Background: The Asynchrony theory suggests that the brain systems of dyslexic readers activated during reading process information on a different time scale. A wider speed of processing gap impairs the between system integration resulting in dyslexic readers. The Acceleration theory maintains that readers at all levels and ages are capable to read faster than their routine reading rate, and thereby enhance their reading decoding and comprehension (Breznitz, 2006). Based on the idea of the brain's plasticity and ability to change, these two theories were combined and had been the bases for the creation of the Reading Acceleration Training Program (RAP) for reading skills enhancement of dyslexics. The current study was design to investigate the RAP effect on immediate and long post retention on brain activity and reading skills improvement in 20 experimental and 20 waitlist dyslexic readers (-1.s.d in reading test). ERP's and behavioral measures were obtained.
Results: Evidence indicated a significant effect of RAP on decoding and fluency skills of the research groups. Furthermore an effect of higher amplitudes of N170 ERP component in the FFA post training was also found. However the retention of these effects after 4 months was moderate.
Conclusions: An immediate effect of the RAP training on the improvement of reading skill and brain activity of dyslexic reader was found. However for long post retention of these effects a booster regime of the RAP training was suggested. Furthermore our results also raised the question of whether remediation induced performance gains, reflect an enhancement of previously established processing routines or rather the establishment of new, alternative, processing routines. This issue is directly related to the acceleration paradigm, since it is conceivable that above a certain stimulus presentation speed the brain cannot handle the information by relying on pre-existing routes and is forced to resort to new solutions.
This study was supported by the Edmond J. Safra Philanthropic Foundation.

The effects of discrimination type and setting on the electrophysiology of speech processing in humans

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Background: Speech discrimination is based on both spectral and temporal acoustic cues. In non-speech auditory stimuli these cues are processed differently in the brain but they have not yet been studied in relation to speech perception.
The electrophysiology and spatiotemporal distribution of speech processing in humans were used to compare processing of consonants discriminated by spectral and temporal cues.
Results: Subjects were presented with series of vowel-consonant-vowel (VCV) stimuli comprised of different stimuli along a temporal continuum between clearly distinguished /

ubu/ and /upu/, with 3 ambiguously distinguished VCV stimuli with intermediate closure durations to determine processing of temporal cues. A series of stimuli along a spectral continuum between clear /ubu/ and /udu/, with 3 intermediate ambiguous VCVs were presented to study processing of spectral cues. Brain potentials include an onset P1, N1, P2 complex and sustained negativity lasting hundreds of msec. While responses to the onset vowel were the same across settings, the consonant-evoked latencies were sensitive to voice-onset time. The sustained negativity was larger in spectral than temporal discrimination and largest in the mixed setting.
Spatiotemporal distributions of brain activity associated with processing consonants vary between spectral and temporal discrimination, and depend on the context in which discrimination is performed, i.e., in temporal, spectral or mixed settings.
Conclusions: Brain activity to speech VCV discriminations is sensitive to spectral and temporal acoustic cues, is associated with different distribution in the brain and is modulated by listening circumstances.

Highly interconnected microvasculature supports restricted blood flow independent of columnar boundaries

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Background: Proper brain function depends on the continuous blood flow supply. Increase in neuronal activity results in a localized vascular response with amplitude and sign dependent on a plethora of factors. Past methodologies used to understand the organization of this interface at the cortical column level lacked the ability to jointly resolve the vascular network structure while directly measuring the location of cortical columns. Here, we obtained complete vascular networks concomitant with the location of all neurons and non-neurons across several cubic millimeters of mouse somatosensory cortex at μm3/voxel spatial resolution. We set to clarify whether the vasculature is organized as units around cortical columns or –alternatively– embedded in a continuum of vasculature. This bears on the interpretations of BOLD-based imaging methods and on the overall control of functional hyperemia.
Results: Three major topologies can be identified in the cortical vasculature: a robust surface network, penetrating vessels and a mesh-like microvasculature. Penetrating arteries and veins show a weak tendency to plunge outside the perimeter of cortical columns. Interestingly, we find less penetrating arteries than cortical columns. Topological analysis and blood flow simulations revealed weakly defined vascular domains with no spatial correlation to cortical columns. Further, point-to-point resistance analysis revealed that the microvasculature behaves as a regular lattice.
Conclusions: Overall, our findings support the alternative hypothesis where cortical columns are embedded in a homogeneous vascular network. We conclude that experimentally observed micro-stroke vascular dynamics results from the discrepancy between the resistance of penetrating arteries and veins vs. the microvasculature. In turn, the combined blood rheology and the vascular structure allows for control of vascular dynamics with minimal changes in capillary diameters.

ApoE4 induces Aβ42, tau, and neural pathology in the hippocampus of young targeted replacement apoE4 mice

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Background: Recent findings suggest that the pathological effects of apoE4, the most prevalent genetic risk factor for Alzheimer's disease (AD), start many years before the onset of the disease and are already detectable at a young age. In the present study we investigated the extent to which such pathological and cognitive impairments also occur in young apoE4 mice.
Results: Our work revealed that the levels of the presynaptic glutamatergic vesicular transporter, VGlut, in the CA3, CA1, and DG hippocampal subfields, were lower in hippocampal neurons of young (4-month-old) apoE4-targeted replacement mice than in those of the corresponding apoE3 mice. In contrast, the corresponding inhibitory GABAergic nerve terminal and perikarya were not affected by apoE4. This synaptic effect was associated with hyperphosphorylation of tau in these neurons. In addition, apoE4 increased the accumulation of neuronal Aβ42 and induced mitochondrial changes, both of which were specifically pronounced in CA3 neurons. Spatial navigation behavioral studies revealed that these hippocampal pathological effects of apoE4 are associated with corresponding behavioral impairments. Time-course studies revealed that the effects of apoE4 on tau hyperphosphorylation and the mitochondria were already apparent at the age of 1 month and that the apoE4-driven accumulation of neuronal Aβ and reduced VGlut levels evolve later and are apparent at the age of 2-4 months.
Conclusions: These findings show that apoE4 stimulates the accumulation of Aβ42 and hyperphosphorylated tau and reduces the levels of VGlut in hippocampal neurons of young apoE4-targeted replacement mice. These neurochemical effects are associated with cognitive impairments. This model is not associated with hypothesis-driven manipulations and is thus most suitable for unbiased studies of the mechanisms underlying the pathological effects of apoE4.

Functional connectivity and mechanisms of synchronization in finite size neuronal networks

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Background: One of the main challenges of modern neuroscience is to understand how network dynamics are related to anatomical connectivity. Recently, it has been demonstrated the existence of functional connector "hubs" in the developing hippocampus where such a function is met by a heterogeneous subpopulation of pioneer GABAergic interneurons that display widespread axonal projections. GABAergic hub cells play a central role in the coordination of early network synchronizations combining high functional, effective and structural connectivity. Are hub neurons common components of all growing neuronal networks or other mechanisms/topologies emerge?
Results: We try to address this question in finite-size neuronal networks grown in culture which may represent a general model of self-organized neuronal circuits not depending on a specific architecture. Given the small size of these circuits, a complete functional-morphological characterization can be obtained through calcium imaging and immunohistochemistry. Similarly to the developing hippocampus, finite networks display spontaneous network synchronizations or bursts. Functional connectivity analysis revealed that cells early activated during global network synchronizations are additionally involved in synchronous inter-bursts events involving a small subset of neurons.
Conclusion: These results suggest that a highly synchronous sub-network might regulate and coordinate global network synchrony. Targeted stimulation through optogenetics will be next implemented to map the effective connectivity and the impact of single cell firing on network dynamics.

Shein-Idelson M. for patterning, Brainis I. for cell culture, David-Pur M. for silicon processing

Occasional access of some trees to conscious awareness with no vision of the forest – insight on PPC contribution to perception from a case study of simultanagnosia

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Background: Patients with Balint syndrome following bilateral parietal damage are typically described as being unable to perceive multiple objects simultaneously, a fact preventing them from understanding the visual scene despite correct identification of individual visual objects (simultanagnosia). Here we report a series of observations with DP, a patient with rare stroke-related pattern of damage affecting the right and left posterior parietal cortex (PPC) that appear to shed some new light on the syndrome and on the role of PPC in conscious perception.
Results: (1) Visual disappearance or fading of salient objects or object parts such as face parts or even a single patch on a blank screen whose alternating onsets and offsets every few seconds could be reported, as well as anti-correlated disappearance of two competing objects such as orthogonal bars (2) Spatial crowding in which a surprisingly intact ability to identify very small digits or color patches was dramatically degraded with flanking patterns. (3) A severe deficit in reporting the relative position of objects or point to marked locations on a touch screen; (4) Preserved ability for perceptual grouping of dot arrays even when partially invisible, in a size averaging task. While some of these findings have been previously reported, the dynamic fading and alternating perception of even an isolated small patch as well as large fragments of the visual scene, coupled with these findings, is novel, and is not consistent with common single-object perception descriptions of this syndrome, and theorizing stressing global/focal imbalance.
Conclusions: We propose that the PPC serves as a short-term data holding mechanism for spatially coded information by which internal and external context factors can modulate perception-action and perception-declaration links. Bilateral PPC damage causes simultanagnosia because of failed maintenance of visual information in spatio-temporal working memory.

Holistic representation of bodies in body-selective occipital-temporal areas

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Background: The discovery of specialized processing mechanisms for human bodies, including body-selective areas in occipital-temporal cortex and the body inversion effect, has led to the suggestion that like faces, bodies are processed by holistic mechanisms. Supporting evidence includes behavioral whole-part and composite effects, and a step-like increase in response of the fusiform body area to large relative to small body parts. Here we used fMRI to examine whether body-selective areas prefer a whole body over the sum of its parts. Subjects were presented with blocks of faceless bodies with and without heads, in either whole or dispersed sum-of-parts configuration.

For each subject we located face, body and object-selective areas with a separate functional localizer scan. **Results**: Body-selective areas showed a higher average response to whole bodies vs. sum-of-parts for both intact and headless bodies. The fusiform face area (FFA) showed higher average response to whole vs. sum-of-parts only for intact bodies, not headless. The occipital face area (OFA) and the object-general areas showed no preference for whole over sum-of-parts. Pattern classification analysis revealed above chance classification of whole vs. sum-of-parts in body-selective areas for both intact and headless bodies. The FFA showed above-chance classification for intact bodies but not for headless, whereas classification in OFA was below chance for both.
Conclusions: These findings suggest that holistic representation of human bodies uniquely exists in body-selective areas, but not in object-general areas. The response of face-selective areas depended on the presence of the head and may reflect face mechanisms, which are more likely to be generated by whole intact bodies than by headless bodies or dispersed sum-of-parts.

Early life stress induces histone modifications in the prefrontal cortex and hippocampus

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Background: Early-life stress programs a life-long risk for developing behavioral dysfunctions and mental disorders. We tested the hypothesis that this vulnerability is mediated by persistent memory traces on our genes, which result in altered neuronal and synaptic development of emotionally relevant brain circuits. Using maternal separation as early life stressor we analyzed two main key players underlying experience-induced synaptic plasticity, ARC and EGR1.
Results: Gene expression analysis revealed elevated ARC and EGR1 mRNA in the hippocampus (HIP) of stressed animals compared to unstressed controls, whereas the prefrontal cortex (PFC) was not affected. Western blot revealed that the protein levels of acetylated histone H3 (Ac-H3) and H4 (Ac-H4) were elevated in the HIP of stressed animals. Using chromatin immunoprecipitation-quantitative polymerase chain reaction (ChIP-qPCR) to investigate the association between histone acetylations and the promoter regions of ARC and EGR1 gene we found that promoter region expressions of ARC and EGR1 gene, which are associated with Ac-H4, were significantly increased in the HIP and PFC of stressed mice. Furthermore, increased expression of EGR1 promoter region was associated with Ac-H3 in the PFC but not in the HIP of stressed mice.
Conclusions: Taken together these results indicate that the stress-induced activation of ARC and EGR1 transcription is presumably regulated by histone acetylations and thereby "reprogram" the development of dendrites and synapses in order to adapt to a stressful environment.
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Acetylcholine receptors and the immune system

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Research done in recent years pointed to a novel function of cholinergic transmission. It has been shown that cholinergic transmission can modulate various aspects of the immune function, whether innate or adaptive. Cholinergic transmission affects immune cell proliferation, cytokine production, T helper differentiation and antigen presentation. These effects are mediated by cholinergic muscarinic and nicotinc receptors and other cholinergic components present in immune cells, such as acetylcholinesterase (AChE) and cholineacetyltransferase. The α7 nicotinic acetylcholine receptor was designated anti-inflammatory activity and has shown promise in pre-clinical models of inflammatory disorders. We studied the various components of the immune cholinergic system, and specifically the immunomodulatory effects of α7 activation. This activation can be accomplished either by direct stimulation or indirectly, by inhibition of AChE. Thus, the presence of the immune cholinergic system can pave the way for novel immunomodulatory agents, or to the broadening of use of known cholinergic agents.
Israel Ministry of Health

Automatic bias of temporal expectation following temporally regular input independently of high-level temporal expectation

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The processing of a target event is facilitated if its timing is known, e.g. if it appears in phase with a preceding temporally regular input. This effect has been attributed to automatic entrainment of internal oscillators to the input frequency and phase (exogenous expectation). However, the timing of an event can also be expected based on voluntary shifting of attention to an explicitly memorized interval, and the involvement of such endogenous factors in facilitation following rhythmic input was not examined. Here, we presented a visual target following regularly flickering stimuli, and examined the facilitative effect of the rhythm (faster responses for target in phase vs. target out of phase) in three block types: 'exogenous', in which rhythm phase was not predictive of target timing;

'endogenous entrainment', in which rhythm phase validly predicted target timing; 'endogenous-exogenous conflict', in which subjects were endogenously cued to attend to a memorized interval, while rhythm phase was not predictive. We found a facilitative effect for the rhythm in the all conditions, with similar magnitude in the exogenous and conflict blocks, but larger than both in the entrainment block. Importantly, the facilitation effect in the conflict block was independent of the interval expected based on the color cue, or its validity effect. EEG analysis revealed that the CNV, a potential assumed to reflect expected interval, was driven by the rhythm, suggesting that the behavioral effect reflected directional bias of temporal expectation by the rhythm, and not general conflict. In a second experiment subjects did not perform endogenous entrainment blocks, thus eliminating the possibility that the exogenous effect in the conflict block results from task confusion. Yet, the results for the exogenous and the endogenous-exogenous conflict blocks were replicated. In conclusion, regular rhythms bias temporal expectation even in the presence of voluntarily high-level expectation.

Modulation of tuberoinfundibular dopamine neurons: novel mechanisms for prolactin control

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Bachground: Pituitary release of the hormone, prolactin, is controlled by tonic inhibition from hypothalamic neuroendocrine tuberoinfundibular dopamine (TIDA) neurons. We recently demonstrated that TIDA neurons discharge in a synchronized gap junction-dependent oscillation (Lyons DJ *et al.*, Neuron, 2010). This finding begs the question: are the network properties of TIDA neurons a target for neuromodulation in prolactin release, and if so, through what mechanisms?
Results: Whole-cell patch clamp recordings were performed on slice preparations of the male rat mediobasal hypothalamus, and ion conductances were identified by pharmacological manipulation and ion substitution experiments. Thyrotropin-releasing hormone, a stimulator of prolactin release, was found to depolarize TIDA cells, shifting phasic to tonic firing, by activating a TRP-like conductance. Administration of prolactin itself caused a similar TRP-dependent depolarization but in addition also spike broadening through inhibition of a Ca2+-dependent K+ conductance. Thus, negative prolactin feedback may involve causing TIDA cells to discharge not only more, but also more efficient action potentials, leading to higher dopamine release. Finally, local application of serotonin, another transmitter that stimulates prolactin release caused TIDA neurons to hyperpolarize, abolishing the oscillation and all action potential discharge. These actions were the result of the opening of G-protein coupled inwardly rectifying K+ channels.
Conclusions: These studies have identified a novel circuit-based control of prolactin that suggests novel therapeutic targets for hyperprolactinaemia and related reproductive disorders. By changes in the discharge pattern and action potential waveform of TIDA neurons, pituitary concentration of dopamine may be tuned to adjust serum prolactin levels to reproductive demands.
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The anticoagulant Protein S mediates TAM signaling in the Retina to prevent photoreceptor degeneration

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Background: The daily Phagocytosis of photoreceptor outer segments is essential for retinal viability, and is mediated by the Mer tyrosine kinase receptor. Mutations in Mer are implicated in retinal degeneration in mice, rats and humans. The two ligands that bind and activate Mer are Gas6 and Protein S. In-vitro experiments suggested that Gas6 is the relevant ligand; however Gas6 KO mice do not exhibit retinal degeneration. The hypothesis that the blood anticoagulant Protein S is a ligand for Mer-mediated photoreceptor phagocytosis was put to test in-vivo.
Results: We generated a conditional KO mouse for Protein S to investigate its role in retinal homeostasis. We generated two mouse lines mediating Protein S deletion in Retinal Pigment Epithelium (RPE) cells, and in the neural retina. These retinas were analyzed for retinal degeneration by histology. We also generated double Protein S and Gas6 KO mice to address potential ligand redundancy. We find that retinal deletion of either Gas6 or Protein S alone does not affect retinal homeostasis up to the age of 12 weeks. However, concerted deletion of both ligands fully reproduces the Mer phenotype, resulting in complete retinal degeneration at the age of 12 weeks.
Conclusions: We have generated a conditional KO mouse model for Protein S. Using this mouse , we show that Protein S is a biologically functional TAM ligand with a key role in maintaining retinal homeostasis. Our results suggest that Protein S and Gas6 act in concert to activate Mer, thus allowing for the successful phagocytosis essential to maintain retinal homeostasis. This raises the possibility that Protein S may function as a signaling molecule to activate the TAM pathway in other biological settings where TAM signaling is activated.
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Metallostasis in Alzheimer's disease and Parkinson's disease

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The brain houses high concentrations of transition metals zinc, copper and iron. Zinc and copper are released during glutamatergic neurotransmission, and their reuptake fatigues with age. This increases the average concentration of extracellular zinc and copper (a phenomenon called "metallostasis") leading to Ab aggregation and downstream pathologies. Intraneuronal cortical iron metallostasis is a feature of aging, and is exaggerated in AD where iron is trapped by tangles. We hypothesized that the main proteins implicated in the pathology of AD and PD are in proximity to these metals because they function to regulate neuronal metal homeostasis.

1. APP is the neuronal ferroxidase partner of ferroportin and is needed for iron efflux. It is inhibited by zinc, which transfers from amyloid collections in AD tissue.
2. PBT2, a zinc/copper ionophore that is in clinical testing, reverses metallostasis.
3. Tau knockout mice accumulate iron in the cortex and nigra, causing neuronal loss, parkinsonism and cognitive loss with advancing age. The neurodegeneration is inhibited by iron-chelator treatment. Soluble (functional) tau levels are decreased in AD and PD.
4. Loss of zinc flux in the glutamatergic synapse causes accelerated age-dependent cognitive decline in ZnT3 ko mice, a phenocopy of AD.
5. Presenilins 1 and 2 play major roles in the uptake and turnover of zinc and copper. The SOD1 activation pathway is sensitive to PS loss.

Metallostasis may be the upstream factor that leads to proteostasis in AD and PD and is an upstream target for new pharmacological approaches.

Facing both foes: phenotypic rescue of a drosophila model co-expressing Aβ and Tau by aromatic molecules

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Alzheimer disease (AD) is characterized by two hallmarks: extracellular amyloid plaques of Aβ42 and intracellular hyperphosphorylated aggregated tau protein. Aβ42 pathology was thought to lie upstream of hyperphosphorylated tau pathology and initiate it, but there is contradictory evidence which shows that Aβ toxicity is actually tau dependent. We aim at unraveling which of the pathologies is upstream in AD - tau or Aβ. For this purpose we use the fruit fly as an AD model. We compared the severity of symptoms of flies co-expressing human tau and Aβ42 to flies expressing either one of these proteins (in the brain/retina). Expression of both proteins in the retina resulted in cell death and neurodegeneration evident as collapsed eye with disordered ommatidia. These are more severe than the symptoms of flies expressing either protein alone. Co-expression of tau and Aβ in the brain led to reduced lifespan and motor abnormalities (e.g. climbing defect), which appear to be more severe as well. The severe phenotype when co-expressing both proteins may suggest a synergistic toxic effect of Aβ and tau. Ongoing analysis on brain extracts from these flies will shed light on the relationship between tau and Aβ. Recently, aromatic residues were identified as key factors in the formation of amyloid assemblies. The stable aromatic interaction between protein monomers enables their assembly into toxic oligomers and fibrils. Therefore, small aromatic molecules have been proposed as a potential inhibitors of amyloid aggregation. We fed animals co-expressing tau and Aβ in the retina or the brain with two small aromatic molecules (NQTrp, Cl-NQTrp) which we have previously shown to ameliorate AD symptoms in Aβ expressing flies and mice. This resulted in marked rectification of eye neurodegeneration, and an increase in longevity of flies, respectively. These results suggest that treatment with NQTrp or Cl-NQTrp can inhibit the synergistic toxic effects of tau and Aβ.

The antiphospholipid syndrome animal model in mice provides clear hypotheses for the study of the human disease

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The antiphospholipid syndrome is closely related to systemic lupus erythematosus and the brain is involved human patients by vascular, inflammtory and antibody mediated processes. Mice immunized with β2-glycoprotein I (β2GPI) are an experimental model of the antiphospholipid syndrome (eAPS) displaying elevated titers of circulating antiphospholipid antibodies (aPL). We studied whether the behavioral hyperactivity and cognitive dysfunction found in eAPS mice is associated with the binding and accumulation of IgG in the brain. eAPS Balb/c mice were immunized with β2GPI and control mice by adjuvant alone. aPL levels in the mouse sera were measured by an enzyme linked immunosorbent assay and behavior was assessed by the staircase test. Immunofluorescence and immunohistochemistry staining was used to evaluate in vivo

accumulation of IgG in brain parenchyma and in vitro binding of eAPS serum IgG. We found a significant correlation between serum aPL levels, total IgG accumulated in the brain homogenates and behavioral hyperactivity. In vivo staining for IgG was significant in neurons and especially inhibitory interneurons (Basket cells) in the hippocampus of eAPS mice as well as in white matter tracts. A cell membrane binding pattern in similar cells was found for eAPS IgG by in vitro immunofluorescence staining of normal brain sections. Penetration into the brain and direct interaction of eAPS IgG with inhibitory interneurons in the hippocampus may explain the hyperactive behavior of the mice. A direct role of aPL in causing CNS dysfunction points to aPL as an important therapeutic target.
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Predictive markers to IFN β therapy in Multiple Sclerosis patients

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Background: Multiple Sclerosis (MS) is a chronic autoimmune demyelinating disease. It is characterized by inflammation, demyelination and primary or secondary axonal degeneration. No clear etiological factor has been discovered. IFN β is the mainstay treatment for MS, but its efficacy varies between patients. Clinical experience suggests that there are IFN 'responders' as well as 'non responders', however clear criteria for such classification are still lacking.
Objective: Our goal was to establish predictive markers of response to IFN β therapy in Relapsing Remitting Multiple Sclerosis patients.
Methods: In order to find an association between a certain genetic profile and clinical response to IFN β, two patients groups were evaluated:

- patients who are treated with interferon (5 betaferon, 4 avonex, 3 rebif) and responded well to the drug (n=12);
- patients who received interferon (4 betaferon, 2 avonex, 4 rebif) but did not responded to the treatment (n=10).

The blood was withdrawed just before the next injection.
The expression of 526 genes was analysed by the next generation nCounter® Analysis System from NanoString on total RNA extracted from peripheral blood mononuclear cells. This assay provides a method for direct counting of the exact number of mRNAs molecules with labeled barcodes called nCounter Reporter Probes without the use of reverse transcription or amplification.
Results: we found a correlation between the expression of genes which belong to three pathways (the interferon pathway, the IL7 pathway and the CCL2 pathway) and the patients 's response to interferon.
Conclusion: Having such an objective tool to predict therapy response is valuable for further decisions concerning therapy in patients with MS and advance our ability towards tailoring the treatment in each individual with MS.

Motherhood alters the balance between excitation and inhibition in the auditory cortex

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Local cortical inhibition is central in shaping neuronal response profiles in the cortex. Diverse response patterns such as lateral inhibition and approximately balanced excitation and inhibition (co-tuning) have been reported. But the precise way in which the excitatory/inhibitory balance affects response profiles remains unclear. Here we studied in detail the response properties of one class of inhibitory neurons, the parvalbumin (Pv)-expressing cells. These inhibitory neurons target the soma and perisomatic compartments of pyramidal cells (Pyr) in the local circuit. We used in vivo multiphoton targeted cell attached recording, in layer 2/3 to compare the response properties of Pv and Pyramidal (Pyr) neurons. We show that Pv neurons provide an unexpected and unique form of inhibition onto Pyr neurons. Moreover, we find that Pv neurons change their inhibitory pattern onto Pyr cells following the transition to motherhood and when multisensory inputs are processed.

Time lapse electrical recordings of single neurons from the mouse neocortex

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The ability of the brain to adapt to environmental demands implies that neurons can change throughout life. But the extent to which single neurons actually change remains largely unstudied. To evaluate how functional properties of single neurons changed over time, we devised a way to perform in-vivo time lapse electrophysiological recordings from the exact same neuron. We monitored the contralateral and ipsilateral sesnsory evoked spiking activity of individual L2/3 neurons from the somatosensory cortex of adult mice. At the end of the first recording session, we electroporated the neuron with a DNA plasmid to drive GFP

expression. Two weeks later, a recording electrode was visually guided in vivo to the GFP expressing neuron for the second time. We found that contralteral and ipsilateral evoked responses (probability to respond, latency, and preference), and spontaneous activity of individual L2/3 pyramidal neurons are stable under control conditions. However, this stability could be rapidly disrupted. Contralateral whisker deprivation induced robust changes in single neurons response profiles. Our experiments provide a framework for studying the stability and plasticity of single neurons over long time scales using electrophysiology.

Stop feeling: executive control attenuates emotional effects

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Background: The relationship between attention and emotion has attracted attention of researchers recently. A major question is: are emotions prioritized so that they have privileged access to our cognitive apparatus or can they be regulated by other systems such as attention? Researchers have reported that emotional stimuli activate sub-cortical structures (e.g., amygdala) that cannot be affected by higher functions or cortical processes. Moreover, it has been suggested that emotional stimuli have automatic effects on our behavior, even when completely irrelevant to the task at hand. However, it makes sense that we should be able to regulate our emotions when they are completely irrelevant to our performance or can interfere with achieving our goals. In the current research we define the specific situations in which the emotional system is down-regulated by executive control—an attentional mechanism that is responsible for monitoring and controlling irrelevant information in order to enable goal-directed behavior. In several experiments we presented a target that activates executive control before or after the presentation of an emotional picture.
Results: We demonstrate that executive control exerts an inhibitory influence on emotion. Namely, the influence of emotional stimuli on performance is attenuated during or after activation of executive processes. This effect was found using different executive tasks (i.e., Flanker, Simon, stop-signal) and was modulated by the relevance of the emotional stimuli to the task.
Conclusions: Our findings demonstrate that during or after activation of executive processes, our emotional system is down-regulated. This down-regulation occurs when the emotional stimulus is irrelevant to our current goals or when it is relevant but can be evaluated as non-threatening. We suggest that the interplay between emotion and executive control is crucial for maintaining adaptive and goal-directed behavior.

Robotic re-embodiment: controlling a humanoid robot by thought using real-time fMRI

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Background: As part of the VERE (Virtual Embodiment and Robotic re-Embodiment) project, which aims at dissolving the boundary between the human body and surrogate representations in immersive virtual reality and physical reality, we are carrying out a number of studies whereby subjects control a virtual character (avatar) or a physical humanoid robot by thought alone, using real-time classification of fMRI signals. We report a robotic embodiment experiment: subjects located in Israel were preceiving through the cameras of a HOAP3 humanoid robot in France and were able to control it using motor imagery.
Method: We first instruct the subject to imagine left-hand, right-hand, and feet imagery upon a predefined cue, and manually (using TurboBrainVoyager, Brain Innovation, Holland) define regions of interest (ROIs), which are delineated by the predictor variables contrast using a general linear model (GLM). This is followed by a baseline. In the task part the subjects saw a video feed taken by cameras located at the eyes of the robot in Beziers, France, and performed three simple navigation tasks. We use a simple classification scheme: at each 2-second repetition time (TR) we calculate the z-score (normalized relative to the baseline values) of each ROI, choose the ROI with highest z-score value, and send the corresponding command to the robot.
Results: Four subjects performed an 8-shape navigation task with a high degree of control on most sessions, despite the hemodynamic delay (which is expected to be 3-8 seconds). One subject used motor imagery only and three others were allowed to use their fingers and toes.
Conclusion: Subjects can navigate a robot by using motor imagination in better-than-chance levels with very little training, based on simple classification method. We are now further exploring the control of avatars and robots by thought using machine learning and more ambitious tasks.
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Early inflammation and NGF deregulation in the amyloid Alzheimer's pathology

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In Alzheimer's disease (AD) the therapeutic "time-window" should be shifted to earlier stages as there is a

decades-long "silent", pre-diagnostic phase. We are investigating this early, "silent" phase of the AD amyloid pathology in transgenic (Tg) models of the AD pathology. Our lab is interested in early pathology. We have observed that preceding the appearance of amyloid plaques there is an abnormal intraneuronal accumulation of oligomeric and prefibrillar forms of Abeta in the cerebral cortex and hippocampus. This phenotype, in the absence of amyloid plaques, was accompanied by cognitive impairments and a pro-inflammatory reaction both in the rat and mouse Tg models. The "pro-inflammatory" process displayed an intermediate activation of microglial cells with their mobilization to Abeta-burdened neurons and elevation of key inflammatory markers in the cerebral cortex and hippocampus. We have reported the existence of an NGF (Nerve Growth Factor) metabolic pathway explaining the mechanisms for its maturation and degradation in the CNS. Our investigations in the human brain revealed that this metabolic pathway is altered in AD. We have found a compromise in the proNGF to mature NGF conversion. Likewise, the degradation of mature NGF in the extracellular space should be enhanced as in both MCI and in AD there is an increment both in protein levels and enzymatic activity of the metalloprotease MMP-9. MMP9 being the protease which terminates NGF action in the CNS. We hypothesize that these consequences of the Abeta oligomer-driven proinflammatory process and deregulation of the NGF metabolic pathway might be amongst the earliest event in the progression of AD pathology. These alterations are likely to aggravate the pathology and have cognitive consequences. These aspects could offer new pharmacological targets as well as diagnostic opportunities for the prevention or diagnosis of the disease.

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Profiling of the placebo responder: personality and cognitive characteristics in Parkinson's disease patients

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Background: The 'placebo response' is defined as a positive outcome in patients who have received placebo (an inactive intervention), over and beyond changes due to the natural course of disease. Although the placebo response is as ancient as the placebo itself, studies attempting to identify the placebo responder are rare and limited. We hypothesize that placebo responders share a psychological and cognitive profile.

Methods: For this aim, we are recruiting patients with Parkinson's (PD) and other diseases who have participated in a previous clinical trial where they received placebo in a double blind manner and their clinical improvement was recorded. To date, we have evaluated 15 subjects with PD, one placebo responder and 14 non-responders who were administered the full Minnesota Multiphasic Personality Inventory (MMPI-2) personality questionnaire and 3 short cognitive tests: RAVLT word list memory, verbal fluency test and trail making test (TMT) A and B.

Results: We found no differences in cognitive nor in personality traits between men (n=11) and women (n=4). However we did find a significant sex difference with men expressing stronger belief in medical treatment (p=0.006). Distress was negatively correlated with the patients belief in medical treatment (p=0.029). In addition, hysteria was found to decrease with age (p=0.012) but fears to increase with age (p=0.005). Marital distress and cynicism were positively correlated with PD severity (p=0.004; p=0.04), respectively, while the need of affection was negatively correlated with PD severity (p=0.011).

Conclusions: Results show the possibility that men have stronger beliefs in medical treatment than women. Our results also indicate that disease severity may differ in its impact on specific characteristics of mood and attitude in PD patients.

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Inosine improves functional recovery after experimental traumatic brain injury

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Background: In spite decades of research, no specific therapy is yet available for traumatic brain injury (TBI), one of the leading causes of mortality and morbidity worldwide. The most prevalent features in TBI survivors are cognitive deficits and motor dysfunction. A potential therapeutic method for improving function of patients following TBI is to restore, at least in part, plasticity to the CNS. The present study was aimed at investigating long-term (up to 35d) effects of inosine, a naturally occurring purine nucleoside that has been shown to promote axon sprouting, on cognitive outcome and levels of synaptic proteins which

promote neurite sprouting and plasticity, in an animal model of TBI.

Results: Experimental closed-head injury (CHI) was induced in mice and rats using a weight-drop device. Inosine (100 mg/kg) was administered i.p. at 1, 24 and 48 hr after CHI. Inosine treatment significantly improved neurological recovery and performance on a non-spatial cognitive task (object recognition). Sensorimotor coordination (evaluated using a rotarod) and spatial cognition (Y-maze) were not affected. Following anterograde tracing with biotinylated dextran amine (BDA), the corticospinal tract (CST) in the lumbar spinal cord contralateral to the injection site was strongly labeled, with some axons crossing the midline, and CHI led to a significant increase in sprouting. Inosine did not increase axonal sprouting further, nor did it increase the levels (Western blot) of the growth-associated protein GAP43 or the presynaptic protein, synaptophysin, in the cortex or hippocampus of injured mice compared to sham controls. Other possible anatomical changes were not investigated.

Conclusions: the results suggest that inosine may have beneficial effects on recovery after TBI. Further research studying longer treatment regimens and more severe trauma is required in order to better detect and explore the mechanisms by which these benefits are exerted.

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Theory and modeling of astrocyte modulation of synaptic release

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Background: The complexity of astrocyte-synapse interactions may seem discouraging when tackled from a theoretical perspective. Computational modeling is challenged by the fact that many details remain hitherto unknown. Supported by experimental evidence is the possibility that astrocytes perform genuine information processing by means of their calcium signaling and are players in synaptic transmission, but the functional implications of this scenario remain elusive.

Results: We devised a novel modeling framework for the study of astrocyte-neuron that can explain several experimental results and is mathematically tractable with potential applications in the study of Artificial Neural Networks. Moreover, our model yields important predictions in support of the physiological relevance of astrocyte-neuron signaling in information processing. In particular, facilitating gliotransmission could underlie bistability of synaptic release, namely, the coexistence of low and high levels of synaptic release for the same stimulus. The occurrence of one mode of synaptic release with respect to the other depends on the history of synaptic activity and could bring forth long-lasting changes of synaptic strength just by mere long-term potentiation or depression of synaptic release probability. This scenario could ultimately provide a novel mechanism to account for the transient increase of neuronal activity following the brief presentation of a stimulatory cue, which underlies working memory.

Conclusions: Our study revealed that astrocyte could affect synaptic transmission in a complex fashion, depending on the rate and nature of gliotransmission. Since gliotransmission could occur either for spontaneous or evoked neuronal activity, astrocytes could physiologically set the tone of synaptic transmission with important implications in information processing and storage by neural networks of the brain.

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CNS-specific immunity at the choroid plexus: a shift towards destructive Th2-inflammation in brain aging

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Aging of the adaptive immune system has been suggested as an important factor in brain senescence. Given

the fact that interactions of neurons or glial cells with T lymphocytes rarely occur within the healthy central nervous system (CNS) parenchyma, the underlying mechanism remains elusive. Here we show that the blood-cerebrospinal fluid barrier, the choroid plexus (CP), is constitutively populated by CD4+ effector memory cells with a T cell receptor (TCR) repertoire specific to CNS antigens. With age, CNS-specificity was largely maintained, while interleukin-4 (IL-4)/interferon-γ (IFN-γ) ratio progressively increased, indicating stepwise Th2 bias in the CP compartment. We found this local cytokine shift to critically affect the CP epithelium, triggering it to produce the chemokine CCL11, recently linked to cognitive dysfunction. Strikingly, partial restoration of cognitive ability in aged mice, by homeostatic-driven proliferation of memory T cells, correlated with reestablishment of the IL-4 / IFN-γ ratio at the CP, and modulated the expression of plasticity-related genes at the hippocampus. Our data indicates that the cytokine milieu of the CP epithelium, the interface between the brain and the blood circulation, is affected by peripheral immunosenescence, with detrimental consequences to the aged brain. Amenable to immunomodulation, such an interface is a novel target for arresting age-related cognitive decline.

The first three authors contributed equally to this study.

Does study episode contribute a constant or a variable increase to familiarity? The contribution of delta-familiarity to recognition memory

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According to dual-process theory, recognition memory comprises two underlying processes: Familiarity and Recollection. Recollection involves conscious remembering of contextual details about the prior learning episode. Familiarity, in contrast, involves a relatively automatic, a-historical assessment of the item's strength, without having available to consciousness any further information about the learning episode. Most dual-process models concur that familiarity is best described using the principles of Signal-Detection Theory (SDT), with some level of familiarity available for every item. According to this notion, in the study episode, familiarity increases for the studied items. A highly influential dual-process model argues that this increase in familiarity is constant to all studied items (Yonelinas, 2001). Other models (e.g., Wixted & Mickes, 2010), however, suggest that this increase might be variable.
To examine this question, we asked participants to provide a subjective familiarity score for each item at both study and test phases of a recognition-memory test. Additionally, for each positively recognized item, participants indicated the quantity of recollection experienced. Difference-in-familiarity was calculated by subtracting the study familiarity score from the test familiarity score. Results support a variable addition of familiarity during the study phase. Moreover, the change in familiarity score was positively correlated with correct recognition. This suggests that positive recognition involves an assessment of the change in familiarity during the study (i.e., delta familiarity), in addition to both item's baseline familiarity and to the recollection of episodic details from the study event.

New herbal treatment for anxiety in comparison to SSRI: high efficacy with minimum side-effects

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Anxiety disorders are prevalent and severe diseases with deleterious impact on patients and society. Selective serotonin reuptake inhibitors (SSRIs) were shown to be effective in treating a wide spectrum of anxiety disorders. Despite their therapeutic actions, SSRIs are associated with a wide variety of side effects such as weight changes, disturbances and sexual dysfunction. Furthermore, recent studies show that their success rates are not high, reaching 50 % at most. Therefore, there is a clear need to explore alternative treatments for anxiety disorders. We have recently produced a novel herbal treatment mixture for the treatment of anxiety disorder. The novel treatment displayed anxiolytic-like effects in treated mice previously exposed to stress. The aim of the present study was to test whether the novel treatment induce two common side effects normally induced by the conventional treatment with the SSRI escitalopram, namely, sexual dysfunction and weight gain. Mice were treated with either: (a) herbal treatment (b) one components of the herbal treatment mixture (c) escitalopram or (d) control group. Following treatment, sexual behavior and weight gain were evaluated in the different groups, as well as changes in prefrontal cortex serotonin transporter levels. We have found that the novel treatment has not altered sexual behavior and did not cause a weight gain, while escitalopram altered these two side effects. Interestingly, serotonin transporter levels in the prefrontal cortex of escitalopram treated group were significantly lower compared to other treatments. These results suggest that the novel treatment may have the same behavioral anxiolytic efficacy as SSRIs, while causing fewer side effects, possibly due to different biological mechanisms. Further studies are now conducted in order to explore the underlying biological mechanisms through which the novel treatment lead to the behavioral anxiolytic effects.

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Abnormal perceptual functions in attention deficit hyperactivity disorder (ADHD)

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Background: Visual crowding, collinear facilitation, and contour integration are visual integration functions (VIF) that are critical for perceptual and cognitive processing. Our recent results support a common early neural basis for the development of VIF in young healthy children. The results show that there is a developmental cascade in which the existence of high levels of crowding in young children limits the developmental onset of collinear facilitation until about the age of 6 years when the crowding decreases to nearly an adult's level. Similarly, the onset of the contour integration skill developed after the maturation of collinear facilitation, between 6 and 9 years. Since development of some of the cognitive functions overlaps with this age period, we hypothesized that the development of VIF in ADHD subjects might be affected. The aim of this study was to explore whether VIF in ADHD subjects during the age of 6-18 years is normal.
Results: We found a high degree of crowding, higher thresholds for contour integration, and reduced collinear facilitation in the ADHD group compared with the age-matched control group. We also found that their thresholds do not improve with age and remain immature, matching the threshold levels of younger children.
Conclusions: Contrary to the visual processing in young normal children, which improves with age, the neural mechanisms underlying global perception are immature in ADHD individuals. These results may suggest that abnormal development contributes to the perceptual processing in ADHD, which in turn may limit the development of some higher cognitive processing.

Translating science: clinical trials for spinal cord injury

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Background: Spinal cord injury (SCI) has devastating and expensive consequences for patients, carers and society. The incidence varies world-wide (Australia: 4.5/million; USA: 25.2-52.5/million) with motor vehicle accidents the major cause. Extensive and promising basic research has yet to be translated into clinical practice.
Results: A search of http://clinicaltrials.gov/, China SCI Net http://www.chinascinet.org/ and the Australian and New Zealand Spinal Cord Registry www.anzctr.org.au was undertaken to map the current global status of clinical trials. Internationally, there are over 100 registered trials covering a wide range of interventions with exercise comprising the majority followed by drug treatments. Cell-based and biologically-inspired drug-based trials are also emerging. Nevertheless, medical management, rehabilitation and exercise are still the predominant treatments. However, strong evidence to support the role of exercise in promoting neurological recovery and overall health is lacking. In Australia and New Zealand, we are undertaking 3 randomized controlled trials, Spinal Cord Injury and Physical Activity (SCIPA), to test novel interventions that move the paralysed limbs and determine whether they improve neurological recovery and overall health. The trials span acute care, in-patients and the chronic phase after discharge and we are also developing a community program to overcome barriers and promote participation and activity. Another Australian trial in the planning stage aims to prevent massive secondary loss of tissue spared by the initial injury by administering immediate hypothermia
Conclusion: The global search to develop effective therapies continues. Rehabilitation is still the main form of therapy and better treatments for acute injury to prevent the catastrophic loss of tissue, as well as for chronic patients living with SCI, are urgently needed.

Similarity of activity-dependent structural changes in synapses formed between identical neurons

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Activity-induced modification of synaptic connections (synaptic plasticity) is widely believed to be a fundamental mechanism for modifying neuronal network function. It is also commonly (often implicitly) presumed that synapses do not change spontaneously or in manners unrelated to their activation histories. Synapses, however, are not static structures, and exhibit significant molecular and cellular dynamics with or without activity on many timescales. An important question thus arises: What is the relative part of specific activity histories in the remodeling synapses undergo?We recorded, for several days, the remodeling of nearby synapses formed between the exact same axons and dendrites, synapses that presumably experience identical activity histories. We then examined the degree to which such synapses changed in a similar manner, and how this covariance was affected by network activity. We found that the covariance of synaptic remodeling in synapses that presumably experienced the same activation histories was only slightly (~12 %) greater that the covariance observed for synapses which did not belong to the same presynaptic neurons. Interestingly this difference disappeared once network activity was silenced. Moreover, silencing activity led to a 20-30 % increase in remodeling covariance between all synapses in the network regardless of their presynaptic identity. These findings indicate that the predominance of specific activity

histories in determining the remodeling synapses undergo might be more limited that commonly assumed.

A genome wide association study of human altruism

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As noted by Darwin in the Descent of Man, "The bravest men, who were always willing to come to the front in war, and who freely risked their lives for others, would on an average perish in larger numbers than other men" and hence the paradox of altruism. Evolutionists propose a number of concepts such as kin selection, direct reciprocity, indirect reciprocity, network reciprocity, and group selection, to resolve the paradox. Notably, the heritability of altruism is comparable to other complex human traits. However, the proximate molecular genetic mechanisms underlying altruism, remains relatively unexplored. To identify loci associated with altruism we conducted the first genome-wide association study (GWAS) using incentivized choice experiment in 1805 Han Chinese samples, observing genome-wide significant evidence of association at ACCN1 rs3744516 ($P=6.87\times10^{-10}$). De-novo replication with was observed in a further Han Chinese sample from Singapore ($N=1052$, $P=0.040$). We identified a locus exceeding the formal threshold for genome-wide significance contributing to altruistic giving that maps to a specific gene *ACCN1*, neuronal amiloride-sensitive cation channel 1. To summarize, by employing the gold standard GWA strategy we have identified a proximate mechanism for altruistic giving, ACCN1 coding for a neuronal cation channel. In particular, *ACCN1* is associated at GWA significance levels with Rawlsian giving, the preference for an egalitarian solution to income distribution. John Rawls, the moral and political philosopher, envisions a society of free citizens holding equal basic rights cooperating within an egalitarian economic system. It appears that evolutionary forces have partially hard-wired Homo sapiens towards attaining the Rawlsian just society.

Olfaction in autism

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The few studies that investigated olfaction in autism combine with anecdotal observations to suggest an "autistic olfactory profile". This is unsurprising considering various links between olfaction and autism. Here we investigate two of these links: First, olfaction depends on precise sensory-motor acquisition, namely sniffing, and indeed, sensory-motor acquisition is impaired in autism. With this in mind, we set out to measure sniffing behavior in children undergoing a diagnostic battery for autism. We tested 20 children (ranging in age from 22 months to 10.6 years) with a computer-controlled air-dilution olfactometer that delivered either pleasant or unpleasant odors through a nasal cannula. The cannula also served to measure concurrent nasal respiration. Odorants were delivered once every 30 seconds, counterbalanced for order. We encountered a major obstacle of compliance: 8 of 20 children refused to participate, and 6 did not complete a minimum number of trials. In turn, in the 6 children with between 6 and 24 trials, there was a striking correlation between autism severity scores (ADOS) and various sniff parameters (overall $r=0.96$, $p<0.03$).

A second link between olfaction and autism is that odors serve social communication, and indeed a characteristic of autism is impaired social communication. With this in mind, we set out to measure the response to chemosignals in young high-functioning adults with autism. Human sweat-bound chemosignals modulate startle response in typically developed adults. Here we will now measure the influence of sweat-bound chemosignals on startle response in high functioning young adults with autism. Together, these results from children and adults will provide an initial characterization of an olfactory profile in autism.

The microglial sensome

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Microglia, the principal neuroimmune cells and sentinels of the brain continuously sense changes in their environment and defend against invading pathogens. Similar to circulating blood monocytes, microglia exhibit plasticity, and can assume various priming states that determine their responses to danger signals. We used direct RNA sequencing to quantify mRNA without amplification or cDNA synthesis, and determined the quantitative transcriptomes of microglia and monocytes of healthy adult and aging mice. We validated our findings with unbiased proteomic analysis. We report that microglia differ significantly from monocytes and express a unique cluster of transcripts encoding proteins for sensing endogenous ligands and microbes, that we term the "sensome". In this presentation we will discuss our findings and their implications for the role of microglia in aging and neurodegeneration.

Genetic ablation of hypocretin neurons alters behavioral state transitions in zebrafish

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Sleep is an essential biological need of all animals studied to date. The sleep disorder narcolepsy is characterized by excessive daytime sleepiness, fragmentation of nighttime sleep, and cataplexy. Narcolepsy is caused by selective degeneration of hypothalamic hypocretin/orexin (HCRT) neurons. In mammals, HCRT neurons primarily regulate the sleep/wake cycle, feeding, reward-seeking and addiction. The role of HCRT neurons in zebrafish is implicated in both sleep and wake regulation. We established a transgenic zebrafish model enabling inducible ablation of HCRT neurons, and used these animals to understand the function of HCRT neurons and narcolepsy. Loss of HCRT neurons increased the expression of the HCRT receptor (hcrtr). Behavioral assays revealed that HCRT neuron-ablated larvae had normal locomotor activity, but demonstrated an increase in sleep time during the day and an increased number of sleep/wake transitions during both day and night. Mild sleep disturbance reduced sleep and increased c-fos expression in HCRT neuron-ablated larvae. Furthermore, ablation of HCRT neurons altered the behavioral response to external stimuli. Exposure to light during the night decreased locomotor activity of wild-type siblings, but induced an opposite response in HCRT neuron-ablated larvae. Sound stimulus during the day reduced the locomotor activity of wild-type sibling larvae, while HCRT neuron-ablated larvae demonstrated a hyposensitive response. This study establishes zebrafish as a model for narcolepsy, and indicating a role of HCRT neurons in regulation of sleep/wake transitions during both day and night. Our results further suggest a key role of HCRT neurons in mediating behavioral state transitions in response to external stimuli.

Novel and familiar taste learning elicit different network

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Learning of novel taste and its value is rapid, robust and ethologically important to survival of the animal. The gustatory cortex (GC) is critically involved in taste memory formation, consolidation and retrieval. In rodents, novel taste learning is associated with biochemical changes in the GC, however, very little is known about the expression of immediate early genes (IEGs) as network activity markers in correlation with novel taste learning.

Here, we used the expression of Activity Regulated Cytoskeleton Protein (Arc) as a marker of neural activation in the GC following incidental taste learning. We found that novel taste did not modulate Arc expression in the GC when sampling both hemispheres, however novel and familiar taste groups have different expression pattern when comparing left and right GC one hour following learning; whereas the novel taste group exhibit clear lateralized pattern of Arc expression, the familiar taste group exhibits no lateralization of Arc expression. Moreover, continuous familiarization with taste reduced the lateralization. For causal experiment we injected the protein synthesis inhibitor anisomycin into the left or right GC and found a pattern of bimodal distribution of animals performing the memory test- one group of animals with clear impaired memory for the aversive taste, and one group of animals with no memory deficit, indicating that one hemisphere predominantly participates in memory consolidation. We found that separate networks for processing of novel or familiar taste exists in the GC and manifested by symmetrical IEG activation for familiar taste and asymmetrical for novel taste learning.

Altered olfactory perception following tDCS

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Background: One of the most important characteristics of odor perception is its hedonic component. Neuroimaging results imply that pleasant odors preferentially activate a region of medial OFC, while unpleasant odors preferentially activate a lateral portion of left OFC. This has merited the hypothesis that activating specific brain regions may change olfactory hedonic perception. To test this, we used transcranial direct current stimulation (tDCS), and measured olfactory perception. The subjects rated the pleasantness and the intensity of 5 different odorants using a visual analog scale (VAS). **Results**: To date, 18 subjects (8 F, mean age=24) were tested. The subjects participated in two conditions: sham and active. We found that the pleasantness rating of Skatole (a feces-like odor) was significantly higher after the active condition compared to baseline (normalized pleasantness before activation: 0.13±0.02, after: 0.18±0.04, $t(15)=-2.6$, $p<0.05$). When we look only at the 1st day, the pleasantness delta (after-before) in the active condition is significantly higher than the Sham delta (Active delta=0.11±0.02, Sham delta=-0.02±0.02, $t(14)=3.5$, $p<0.004$). As for Hexanoic-

acid (a goat- like odor), the pleasantness rating was significantly higher only after the active condition compared to baseline (before: 0.15±0.04, after: 0.21±0.04, t(15)=-2.1, $p<0.05$). In contrast, pleasantness ratings of the pleasant odors were unaffected by tDCS. The Intensity ratings of all the odorants were unaffected as well.

Conclusions: These results suggest that olfactory perception can be modulated using tDCS. Beyond probing brain representation of olfactory information, the possibility of predictably modulating odorant pleasantness has tantalizing implications and possible applications.

Operant conditioning of LFP gamma oscillations via Brain-Machine Interface: emergence of precise spike synchrony

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Background: Neuronal oscillations in the low-gamma band (30-50 Hz) are thought to reflect synchronized activity in the brain and have been associated with numerous cognitive and computational roles. In particular, various clinical disorders have been linked with abnormal low-gamma activity such as ADHD, Autism, Schizophrenia, Epilepsy and others. These abnormalities are thought to reflect in turn abnormalities in the degree of neural synchronization in either a local or distributed manner. The precise role of these oscillations, however and the extent of their contribution to single neurons' synchrony in a behavioral context remains unclear.

Results: In this study we used a Brain-Machine Interface (BMI), to train monkeys to specifically increase the power of the 30-43 Hz band in selected sites of motor cortex. Over the course of several sessions the monkeys learned to use the BMI to move a cursor on the screen and obtain a reward. The evoked activity was oscillatory in nature, band specific and clearly apparent on a single-trial basis. The increase in the LFP band power was accompanied by a dramatic increase in the amount of neural synchrony, allowing previously uncoordinated pairs of neurons to fire together in a time-precise manner. Furthermore, we found a tight relationship between the spatiotemporal patterns of gamma oscillations and the patterns of spike synchrony. Finally, the level of gamma oscillations was directly related to the size of the synchronized neuronal ensembles.

Conclusions: Our findings have a two-fold significance: On the clinical side, they stand as an important step in the development of treatments for a wide variety of conditions in which the level of neural synchrony is impaired. From a neurophysiological perspective, we have shown a causal link between LFP oscillations, neural synchrony and behavior, suggesting that oscillatory synchrony can be used in a behavioral context as a substrate for neural computations.

This work is dedicated to the memory of Dr. Dmitry Davidov

Spike shape of human pyramidal cells and the tracking high input frequencies

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A spike is a spike is a spike. Indeed, the spike is generally considered to be a binary signal. Yet, in various neuron types and in different animals, spikes appear in an assortment of shapes and amplitudes. Interestingly, recent theoretical studies have demonstrated that the steepness of the spike onset is highly correlated with the capability of the neuron to track high frequency input fluctuations. This was confirmed in the present modeling study using detailed conductance-based Hodgkin-Huxley-based model of 3D reconstructed pyramidal cells of both human and rats. In the H&H model, the steepness of the spike onset is determined by the steepness of the Na+ activation curve and by its maximal conductance value. Pyramidal cells in the rat neocortex can track input frequencies up to 200 Hz and time their spiking accordingly (Koendgen et al., 2008), whereas human pyramidal cells can track input frequencies up to and beyond 1000 Hz (Testa-Silva et al., submitted). To explore this surprising result we have analyzed the shape of spikes in rat versus the human, using phase plots. We found that the human spike is not steeper than that of the rat. Thus, contrary to our initial expectations, the ability of human cells to track higher frequencies, as compared to the rat, is not explained by differences in the spike rapidness. We are currently further exploring what could be the alternative explanation for the superiority of human pyramidal cells in tracking high input frequencies.

GABAA receptor α2 but not α1 subunit knock down in dentate gyrus reduces inhibition activity and improves learning abilities of rats

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In the current study, the GABAA receptor α1 or α2 subunit was knocked down by injecting a viral vector into the dentate gyrus (DG) of juvenile rats. A sustainable expression of infection could be found in DG for more than 8 weeks after the injection. To examine the possible alterations in local circuit activity after DG GABAA receptor α1 or α2 subunit knock down, frequency dependent inhibition (FDI) and paired pulse stimulation protocols were employed. Briefly changing stimulation frequency from 0.1Hz to 1.0Hz, a strong inhibition of population spike (PS) could be observed in both control rats and α1 or α2 subunit knock down rats, but the ratio of inhibition was significantly decreased in α2 subunit knock down rats. Paired pulse stimulation with an interval of 15 ms resulted in the inhibition of the second PS and this inhibition was also significantly reduced in α2 subunit knock down rats compared to control rats. To test the potential behavioral effects of GABAA receptor subunit knock down, rats were tested in the elevated plus maze (EPZ) and on a novel object recognition task. No differences were found between the groups in the EPZ. In the novel object recognition task the α2 subunit knock down rats exhibited significantly longer time compared to both control and α1 subunit knock down rats of novel object exploration. The results suggest that knocking down of GABAA receptor α2 but not α1 subunit has significant effects on learning but not on emotional behavior. The associated induced alteration of DG local circuit activity in α2 subunit knock down rats suggests that DG local circuit activity is important for hippocampus-dependent learning.

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The effects of stress in adulthood, following sleep restriction or stress in juvenility, on body temperature and activity level

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Background: The effects of stress in adulthood, following sleep restriction or stress in juvenility, on body temperature and activity level in rats were studied by means of radiotelemetry.
Methods: Rats were stressed in juvenility using a protocol of three-day exposure to different stressors. In adulthood rats were subjected to 8 days of sleep restriction (SR) using activity wheels. Immediately following the last day of sleep restriction they went through the underwater trauma (UWT), an acute stress procedure. Core body temperature was measured before and during the SR protocol and following the UWT, using radiotelemetry.
Results: During SR protocol, sleep restricted rats had higher body temperature throughout the protocol, and juvenile stressed rats had higher body temperature only while on wheels. Juvenile stressed rats were also more active during the dark phase of the SR protocol. Following SR protocol and the UWT, during the light phase, all rats including controls had lower body temperature, except for the rats that went through the UWT procedure and no SR, which had no change in body temperature compared to baseline.
Summary and Conclusion: Sleep restriction had only a short-term effect on body temperature that was compensated in the days following the protocol. UWT resulted in elevated body temperature for a few days, an effect that was abolished by sleep restriction. Juvenile stress, in contrast, had a prolonged effect on thermoregulation and activity, even a month following the juvenile stress, when the rats were either on voluntary activity wheels or motorized ones. The results demonstrate yet another aspect of the longevity of the effects of exposure to stress in juvenility.

The importance of P75NTR receptor in mediating microglia activity in Alzheimer's disease

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Background: It has been recently postulated that there are different microglial cell phenotypes that have the potential to be beneficial or harmful in Alzheimer's disease (AD). We have recently shown that gamma-secretase inhibitors impair microglial activity as measured in gene expression, protein levels, and migration ability. (Farfara et al., Ann Neurol 2011). Furthermore, dysfunction in gamma-secretase catalytic site led to impairment in clearing insoluble amyloid β from brain sections taken from an AD mouse model compared to microglia from wild-type mice. Gamma-secretase is also known by its ability to cleave intra-membrane type-1 receptors, such as $P75^{NTR}$. $P75^{NTR}$ is a neurotrophin receptor which binds to different neuro-growth factors such as NGF and BDNF. It was previously reported that $p75^{NTR}$ is highly expressed in microglia cells. Here we aim to investigate the role of $P75^{NTR}$ in microglia cell activation towards Amyloid-β.
Results and conclusions: We discovered that microglia cell line transfected with shRNA $P75^{NTR}$express higher levels of CD11b, marker for microglia activation, when stimulated with Alzheimer's disease beta amyloid 1-42 peptide.

Furthermore, shRNA $P75^{NTR}$ microglia has an increased expression of specific pro-inflammatory activation markers such as CD11b, IL-6, SRA, LRP and TLR4. Interestingly, there was significantly reduction in expression and secretion of important anti-inflammatory factor IL-10 and in expression levels of Abeta degrading enzyme such as Insulin degrading enzyme (IDE). Our findings suggest the importance of signaling through $P75^{NTR}$ in microglia cells in shaping their activity in neurodegenerative diseases such as Alzheimer's disease.

Alzheimer's association, HFSP and ISF

Selective glycolipid accumulation correlates with distinct brain pathology in a mouse model of a lysosomal storage disorder

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Background: Gaucher disease (GD), the most common lysosomal storage disorder, is caused by defective activity of the lysosomal enzyme glucocerebrosidase (GlcCerase), which results in accumulation of the glycolipids glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph). The rare neuronopathic forms of GD are characterized by devastating neurological disease and neuronal cell death, but little is known about the neuropathological changes that underlie these events.

Results: We systematically examined the onset and progression of various neuropathological changes in a mouse model of neuronopathic GD, defined the specific brain areas involved (some of which were also reported to be involved in the human disease) and established that localized microglial activation and astrogliosis are spatially and temporally correlated with selective neuron loss (Farfel-Becker et al., 2011). To understand why only specific brain areas are affected, we used periodic acid-schiff (PAS) reaction and mass spectrometry (ESI-MS/MS) and determined that glycosphingolipid accumulation occurs only in specific neuronal populations in the same brain areas that showed neuron loss and neuroinflammation. Remarkably, a two-fold elevation in GlcCer levels in the VPM/VPL of the thalamus did not cause any transcriptional alterations (as determined by a microarray experiment) in pre-symptomatic mice, suggesting that a certain threshold of GlcCer or GlcSph levels must be met in order to elicit the massive neuron loss and inflammation detected in this brain area in later stages of the disease.

Conclusions: Glycolipids accumulate to a different extent in different brain areas and in different neurons within the same area in Gaucher brains, which explains the specific pattern of neuroinflammation and neuron loss seen in those brains. The mechanism underlying the specificity of storage build-up is, as yet, unknown.

Selective lentiviral mediated targeting of glia cells in the central nervous system

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Background: In a complex tissue of the central nervous system (CNS), cell cross-talk is essential to preserve normal functions. Current tools for dissecting the molecular mechanisms that mediate cell-cell interactions within the brain include molecular genetics, imaging and use of transgenic animals. However, these are technically challenging, time consuming and difficult to control. In this study we report the establishment and validation of a lentiviral-mediated gene-targeting platform to specific cells in the CNS. It combines unique features of self-inactivated lentiviruses that promote stable gene delivery into non-dividing cells and efficient display of single-chain variable region human fragments (scFv) or soluble IgG on the surface of viral particles.

Results: In vitro, cells that express the receptor-binding domain of the SARS CoV spike glycoprotein were targeted by engineered sindbis pseudotyped lentiviruses that incorporate specific scFvFc attachment moieties. Additionally, in vitro targeted gene expression to primary astrocytes was also demonstrated, using engineered lentiviruses that incorporate Aquaporin 4 and GLAST (ACSA-1: Astrocyte Cell Surface Antigen-1) IgG. In vivo, lentiviral targeting of astrocytes and oligodentrocyes progenitor cells (OPCs) that express the chondroitin sulfate proteoglycan, NG2 was obtained using viral particles that display an anti GLAST and anti NG2 IgG antibodies, respectively.

Conclusions: We conclude that this genetic delivery tool can be used for specific targeting of several genes into different cell populations. Moreover, it will enable efficient fating and imaging studies during CNS development, as well as enhance the understanding of the molecular mechanisms that mediate cell communication in healthy and diseased brain. This novel approach will be implemented in model of epilepsy to study the role of astrocytes in the pathogenesis of the disease and challenge its use as a therapeutic tool.

Towards a breath test for early Parkinson's disease: nanomaterial-based sensors for detecting nigro-striatal dopaminergic lesion in rats

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Background: Symptoms of Parkinson's disease (PD) occur only after 50-70 % of nigrostriatal dopaminergic neurons have already been lost. It is therefore a prime effort in PD research to identify at-risk subjects as early as possible, with the future goal of instigating neuroprotective therapy before large scale neurodegeneration takes place. Recently the analysis of volatile organic compounds (VOCs) in exhaled breath has attracted much interest as a possible method to rapidly detect a variety of medical conditions. The aim of this study is to identify the VOC pattern of early-stage nigrostriatal dopaminergic lesion in rats with a new nanomaterial-based breath test.
Results: Exhaled breath was collected from rats that were previously administered 6-hydroxydopamine (6-OHDA) intracerebroventricularly (i.c.v.) at different doses (125 to 325 μg) in order to cause different degrees of dopaminergic neuronal loss, or with 5,7-dihydroxytryptamine (5,7-DHT) or saline as specificity and operational control substances respectively. The breath samples were analyzed using an array of organically functionalized carbon nanotube and gold nanoparticle sensors. Discriminant factor analysis detected statistically significant differences between the study groups and a classification accuracy of over 80 % was achieved using leave-one-out cross-validation. The chemical composition of the breath samples was studied using gas chromatography/mass spectrometry. Significant concentration differences of 4 VOCs were found among the sub-populations.
Conclusions: The source of the altered VOC metabolism in PD is unknown, but other studies have shown that increased oxidative stress can change production of VOCs from cell membrane lipids. The results indicate the feasibility of future development of this non-invasive technique for early PD detection.

Australia: Neuroscience, Research and Innovation

Finkel A.
AM FTSE – President-Elect, the Australian Academy of Technological Sciences and Engineering (ATSE) and Chancellor, Monash University.

Neuroscience research in Australia is running strong, as will be apparent during the presentations by the Australian delegation at the ISFN meeting. We are grateful for the opportunity to participate so fully in this meeting.

The neuroscience research capability in Australia is backed by a considerable investment in infrastructure, such as can be found at the Florey Institute in Melbourne, the Queensland Brain Institute in Brisbane, Neuroscience Research Australia in Sydney, the Hunter Medical Research Institute in Newcastle and the John Curtin School of Medical Research in Canberra. The advanced imaging equipment at these research centres is backed up by capabilities at the Australian Synchrotron at Monash University in Melbourne, including a new medical beam line, as well as other infrastructure capabilities around the country in hospitals and universities, ranging from X-ray crystallography to automated antibody manufacturing.
But we face challenges. On the plus side, Australian scientific research is cited at twice the rate of the OECD average. On the negative side, Australia has not been able to convert its research output into commercial outcomes at the same rate as other developed countries. Indeed, the rate of multi-country patents for Australian inventions is about one third of the OECD average. This means that there is enormous opportunity for Australia to achieve more in translating its strong research base into commercial outcomes. This is true in neurosciences as much as it is in IT and mining automation.
There are numerous existing collaborations between Israeli and Australian neuroscience researchers, and we hope that through the visits made by the Australian delegation and our participation at the ISFN meeting we will discover new opportunities for effective collaborations between outstanding neuroscience researchers in our two countries. A brief overview of the research interests of the delegation will be presented, along with some additional fields of relevant research not directly represented by the delegation.
The Australian delegation is being managed at the Australian end by the Australian Academy of Technological Sciences and Engineering. ATSE is an independent, non-government organization that promotes the development and adoption of existing and new technologies to improve Australia's competitiveness, and Australia's economic, environmental and social well-being.

3-D neural-compass: head-direction cells in the bat presubiculum

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'Head-direction cells' are neurons that become active whenever the animal's head points in a specific direction in space (like a compass), and they were suggested to be a key component of the mammalian navigation system. Directional tuning of rodent head-direction cells was previously characterized only for the head azimuth (yaw), and it is unclear whether they may

also encode elevation (pitch). Here we asked whether 3-D head-direction tuning exists in mammalian brains, by recording from Egyptian fruit bats, mammals which are well adapted to 3-D behavior. To this end, we developed a custom 3-D tracking apparatus that allowed monitoring the three head-rotation angles: yaw, pitch and roll, in freely moving animals. We conducted single-unit tetrode recordings in bat presubiculum, yielding more than 300 neurons – 32 % of which were tuned to head direction – from 4 bats, while the animals were actively crawling in an open-field arena, or were passively moved while being held upside-down. We found that head-direction cells in the bat were tuned to one or more of the three Euler rotation angles (yaw, pitch, and roll), with some neurons showing clear tuning to all the 3 angles – including pitch and roll. Population analysis showed that while the bat was held upside-down, a substantial fraction of neurons retained a clear directional firing, but surprisingly, the best tuning in azimuth was often shifted by 180 degrees compared to the upright position, suggesting a torus-like continuous representation of 3-D head-direction. Taken together, our results demonstrate for the first time a 3-D head-direction mechanism in mammals, which may be part of a broader neuronal network supporting navigation in 3-D space.

Carbamate derivatives of indolines as cholinesterase inhibitors and antioxidants for the treatment of Alzheimer's disease

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The cascade of events that occur in Alzheimer's disease (AD) involving oxidative stress and the reduction in cholinergic transmission can be better addressed by multifunctional drugs than by cholinesterase inhibitors alone. For this purpose we prepared a large number of derivatives of indoline-3-propionic acids and esters that showed antioxidant activity both in solution and against cytotoxicity in cardiomyocytes and primary cultures of neuronal cells exposed to reactive oxygen species (ROS).

Conclusion: Indoline derivatives having a carbamate in position 4 were found to be more potent acetycholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitors than those substituted at positions 6 or 7 while the corresponding 3-propionic acid esters, were more potent than their respective acids. Compounds with an (N-methyl,N-ethyl)-carbamate substituent were more potent inhibitors of BuChE than of AChE. The most potent AChE inhibitors were AN-890 (3-(2-aminoethyl)-indolin-4-yl-ethyl(methyl) carbamate dihydrochloride), and AN-819 (3-(3-methoxy-3-oxo-propyl)-4-(((4-methoxyphenyl)(methyl)carbamoyl)oxy)indolin-1-ium hydrochloride) with IC50s of 0.4 and 1.2 μM, respectively. Almost all the carbamates tested showed anti-oxidant activity against ROS at concentrations similar to or lower than those inhibiting AChE. Carbamoylation of the AChE enzyme releases the respective 4- or 6-OH indoline analogs. These compounds were found to be as good as or even better than the parent carbamates at scavenging ROS. Many of the compounds were able to reduce cytotoxicity induced by H2O2 in cardiomyocytes at concentrations ranging from 1 pm-100 nM, which act by reducing the fall in the mitochondrial potential. Thus, several of these novel compounds possess advantages over existing AChE inhibitors for the treatment of AD since they interact at relevant concentrations with several important targets to reduce the pathological changes occurring in this disease.

Novel multi-functional drugs for the treatment of neurodegenerative diseases

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Background: In Alzheimer's disease (AD), oxidative stress, (OS) glial activation and formation of plaques and tangles are believed to contribute to progressive neurodegeneration. None of the acetylcholinesterase (AChE) inhibitors currently in the clinic are able to reduce OS and inflammatory processes at doses used to treat AD. Therefore, there is a need for a drug which inhibits AChE and butyrylcholinesterase (BuChE), has anti-oxidant and anti-inflammatory activities. Indole propionic acid (IPA) prevents oxidative stress and death of primary neurons and neuroblastoma cells exposed to H_2O_2 or amyloid beta. Derivatives of indoline propionic acid (InPA) were found to be more potent anti-oxidants than those of IPA in cell culture. Therefore, a series of novel carbamates was synthesized based on the structure of InPA and their AChE, BuChE, anti-oxidant and anti-inflammatory activities were evaluated.

Results: Two compounds: 3-(2- (methoxycarbonyl) ethyl)-indolin-4-ylethylmethylcarbamate (AN-827) and 3-(2-(methoxycarbonyl)ethyl)-1-indoline-6-ylethylmethylcarbamate (AN-680) prevented cytotoxicity induced by OS and the release of cytokines from activated microglial cells at concentrations at, or lower than those inhibiting AChE. They inhibited AChE in rat brain and reduced lipid peroxidation and formation of nitrites in mouse brain after injection of lipopolysaccharide (LPS). When injected together with LPS,

AN-827 andAN-680 lowered the levels of pro-inflammatory cytokines (IL-6, IL-1β and TNF-α) in the cortex, subcortex and spleen. The mechanism of anti-inflammatory activity was evaluated in BV2 cells activated with LPS and shown to occur through reduction in phosphorylation of p38 and activation of the transcription factor AP-1.
Conclusions: Two derivatives: AN-827 and AN-680, which display anti-oxidant, anti-inflammatory and AChE inhibitory activities *in vitro* and *in vivo*, may have potential use for the treatment of AD and other neurodegenerative diseases.

Head motion in children with ADHD: how it affects connectivity results in neuroimaging studies
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Background: Recent reports have suggested that spurious but systematic correlations in resting state functional connectivity MRI (fcMRI) may arise from subject motion to the sensitivity of resting state data, typical preprocessing methods such as motion correction, regression of confounding signals and bandpass filtering are not sufficient to eliminate signal corruption caused by head movement. Here we analyzed the impact of head motion on seed-based functional connectivity. Data from the ADHD200 Consortium, comprising children and adolescents with ADHD and healthy controls, were used to estimate subject motion based upon head realignment using a rigid body six-parameter affine transform, summing the displacement at each TR. Mean displacements were calculated for translation and rotation. FcMRI was calculated between two seeds within the DMN, the medial prefrontal cortex (mPFC) to the posterior cingulate cortex (PCC). A linear stepwise regression with rs-fcMRI as the dependent variable and age and translation as independent variables was calculated.
Results: A total of 421 children (119 drug-näive and 302 controls) were included in this study. No statistical difference in age and IQ were observed groups ($p>0.1$). Children with ADHD exhibited excessive motion compared to controls within both modalities ($p<0.05$). Increased functional connectivity between the mPFC and PCC was observed within controls compared to patients ($p=0.036$). Regression analyses showed that difference in rs-fcMRI between groups was lost ($p=0.091$) when age and movement were incorporated in the analysis.
Conclusions: Head motion is one of the greatest factors that degrade fMRI data quality. Typically data with large displacements are discarded; however, discarding such data may induce selection bias. These results suggest that optimal handling of fcMRI data will need to take into account the consequence of motion artifacts to avoid the report of artifactual patterns of correlation.
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New insights into links between glia function and the development of Alzheimer's disease pathology
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Background: Glial cells maintain brain plasticity, as well as protect the brain for functional recovery from injuries. Dysfunction of glial cells may promote neurodegeneration and, eventually, the retraction of neuronal synapses, which leads to cognitive deficits that are found in neurodegenerative diseases such as Alzheimer's disease (AD). AD patient brains demonstrate a significantly higher degree of glial cells dystrophy than non-demented individuals. We aim to investigate the role of glial cells in the progression of AD.
Results and conclusions: The majority of the early-onset familial AD genetic cases (75 %) relate to the presenilin 1 (PS1) and presenilin 2 (PS2) genes that are considered important determinants of g-secretase catalytic site. We have demonstrated that g-secretase inhibitors (GSIs) can lead to impairment of microglial cell activity, which resulted in a reduction of phagocytosis of Aβ (Farfara et al. 2011). The accumulation of amyloid deposits on the cerebral blood vessels, known as cerebral amyloid angiopathy (CAA), is associated with cognitive decline and is one of the hallmarks of AD pathology. We recently demonstrated (Weiss et al.BBI 2012; Lifshitz et al Neurobiology of Aging 2012) that TGF-beta affects astrocyte and endothelial cell interaction, which as measured, resulted in an acceleration of a CAA-like pathology. Furthermore, we have shown that tau hyperphosphorylation in astrocyte leads to acceleration in AD pathology in a new mouse model that contains most of the features of AD pathology including CAA and neurodegeneration. Understanding the molecular pathway of glial cell activation will not only shed light on the pathogenesis of AD but also help to develop novel therapeutic applications in AD treatment.
Alzheimer's association, HFSP orginization and ISF

Alleviating tauopathy symptoms in a Drosophila model using aromatic inhibitors of amyloid aggregation
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In spite of the fact that various amyloid-forming proteins do not share simple sequence homology, all amyloid assemblies have common ultrastructural and physiochemical properties. We and others have identified a central role of specific interactions between aromatic residues in the recognition and self assembly process leading to the formation of various amyloid aggregates. Therefore, aromatic aggregation inhibitors, which would compete for the aromatic interactions between amyloidogenic proteins themselves, may serve as general anti-aggregation inhibitors for various amyloid proteins. Indeed, our in vitro studies have shown that NQTrp, a small aromatic molecule composed of a quinone-tryptophan hybrid, inhibits aggregation of various amyloidogenic proteins including Aβ, alpha-synuclein and lysozyme. Based on this, we have shown that NQTrp can cause complete phenotypic recovery of an Aβ-Alzheimer's disease (AD) Drosophila and mouse models. To test whether this generic inhibition potential is effective also in vivo we began to explore NQTrp as potential inhibitor of tau aggregation in a Drosophila tauopathy model. The microtubule-binding protein tau is a component of neurofibrillary tangles in AD and related disorders that are collectively referred to as tauopathies. In an available Drosophila model of tauopathies, overexpression of wild-type human tau in the fly retina resulted in neurodegeneration which is manifested as a 'rough' eye phenotype with disordered ommatidia. Utilizing this model we found dramatic reduction in the flies' eye neurodegeneration when fed with 0.75 mg/ml NQTrp in the culture medium throughout their lifetime. Likewise, NQTrp alleviated the locomotion defects typical of targeted overexpression of wild-type human tau in the fly CNS. These results support the notion that aromatic aggregation inhibitors can work efficiently on various amyloidogenic proteins in vivo. Testing inhibition of in vitro tau aggregation using NQTrp is underway.

Evidence for similar early but not late representation of possible and impossible objects

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Impossible objects are defined as 2D drawings that represent 3D objects that could not exist in real space. Yet, despite being perceived as exceptionally unusual, impossible objects still possess fundamental Gestalt attributes, such as closure, distinguishable surfaces and volume properties. Based on this notion and on recent neuroimaging findings from our lab, we hypothesized that the initial perception of impossible objects will involve common mechanisms to those mediating typical object perception. Furthermore, the perceived differences between the two classes of objects would only emerge later along the processing hierarchy. Experiment 1 utilized the object-based attention paradigm to show that impossible and possible objects are represented similarly such that for both object categories processing features belonging to the same object was enhanced compared to features belonging to two different objects. Yet, responses for impossible objects were overall slower compared to possible objects. The goal of Experiment 2 was to examine whether these differences could be attributed to early versus late processing by manipulating exposure duration. Importantly, differences in accuracy between possible and impossible objects emerged only for long stimulus exposures thus verifying our working hypothesis. Overall, these findings suggest that the visual system utilizes intact shape attributes to create an organized representation of impossible objects and highlight the importance of these attributes for perceptual organization.

Using machine learning to identify patients with syslexia disability

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Background: Dyslexia is a learning disability that impairs a person's ability to decode words accurately and fluently. This deficit can manifest itself in the language-related domain as difficulties in phonological and orthographic working memory, brain systems asynchrony, poor executive function skills and/or poor rapid naming processing. However it is not clear yet whether the dyslexia phenomenon is only related to language or if it can also be seen as a non-language deficit. Moreover, if it is also related to non-language activity, it is important to verify if it is possible to identify dyslexic readers at the earliest stage of information processing for better and effective remediation. Based on this, an effective algorithm was developed for analysis and classification of subjects as either Regular Readers or Dyslexic Readers, by using EEG recorded channels with Event Related Potentials (ERP) methodology during an auditory, short non-linguistic, simple, subphonetic choices reaction time task.
Results: Three results are presented: (i) the ability to successfully identify readers using the single feature, taking advantage of only three out of 64 electrodes, reached 80 % accuracy, (ii) using an ensemble of classifiers, lead by a majority voting mechanism (each classifier trained separately on a different feature – electrodes pairings) 85 % accuracy reached, (iii) we show that the majority of differences lie in the left hemisphere.

Conclusions: Successful classification at such an early auditory processing stage may indicate the origins of the dyslexia phenomena. Another interesting conclusion was that each feature could successfully be separated using different electrode leads, i.e. there exist wide differences in information processing and different brain areas may indicate that there are different causes of the same problem, perhaps the existence of different subtypes of dyslexia.

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Chronic inflammatory pain and morphine analgesia: Involvement of microglia and interleukin-1

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Background: Peripheral inflammation induces changes in the central and peripheral nervous system, which are (mostly) associated with hyperalgesia, and accompanied by activation of spinal glia cells and the release of interleukin-1 (IL-1). In naive mice, IL-1 has been shown to mainly induce hyperalgesia and to counter-regulate morphine analgesia. In contrast, accumulating evidence suggests that in states of peripheral inflammation IL-1 may contribute to hypo-algesia, via changes in peripheral opioid mechanisms. The present study examined the involvement of IL-1 and microglia in pain sensitivity and in opioid analgesia in a state of chronic peripheral inflammation.
Methods: Inflammation was induced by sub-dermal injection of complete Freund's adjuvant (CFA) at two sites around the left ankle in mice. Animals were assessed for mechanical allodynia, mobility, swelling, and hind-paw histology.
Results: (A) Morphine analgesic efficacy was extended by peripheral inflammation;(B) Neither genetic nor pharmacological blockade of IL-1 signaling impeded the development of allodynia in the inflamed paw; (C) Genetic and pharmacological blockade of IL-1 prevented the potentiated morphine analgesia;(D) Pharmacological blockade of microglia prevented the potentiated morphine analgesia; and (E) Morphine injection reduced histological markers of inflammation around the joints by 24 hrs post-injection.
Conclusions: These findings indicate that morphine analgesia is potentiated in a state of chronic peripheral inflammation and that IL-1 (possibly released by microglia) is involved in this potentiation. Furthermore these findings indicate that morphine plays an anti-inflammatory role in a state of chronic peripheral inflammation.

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ADHD subjects fail to suppress microsaccades and eye blinks during anticipated stimulus presentation

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Background: ADHD is the most prevalent psychiatric disorder, estimated to affect about 10 % of the population. Currently, the diagnosis is based mainly on subjective parameters, though there are several computer-based tools, such as TOVA, to support the diagnosis. However, no objective tool based on physiological measurements is available for diagnosing ADHD. It was previously shown that several ocular parameters correlate with attention. We thus aimed to search for objective markers of ADHD based on ocular parameters.
Methods: Twenty subjects diagnosed with ADHD and 20 control subjects performed 2 sessions of TOVA, while their eye movements were tracked. ADHD subjects performed the first session un-medicated and the second session 1.5 hours after taking medication (Ritalin). Control subjects performed the second session 1.5 hours after the first, both without medication. We measured the average rates of eye blinks and microsaccades during the time interval -75 to 150 milliseconds relative to stimulus onset (peri-stimulus).
Results: We found that un-medicated ADHD subjects have a significantly higher average blink rate than control group during the peri-stimulus interval; this average rate is significantly reduced with medication, but still remains significantly above the control rate. We also found that the average rate of microsaccades in ADHD group in the un-medicated session during the peri-stimulus interval is significantly higher than in the control group and that is reduced to the level of the control group after medication.
Conclusions: These results suggest that un-medicated ADHD subjects fail to suppress both microsaccades and eye blinks during anticipating the stimulus presentation. We also show that medication increases the suppression capacity of ADHD subjects towards the normal range.

The romantic OdorSpace

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Olfaction and the MHC family of genes influence mate selection. MHC is both linked to the individual olfactory genome, and also influences body odor. Therefore, exploring the olfactory preferences of individuals has the potential of foreseeing their mate selection preferences. To test this hypothesis, we used a web-based platform developed in our lab called OdorSpace. The basic idea involves dispensing odor kits, and rating a series of psychophysics measures regarding each smell. We micro-encapsulated four different odors (cis-3-hexen-ol,

isoamyl acetate, methyl anthanilate and isovaleric acid) packed in a kit and asked romantic couples to log in to site (www.odorspace.com), where they were asked to fill in a questionnaire. They were asked to enter general demographic data, to rate their overall relationship quality as well as the quality of their sexual relationship, on a 1 to 100 visual analog scale (VAS). They were then asked to rate 30 descriptors for each of the odors in the kit (for a total of 120 ratings, on a similar VAS). Typical descriptors were "To which extent is the odor edible", "How fresh is the odor", etc. Both partners filled the same questionnaire consecutively, albeit with a scrambled order of descriptors. We calculated the correlation between the answers of both partners, and correlated that number with the rated overall and sexual quality of the relationship, as provided by the subjects. So far we received entries from 18 couples. Rated quality of the relationship positively correlated with the smell match correlation for the romantic couples (R=0.556, p<0.0005). Rated sexual quality also positively correlated with smell match correlation but was weaker (R=0.47, p<0.005) (Pearson's correlation). There was no significant correlation between the length of relationship to neither the smell matching score nor the rated qualities.

Neural signature of change of intentions

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Intention is an intermediate concept between will and action and is defined in this work as conscious or non-conscious preparation to act. The goal of this work is to identify a neural index of change of intention and characterize the conditions that lead to it. In order to obtain an electro-physiological model for 'change of intention' we used a masked priming paradigm while recording EEG. The task was to press a right or left button following either a visible arrow cue ('instructed condition') or a visible 'free-choice' cue. The subjects were unaware of the presence of the masked prime, nevertheless we observed a behavioral effect of the prime: on Instructed trials performance was slower and less accurate when the prime and instruction cue pointed in different directions (i.e., incongruent trials), than on congruent trials; on free-choice trials performance was slower in the incongruent cases, and primes significantly biased freely chosen responses in the direction of the prime. We revealed a spatio-temporal electrophysiological signal around 250-350 ms after prime onset which we interpret as an EEG signal induced by the prime, representing preparation to move right or left according to the prime cue direction. This signature allowed us to explain the behavior cost of incongruence, both in Instructed as well as in free-choice trials, by a 'change of intention' scenario rather than confusion or hesitation: the subject prepares the type of action indicated by the prime but 'changes his/her mind' and actually acts differently. In this experiment, the 'change of intention' is composed of an initial intention prompted exogenously by a masked prime, which is then overruled either by an exogenous instructing arrow in the Instructed case, or by an endogenous intention in the free-choice case. The results allowed us to reveal the process of change of intention in a second experiment in which both the initial and the overruling intention are endogenous.

Aversive olfactory memories with different reinforcers

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Drosophila melanogaster flies show complex behaviours like associative learning. Using the available genetic tools combined with behavioural measures allows us to study the specific neuronal circuit of learning and memory. In olfactory conditioning, flies are simultaneously presented with odour and reinforcement, and their associative memory is tested later by the degree of odour avoidance. Using olfactory conditioning with different aversive reinforcers, we directly compare the neuronal circuit of different aversive memories (i.e. heat and electric shock). We found that flies avoid the conditioned odour that has been paired with the heat, while too high temperature leads to impairment of the performance. Calibration of reinforcement intensities revealed that the memories of heat and shock share commonalities. We identified responsible neurons that are selectively required for the heat, but not shock memory. Furthermore, we found that conditioned odour avoidance with both heat and shock requires intact dopamine neurons. These results imply that these two noxious stimuli are perceived using different receptors but commonly recruit the same neurotransmitter system to signal aversive reinforcement.

Extracellular pH regulates the ZnR/GPR39-dependent Ca++ responses in primary hippocampal neurons

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Background: Zinc ion is the second most important element in the body and is abundant in the brain, with very high concentration in the hippocampus, among other brain regions. Zinc is selectively stored in presynaptic vesicles and has been shown to be released in a calcium- and activity-dependent manner. Recent studies have demonstrated that synaptically released zinc can act on a post-synaptic metabotropic zinc receptor/G protein-linked receptor 39 (mZnR /GPR39)that is localized in CA3 neurons.

Activation of GPR39 triggers a Zn-dependent metabotropic Ca++ response which then regulates Cl transport in the post synaptic cells.

Results: We have developed a primary culture of hippocampal neurons in which we are able to monitor ZnR activity. Cultures obtained from GPR30 KO mice do not exhibit a Zn-dependent Ca++ response. . Zn binding is mediated by histidine and aspartate residues on GPR39, these residues are often implicated in pH sensing. Localized pH changes have been suggested to occur in the brain during normal function or pathologic conditions. Using calcium imaging, we show that the neuronal mZnR response is regulated by pH. Our preliminarily results show that the mZnR/GPR39-dependent Ca2+ response is reduced at pH 8 and abolished at pH 6.5 on WT cultured neurons.

Conclusion: In this study, we will focus on the role of ZnR/GPR39 in regulating a major Ca2+ signaling pathway that is sensitive to extracellular pH.

Feed-forward and top-down somatosensory body processing in the human brain

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We perceive ourselves as single individuals, each an inseparable combination of body and mind. Key to this perception is the brain's ability to maintain the Holistic Body Representation (HBR), which combines information from a variety of body parts, sensory input modalities and higher cognitive sources. Yet, it is not clear how all these sources of information converge and the neural correlates of HBR remain elusive. Our goal is to reveal the networks underlying HBR.

This study focuses on the neural correlates of HBR using fMRI in humans. We combine tactile perception and imagery paradigms with a visual-based mental body transformation task to examine feed-forward (body parts to brain) and top-down (higher cognitive function to body part) processing contributions to the HBR in humans. Specifically we focus on the integration of bottom-up and top-down somatosensory and visual information of the whole body.

The ventral and dorsal premotor (PM) cortex and the anterior intraparietal sulcus (aIPS) were the main areas involved in HBR. We show that information from several body parts converges in these areas. The aIPS was the major focus of activation for all aspects of HBR, integrating whole-body processing in tactile perception and tactile imagery and showing equal feed-forward and top- representation. The Parietao-Occipital Sulcus showed a unique preference for HBR imagery selectively. Based on our findings, we suggest an integrative framework for the cortical network which subserves HBR.

Effects of sensory modality and flight kinematics on 3-D spatial codes in bat hippocampus

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Hippocampal neural recordings are an important model system for understanding spatial cognition: The ensemble activity of hippocampal 'place cells' encodes the location of an animal within its environment. However, little is known on how inputs from different sensory systems affect hippocampal spatial representation. Here we set out to dissociate the effects of using two long-range sensory systems – vision and echolocation – on hippocampal neural activity in a unique animal model, the Egyptian fruit bat. We trained bats to orient using vision without sonar – in a lit environment, and by sonar without vision – in the dark. Through simultaneous recordings of multiple cells in the hippocampal CA1 region of flying bats, we are in the process of characterizing the differences in the neural codes for space of individual cells, and in the ensemble activity, based on the two sensory systems. Preliminary results from hippocampal recordings in flying bats showed clear three-dimensional (3-D) place fields in the light, and in the dark. Some cells showed clearly reproducible 3-D place fields between two consecutive flight sessions in light conditions, while exhibiting consistent 'remapping' when switching from light to dark conditions (that reverted when switching back to the light condition).

We will also discuss the selectivity of place-cell firing to the 3-D-directionality of flight, and the possible dependence of the neural activity on flight curvature. So far, we have found that some cells show clear preferences for left-right flights or for right-left flights – similar to previous reports in rats.

A novel sarcosinyl-linked Olanzapine antipsychotic agent, PGW5, exhibits high efficacy with no metabolic side-effects in rodent models

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Background: Schizophrenia is a chronic disease associated with hypo function of glutamate transmission. Psychotic symptoms are induced by NMDA antagonists. Atypical

neuroleptics induce weight gain and metabolic syndrome associated with the development of medical comorbidities (atherosclerosis, hypertension, dyslipidemia, diabetes) as well as depression, and eating disorders. We have developed a novel antipsychotic drug, PGW5, possessing an olanzapine moeity linked to positive modulators of NMDA sarcosinyl. Objective 1. Evaluate the efficacy of PGW5 in mice models of schizophrenia. 2. Determine the metabolic profile of PGW5 compared to Olanzapine in a rat model of weight gain.

Results; Efficacy studies were performed in male mice (Balb/c or C57bl) exposed to MK801 or PCP. PGW5 (12.5-50.0 mg/kg) was administered orally. In open field tests, PGW5 effectively antagonized MK801-induced hyperactivity up to 6 hr. At effective doses, PGW5 was not sedative, and demonstrated significant anxiolytic activity. In a subchronic study, PGW5 but not Olanzapine antagonized PCP-induced impaired social preference. In adult female Wistar rats, PGW5 (25 mg/kg/d) ingested daily (over 14 of 16 days, dissolved in 10 ml of Ensure Plus Chocolate), as opposed to Olanzapine, did not induce weight gain or alteration in lipid profile. This subchronic administration of PGW5 was accompanied by an increase in the neurotrophic factor BDNF in the cortex and hippocampus, whereas Olanzapine but not PGW5 increased the hippocampal expression of the NPY receptor Y5.

Conclusions: PGW5 is a novel neuroleptic, potentially efficacious (according to research in mouse models) against positve and negative symptoms of schizophrenia. PGW5 administration, in contrast to Olanzapine was not associated with weight gain. The possible mechanisms underlying the differential effects of the drugs involve brain BDNF and NPY regulation.

Zn2+ neurotransmission during kainate-induced in-vitro seizure-like activity results in upregulation of KCC2 activity via mZnR/GPR39

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Background: Synaptic Zn^{2+} is stored in pre-synaptic vesicles and is co-released with glutamate in a sub-population of glutamatergic nerve terminals. A distinct metabotropic Zn^{2+}-sensing receptor (mZnR), was shown by our lab to trigger intracellular Ca^{2+} rise following synaptic Zn^{2+} release in CA3 hippocampal neurons. We have shown that exogenous Zn^{2+} or Zn^{2+} released by physiologic stimulation of hippocampal mossy fibers upregulates KCC2 activity via mZnR/GPR39 by increasing its surface expression. KCC2 is the principal Cl^--outward transporter in mature neurons and its upregulation by mZnR/GPR39 signaling is sufficient to produce a hyperpolarizing shift in GABA reversal potential (E_{GABA}) and may thus alter neuronal excitability.

Results: KCC2 activity was monitored by measuring the rate of NH_4^+ influx into neurons using fluorescent imaging. Mouse brain slices from mZnR WT animals incubated with the excitotoxin kainate demonstrated a nearly two-fold increase in KCC2 activity in CA3 hippocampal neurons compared to controls. This upregulation of KCC2 activity was abolished in slices treated with the cell impermeable Zn^{2+} chelators CaEDTA and tricine. Furthermore, kainate treatment did not change KCC2 activity in the presence of Gαq, PLC and MEK1/2 inhibitors that eliminate GPR39/mZnR signaling. Importantly, in slices from mZnR KO animals kainate did not significantly change KCC2 activity.

Conclusions: GPR39/mZnR activation by Zn^{2+} during kainate-induced seizure-like activity results in upregulation of KCC2 activity in CA3 hippocampal neurons. We suggest that synaptic Zn^{2+} released during excitatory activity may initially enhance inhibitory tone, providing an intrinsic homeostatic mechanism.

Resting state patterns reflect functional abnormalities in human visual cortex

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Even in the absence of stimulation or task, the cerebral cortex shows an incessant pattern of ultra slow fluctuations which are coherent across brain regions. In the healthy brain these coherent patterns (also termed resting state functional connectivity) often exhibit spatial similarity to the large scale organization of task-induced functional networks. However, it is not clear to what extent the resting state patterns can also reflect task-induced abnormalities in cortical activations which are often detected in various brain pathologies. Here we examined whether an abnormal visual activation pattern is recapitulated in the resting state functional connectivity. We examined LG, a sighted young adult with developmental object agnosia and no apparent cortical structural abnormality. We have previously reported that upon visual stimulation, LG's intermediate visual areas (V2, V3) are paradoxically deactivated. Here, examining LG's resting state functional connectivity revealed the same pattern of functional abnormality- including a strong atypical decorrelation between areas V2-V3 and the rest of the visual system. Thus, our results suggest that resting-state functional connectivity could provide a powerful tool for detecting task-related abnormalities in cortical activity without resorting to task performance.

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Biological motion perception in individuals with form perception deficits

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What neural computations underlie the perception of biological motion is a key question in vision science and neuroscience. The classical point-light biological motion stimuli used in most studies not only incorporate the dynamics of animate motion, but also evoke the percept of bodily form. Psychophysical and neuroimaging studies have provided support for the involvement of both form and motion-based processing in perception of these stimuli. Here, we explored whether biological motion perception critically relies upon form processing. We examined individuals with form perception deficits (ventral visual brain-damaged patients and a developmental visual agnosic with no apparent brain damage), and matched controls (healthy individuals and brain damaged patients without form perception deficits whose lesions were in the MCA territory and did not include ventral temporal cortex). In a series of experiments using established noise-masking methods, we adaptively measured perceptual thresholds in detecting point-light biological motion. Perception of non-biological form-from-motion was also assessed. We found that patients and individuals with form perception deficits were not obviously impaired in their biological motion perception, but were impaired in non-biological form-from-motion tasks. Critically, biological motion perception of ventral patients did not differ from those of MCA-territory lesioned patients on average, and was better than patients whose lesions included premotor or superior temporal cortex. Thus, our data suggest that biological motion processing relies on a broad network of brain regions, where ventral visual cortex is not as critical to biological motion perception as frontal or superior temporal brain regions.

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Neuro-responsive media: SSVEP-based interactive experiences

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Background: There is now wide interest in controlling external devices using brain-computer interface (BCI); we are aiming at extending BCI to interactive media experiences. Our method uses the steady state visually-evoked potential (SSVEP) paradigm, which is based on detecting occipital activation that resonates to flickering visual stimuli. Typical SSVEP-based methods use analog stimuli at low frequencies (5-20 Hz), whereas we embed the SSVEP cues naturally inside the interactive media at high frequencies close to the fusion flicker threshold using a digital display. This allows for a user-friendly interactive experience that can be used for classic BCI as well as novel applications.

Method: EEG was recorded using 8 electrodes positioned at occipital locations. Amplification, analog and digital filtering, and algorithms were computed using Matlab, Simulink (MathWorks, USA), and hardware and software from g.tec (Austria). Stimuli were presented on a back projected large screen at 120 FPS, at 30,40 and 60 Hz, generated using Unity (Unity Technologies, USA) game engine. A classifier was first obtained by exposing the subject to simple stimuli using the minimum energy EEG method (Friman et al., 2007). A rerun verified accuracy of at least 90 %, followed by the interactive experience. We explored various types of stimuli: simple shapes, images, and an interactive scenario that included four star-shaped stimuli. The subjects selected one of the stars and had to maintain attention to it after it started moving around the screen.

Results: Ten subjects participated in the pilot, and the system was able to classify their SSVEP responses at 90 % accuracy or higher in the interactive experiences.

Conclusion: SSVEP responses can be classified with cues that are embedded naturally in an interactive media in high frequencies. We are now exploring the psychological aspects of this effect in terms of the sensation of agency and the emotional relevance of the stimuli.

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Therapeutic potential of combining the multi-target neuroprotective compound M30 with a fortified high calorie/energy diet in a transgenic mouse model of ALS

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Background: Given the multiplicity of pathological mechanisms in Amyotrophic lateral sclerosis (ALS), the management of the disease nowadays is based on the recognition of the importance of a multiple target and multidisciplinary care including the energy intake and expenditure of patients. Recently, we demonstrated that the multi-target, brain permeable iron chelator M30, carrying the propargyl moiety of our neuroprotective anti-Parkinsonian drug rasagiline and the iron-chelating moiety of VK28, conferred a significant improvement in survival time and motor performance of

G93A-SOD1 Tg ALS mice. Goal: Our experimental protocol aims to test the possibility that strengthening the basal energy status of G93A-SOD1 Tg ALS mice would provide a supportive basis for optimization of the neurorestorative efficacy of M30. For this purpose ALS mice are administered a combination of M30 and a high **c**alorie/**e**nergy supplemented**d**iet (M30 + CED), starting at the 56th day of birth until death.
Results: We demonstrated that the M30 + CED cocktail significantly delayed the onset of dysfunction compared to each individual treatment. Furthermore, the combined formulation showed superiority in extending the lifespan of the ALS SOD1 mice compared to the effect of each of the individual components, suggesting a synergism between M30 and the CED. Lastly, gene expression analysis of genes related to energy homeostasis and lipid and glucose metabolism in the gastrocnemius muscle, liver and brain samples, showed significant tissue-specific changes by the M30 + CED treatment compared to either M30 or CED alone, further supporting their protective complementary action.
Conclusion: This study supports the current assumption in the treatment of ALS, stating that combining therapeutic agents with different mechanisms of action may be superior to monotherapies and provides a novel design for a multiple-target therapeutic protocol for clinical trials in ALS.

The mere co-presence: studying the physiological effects of the presence of others
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An extensive effort is currently invested in revealing the biological mechanisms involved in social interactions. Recently it has been proposed that the biological signals of two interacting individuals exhibit joint, temporally aligned response patterns (Hasson et al. 2012), aka *physiological coupling*. Thus, people not only couple together on the behavioral and emotional levels during interaction, but also enter a state of biologically maintained interpersonal resonance in which various somatic and neuronal processes show similar dynamical changes. A series of recent studies demonstrated that *physiological coupling* in the neural and autonomic domains accompanies different forms of interpersonal information exchange. In the current study we explored whether *physiological coupling* occurs when individuals are merely co-present, without directly exchanging information. To that end we recorded continuous autonomic signals of subjects while they watched a movie together with other people or while they watched a movie alone. We hypothesized that subjects who shared both the input (a movie) and the physical presence with each other will show higher levels of *physiological coupling* relative to those who only shared the input, marking the physiological effect of co-presence.
In accordance with our hypothesis, subjects who watched the movie together showed significantly higher levels of *physiological coupling* then those who watched the movie alone or those who watched the movie with a different partner, on a different occasion. In addition, we revealed that collective movie watching involves a specific physiological state, marked by heightened levels of arousal during emotional scenes.These results support the hypothesis that other people distinctively affect our biological responses to external stimuli, even when there is no direct exchange of verbal information. Moreover, it suggests that*physiological coupling* is one of the biological processes underlying this phenomenon.

An integrative metabolic analysis of mesial temporal epilepsy
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Background: Mesial temporal lobe epilepsy (MTLE) is a chronic disease which is acknowledged as the most prevalent of all focal epilepsies. While there is a vast amount of knowledge regarding the anatomical, physiological and cellular aberrations of the disease, very little progress has been made in understanding its underlying mechanism and in discovering possible pharmaceutical treatments. The main purpose of this project was to study the metabolic aspects of the disease using a state of the art method - the integrative metabolic analysis tool (iMAT).
Results: By integrating raw transcriptomic data from the CA1 sub-region in the hippocampus, we have portrayed an integrative metabolic description of the different stages of MTLE. We have successfully replicated many experimental results on known aberrations of the disease in the metabolic level and have shown for the first time that some of them are noticeable already in very early stages. We further study which metabolic genes and pathways are strongly associated with MTLE and compose an integrative overview of the disease. In addition, a list of suggested metabolic biomarkers and drug targets was prepared.
Conclusions: This discovered biomarkers and drug targets may be further validated experimentally and by doing so offer significant progress in the treatment of MTLE such as early discovery of the disease, novel pharmacological treatments and better detection of the severity of MTLE and the state of its progression.

Neurobehavioral dissociation of reinforcement sensitivity and its relation to personality traits
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Background: Motivation is defined as the drive to facilitate or inhibit behavior in response to environmental cues. The "Reinforcement Sensitivity Theory" is a neurobehavioral model for motivational processes postulating three neural systems mediating the response to reward and punishment, and implies correspondence of these systems to core personality traits of Sensitivity to Punishment (SP) and Reward (SR). However, this relationship has been scarcely examined at the neural level. One obstacle for such investigation is that sensitivity to reinforcements carries two behavioral aspects of motivation: 'liking' (i.e. hedonic) and 'wanting' (i.e. incentive). We aimed to dissociate these elements by measuring brain activity via fMRI and to further inspect the relation to SP and SR personality traits.
Methods: 46 subjects were scanned while playing an ecological computer game constructed to manipulate motivational tendencies, with random events of rewards and punishments allowing for subtraction of the hedonic (uncontrolled) element from the incentive (controlled) process. Results: GLM analysis of controlled vs. uncontrolled events enabled to identify an incentive network, including regions related to action (e.g. M1, SMA) and arousal (e.g. hypothalamus, PAG). Importantly, we found differences in activation between high and low SP/SR traits: higher SR was related to less activation of punishment related areas, and vice-versa.
Conclusions: Our paradigm enabled to neurally dissociate the incentive and hedonic elements in the response to reinforcement, thus allowing for inspection of personality traits related to incentive motivation. This approach revealed that these traits are mediated by differential activation in several motivation systems, and not simply in one system or another. Such neurobehavioral distinction can provide new avenue for the diagnosis and therapy of psychopathologies, which can be often characterized along the hedonic and incentive dimensions.
The Levie-Edersheim-Gitter Institute for functional Brain imaging

An active perception model for whisking humans
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Background: Perception involves motor control of sensory organs. However, the dynamics underlying emergence of perception from motor-sensory interactions are not yet known. We studied the closed-loop scheme of motor-sensory interactions using a novel experimental paradigm in which human participants localized objects using artificial whiskers. The setup enabled monitoring all relevant motor variables, such as hand velocity and synchronization and sensory variables, such as position and contact-induced force.
Results: We found that motor variables were dynamically controlled within each perceptual trial, such that they gradually converged to steady values. We constructed a model wherein perceptual confidence increased via Bayesian update rules and extracted internal parameters of the subjects, such as sensory noise and intrinsic confidence thresholds, by fitting the model prediction to the subjects' performance. A perception-oriented optimal control formalism, with a novel processing cost term, was then applied and correctly described the behavioral converges of the "whisking humans". A corollary result of the new framework is that the update flow of information is actively maintained constant.
Conclusions: We believe that the novel experimental paradigm can serve as a fully monitored testing bed for future research of active sensing in humans. Furthermore, we believe that the developed theoretical active perception framework can be applied to many other modalities and behaviors and is a key principle in active perception in humans and animals.

Activity-dependent neuroprotective protein (ADNP) and ADNP2: brain and blood regulation
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Activity-Dependent Neuroprotective Protein (ADNP) and ADNP2 are members of a protein family, containing zinc-finger motifs and a homeodomain profile. ADNP knockout in mouse results in failure of cranial neural tube closure and embryonic death. Partial knockdown of mouse ADNP results in age-dependent neuronal cell death as well as astrocyte tau pathology coupled to cognitive and social deficits. At the cellular level, partial knockdown of ADNP is associated with inhibition of neurite formation as measured by decreases in microtubule-associated protein 2. Similarly, silencing of ADNP2 RNA renders the cells more susceptible to oxidative stress. ADNP was identified as a chromatin accessory protein, interacting with components of the SWI/SNF chromatin-remodeling complex, including Brg1. Our current studies show that ADNP2 is also interacting with the SWI/SNF complex. Previous studies have demonstrated that 1] the SWI/SNF complex is critical for neuronal differentiation and 2] Brg1 is involved in

erythropoiesis regulation, and is recruited to the β-globin locus by selective association with zinc-finger containing transcription factors. Here, chromatin immunoprecipitation (ChIP) assays revealed, for the first time, specific recruitment of ADNP as well as Brg1 to the mouse β globin promoter in murine erythroleukemia cells. Furthermore, specific down-regulation/silencing ADNP or ADNP2 in zebrafish embryos or mouse erythroleukemia cells inhibited erythroid maturation, which is critical for survival in the externally developing fish larvae (1). Thus, ADNP and ADNP2 play an important role regulating development, from fish to mammal.

Reference: (1) Efrat Dresner, Anna Malishkevich, Shelly Leibman Barak, Shahar Alon, Carmit Arviv1, Rivka Ofir1, Yoav Gothilf and Illana Gozes. Novel Evolutionary-Conserved Role for the ADNP Protein Family that is Important for Erythropoiesis. J. Biol. Chem. EPUB, 2012).

Gildor Chair, Adams Super Center, AMN, CFTAU, Allon Therapeutics (IG, Director, Founding Scientist).

Similar dynamics for categorization and exemplar discrimination in human face-related cortex

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Humans are faster in categorization (i.e., differentiation between faces and houses) compared to identification (i.e., differentiating between individual faces). However, it is unclear whether this behavioral difference is reflected in the neuronal dynamics in the visual cortex. Here, we utilized the millisecond temporal resolution of electrocorticographic (ECoG) recordings obtained from face-related areas in human patients. The dynamics of differential ECoG responses to categories of objects, including faces, was compared to that of individual face exemplars. The neural differentiation in the Gamma-band between categories and exemplars emerged rapidly (~100 ms latency) and simultaneously, despite a substantial difference in amplitude. Differential responses appeared earlier in lateral face regions compared to ventral regions (fusiform gyrus). The latency of visual evoked potentials (VEPs) coincided with that of Gamma-band responses, but VEPs exhibited lower category and exemplar decoding rates. Our results argue against a strict sequential process of face categorization preceding exemplar discrimination. They also shed light on the information flow within the human face processing network.

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Proinflammatory cytokines activate nociceptors by 38-MAPK-dependent relief of slow inactivation of TTX-resistant sodium channels

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Proinflammatory cytokines, interleukin-1 β (IL-1β) and tumor necrosis factor α (TNFα) not only sensitize nociceptors via gene regulation, but also rapidly and directly activate them, generating action potentials and inducing acute pain hypersensitivity. We have previously demonstrated, that IL-1β acts via p38 mitogen-activated protein kinase (p38 MAP kinase), to increase the excitability of nociceptors by relieving resting slow inactivation of tetrodotoxin-resistant (TTX-r) voltage-gated sodium channels. In the current study we examined whether this p38 MAP kinase-mediated modulation of slow inactivation is a common mechanism of proinflammatory cytokines to induce acute inflammatory pain.

We show that a short exposure to TNFα (1 min) produced a significant increase in peak amplitude of TTX-r sodium currents. This increase was not accompanied by changes in voltage dependence or kinetics of activation and fast inactivation. Similarly to the effect of IL-1β, application of TNFα caused a significant relief of slow inactivation, thereby increasing the amount of sodium channels available for activation from subthreshold voltage potentials. Both TNFα-mediated increase in TTX-r sodium current and TNFα-mediated relief of slow inactivation were prevented by application of the p38 MAP kinase inhibitor (SB-202190), implying the essential role of p38 MAPK in this TNFα-sodium channel interaction. Our results suggest that a relief of slow inactivation is a common mechanisms for cytokine-induced nociceptive hyperexcitability. Furthermore, we demonstrated that modulation of this mechanism by lacosomide (an anti-epileptic agent) which enhances slow inactivation of TTX-r sodium channels, reverts cytokine-mediated changes in neuronal activity. These data suggests that lacosamide, could be used clinically to attenuate inflammatory pain.

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Distributed coding in the trigeminal system

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Untangling the neural code underlying sensory perception requires the mapping of physical stimulus parameters to neuronal responses. The speed by which rodents discriminate between tactile stimuli, and neuronal response reliability in the whisker somatosensory system suggest that temporal coding might be used to encode sensory stimuli. The interaction between whiskers and object surfaces induces a complex temporal pattern of whisker vibration which may carry important tactile information. To determine the temporal kinetic features of whisker motion that are represented by first-order sensory neurons, we recorded from trigeminal ganglion neurons (TG) during stimulation with complex pattern of whisker vibration. We find that each of the different TG mechanoreceptor subtypes transmits a distinct kinetic feature of the stimulus. Our results suggest that TG neurons transmit a distributed representation of whisker motion, based on tactile kinetic features.

Long-term social recognition memory is mediated by molecular processes in the medial amygdala

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The ability to remember and recognize specific individuals is fundamental to vertebrate social behavior,especially for the establishment of social structures such as family,pack or clan.Most mammals largely rely on olfaction for social recognition, using mainly the main (MOS) and accessory (AOS) olfactory systems, which project converging inputs to the medial amygdala (MeA).Several lines of evidence indicate that the MeA is indeed involved in social recognition memory (SRM),but its exact role is unknown.In the presented study we first established that adult male rats do show short-(30 min) as well as long-term (>24 h) SRM using the social discrimination task,which is based on the difference in the time spent by the subject on olfactory investigation of a familiar and a novel juveniles, simultaneously presented to it.We then examined the dependence of this memory on protein synthesis in the MeA by locally blocking MeA protein synthesis during SRM acquisition.SD rats received bilateral saline or anisomycin (50 ug) injections into the MeA ten minutes before the first exposure to the social stimulus and SRM was tested 30 min or a day later by the social discrimination task.We found that anisomycin injection completely blocked long-term SRM acquisition,while no effect was observed when saline was locally injected.Moreover, anisomycin administration did not affect short-term SRM acquisition at all.Thus,protein synthesis in the MeA is required for long- but not short-term SRM acquisition.In order to further validate the susceptibility of MeA neurons to long-term plasticity we used theta burst stimulation in the AOB to induced long-term electrophysiological changes at the AOB-MeA synaptic pathway *in vivo*. Surprisingly,we found that MeA neurons underwent LTD following this type of stimulation,widely used for LTP induction.Altogether,our results indicate that the MeA is a place of long-term plasticity,where protein synthesis is required for the acquisition of long-term SRM.

GABA-related gene expression alterations in dorsal and ventral hippocampus and the amygdala in response to stress in juvenility and 'controllable / uncontrollable stress' in adult

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An exposure of rats to stress during juvenility (i.e. juvenile stress model) was found to impair the ability of animals to cope with stressful challenges in adulthood. Moreover, these behavioral manifestations were associated with lasting alterations in the limbic system, such as GABAergic system functioning and alterations in levels of circulating CORT (Horovitz et al., in press), neuromodulatory pathways and alterations in the expression of cell adhesion molecules. These findings suggested that exposure to stress during juvenility may lead to altered limbic functioning, possibly by dysregulating maturational processes in these regions. These alterations may result in mood and anxiety symptoms, particularly in association with additional exposure to stressors in adulthood (Avital and Richter-Levin, 2005; Avital et al., 2006; Ilin and Richter-Levin, 2009; Jacobson-Pick et al., 2008; Tsoory and Richter-Levin, 2006; Tsoory et al., 2007, 2008a,b).
A previous study demonstrated alterations in GABAergic interneurons' related genes in hippocample sub-regions and in the BLA following learning the water maze task (Hadad et al., in preparation). We now investigate potential alterations of expression of these genes following exposure to juvenile stress. The current study focuses on long-term effects of 'Controllable vs. Uncontrollable stress' in the TWS on gene expression alteration in different regions of the hippocampus and the amygdala on the background of exposure to 'Juvenile-stress'.

Increased resting state inter-hemispheric coherence in high functioning subjects with Autistic Spectrum Disorder

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Analysis of BOLD- resting state patterns is rapidly advancing as a potential diagnostic tool for a variety of brain disorders. In particular, resting state inter-hemispheric (IH) functional connectivity has proven to be a sensitive marker for neural aberrations. Here, we examined the IH connectivity of adult, high functioning individuals with Autism Spectrum Disorder (ASD) in comparison to age- and IQ-matched controls participants. We report an IH connectivity increase in the ASD group in the Ventral Premotor Cortex, a region associated with the language related fronto-prietal network. This VPM IH increase was also correlated with the degree of communication deficit in the ASD participants. As communication deficits are an important diagnosis criterion for ASD, we thus suggest that increased IH connectivity of the VPM may serve as a marker for high functioning autism in the adult brain.

Sleep shapes the brain: a potential mechanistic role for sleep in mediating risk in children of alcoholics

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Background: Reduced quality or amount of sleep in childhood is associated with impaired academic performance, poor impulse control, and impaired social functioning, and predict the development of emotional and behavioral problems including depression, anxiety, hyperactivity, and substance use problems. Despite such evidence, a mechanistic link between sleep and developmental risk remains elusive. Here we provide additional evidence linking sleep with psychopathology by associating sleep patterns with environmental and behavioral risk markers on the one hand, and with brain morphology and function in regions involved in affect regulation and impulse control, on the other.
Results: 72 children, 8-12, from the Michigan Longitudinal Family Study (N=59 children of alcoholics (COAs), N=13 non-COAs) participated in the study. COAs slept less compared to non-COAs. Within and across groups, less sleep correlated with more conflict at home, as reported by the children, and more behavioral problems at school as reported by the teachers. Further, the volume of the right hippocampus positively correlated with amount of sleep, while the thickness of the right anterior cingulate correlated positively with delayed sleep onset, a marker for insomnia. Teacher-rated externalizing negatively correlated with both left and right hippocampal volumes, while conflict in the home correlated positively with the volume of the right nucleus accumbens (NAcc). We then considered whether sleep was associated with neural responses to rewarding stimuli in the NAcc, finding that more sleep was associated with greater activation in the presence of reward.
Conclusions: These observations suggest that reduced amount of sleep is associated with functional and structural changes in neural substrates involved in affect regulation and impulse control, supporting the notion that sleep mediates the effects of environmental risk factors in the development of behavioral problems.
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Differences between adults who do and do not stutter in fMRI activation during speech perception

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Background: Stuttering is a developmental speech impairment, manifested as blocks, prolongations, and repetitions of sounds and syllables in speech production. Several neuroimaging studies have attempted to characterize differences in brain activity between people who stutter (PWS) and fluent speakers while producing speech. Only a few studies focused on cortical differences during speech perception, reporting mixed results (Loucks et al, 2011; de Nil et al, 2008). The current study used fMRI to investigate neural differences between PWS and fluent speakers while performing a speech perception task. We examined brain activity while subjects (11 PWS and 25 controls, ages 19-53) were listening to short Hebrew paragraphs or to auditory baseline epochs (signal-correlated noise). We used an incidental sound detection task to monitor subject's attention throughout the scan.
Results: We analyzed BOLD signals in three bilateral brain regions: inferior frontal gyrus (IFG), posterior superior temporal sulcus (pSTS), and Heschl's gyrus (HG). PWS exhibited significantly stronger brain activity within the right IFG and within the left HG in comparison to fluent speakers. In the right IFG, PWS presented a bilateral activation pattern, while controls showed significant left lateralized activation.
Conclusions: Neural differences between PWS and fluent speakers are not restricted to speech production but are also evident in a speech perception task that does not involve speaking. Results suggest that right IFG serves as a general compensatory region in adult PWS, showing increased activation in both production and perception tasks. The over-activated auditory cortex in PWS contrasts with typical under-activation of that region in PWS during production. Within the "efference copy" model of stuttering, our finding suggests that HG enhances its perceptual responsivity to

overcome the inhibitory effect of the exaggerated efference copy delivered from the motor system during production.
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Location specificity in perceptual learning is a result of sensory adaptation

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Background: In perceptual learning (PL) practicing visual tasks improves sensitivity to the trained stimulus in a highly specific manner. Conversely, Performance deterioration was shown following intensive training, comprised of many repetitions. The suppressive effect of excessive training trials has been attributed to sensory adaptation, a selective sensitivity reduction. Harris et al. (Current Biology, 2012) found, using the standard texture discrimination task (TDT) that location specificity, a defining yet limiting feature of perceptual learning, is absent when adaptation is removed. To remove adaptation, we added task-irrelevant ("dummy") trials with the texture oriented ±45° relative to the target's orientation. Here the newly proposed link between learning specificity and sensory adaptation is challenged using a different training procedure that enhances adaptation. One group of observers was trained with the standard TDT training paradigm while another group was trained with reduced adaptation. To maximize adaptation, stimulus onset asynchrony (SOA) was gradually decreasing from high to low, until chance level performance was reached.
Results: Results show (1) within-day deteriorations are more dominant in the enhanced adaptation conditions and are modulated by the presence of "dummy" trials (2) the effectiveness of "dummy" trials in reducing adaptation was evident under the enhanced adaptation training procedure (3) performance level at the transfer location was better for the reduced adaptation group comparing the standard training group.
Conclusions: We suggest that adaptation interferes with invariant pattern-discrimination learning by inducing network-dependent changes in local visual representations. Moreover, applying adaptation based predictions on PL specificity holds for several training procedures.

Effective learning and retention of Braille letter tactile discrimination skill in dyslexic children

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Introduction: Perceptual and motor training can dramatically improve performance on a given task, and lead to the establishment of long-term procedural (skill) memory. Studies suggest that children with developmental dyslexia (DD) may differ from typical readers in aspects other than reading; the notion of a core deficit in the ability to acquire and retain procedural knowledge as procedural memory has been advanced.
Methods: Forty 10-11 year-olds were assigned into two groups, according to their reading abilities (DD, typical readers), matched in age and IQ and received structured training in tactile discrimination of Braille letter pairs, while blindfolded. In each trial, participants were asked to report whether the target stimuli were identical or different from each other. The initial training session was followed by two additional sessions, 24-hours and two weeks later.
Results: Both groups improved robustly. In session 1, dyslexic children started significantly less accurate and slower but showed rapid learning and successfully closed the gap. At 24 hours post-training both groups showed robust, delayed ("offline") gains in accuracy. In addition, the dyslexics were able to effectively retain the gains in speed and accuracy even after two weeks.
Conclusions: Children with DD are as effective in the acquisition and retention of tactile discrimination of Braille litters as regular readers of the same age. The notion of a general procedural learning disability in DD is not supported.

Head saccades in barn owls: the role of area centralis in acquiring targets.

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In our lab we study active vision in the barn owl. Barn owls are known for their rich repertoire of active vision behaviors and their very limited eye movements which are compensated by conspicuous head movements. These properties provide a substantial experimental advantage since head motions are much easier to track than eye movements. However, barn owls like all birds lack an anatomical structure of a fovea in their retina. It is an open question to what extent barn owls foveate targets and what part of the retina is used. The goal of this study was to provide evidence that area centralis (a retinal area with a maximal density of photoreceptors) is used as a functional fovea in barn owls. For this purpose we attached miniature wireless video cameras on barn owls' head. Cameras were adjusted to point in the general direction of the gaze. Owls were positioned on a high perch and food targets were scattered on the floor. Video sequences were taken while the owls spontaneously scanned the room. These videos were analyzed offline. First, frames of fixation periods were isolated, then, by averaging fixation images the position in the frame with the highest probability to contain a

food target was extracted. We show, in two owls that the area with high probability was invariant across trials indicating the existence of a single functional fovea in the barn owl's retina. In the second part we used an optalmoscope to map the projections of known retinal landmarks on the video frames. From these we derived the expected projection of area centralis. We show that the position of area centralis matched, to a good approximation, the position of the behaviorally determined functional fovea. The findings that barn owls use head saccades to accurately and consistently foveate targets will promote further comparative studies on visual search in barn owls.

Network probing of emotional dynamics in schizophrenia patients and their healthy siblings

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Dynamic functional integration of distinct neural systems plays a pivotal role in the formation of emotional experience. Schizophrenia patients often exhibit flatten and/or inappropriate affect, suggesting a dysfunctional processing of emotional cues and their meaning. We propose a new tool to probe changing interactions within and between emotional and cognitive related networks using fMRI. The approach is based on continuous computation of an index of network cohesion, which is sensitive to both strength and variability of signal correlations between pre-defined regions. Schizophrenia patients and their siblings were compared to healthy with regard to passive viewing of emotional film excerpts. To depict the individual variation in network dynamics during the emotional cinematic experience, a comparison between each viewer's time courses of rated emotion intensity, parasympathetic and neural indices were calculated. Thus, the limbic-cognitive inter-network cohesion indices at specific points of difference between the patients and healthy groups can typify abnormality in the dynamics of cognitive driven emotional regulation.

Detection of tone in noise in rat auditory cortex

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Sounds in natural settings always appear over a noisy background, and the way the auditory system extracts sounds from such backgrounds is of extreme importance both theoretically and practically. The masked threshold (lowest level at which the presence of a tone can be detected in the presence of a masker) increases with noise level. Such results can be explained by energy masking in the peripheral auditory system: once the signal-to-noise ratio within the critical band centered at the target tone frequency is large enough, the tone is detected. However, when additional information is supplied to the auditory system, for example by slowly modulating the masker over a wide frequency range or adding a co-modulated sideband, masked thresholds can be reduced substantially below the values expected from pure energy masking. We have previously demonstrated correlates of the reduction in masked thresholds for tones in modulated maskers (comodulation masking release, CMR) in the neuronal responses of cat auditory cortex (Las et al. 2005).

Here we are using intracellular recordings *in vivo* in rat auditory cortex in order to study neuronal responses in the auditory cortex to tones masked by broadband noise or by slowly fluctuating broadband noise maskers. We characterized the responses of neurons in auditory cortex to pure tones, broadband maskers, amplitude-modulated broadband maskers, and narrowband maskers with and without comodulated side bands, as well as their combinations with tones of varying levels. The main effects of noise on tone responses are consistent with energetic masking. While we found release from masking when using modulated broadband noise maskers compared with unmodulated noise maskers, we did not observe in the rat the 'hypersensitive locking suppression' observed in cat intracellular recordings, possibly because the locking of the neuronal responses to the amplitude modulation pattern was weak.

fMRI dependent components analysis reveals context effects on the cortical networks dependency structure

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One of the major benefits of whole brain fMRI is the detection of functional large scale cortical networks. Dependent Components Analysis (DCA) is a novel approach to extract both cortical networks and their dependency structure. DCA is fundamentally different from the prevalent data driven approaches, i.e. spatial ICA, as instead of maximizing the independence of components it optimizes their dependency (in a tree graph structure, tDCA), allowing cortical areas to be part of multiple cortical networks. tDCA was used

to examine changes in cortical activity when learning visual to an auditory sensory substitution algorithm originally employed as a rehabilitation tool for the blind. A learning effect was manifested primarily in changes in the dependency structure, in that auditory networks became directly dependent on object recognition networks. tDCA may prove a useful and robust tool that provides a rich description of task related brain activity, ,mental states and neural disorders.

The haptic loop: top-down processes control unaware motor responses to colors with embodied metaphoric content

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Background: Bodily interactions are regulated by the haptic loop, in which applied forces to objects, changes in response to sensory stimuli that in turn changes the sensory input, and so on, generating a haptic cycle. Humans often metaphorically associate visual stimuli, including colors, to physical properties, such as temperature, weight, and softness. We ask whether metaphorical associations of stimuli are reflect patterns of motor response, and examine whether visual exposure to colors that were mentioned in the literature as linguistic metaphors of softness or hardness, are correlated with different patterns of motor responses, in accordance with their metaphorical significance.
Results: Using a touch-enabled, immersive virtual environment, we found that people that explore haptically virtual surfaces with the identical physical qualities of roughness and hardness, but with metaphorically different colors, namely “hard” colors and “soft” colors, differed significantly in the applied average normal forces, according to the color of the surface. The participants were not aware of the metaphorical significance of the colors. The differences in forces applied on surfaces with colors of similar metaphorical meaning were not significant. On average, participants applied weaker forces to surfaces with hard colors.
Conclusions: Results suggest that the metaphorical difference in colors, have an impact on motor behavior, which participants are unaware of. Colors that belong to a metaphorical category are associated also, with similar motor-response patterns, and form a similar action category. This provides support for the top-down hypothesis in perception-action, and points at perceptual embodied metaphors, to be a factor in action. This study integrates semantics into the haptic loop; it shows that motor components of the cycle, are correlated with the nature of the color of surfaces, and constitute a central component in the haptic cycle of unaware perception.

Short term learning induced white matter plasticity in the fornix

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Diffusion tensor imaging (DTI) is a diffusion MRI method sensitive to the tissues micro-structure. Previous studies in our lab discovered that short-term spatial learning tasks, both in humans and rats, can lead to changes in diffusion parameters, indicative of structural neuroplasticity. Mean diffusivity (MD) decrease was found in the hippocampus after 2 hours of training in a car racing game. Rats undergoing 1 day of Morris water maze (MWM) training showed similar MD decrease in the hippocampus and septum. In line with these results we aimed to investigate structural changes in the fornix of humans and rats, the main hippocampal projection known to be involved in memory. Maps calculated from DTI were processed with a common method for studding white matter: TBSS.
Results: Human group: Voxel based statistics revealed a group (learning (n=36) vs. control (n=14)) by time (scan time) interaction (clusters≥16, p<0.05, uncorrected). MD decreased in the learning group by 3.82 %. The hippocampal MD decrease was positively correlated with changes in MD in the fornix (r=0.61, p<0.05 corrected). Rats groups: Group (learning (n=19), control (n=7) and naïve (n=4)) by time interaction was found (p<0.05, corrected). MD decreased in the learning group by 3.46 %. Changes in MD in the hippocampus were found to correlate with MD change in the fornix (r=0.76, p<0.05, corrected), and reduction in the time required to reach the platform was found to correlate with MD change in the fornix (r=0.76, p<0.05,corrected).
Discussion: This work provides the first indication of white matter plasticity in the fornix following a spatial learning task in both humans and rodents. It appears that structural changes in the white matter can occur in short time scales and can be detected with DTI. Results found in the fornix are complimentary to the hippocampus, the fornix's origin. Not only that both structures are involved in this task, the extent of change they undergo is connected.

Plasticity in auditory perception: exposure to the speech nature of sine-wave stimuli modifies brain activity

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Sine-wave speech (SWS), in which speech formants are replaced by 3 tones, can be perceived either as speech or non-speech, depending on listeners' expectations about the nature of the stimuli, providing a tool to study neural activity specific to speech using identical acoustic stimuli.

Auditory Evoked Potentials (AEPs) were recorded from 61 scalp electrodes of 19 subjects in two sessions, during active discrimination of SWS stimulus pairs using spectral (/ubu/ - /udu/) or temporal (/ubu/ - /upu/) cues. In the first, "non-speech" session, subjects discriminated between SWS stimuli, unaware of their speech-like nature. In the second, "speech", session, the same subjects were first exposed to the natural speech counterparts of the SWS and came to perceive the SWS as speech. Then they performed the same discrimination task. Electrophysiological responses to the first stimulus in the pairs were analyzed and sLORETA current density source estimation was carried out to derive statistical activation difference maps when the very same physical stimuli were perceived as speech or non-speech, and the distribution of brain activities were compared. Perceiving the very same stimuli as speech or non-speech was associated with significant voltage differences around the main scalp recorded AEPs peaks. sLORETA source estimation revealed higher activation of auditory cortices to "speech" stimuli at early (around 230 ms) stages of processing, and at the time of a sustained negativity (340-500 ms), stronger activation to "non-speech" stimuli, reflecting later processing stages. Differences were prominent mainly within the right superior temporal cortex and the right prieto-temporal junction. Right hemisphere activity was lower when stimuli were perceived as speech compared to non-speech, while left hemisphere activity did not differ. Our data provide evidence for changes in brain distribution of processing non-speech sounds following a single exposure to their speech nature.

Stress exposure and GABA-aα2 receptor protein expression in emotional neural circuits

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Human studies suggest that childhood trauma pre-disposes individuals to develop stress-related disorders. In line with that, an acute exposure of male rats to 'Adult stress' on the background of an exposure to post weaning, pre-puberty (juvenile) stress resulted in altered behaviors which were reminiscent of trauma-related symptoms in humans (for a review: Horovitz et al., 2012). These altered behaviors were also linked to activation of core sub-cortical emotional neural circuits such as the amygdala and the Periaquaductal Gray (PAG). GABA seems to play a crucial role in the pathogenesis of several stress-related disorders (Petty, 1995). Specifically, GABA-A receptor subtypes are associated with regulation of neuronal excitability and rapid changes in anxiety, panic, and acute stress responses (Petty, 1995). In the current study, we examined possible alterations in GABA-Aα2 protein levels in emotional neural circuits following an exposure to stress in adulthood on the background of previous exposure to stress in juvenility. Results indicated that exposure to stress in juvenility exacerbated the effects of an exposure to stress in adulthood. In accordance with our hypothesis, an exposure to stress altered the GABA-Aα2 protein levels in core emotional brain regions, mainly in the amygdala and PAG. Maps of region-specific alterations of GABA-Aα2 expression differed between control, juvenile stress, adulthood stress or juvenile +adulthood stress groups, indicating that emotional circuits in the brain have unique pattern of response under each condition. The results indicate that classification and segregation of behavioral performance together with biochemical markers should be carried out at the system level. Any description at the level of a single specific region is inaccurate.

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Brain connectivity in prenatal stressed rats: a rest functional connectivity MRI study

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Background: Chronic stress during pregnancy has been shown to affect offspring development and behavior at adulthood. In rats, prenatal stress alters brain morphology and induces anxiety and depressive-like behavior in adulthood. Citalopram given to the pregnant stressed mothers did not significantly affect behavior of prenatally-stressed (PS) male rats and even induced anxiety and depression in offspring of unstressed mothers. We tested whether this change in behavior was correlated with neuronal nodal connectivity - a new method to estimate the global effective connectivity of a region, as measured by a non-invasive resting state MRI (rs-fcMRI).

Results: Eleven different brain circuits/structures were included in the analysis. Significant differences between Control and PS rats were found in motor, pre-frontal cortex, insula and sensory areas. Offspring of citalopram-treated control mothers showed significantly lower nodal connectivity at multiple systems compared to untreated controls, but were similar to the pattern seen in untreated PS rats with the exception of the hypothalamus where a higher nodal connectivity was observed. Also, the only significant difference was expressed in the reward-circuit. On the other hand, offspring of stressed dams given citalopram showed major differences in nodal connectivity compared to untreated PS rats.

Conclusions: Behavioral data and nodal connectivity estimates correlated well in the untreated PS group and citalopram-treated controls but not with PS citalopram-treated group. This suggests that the relation between behavior and neuronal connectivity is a complex one and that

the effect of the drug administered to the mothers can be expressed in alterations of neuronal connectivity that may not always correlate directly to behavior.

Connectivity analysis of resting state EEG recordings of patients with temporal lobe epilepsy (TLE)

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Background: Epilepsy is a common brain disorder with 0.5-1 % prevalence in the population. Temporal lobe epilepsy (TLE) is the most common focal type of epilepsy. Functional connectivity analysis reveals the extent to which brain areas function together and therefore might comprise an emerging neural network. Our objective was to study functional connectivity in patients with TLE.
Methods: In our study we apply dynamic causal modeling (DCM) to resting state of routine EEG recordings in 7 TLE patients and 3 controls. We explore the intra-hemispheric connectivity, and compare it with the controls and between the two hemispheres: the epileptic focus hemisphere versus the non-epileptic focus hemisphere. We then study the findings in light of the clinical data
Results: We present our preliminary results pointing out a difference in the connectivity strength between the medial temporal lobe (MTL) and other intra-hemispheric nodes, in the epileptic focus hemisphere versus the non-epileptic focus hemisphere. Moreover, the results show a notably large variability in the connectivity maps between subjects, as expected from the variability in the nature of the disorder and the compensatory mechanisms of the brain between subjects.
Conclusions: Dynamic causal modeling of resting state EEG activity reveals in subjects with TLE different connectivity patterns in the epileptic focus hemisphere in comparison to the non-epileptic focus hemisphere, in a subject specific manner. These preliminary results are an initial and promising step towards an improved lateralization of the epileptic focus and determination of other individualized characteristics as pathway of spread and generalization.

Spatial attention across perception and action

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Converging evidence in cognitive neuroscience has generated the notion that perception and action may share the same spatial representation, on the neuronal level as well as the cognitive level. The Simon effect (Simon, 1969) demonstrates this complex relationship between perception and action. According to this phenomenon, spatial relation between perception and action (stimuli and response) can affect performance even when the spatial information of the stimulus is irrelevant to the task. In our study subjects performed two tasks, either separately (in the single task condition) or simultaneously (in the dual task condition). In the first task (the shape task), two stimuli were presented bilaterally - two distinct shapes (circle and triangle) that were colored in either red or blue. The subject's task was to name one of the shapes according to its color (e.g., to name the red shape) and ignore the other shape. In the second task (the tone task) subjects were required to respond with either a left or right button according to the pitch of a tone. The input for both tasks appeared simultaneously, and subjects were instructed to respond to both tasks as fast as possible, without prioritizing either of them. We found a sizable dual task cost when the two tasks were performed simultaneously. Moreover a significant compatibility effect was found between the side of the relevant shape and the side of the correct response in the tone task, for both tasks- a between tasks Simon-like effect. These results demonstrate an obvious overlap between representations of space in perception and action, and lead us to the notion that perhaps both perception and action use the same spatial template in the brain for spatial coding, even when the spatial information comes from two distinguished tasks. Spatial information seems to be difficult to ignore, and it might be coded automatically, as a basic feature of an object.

Sensorimotor synchronization and working memory

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Traditionally, sensory and motor tasks were considered related to low-level processing. Reverse Hierarchy Theory, suggested by Ahissar and Hochstein (1997), challenges this view by emphasizing the importance of top-down processes in sensory tasks that were traditionally considered as low level. In this study, we give evidences that a motor task, sensorimotor synchronization (SMS) is also linked with high-level processes, mainly ones that involve working memory.
SMS, the temporal coordination of a rhythmic movement with an external rhythm, is studied experimentally by tapping experiments (Repp 2005) in which subjects are required to finger tap in synchrony with an auditory stimuli. One type of tapping experiments is the step-changes experiment, where subjects are required to adapt their taps to a metronome alternating between two tempi. Subjects (N=30) performed a battery of cognitive and sensory tasks, and two-step tapping experiments. We found high positive inter-subject correlations between successful performance in the tapping experiment (decreased tapping variance) and working memory related tasks, the highest correlation to an n-back auditory task, in which subjects are required to report

whether the current tone matches a tone n-steps earlier (n is changed adaptively). We also found significant correlations to other tasks that pound on verbal or tonal memory. However, the Block Design task, a standard spatial-reasoning visual task, usually considered to measure general cognitive abilities and not directly related to working memory, did not show a significant correlation. We propose that these correlations can reflect the involvement of high-level working memory mechanisms for the representation of tempo in the SMS control loop, and therefore in line with the Reverse Hierarchy Theory's predictions.

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Auditory ERP marker for automatic structural regularity detection predicts word recognition performance

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Detection of repeated stimulation patterns (stimulus regularities) is an important learning mechanism, which is largely automatic. In the auditory system it is often tapped by ERP components as mismatch negativity peaking ~150 ms from regularity violation, and early left and right anterior negativities peaking ~200 ms from linguistic and musical structural violations, respectively. We now asked whether structural regularities introduced into a simple paradigm of 2-tone frequency discrimination can also be detected automatically, and whether the ability to automatically detect such a structural regularity predicts the individual's aptitude for regularity detection in other contexts.

We administered two protocols of 2-tone frequency discrimination. Each protocol had a simple structural regularity – in each trail one of its two tones was fixed across trials (i.e. REFERENCE) and the other was higher or lower. In protocol 1 it was the 1st tone whereas in protocol 2 it was the 2nd. Our previous behavioral data (Nahum et al., J Neurosci 2010) indicated that protocol 1 was performed significantly better even though its objective complexity is equal to that of protocol 2. Participants' automatic ERP response at ~200 ms from the onset of the 1st stimulus (P2) was larger in protocol 1, where the 1st tone is the repeated reference than in protocol 2. This difference indicates that participants detected the structure of protocol 1. Our participants were also tested with few cognitive tasks. Their automatic sensitivity to the auditory structure was correlated with their sensitivity to visual regularities in word recognition, i.e. their rate of discriminating correct versus incorrectly spelled frequent words. These findings reveal that automatic regularity detection can be tapped even without structural violation. Moreover, automatic sensitivity predicts behavioral success in a range of tasks, both at the group (protocol asymmetry) and at the individual level.

A novel genetic animal model for bipolar disorder

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Genetic predisposition and dysfunction of monoaminergic neurons are thought to play a critical role in bipolar disorder. However, how these factors interact in the pathophysiology and pharmacotherapy of this disease is poorly understood. Previously, we demonstrated that the embryonic mid-hindbrain organizer, which is composed of a transient cell population in the brainstem, controls the development of dopaminergic and serotonergic neurons. Recently, mid-hindbrain organizer
associated genes have been suggested as susceptibility genes for bipolar disorder. The aim of the present study was to test the face and predictive validity of mid-hindbrain organizer mouse mutants as a model for bipolar disorder. To this
end we investigated manic- and depressive-like behaviour in these mutants and studied whether these behaviours can be reversed by mood stabilizing drugs. In addition, neuropathological changes that have been associated with bipolar
disorder were studied in these mice, providing insights into the molecular basis of the altered behaviour of the mutants. We found that mutants are hyperactive and showed increased risk taking behavior. Importantly, mutants showed in contrast to wild-types intra-individual fluctuations in their locomotor activity, hedonic and risk taking behavior. In addition, mutants showed an increase in risk taking behaviour. Olanzapine and lithium, which are used for the treatment of mania, reversed some of behavioural alterations in mutants. The establishment of mid-hindbrain
organizer mutants as a model for bipolar disorder will provide a tool to investigate particular aspects of the pathophysiology of this devastating disease and will serve a rationale towards the development of novel and efficient mood stabilizing drugs.

Vomeronasal responses to vaginal secretions in male mice

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Male mice show a preference for the voided urine of estrus females over that of non-estrus females. However, this preference is absent for bladder urine, suggesting that other secretions along the urogenital tract confer the estrus dependent preference. Because the mouse vomeronasal system is highly sensitive to various socially relevant secretions, we set out to

study its role in mediating this preference. We stimulated the vomeronasal organ of male mice with vaginal secretions and measured responses in the accessory olfactory bulb using multi-site extracellular electrodes. We found that vaginal secretions indeed activate the mouse vomeronasal organ in a strain specific manner. Furthermore, individual AOB neurons can discriminate between estrus and non-estrus secretions from an individual female. Finally, we show evidence that, at least in some cases, responses to urine and to vaginal secretions involve distinct chemical substances. These results suggest that the vomeronasal system in male mice plays an important role in detecting the reproductive state of female mice, a crucial ability for directing efficient reproductive behavior.

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Representation of conceptual size in the ventral visual cortex

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Background: It has recently been argued that objects are represented in the ventral temporal cortex according to their real-world size (Konkle & Oliva, 2012). Size representation was investigated using images of small and big objects of equal retinal size (e.g., a paperclip and sofa, respectively). A possible confound in such studies is that small and big stimuli typically belong to object categories that differ in shape and function (e.g., small objects are typically graspable and/or manipulable, while big objects often have a more static nature). The present study aimed to control for these confounding factors by using abstract, meaningless shapes, which were associated with specific size representations by virtue of extensive training.

Method: Participants implicitly learned a 10-point size scale composed of 5 animals, organized along the scale by real-world size, and 5 abstract shapes, arbitrarily distributed in-between the animal points along the scale. All stimuli were presented in the same retinal size. Following training, a functional magnetic resonance imaging scan was conducted while participants made a conceptual size discrimination task on the abstract shapes.

Results: A region-of-interest (ROI) analysis revealed larger responses to "big" than to "small" shapes within the parahippocampal place area (PPA), but not within the fusiform area (FFA). In addition, a whole-brain analysis showed larger BOLD responses to "big" than to "small" objects in primary visual areas.

Conclusions: Our findings support earlier findings of medial-to-lateral organization of big and small object preferences in the ventral temporal cortex. By using abstract shapes, we minimized categorical and semantic influences on fMRI measurement, further providing "pure" evidence for object size representation in visual cortex.

The effect of malfunctioning DNA damage response on neuronal-glial circuits: altered neuronal synchronizations and atrophied astrocytic morphologies in cerebellar cultures from Atm-deficient mice

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Background An aberrant response to DNA lesions is implicated in many human neurodegenerative disorders. In healthy cells, the accumulated DNA damage is rapidly detected, leading to the activation of a web of signaling pathways known as the DNA damage response (DDR). In cells with neurodegenerative dysfunction some components of the DDR machinery are impaired and the gene coding for the ATM protein is mutated in the human genetic disease Ataxia Telangiectasia (A-T).

Results In order to study the effect of impaired DDR on neuronal circuits, we used calcium imaging and immunohistochemistry to compare the morphology and dynamics of primary cerebellar cultures grown from postnatal ATM-deficient and wild-type (WT) mice. Cerebellar network exhibited spontaneous network synchronizations after two weeks in-vitro. Compared to WT circuits, ATM-deficient circuits displayed a lower number of global synchronizations and a larger number of sparse synchronizations, i.e. synchronous events involving less than a dozen of cells.To relate the different circuit synchronization dynamics to altered morphological structures, we tested the hypothesis that A-T is at least partially a glial disease. staining of astrocytes revealed a less complex cell arborisation in ATM-deficient versus WT circuits as measured by number of branches originating from the cell bodies.

Conclusion We present evidence that malfunctioning DDR affects neuronal synchronization and astrocyte morphology. In ATM-deficient circuits, sparse synchronizations that are not capable to propagate through the rest of the circuit might represent network failures. The reduced astrocytic branching arborization result in an atrophied structural organization of the astrocytic network functionally coupled with neuronal circuits. These results support the idea that neuronal network failures in genetic neurodegenerative diseases are correlated to the "breakage" and impairment of the astrocytic network.

An introduction to Neuroimmunology: Overview of the various types of neuroimmunological diseases and the distinct immunopathogenetic mechanisms involved in them

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The field of Neuroimmunology which investigates the reciprocal relations between the immune system and the nervous system in health and disease, has been largely expanded during the last decades. Neuroimmunological diseases are defined as those in which immune mechanisms (mostly autoimmune ones) play a role in their pathogenesis. The prototype of such a neuroimmune diseases is myasthenia gravis (MG) where a known autoantigen (AchR) has been clearly defined and the cascade of events leading to neuromuscular dysfunction mediated by these anti-AchR antibodies have been investigated in depth. Moreover, the transfer of such antibodies in animals can produce a similar to human MG, disease. Other examples of neurological diseases with an obvious (auto)immune pathogenesis include the various anti-gangliosode polyneuropathies. However, not all of the, currently classified as neuroimmune, diseases have such a well-defined underline autoimmune mechanism. For example, multiple sclerosis (MS) is widely perceived as an autoimmune neurological disease, but the target antigens in MS and the relevance of the immune mechanism in this disease remain largely obscure, at least in terms of their direct and primary involvement and its pathogenesis. A plethora of neurological conditions, previously considered as "idiopathic" are now included in the extended lists of diseases with a primary or secondary immune-mediated pathogenetic mechanism. Of particular interest, is a new group of neuroimmune diseases in which the primary immune stimulus is known (ie a virus, vaccine or even a cancer cell) and the inflammatory neurological disease evolves as a secondary event (post-viral, post-vaccination and paraneoplastic diseases). But even in purely "neurodegenerative" diseases or vascular ones, such as Alzheimer's disease or stroke, immune mechanisms palying a crucial role during the course of the disease, have been now recognized and identified. All of the arms of the immune system, including innate, humoral and cellular adoptive immunity have been shown to be involved in neuroimmunological diseases. The development of various immunotherapeutic approaches targeting distinct elements of the immune system for such diseases with primary or secondary neuroimmunological pathogenesis, represents a great challenge and may offer novel treatment approaches for diseases which in the past, were considered as incurable.

Visual perception of order-disorder transition

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Background: An open question in neuroscience is the functional role of sensory receptive-fields. Here we ask to what extent visual receptive fields are sensitive to qualitative changes in visual textures. We employed a set of textures generated from different homogeneous Markov Random Fields (MRF). Changing a one-dimensional parameter (analogous to the thermodynamic temperature in Boltzmann distribution), the generated textures vary from random (independent identically distributed amplitudes, IID) to ordered – gratings of different orientations, blobs of different sizes or uniform intensity. We measured perceptual thresholds (characterized by the MRF parameter) for detecting an MRF generated texture embedded in one quadrant of IID random display (4AFC task). The characteristic feature of the order-disorder phase transition is the divergence of the order parameter, in particular, the correlation length. This method allows us to compare human performance to that of an ideal observer based on sufficient statistics (the most informative representation of MRF textures) and on correlation lengths computed for the generated images.
Results: All human observers ($n=5$) were substantially outperformed by an ideal observer based on bootstrapped likelihood ratios between sufficient statistics. Moreover, a linear regression between perceptual thresholds and order-disorder phase transition thresholds produced a slope close to one, but with an additional observer-dependent constant shift toward the disordered phase, corresponding to the lower perceptual thresholds.
Conclusion: Our results suggest that the human visual system lacks the flexibility required to form an efficient representation (sufficient statistics) for the given task. On the other hand, it is probably tuned to qualitative changes in images, corresponding to order-disorder transitions or transitions between different kinds of order (gratings, blobs, etc.), and not that much to changes in the degree of disorder.
Thie study was supported by ISF

A special electrode holder for simultaneous intracellular patch recording and optical stimulation

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Optogenetics has rapidly become a standard tool in neuroscience research and thus new tools to support this rising experimental field are developed. However, until now simultaneous intracellular recording and light stimulation were only possible by using two different positioning systems. To overcome this, we have developed an optopatch device, which is a glass pipette holder that contains an additional port for the insertion of fiber optic into the pipette. This optopatch allows

performing whole cell patch recording simultaneously with a direct light illumination from the recording pipette. The holder spares the use of additional manipulator and thus enables a much more accurate, stable and reproducible illumination. In addition, replacement of standard pipettes is easily done as with available commercial holders. Here we used the optopatch in-vivo to record the membrane potential of neurons from different cortical layers of the motor cortex in optogenetically-mutated mice. Using the optopatch we demonstrated both direct and indirect disynaptic activation of the intracellularly recorded cells by the light illumination.

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Loss of orexine neurons in the hypothalamus and narcolepsy-like behavior induced by autoantibodies in mice

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Background: Narcolepsy is a sleep disorder characterized by abrupt attacks of somnolence caused by the loss of orexine neurons in the hypothalamus. Autoimmune mechanisms are implicated in narcolepsy byincreased frequency of specific HLA alleles and the presence of specific autoantibody (anti- Tribbles homolog 2 protein antibodies) in the sera of narcolepsy patients. The aim of the present study was to assess whether experimental narcolepsy can be passively transferred to mice.

Methods: We examined behavior and brain pathology of naive C3H mice injected intra-cerebra-ventricularly (ICV) with pooled IgG from narcolepsy patients positive for anti-Trib2. Control mice were injected with pooled matched healthy control IgG. Mice were filmed and analyzed for immobility attacks weekly before and after ICV injection by using Noldus PhenoTyper cage and EthVision software. Mice were also examined for behavior and cognition in the staircase, novel object recognition and Y-maze tests. Brains were removed and analyzed by immunofluorescence for neurodegeneration in the hypothalamus.

Results: We found loss of neuronal marker (NeuN) and synaptic marker (synaptophysin) staining in the lateral hypothalamus area in narcolepsy-injected mice compared to controls. A specific loss of orexine-positive neurons in narcolepsy-IgG was found. We observed narcolepsy-like immobility attacks in narcolepsy injected mice 4 weeks post injection but not before. We found that narcolepsy-injected mice were significantly hyperactive in the staircase test and had significant short memory deficits in the Y-maze test compared to controls. The behavioral and cognitive results are similar to those observed in line narcolepsy patients.

Conclusion: This is the first report of passive transfer experimental narcolepsy induced by autoantibodies and supports an autoimmune pathogenesis of narcolepsy.

Brain tumour biology and development of new therapies

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Despite the introduction of the Stupp Protocol utilising concomitant radiation and temozolamide chemotherapy following surgery for high-grade cerebral glioma, there has been little substantial improvement in the prognosis for of these tumours over the past three decades. The median survival for high-grade glioblastoma multiforme remains around 12-14 months. However, there has been substantial progress in understanding the cell and molecular biology of cerebral glioma, and in particular, the critical intracellular signalling pathways that underpin the major biological processes in the development of cancer. These include cellular proliferation, control of apoptosis, induction of angiogenesis and cell migration and metastasis. In addition, new technologies have enhanced our understanding of the molecular genetics of cerebral glioma. Numerous chromosomal abnormalities have been identified, and in some tumours, it appears that there is a step-wise process of chromosomal instability in the genesis of high-grade glioma. Epidermal growth factor receptor amplification is present in nearly 80 % of high-grade cerebral gliomas. Loss of tumour suppressors, such as PTEN occur as an initial process in the development of nearly all cerebral glioma. In addition, the AKT-mTOR pathway is known to be particularly important in the control of cellular growth and proliferation, and in the development of resistance to therapies. A number of critical targets for biological therapies have been identified and many biological inhibitors are already in clinical trials. These therapies potentially offer the possibility of control of these otherwise fatal tumours.

Neurophysiological investigation of spontaneous correlated and anticorrelated fluctuations of the bold signal

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Background: Correlated fluctuations of the BOLD signal measured at rest directly relate to fMRI activation. As the BOLD signal represents an indirect measure of neural activity, the neurophysiological underpinnings of these correlations must be elucidated. The origin of antiphase fluctuations in BOLD ('anticorrelations') is an area of intense debate. While some believe this measure is artificially induced by removal of the global BOLD signal, others argue for its existence and significance in disease states. Here, by measuring ECoG and BOLD signals from the same individuals, we tested the hypothesis that BOLD anticorrelations correspond to anticorrelations in high-frequency ECoG power. A better understanding of anticorrelations will aid in our understanding of this signal in disease states.
Methods: Pre-operatively, a resting state fMRI was recorded in 5 patients with epilepsy undergoing surgical evaluation of seizure foci. Following implantation of subdural grids and strips, we recorded ECoG during a 3-5 minute period of rest where subjects were instructed to lay quietly with their eyes closed. Data was filtered into the high gamma band (50-150Hz), enveloped, and smoothed to obtain the high gamma power signal. Pair-wise correlations of electrodes were performed, and spatial maps of HGP and BOLD correlations were compared.
Results and conclusions: 1) A strong correspondence was found between HGP and BOLD correlations regardless of network sampled, supporting and extending previous studies with whole brain intra-individual neuronal and hemodynamic measurements. 2) A small but significant subset of networks exhibited neuronal anticorrelations; 3) neuronal anticorrelations exhibited a spatial selectivity to regions of anticorrelated BOLD fluctuations. Together, these findings suggest that BOLD correlations and anticorrelations have neurophysiological correlates that are reflected in fluctuations of neural activity.
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Texture coarseness coding in the secondary somatosensory cortex (SII) of the rat
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Background: The role of the secondary somatosensory cortex (SII) in somatosensory processing is poorly understood.We investigated texture coding in SII.
Results: We performed single unit recordings from layers 2-5 of SI and SII in anaesthetized rat during artificial whisking against sandpapers with different coarsenesses. For SI recordings only the principle whisker was left intact,while for SII recordings,a whole row was left intact with 3 whiskers palpating the textures. Selectivity indexes (S.I.); the Response for texture X divided by the average response of all the textures, were calculated for each texture, and the preferred texture was determined. When we calculated the averaged S.I. and the ratio of highly selective cells in each layer we obtained a texture selectivity hierarchy in the somatosensory SI and SII cortexes: L4(SI)<L2-3(SI),L5 (SI) and L4(SII)<L5(SII)<L2-3(SII). To ensure that the differences between SI and SII were not due to differences in the stimulus paradigms we performed control experiments in which only a single whisker was left for SII experiments and a whisker row was left intact in SI experiments. In SI no significant changes were observed in layer 4 neurons, but a significant decrease in selectivity in layers 2-3 and 5 neurons.In SII the response magnitude decreased,yet the texture selectivity did not change significantly in layer 2-3,increased in layer 4 and dropped in layer 5. We performed two-photon imaging from the upper layer2-3 of SII, the most selective for textures, in order to investigate the neurons' functional mapping.Our results showed that neurons tend to cluster according to their preferred texture.Moreover, functional cortical columns were observed in which the preferred texture was significantly similar across layers 2-5.
Conclusions: Texture coarseness coding is sharper in SII compared to SI.These findings suggest that SII and especially layer 2-3 of SII serve as a higher processing station for texture coding.

Stimulus-specific adaptation in inferior colliculus does not index deviance detection
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The auditory system differentiates rare from common sounds by decreasing responsiveness to common and thereby emphasizing responses to rare sounds - a phenomenon that (on the neuronal level) is called Stimulus Specific Adaptation (SSA). SSA has been demontsrated at the level of the auditory midbrain (Inferior Colliculus, IC), the medial geniculate body, and the Auditory Cortex (AC). SSA as usually tested may result from neural fatigue (e. g. due to adaptation of excitation of narrowly-tuned inputs). Such a mechanism, however, is not truely sensitive to the deviance of the rare sound with respect to a predictable background. To differentiate between true deviance sensitivity and

adaptation due to neural fatigue, we employed a set of control stimuli and compared neural responses recorded from AC and IC to predictions of a feed-forward model with adaptation of exciation in narrowly-tuned inputs. In line with previous results, we found substantial SSA in a subset of neurons recorded in the IC. Neurons showing substantial SSA were sensitive to a wide range of tone frequencies, while neurons showing little or no SSA showed narrow frequency tuning. Moreover, SSA in IC was well in line with the predictions of the adaptation of excitation model. In contrast, cortical responses to deviant sounds were stronger than predicted by the model. Our results suggest that (1) SSA in IC results from adaptation of excitation in narrowly tuned inputs, (2) SSA in IC does not encode deviance; and (3) true sensitivity to stimulus statistics only emerges after additional layers of processing (potentially in the auditory thalamus, but certainly in auditory cortex).

Predicting layer-specific genes in the mouse cerebellum using ISH images

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Background and Methodology: Understanding the patterns of the transcriptome in the brain is particularly hard since brain tissues mix numerous types of neurons and glia, and little is known about which genes are expressed in which cells and brain layers. Here, we describe an approach to detect genes whose expression is primarily localized to a specific brain layer and apply it to the mouse cerebellum. We learn typical spatial patterns of expression from a few markers that are known to be localized to specific layers, and use these patterns to predict localization for new genes. We analyze images of in-situ hybridization (ISH) experiments and train classifiers for four layers of the cerebellum: the Purkinje, granular, molecular and white matter layer.
Results: On held-out data, the layer classifiers achieve accuracy above 94 % (AUC) by representing each image at multiple scales and by combining multiple image scores into a single gene-level decision. When applied to the full mouse genome, the classifiers predict specific layer localization for hundreds of new genes in the Purkinje and granular layers. Many genes localized to the Purkinje layer are likely to be expressed in astrocytes, and many others are involved in lipid metabolism, possibly due to the unusual size of Purkinje cells.
Conclusions: Gene expression can be accurately localized to brain layers, using ISH images in an automated way. Also, we find a surprisingly large fraction (3.4 %) of the mouse genome localized to the Purkinje layer. This suggests that many molecular functions have special variants restricted to this thin layer. Specifically, we identify the Bergmann glia, an astrocyte, as a main actor in the Purkinje layer of the mouse cerebellum.

Learning of grammatical structure: a biologically inspired learning mechanism and its application to language acquisition

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Background: The brain has evolved mechanisms for learning the organism's environment by finding recurring patterns, representing them in memory, and acting upon this knowledge to generate adaptive behavior. We used insights from several traditionally disparate fields to construct and implement a learning mechanism which is biologically realistic in that it is incremental, uses limited memory and computational resources, and is composed of biologically-inspired building blocks. This implementation may explain a variety of phenomena in tasks ranging from learning of language in humans, through learning of birdsong, to animals' learning of regularities in foraging environments. In the work I currently present I focus on results from language learning.
Results: To assess the model's performance, we subjected it to an extensive series of tests. These included the replication of fifteen published results in sequence segmentation, artificial grammar learning, and structure dependence, and the estimation of the model's ability to learn a generative grammar from a corpus of natural language. In its generative abilities, the model compares favorably to a standard trigram model, achieving much higher scores on precision, but performing less well in perplexity scores. It was also found to categorize linguistic units fairly well, showcasing its exemplar-based learning and its equal treatment of syntax and semantics, which occasionally results in units that straddle traditional boundaries of constituency. Our model successfully reproduced the reported effects in all but two of the experiments.
Conclusions: We propose a general model of learning, which is biologically motivated and is applicable to a wide spectrum of animal learning tasks, and successfully apply it to language learning. Within the field of language learning, this is the first model to accommodate such a wide range of tasks while preserving a modicum of biological realism.

Intra-individual variability of reaction time differentiates between attention and reading disorders

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Background: Attention deficit/hyperactivity disorder (ADHD) is one of the most prevalent developmental disorders. Intra-individual variability of reaction time (IIV of RT), also conceptualized as an index of sustained attention ability, has been demonstrated in ADHD in a variety of tasks and has been suggested as a candidate endophenotype of ADHD. However, it is questioned whether IIV of RT is specific to ADHD, rather than a more general characteristic of clinical groups, as for example is the case with slow RT. In this study we aimed at demonstrating specificity by comparing IIV of RT of adults with ADHD with that of adults with reading disorder (RD), the most prevalent disorder co-occurring with ADHD. IIV of RT was assessed using the standard deviation of RT (SD of RT) in a conjunctive continuous performance test (CCPT), designed to measure sustained attention. The CCPT - a long monotonic task with a low frequency of target stimuli to which a response is required, poses difficulty to maintain a constant level of performance, while minimizing the involvement of working memory and other cognitive factors.
Results: Participants with RD performed equally well as control participants in all measures of the CCPT, including SD of RT- reflecting low IIV of RT, although reporting a high rate of behavioral symptoms of inattention. The IIV of RT of participants with ADHD was significantly higher than of participants with RD and controls. Interestingly, IIV of RT in the co-morbid group (participants with ADHD+RD) was significantly lower than in the ADHD group.
Conclusions: Pure sustained attention deficits, as reflected by high IIV of RT, are unique to ADHD. Symptoms of inattention experienced by participants with RD do not stem from deficient sustained attention, and may be the outcome of reading difficulties rather than their cause. It is recommended to use tools such as the CCPT in order to obtain a discriminative diagnosis of attention and reading disorders.

Kinematic strategies underlying improvement in the acquisition of a sequential finger task with self-generated vs. cued repetition training

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Many motor skills, such as typing, consist of articulating simple movements into novel sequences that are executed faster and smoother with practise. Dynamics of reorganization of these movement sequences with multi-session training and its dependence on the amount of self-regulation of pace during training is not yet fully understood. In this study, participants practiced a sequence of key presses. Training sessions consisted of either externally (Cued) or self-initiated (Uncued) training. Long-term improvements in performance speed were mainly due to reducing gaps between finger movements in both groups, but Uncued training induced higher gains. The underlying kinematic strategies producing these changes and the representation of the trained sequence differed significantly across subjects, although net gains in speed were similar. The differences in long-term memory due to the type of training and the variation in strategies between subjects, suggest that the different neural mechanisms may subserve the improvements observed in overall performance.

Auditory response adaptation is not specific to the direction of auditory motion

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Two alternative hypotheses have been suggested with regard to auditory motion processing. The first hypothesis suggests that there is no dedicated auditory motion processing circuitry in the brain and that motion is encoded as a series of static localizations. A prediction of this hypothesis is that the neural responses to motion are inseparable from the neural responses to static stimuli. The alternative hypothesis is that the central auditory system contains neural circuitry that is dedicated to auditory motion processing and is exclusively sensitive to parameters such as direction and velocity. In this study we aim to examine the later hypothesis that sound motion is independently encoded in the brain. We used adaptation paradigms such as the oddball paradigm. In the oddball paradigm, rare stimuli (deviants) are embedded in a long sequence of common stimuli (standards). The role of the standards and deviants is then switched, and neural responses to a stimulus when rare are then compared with the responses to the same stimulus when common. The standard stimulus was an auditory stimulus starting at a position outside the auditory receptive field (ARF), moving in a straight line through the ARF and ending at a position outside the ARF. The deviant was a stimulus moving at the same velocity but in opposite direction starting at the end-point and ending at the start-point of the standard. Auditory stimuli were presented in virtual acoustic space. The results of these experiments did not show specific adaptation to the direction of motion, the neural responses to deviant and standard directions were on average similar. This was in marked contrast to the results obtained using the same adaptation paradigms but using static stimuli with standards and deviants differing by the location of the sound. Our results therefore argue against a specialized auditory motion processing circuitry. *This work was supported by a grant from the ISF.*

Protective effects of the novel multi-target iron chalator / monoamine oxidase inhibitor drug, VAR, on age-related neurodegeneration: regulation of BDNF/CREB signaling

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Background: Brain-derived neurotrophic factor (BDNF)/ tropomyosin receptor kinase B (TrkB)/cAMP response element-binding protein (CREB) signaling pathway has been shown to play a pivotal role in neuronal survival, differentiation and synaptic plasticity, be highly implicated in the pathophysiology of aged-related cognitive decline and be positively regulated by long-term antidepressant treatment. The main aim of this study was to investigate whether the positive impact of our novel multi-target monoamine oxidase inhibitor and antidepressant iron chelator, VAR, on cognitive deficits and brain morphological deteriorations are accompanied with BDNF/ TrkB/ CREB pathway regulation and synaptic integrity preservation in the hippocampus of the aged rats.
Results: Here, we report that a chronic systemic treatment of aged rats with VAR(5 mg/kg; 4 times weekly for 6 months), had a significant positive impact on anxiety levels and cognitive age-related impairment, as revealed by forced swim, object recognition and open field tests. This effect was accompanied by a marked brain MAOA and B inhibition and significant increase in hippocampal catecholamines levels. Histochemical studies showed that VAR increased the number of viable cells detected by Nissl staining, as well as the levels of BDNF and phosporylated CREB in hippocampal CA3 and dentate gyrus regions, compared with aged control rats. We have found thatVAR induced hippocampal levels of TrkB, growth associated protein (GAP) 43, synaptophysin and nerve growth factor (NGF). VAR also significantly enhanced the levels of phosphorylated extracellular-signal-regulated kinase (ERK) and Bcl2/Bax ratio in the hippocampus of aged rats.
Conclusion: Our results indicate that VAR-induced neuroprotection against age-related neurodegeneration and preservation of hippocampal neuronal integrity might be exerted by enhancing the BDNF/TrkB/CREB signaling pathway in aged rats.

Microvibrissae based texture coding

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In their natural environment, rodents use their whiskers to locate and distinguish between objects of different textures and shapes. They do so by moving their whiskers actively as well as passively, through body and head movements. An alternative and relatively unexplored strategy for texture and object discrimination may involve microvibrissae- and non-whisker tactile based discrimination. To determine whether the somatosensory cortex can code for surface coarseness through the microvibrissae, we recorded from the cortical area representing the frontobuccal pad while presenting moving textures with varying coarseness. We found that surface coarseness is coded by the discharge rates of frontobuccal pad cortical neurons. This suggests that microvibrissae or skin/fur cues can provide salient texture information.
Supported by ISF to RA

K shell decomposition reveals the functional hierarchy of information integration in human brain

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The human brain has been shown to feature small world network characteristics. In order to further analyze the unique structure of this network we applied a k-shell decomposition analysis on a structural human brain network, derived from DTI\MRI imaging of 5 subjects. In this technique, 998 cortical ROIs were used to construct the nodes of each network and 14,865 edges were derived from white matter fibers. We confirmed that the whole network features a 'small world network' and that the cortical network is highly resilient. Using the K-shell decomposition analysis we were able to reveal shells of growing connectivity within the network. In this way we identified that each shell can be attributed to specific functional network alongside its corresponding organizational hierarchy. we revealed that the shells can be grouped into three hierarchial clusters. For instance, primary visual areas were found in the lowest functional cluster (lower k-shells) while higher visual associative areas were found in the highest cluster that we called the nucleus (highest shell). Furthermore, all known consciousness supporting networks were included in the nucleus. it can be assumed that information flow in the brain starts from the lowest functional cluster while being more and more integerated in the higher clusters.

Effects of gestational exposure to chlorpyrifos on motor development and social behavior in C57BL/6 J mice

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Background: Chlorpyrifos (CPF) is a widely-used organophosphate insecticide suspected to be a risk factor for autism. Exposure to CPF in gestation was linked to lower birth weight, abnormal reflexes, increased risk for pervasive developmental disorder and lower IQ in children. In rodents gestational CPF elicited decreased vocalizations in pups and enhanced agonistic responses in adults. In this study the long-term effects of gestational exposure to CPF on early motor development and social behavior, in C57BL/6 J male mice were tested.
Method: Pregnant female mice were randomly assigned to one of the four treatments: 5 mg/kg, or 2.5 mg/kg CPF, vehicle (oil) and no treatment, administered by gavage on gestational days 12 to 15. In order to test whether maternal behavior was impaired by CPF, on postnatal day (PND) 5 maternal retrieval was tested. On PND 5-12, 3 neonatal reflexes were tested: righting, negative geotaxis and cliff avoidance. On PND 90 the social preference (SP) & social novelty (SN) tasks were administered. Preference toward a conspecific was measured by time spent in either chamber of a three-chambered box, in which the two side chambers contained either an unfamiliar conspecific an inanimate object (SP task). Thereafter, SN was measured by comparing time spent in a chamber with an unfamiliar mouse as opposed to a chamber with the familiar mouse.
Results: CPF treatment did not impair maternal retrieval, suggesting delayed development of CPF exposed offspring was unlikely to be due to maternal behavior. Both doses of CPF resulted in delayed development of reflexes: righting reflex ($F(21,98)=2.21$, $p<.05$), the negative geotaxis reflex ($F(3,14)=12.87$, $p<.05$) and cliff avoidance ($F(3,15)=14.06$, p.05), but were not impaired in the SN task.
Conclusion: Gestational exposure to CPF elicits deficits in social behavior and motor development.
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Attentional Sampling: lessons from psychophysics and MEG

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Overt exploration or sampling behaviors, such as whisking, sniffing, and saccadic eye movements are often characterized by a theta rhythm (4-10Hz; Otero-Millan, Troncoso, Macknik, Serrano-Pedraza and Martinex-Conde, 2008; Buzsaki, 2006). In addition, the electrophysiologically recorded theta or alpha phase predicts global detection performance (Busch Dubois and VanRullen, 2009; Methewson, Gratton, Fabioani, Beck and Ro, 2009). These two observations raise the intriguing possibility that covert selective attention samples from multiple stimuli rhythmically. To investigate this possibility, we measured change detection performance on two simultaneously presented stimuli, after resetting attention to one of them. After a reset flash at one stimulus location, detection performance fluctuated rhythmically. Additionally, different locations were associated with different phases of the rhythmic sampling supporting a sequential model of exploration. This suggests that selective attention entails exploration rhythms similar to other exploration behaviors. In my presentation, I will report new findings combining the psychophysical task with MEG recordings. We utilized stimuli that elicit a strong sustained gamma band response in visual areas. Previously gamma band synchronization has been proposed as a mechanism supporting inter areal communication of behaviorally relevant stimuli. In our study, we investigated the possibility that MEG responses measured from visual areas might display cross frequency interactions reflecting both sustained neural synchrony at higher frequency as well as slower rhythmic modulation that supports attentional sampling.

Exploring the role of synaptic proteins in tuning synchronous neuronal network activity

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The plasticity of the brain plays a key role in shaping our behavior, learning and memory. It is well known that plasticity is associated with alteration in synaptic strength and efficacy. Some of these effects correlate with changes in the levels of synaptic proteins. However, the implications of genetic alteration in synaptic proteins on the network activity of neurons are not known. We previously used the MicroElectrode Array (MEA) technology to examine the effect of DOC2B manipulation, a synaptic neuronal Ca2+ sensor that is known for its ability to alter synaptic transmission, on neuronal network activity. We found that overexpression of DOC2B lead to a distinctive increase in the spiking activity and noticeable increase the participation rate of neurons in the network burst. In this work, we used a unique in silico neuronal network to simulate the effect of DOC2B on network activity. Our model takes into account both cellular and network parameters in order to understand the impact of DOC2B overexpression on the activity of the neuronal network. Preliminary results suggest that DOC2B's effect on neuronal network bursting activity might be explained by its ability to increase

spontaneous neurotransmitter release in a calcium-dependent manner. Furthermore, our network model suggests that DOC2B might exert its physiological effect through localized buffering of pre-synaptic calcium. This approach extends our understandings of the role of DOC2B in synaptic transmission and as suggested before by London et al., demonstrates how small changes in the cellular level can be translated to significant changes in the network level. This stresses the importance of understanding synaptic proteins in the network frame of work.

Early neural lesions following organophosphate poisoning in the rat: propagation of damage

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Sarin, a highly toxic cholinesterase inhibitor, administered at near 1LD50 dose causes severe signs of toxic cholinergic hyperactivity in both the peripheral and central nervous system. The early histopathological consequences occurring following sarin exposure have not been fully characterized. In the present study, we analyzed the early histopathological and biochemical events occurring following sarin exposure. Male Sprauge-Dawley rats were exposed to 1LD50 of sarin (75 μg/kg, i.m.). Brains were removed 1, 2, 6, 24 and 48 hours following sarin intoxication and processed for biochemistry analysis and immunohistopathology examination. Results showed maximal ChE inhibition (97 %) within 1 h post exposure that remained elevated at 48 h. Translocator protein (TSPO, a well established marker for brain damage) mRNA reached maximal level 24 h post exposure while maximal receptor density observed at 48 h. Immunohistopathologic examination revealed a marked increase in astrocytes (GFAP staining) already 2 h post exposure in all brain regions. This elevation was particularly higher in the piriform cortex area. A sharp decrease in intact neuronal cells (NeuN staining) was noted as soon as 1 h post exposure in the piriform cortex, frontal cortex and thalamus regions and 2 h post exposure in the hippocampus. A time dependent reduction in MAP2 (microtubule-associated protein 2) labeling indicated a propagating damage to the nerve dendrites and spines. These results suggest an immediate onset of a propagating deterioration cascade of nerve cells damage following organophosphate exposure.

Interaction between nerve growth factor (NGF) and alfa9beta1 integrin in glial tumor angiogenesis*

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NGF is a neurotrophin for which the role in the promotion of angiogenesis in neuronal tissue is still not completely understood. We found that NGF promotes the pathological neovascularization process in glioma through a direct interaction with α9β1 integrin, which is up-regulated on microvascular endothelial cells in human glioblastoma brain tumors. We isolated from these tumors microcapillaries and derived endothelial (gHMVEC) primary cells using a new method of immune-selection. These cell clones demonstrated in vitro α9β1 integrin-dependent binding of NGF in a cell adhesion assay. Moreover, NGF induced gHMVEC proliferation and chemotaxis, processes inhibited by specific blockers of α9β1integrin, such as MLD-disintegrin (VLO5) and monoclonal antibody Y9A2. A matrigel tube formation assay revealed that NGF significantly increased capillary-like growth from gHMVEC to a level comparable to treatment with vascular endothelial growth factor VEGF. The snake venom disintegrin VLO5, inhibited the angiogenic effect of both growth factors, whereas the effect of Y9A2 was not statistically significant. Angiogenesis exogenously induced by NGF was also α9β1-integrin dependent in an embryonic quail chorioalantoic membrane system. However, angiogenesis pathologically induced by developing glioma tumor in this system was only sensitive for inhibition with VLO5, suggesting a more complex effect of cancer cells on the neovascularization process. The anti-angiogenic effect of VLO5 is probably related to its proapoptotic activity in activated tumor capillaries endothelial cells. These findings extend NGF effects from neurons and glia to capillaries endothelial cells emphasizing the important role of this neurotrophin on the brain neurovascular unit. Moreover, the ability of VLO5 to antagonize NGF-induced angiogenic effect may be useful for developing new angiostatic pharmaceuticals for application in glioma therapy.

* Walsh, E.M., Kim, R., Del Valle, L., Weaver, M., Sheffield, J., Lazarovici, P. and Marcinkiewicz, C. Importance of interaction between nerve growth factor and α9β1 integrin in glial tumor angiogenesis. Neuro Oncol. 14:890-901. 2012

Single-digit multiplication in Generally Gifted and Excelling-in-mathematics adolescents: ERP study

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Background: This paper presents a small part of a larger interdisciplinary study that investigates brain activity (using ERP methodology) of mathematically talented adolescents when solving mathematical problems of different types. The present study aimed to examine the differences in time course and form of activation between four ability groups of high school students according to the combination of G (giftedness) and E (excellence in mathematics) factors. ERPs

were used in order to compare the process of brain activation when students perform single-digit multiplication tasks.

Results: P1, N2, P3, N4 and P6 ERP components were identified in the RMS, and peak detection was performed for the chosen electrodes. Significant effect of E factor on differences in amplitudes and latencies of the peaks was found. Gifted (G) student differed from non-gifted (NG) ones only on P1with significantly longer latency for students from group G as compared to students from group NG. Significant main effect (with repeated measures MANOVA) for E factor in the amplitude measures ($F(1,74)=5.036$, $p=.028$) of all ERP components with larger amplitudes for students from group E as compared to group NE was found. Significant interaction between all selected electrodes and E factor ($F(1.782, 133.930)=6.497$, $p=.003$) was also obtained.

Conclusion: G factor does not affect performance on relatively simple arithmetical tasks. At the same time, effect of E factor is associated with the automatic retrieval of information performed by E participants, and producing calculations by NE participants. The difference in amplitude and latency of the N2 component may reflect the difference in the attention mechanism between E and NE participants. For E students the solution process is faster with higher amount of activity and use of more areas but for less time.

Neurexophilin 3 is expressed rhythmically in the suprachiasmatic nucleus (SCN) in vivo and in immortalized SCN2.2 cells and is colocalized with membranal but not intracellular Neurexin2-α

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Background: Neurexophilins (NXPH1/2/3/4) are secreted neuronal glycoproteins, primarily expressed in mammals. NXPH1/2/3 (but not NXPH4) bind specifically to Neurexins 1/2/3-α (NRXN1/2/3-α). NRXNs are members of a gene family encoding hundreds of alternatively spliced isoforms of presynaptic proteins that are involved in neurosecretion and excitatory/ inhibitory synapse specification and mental disorders, e.g. autism and schizophrenia. The role of NXPHs in NRXNs' functions is largely unknown.

We have recently shown circadian oscillations in NRXN1/2-α in the suprachiasmatic nucleus (SCN) of the hypothalamus, that function as the main circadian clock *in vivo* and in immortalized SCN cells (SCN2.2 cells), which retain the rhythmic properties of the SCN, *in vitro*. Bioinformatic search suggested that NXPH1 might be a clock controlled gene. We thus explored circadian rhythms in NXPH1/2/3 in the SCN *in vivo* and SCN2.2 cells *in vitro*.

Results: NXPH1 and NXPH3 were expressed in SCN cells both *in vivo* and *in vitro* but only NXPH3 mRNA showed strong and significant rhythm in both. *In vivo*, NXPH3 peak lagged two hours after NRXN1-α and NRXN2-α mRNA peak, while in the SCN2.2 cells, NXPH3 and NRXN1/2-α expression patterns were similar.

Immunofluorescence labeling demonstrated colocalization of NXPH3 and membranal NRXN2-α at all time points, although NXPH3 levels varied diurnally in agreement with the mRNA temporal expression pattern.

Conclusions: These results show for the first time that NXPH3 is transcribed rhythmically in the SCN *in vivo* and in SCN2.2 cells *in vitro*. Furthermore, we show that endogenous NXPH3 and NRXN2-α colocalize in SCN2.2 cells, with different levels of NXPH3 expression throughout the day. These results suggest that NXPH3 may have a role in the circadian rhythm disturbances typically seen in ASD and schizophrenia.

Breakdown of temporal hierarchy in neural processing of natural information: evidence from schizophrenia

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Background: Real-life events, such as listening to a speech or watching a movie, unfold over many minutes. During such events, our brains absorb information continuously for the duration of the experience. However, the information gathered at each particular moment only becomes meaningful in the context of previous events. The capacity to accumulate information over time, thus, is crucial to our functioning in an ever-changing world. Yet our knowledge about gathering and parsing information over time is surprisingly limited. Recently, in healthy subjects, we revealed hierarchy of information processing over time from early sensory areas toward high order perceptual and cognitive areas. Here, we investigate the issue in first-episode schizophrenia patients, who are known to exhibit deficient information processing.

Results: Results were derived from inter-subject correlation analysis, which measures the reproducibility of neural responses across participants evoked by continuous and complex stimuli, such as stories and movies. The time-courses within each brain area in schizophrenia patients were estimated against healthy controls and unaffected siblings of the patients, which are known to be more prone to the disease. Results in patient group demonstrated impaired hierarchy with processing intact in low level but disturbed in high level, in both visual and auditory modalities. The sibling group showed an intermediate effect.

Conclusion: We believe that better understanding of the underlying neural circuit involved in information

processing in schizophrenia patients may assist in early identification of functional neural markers for the disease and facilitate development of improved methods for early diagnosis.

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Dietary sodium, added salt - associations with depression in NHANES

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Background: The possibility that enhanced salt intake protects against stress is a long-standing and attractive hypothesis deriving from the commonality of adrenal corticoids mediating both salt appetite and stress response, and the intertwining endocrine systems regulating sodium appetite, serum sodium concentration, fluid volume, and sympathetic tone. Mineralocorticoids and angiotensin II are activated by sodium deficiency and are anxiogenic. ACTH activation increases sodium intake in some species but not others, including humans. Rats on a sodium restricted diet, sodium depleted, or with endocrinologically-mimicked sodium depletion, evince increased modeled anxiety and depression (reduced sweet hedonics and electrical brain self-stimulation). Here we examined the possible relationship of salt intake and depression in humans,

Method: We analyzed the National Health & Nutrition Examination Survey (NHANES) 2007-2008 US database of ~10,000 people for the relationship of dietary sodium, reported table salt use, and depression.

Results: We find, in women only, that depression is inversely related to dietary sodium intake, and positively related to table salt use.

Conclusions: It is possible that depression-induced anhedonia may reduce choice of foods with sodium enhanced flavor. We have shown that rats in the chronic unpredictable stress model of depression consume less sweet and less salty solutions, even when sodium restricted. On the other hand, our findings can suggest that men are protected against depression by their higher sodium intake, while in women low sodium intake increases rates of depression. Adding salt might be self-medication. Although the data are correlative, these possibilities should not be ignored.

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Training on visual masking improves visual functions in fovea and periphery

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Background: Crowding impairs the ability to recognize an object in clutter. Visual masking refers to impaired performance on a target stimulus when a mask stimulus is briefly presented before, during, or after the target, at the same, or at flanking locations. Each crowding and visual masking effect represents a very important stage in visual processing and both are widely used as a tool to study visual processing in the brain. Yet the relation between crowding and lateral masking is unclear. In our previous studies we showed that crowding is correlated with masking; a higher degree of crowding correlates with higher masking. Previous studies showed that training on lateral masking improves some visual functions but the effect on crowding is not yet clear. Here we explored whether training on lateral masking can reduce the crowding effect as well as improve other visual functions in the fovea and the peripheral.

Methods: Subjects were tested before and after undergoing training in visual acuity, stereo acuity, letter crowding, spatial alignment, and contrast sensitivity. The subjects were trained on detection tasks and on two types of masking (simultaneous, temporal). The target appeared randomly either at the fovea or at the periphery (right or left).

Results: During the training sessions the extent of spatial and temporal masking was reduced. After training, the group improved in visual acuity, spatial alignment, and contrast sensitivity at all locations. In addition, stereo acuity was tested and it improved in the fovea and crowding was reduced at the periphery.

Discussion: The results indicate that training that reduces the masking effect is transferred to reduction in the crowding effect. Thus, the results support our hypothesis that crowding and lateral masking share similar mechanisms. The improvements in all trained locations, using lateral masking, support our suggestion that similar basic processing takes place in both peripheral and the foveal vision.

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A mouse model of the gateway hypothesis: nicotine and cocaine

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We present the results of mouse models of the Gateway Hypothesis, an epidemiological finding that describes the progression from nicotine or alcohol to marijuana to the use of illicit drugs in human populations. We designed an alternate sequential treatment procedure involving nicotine and cocaine and examined the behavioral, electrophysiological and molecular effects of sequential treatments. Pretreatment with nicotine alters the response to cocaine of both addiction-related behavior and synaptic plasticity in the striatum, a region critical for addiction. The ordering effect from nicotine to cocaine is unidirectional; there is no effect of cocaine on nicotine. Nicotine alters addiction related behavior and cellular physiology of LTP in response to cocaine. Nicotine produces these effects by initiating global histone acetylation, which leads to greater transcriptional activation of the fosB gene, a molecular marker for addiction. Pretreatment with the HDAC inhibitor SAHA produces an enhancement of the effect of cocaine very similar to that produced by pretreatment with nicotine. Conversely, decreasing histone acetylation leads to a decrease in the effects of cocaine electrophysiologically and in fosB expression. Histone acetylation is reduced genetically by using a mouse which lacks one functional allele of CBP (a histone acetyl transferase), or pharmacologically, by infusing low-dose theophylline (an HDAC stimulator) to the nAC. Nicotine enhances the effects of cocaine only when it is administered for several days prior to cocaine treatment and is given concurrently with cocaine. A new analysis of epidemiological data indicates that the majority of cocaine users initiate cocaine use while still smoking actively, and that initiation of cocaine after smoking increases the risk of becoming dependent on cocaine compared with initiation prior to smoking. The HDAC inhibitory properties of nicotine provide a possible molecular mechanism for the Gateway Hypothesis.

Impaired network stability in Schizophrenia

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Background: Schizophrenia is a serious mental illness that has been mostly studied from a bottom-up, biological, anatomical, or neuropsychological approach. Recently, the urgent need for top-down approaches has become evident, since abnormalities in global, emergent brain properties such as connectivity have been implicated in schizophrenia. Indeed, a growing body of work is concentrating on global network metrics and on dynamic systems computations to characterize abnormalities in schizophrenia. Recently, we have undertaken a perturbational approach using transcranial magnetic stimulation (TMS) as a means to study stability and dynamics of the schizophrenia network and suggested that TMS perturbations have considerably greater effects on schizophrenia participants than on controls. Here we combine TMS with electroencephalography (EEG) to measure the brain response to TMS perturbations in schizophrenia and in healthy controls. Using complexity system approach we characterize the effect of these TMS perturbations on the dynamics and stability of the underlying networks.
Results: While in the Sham condition the schizophrenia brain network had less links than the control network, following TMS perturbations the schizophrenia network exhibited more links than the TMS-perturbed healthy network. When analyzing the robustness of the schizophrenia and control networks to intentional attack and to network failure (when nodes are removed in decreasing order of their degree or in a random manner, respectively), both healthy networks (Sham and TMS) behaved as expected from a scale-free network dominated by hubs. However, while the Sham schizophrenia network was even less robust than the healthy network to intentional attack, the TMS-perturbed schizophrenia network behaved like a random network.
Conclusions: 7TMS perturbations applied to the schizophrenia network lead to an abnormal increase in effective connectivity and shift the network to a random-like network dynamics.

Font size effect on risk preferences

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Background: Many things influence risk preferences such as the magnitude of the reward to be chosen, its probability to occur and even the current and global wealth of the decision maker. Other more context dependent effects and higher order cognitive effects like reference points, stress, framing of the questions and even the subject's internal state have been found to influence risk preferences. However, much less is known if and how low-level sensory attributes influence risk preferences. In this study we examined the effect of a low level visual attribute on subjects' risk preferences.
Methods: Subjects were asked to choose between a certain small monetary reward ('reference') and a stated probability of either winning a larger amount of money or getting nothing ('lottery'). In all trials the reference option was always the same font size (22-meduim) while the lottery option could take one of three different font sizes: 18-small, 22-medium, or 27-large. Subjects faced the same choice options for all three font sizes. From these trials we estimated each subject's risk preferences for each off the three font sizes.

Results: We found a systematic effect of font size on risk preferences. As the font size of the lottery option increased the propensity to choose the lottery option increased. Interestingly, this effect was still evident even after we controlled for the difference in reaction times between the three conditions.
Conclusions: A low level visual attribute affected subjects' risky behavior. This suggests that brain areas that encode low-level visual attributes participate in value representation and choice. However, further studies need to be conducted using additional visual attributes like contrast, and frequency, inside the fMRI scanner to examine if the effect we observed is because value is represented already at the level of sensory areas or rather the sensory areas send sensory information to value areas per se.

Scavenger receptor A enhances disease progression in MS mouse model through CD4+ T-cells activation

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Background: Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by damage to the neuronal myelin sheath. The class A scavenger receptor (SRA), constitutively expressed on antigen-presenting cells (APCs) in peripheral tissues and the CNS, was shown to play a role in the phagocytosis of myelin; however, the role of SRA in the development of experimental autoimmune encephalomyelitis (EAE) and autoimmune reaction in the periphery has not yet been studied. We measured the clinical score of EAE induced C57BL/6-WT and $SRA^{-/-}$ mice and characterized CNS pathology using immunohistology staining. Furthermore we assessed pro-inflammatory cytokine response in cell cultures and measured SRA expression levels using RT-PCR and immunohistochemistry;
Results: We discovered that EAE progression and CNS demyelination were significantly reduced in $SRA^{-/-}$mice compared to WT mice. In addition, there was a reduction in infiltrating peripheral immune cells into the CNS lesion of $SRA^{-/-}$ mice, which was associated with reduced astrogliosis. Immunological assessment showed that SRA deficiency resulted in significant reduction of pro-inflammatory cytokines, such as IL-2, IFN-γ, IL-17 and IL-6. Furthermore, we discovered that $SRA^{-/-}$ APCs showed impairment in activation and in their ability to induce $CD4^+$ T cell proliferation. Recently, we have shown development of brain lesions in EAE induced non obies dibetic (NOD) mice (Levy et al 2010). Here we present an increase in SRA expression in infiltrated cells surrounding the brain lesion in these mice.
Conclusions: Elevation of SRA enhances EAE progression by expresing SRA on APCs to $CD4^+$ T-cells and increases their proliferation. Further studies of SRA-mediated cellular pathways in APCs may offer useful insights into the development of MS and other autoimmune diseases, providing future avenues for therapeutic intervention.

Do past negative life events affect generalization learning and symptoms improvement after cognitive behavioral therapy (CBT) in individuals with post traumatic stress disorder (PTSD)?

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Our previous studies have shown that Individuals with PTSD have a selective impairment in generalization learning. Most treatments for PTSD patients involve CBT. This method is based on principles of associative learning and generalization. Individual differences in generalization learning may influence the degree to which different PTSD patients are likely to benefit from CBT. The aim of the present study was to test the connection between generalization learning and responsiveness to CBT, and its correlation with past negative life events. We used a novel generalization task. The first phase of the task includes a discrimination learning procedure in which stimuli consisting of a cue and a context predict a specific outcome (reward/punishment). In the subsequent reversal phase, there are two possibilities: (1) the cue is unchanged but appears in a new context; (2) a new cue is presented in the original context. The new stimuli are associated with the opposite outcome relative to the stimuli in the first phase. Participants must reverse the original discrimination rule in order to adapt to the new condition. 30 PTSD and 30 trauma-exposed non-PTSD participants were tested in two points of time. Participants with PTSD had significantly more negative life events prior to trauma exposure compared to trauma-exposed non-PTSD participants. These results may suggest that a history of negative events increases risk for later PTSD. In addition, as predicted PTSD participants showed a significant deficit in generalization learning specifically when had to reverse aversive context. At this stage all PTSD participants went through a three months of CBT including a total of 24 45-minutes individual sessions. Improvement was defined as a reduction of 50 % in PTSD symptoms as measured by the Clinician-Administered PTSD Scale (CAPS). Results show a possible connection between past negative life events, generalization learning and symptoms improvement after CBT.

Translational and genomic approaches to obesity, depression and their interface

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Drugs have been used by individual clinicians and medical areas to treat all sorts of ailments for millennia. After World War II the emergence of an organized academic medical discipline of pharmacology led to a revolution in therapeutics. Likewise, translation of discovery into treatments occurs daily throughout the world as the outcome of cottage industries working in a highly fragmented manner. The efficiency of translational outcomes must be optimized. There is an emerging concept worldwide that as its logical outcome would lead to the creation of translational science as a novel bona fide, self-standing academic medical discipline aimed at facilitating and fostering translational outcomes across the full spectrum of medicine, in integration with pharmacogenomics aimed at improving and personalizing treatment outcomes. In our own work we have focused on two common and complex diseases of gene environment-interactions, depression and obesity, as well as their interface, as case examples of how to approach translation both from bench to bedside and bedside to bench. This work includes novel and provocative findings on the phenomenon of antidepressant-induced weight gain. In these two disorders that are rare cases with a strong genetic basis and other cases of clear environmental impact. We need to reframe the continuum of gene-environment interactions in the causes and treatments of common and complex diseases from a challenge to an opportunity for a variety of exciting translational approaches that will lead to better and personalized preventive and treatment strategies.

Learning 2–tone frequency discrimination – is fast improvement an indication of success or a cause of alarm?

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Two-tone discrimination is traditionally viewed as a simple discrimination task. However, it was recently shown that its performance varies substantially with the implicit strategy chosen by listeners. Introducing regularities, such that a reference tone is presented in a fixed position (first or second in every trial), enables listeners to categorize the informative tone rather than compare the tones, leading to substantially improved discrimination ability. Having found that we can benefit by training with specific structural regularities, we now ask whether learning transfers to novel contexts. Namely, whether regularity is a means for facilitating a broader learning process (like a gating mechanism) or, whether learning is specific to the trained regularity. Participants were randomly divided to 6 groups, each practicing the same task and same stimuli and procedure, but with different proportions of trials with Ref 1st versus Ref 2nd (0, 20 %, 50 %, 80 %, 100 %, and without reference). After completing a 300 trials training stage, they were all tested (in the following 100 trials) on the same task 50 % Ref 1st and 50 % 2nd trials. Performance in Ref 1st trials improved linearly across groups as the number of Ref 1st trials increased, regardless of the intervening Ref 2nd trials. Although performance was maximally improved when training with Ref1 only, this improvement was structure specific, and was substantially hampered in the test phase (50-50). Performance in Ref 2nd trials improved only when there were no intervening Ref 1st trials (i.e. 100 % ref 2nd), but showed more transfer to the mixed condition. Our inability to obtain low thresholds in both structures suggests that the mechanisms "seeking" structure are competitive, biased in favor of the Reference 1st structure. Training with "favorable" structures, as evident by their quick improvement, may block the improvement with other structures.

The role of TGF-β signaling in mediating cerebrovascular pathology: from cell culture to mouse model

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Background: The accumulation of amyloid deposits on the cerebral blood vessels, known as cerebral amyloid angiopathy (CAA), is associated with cognitive decline and is one of the hallmarks of Alzheimer's disease (AD) pathology. Transforming growth factor beta 1 (TGF-β1) expression levels correlate positively with the degree of cerebrovascular amyloid in AD cases. Furthermore, expression of TGF-β1 under GFAP promoter in mice leads to an age-related deposition of amyloid, such as β-amyloid (Aβ), around cerebral blood vessels. We aim to define the role of TGF-β1 in mediating endothelial cells pathology related to CAA.
Methods: We isolated EC from CAA mouse model and human CAA patients in order to target EC genes that related to CAA pathology. We applied shRNA approach in mouse EC cell line in order to identify the contribution of different TGF-β1/Smad dependent signaling in ECs.
Results: Using specific endothelial cells gene array we have identified genes that are regulated by TGF-β1 and may play a role in disease progression in a mouse model with CAA pathology. Using shRNA Smad2 and specific inhibitor we have shown

the important role of Smad1/5/8 pathway in mediating changes in the selected genes in EC line and in TGF-β1 mouse model.
Conclusion: We suggest the important role of TGF-β1-Smad1/5/8 signaling in the progression of CAA and we identify new target genes that may be used for future therapeutic intervention or for early diagnosis of CAA.
Alzheimer's association, HFSP and ISF

Repeated checking primes inhibition in healthy participants

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Repeated checking is a common symptom of Obsessive Compulsive Disorder (OCD)—an anxiety disorder characterized by intrusive thoughts that are followed by compulsive acts aimed to reduce anxiety. Various studies used a repeated-checking manipulation to demonstrate that relevant checking affects subjective memory but does not harm memory accuracy. This effect of repeated checking was found to be larger in individuals with poor inhibitory control. The current study aimed to reveal how repeated checking affects inhibition. Two groups of healthy participants completed either a repeated-checking task or a simple detection task. Both tasks were followed by a stop-signal task designed to measure inhibition of a pre-potent response. Results revealed that the repeated-checking task improved performance of the stop signal. It can be assumed that at least in healthy participants, repeated checking primes inhibition, thus making easier for the participants to recruit cognitive control in the stop-signal task. Implications for neuropsychological characteristics and theories of OCD are discussed.
Meloul Desiree

Dynamics of gene expression divergence during mammalian brain development follow an 'hourglass' shape

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Background: The transcriptome of the brain changes during development and across brain regions, reflecting processes that determine the structure and function of its circuitry. Despite the importance of these changes, little is still known about how brain regions become specialized in terms of their transcription profiles during development. We use gene expression measures from in situ hybridization across the full developing mouse brain to quantify the specialization of regional gene expression profiles.
Results: We quantified expression specialization as the dissimilarity in expression profiles across brain regions and looked at dissimilarity dynamics over development. Surprisingly, during the time that the brain becomes anatomically regionalized in early development, its transcription specialization decreases, reaching a low point around birth, and then rises postnatally. This hourglass shaped profile spans many genes and brain regions. The early decrease of specialization is mainly due to biological processes that are involved in constructing brain circuitry, like axon guidance, while the rising post natal specialization is largely attributed to plasticity and neural activity processes. Post natal specialization is particularly significant in the cerebellum, whose expression signature becomes increasingly different from other brain regions. This effect is also observed in the human cerebellum during the parallel developmental period.
Conclusions: Neural transcriptome diversity is minimized around birth, due to reduction of spatial divergence of genes important in nervous system structure and function. The fact that the cerebellum mostly develops after birth and becomes functional following post-natal inputs is reflected in an abrupt change in its gene expression profiles, and a similar trend is observed in parallel human data, suggesting that similar specialization profiles of brain development may be abundant in mammals.

Convolution models for induced electromagnetic responses

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Time-frequency analysis is a widely used method for studying event-related (induced) neural responses. Conventionally, event-specific time-frequency images are computed by averaging time-frequency decompositions of data epoched around the event in question. However, averaging of this sort fails when the induced responses overlap or when there are multiple response components that have variable timing within each trial (for example stimulus and response components associated with different reaction times). In these situations, it is advantageous to estimate response components using a convolution model of the sort that is standard in the analysis of fMRI time series. Here we describe one such approach, based upon ordinary least squares deconvolution of induced responses to input functions encoding the onset of different components within each trial. There are a number of fundamental advantages to this approach: for example; (i) one can disambiguate induced responses

to stimulus onsets and variably timed responses; (ii) one can test for the modulation of induced responses – over peristimulus time and frequency – by parametric experimental factors and (iii) one can gracefully handle confounds – such as slow drifts in power – by including them in the model. We illustrate the utility of deconvolution estimators using simulated and real MEG data.

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Self-monitoring of social facial expressions in the primate amygdala and cingulate cortex

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Keeping track of self-executed facial expressions is essential for the ability to correctly interpret and reciprocate social expressions. Yet, little is known about neural mechanisms that participate in self-monitoring of facial expression. We designed a natural paradigm for social interactions where a monkey is seated in front of a peer monkey that is concealed by an opaque LCD shutter positioned between them. Opening the shutter for short durations allowed the monkeys to see each other and encouraged facial communication. In order to explore neural mechanisms that participate in self-monitoring of facial expression we simultaneously recorded the elicited natural facial interactions and the neural activity of single neurons in the amygdala and the dorsal-anterior-cingulate-cortex (dACC), two regions that are implicated with decoding of others' gestures. Neural activity in both regions was temporally locked to distinctive facial gestures and close inspection of time-lags revealed activity that either preceded (production) or lagged (monitor) initiation of facial expressions. This result indicates that single neurons in the dACC and the amygdala hold information about self-executed facial expressions and demonstrates an intimate overlap between the neural networks that participate in decoding and production of socially informative facial information.

In vivo sensory physiology of adult-born neurons

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The adult mammalian olfactory bulb (OB) is supplied with adult-born neurons (ABNs) throughout life. ABNs are thought to have a special role in OB plasticity. However, their actual involvement in odor processing remains elusive, partly because even the basic odor response profiles of ABNs have never been documented. Here, we provide the first characterization of odor responses of ABNs in the mouse OB. To do so, we performed *in vivo* two-photon-targeted juxtacellular recordings from virally labeled ABNs, and resident OB neurons. This approach allows us to address fundamental questions in the field of adult neurogenesis – do ABNs mature to become like resident neurons, or do they form a special subpopulation? Does their contribution to odor coding change as they mature? We find that ABNs clearly respond to sensory stimuli, suggesting that they are an integral part of OB odor coding. Their spontaneous firing characteristics do not substantially change during the final stages of development. In contrast, we find that odor responsiveness and selectivity reach a peak during the final stages of development, and then eventually become similar to that of resident neurons. Our results suggest that ABNs mature to become like any other OB neuron. The heightened responsiveness and selectivity during development suggest that they contribute differently to odor coding as they mature, and might also subserve an experience-dependent mechanism of survival.

Effect of injury severity on brain activation patterns in survivors of traumatic brain injury: an fMRI study

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Survivors of Traumatic brain injury (TBI) suffer from a range of cognitive deficits. Our objective was to assess the influence of injury severity determined by initial Glasgow Coma Scale (GCS) on patterns of brain activation during a working memory (WM) task in TBI survivors compared to age and sex matched healthy controls.

Brain activations were assessed with functional magnetic resonance imaging (fMRI) using a 3 T MRI system (GE, HDxt). Twelve mild (mTBI), 10 moderate-severe (msTBI) patients and 19 controls were scanned while performing an N-back task for letters. The task (0-, 1- and 2-back conditions) was presented using E-Prime software and results were analyzed using SPM8. Activations in the low memory load (1-back vs 0-back condition, p Overall, activation patterns were more dispersed and less lateralized in the TBI groups compared to controls. These results indicate that TBI severity influences the pattern of brain activation, with moderate-severe but not mild head injury associated with more dispersed and less lateralized activations in response to a WM task compared to healthy controls.

Modification of neurotransmitters expression in various brain areas of transgenic mice for APP or/and Dyrk1A, two chromosome 21 genes involved in Alzheimer disease and Down syndrome

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Background: Expression of APP (Amyloid Precursor Protein) and Dyrk1A (Dual-specific tyrosine phosphorylation-regulated kinase) genes is increased in the brain of patients with Alzheimer disease (AD) or Down syndrome (DS). Deficits in serotonine, dopamine or noradrenaline systems have been evidenced in post-mortem brain tissue samples from AD and DS patients and also in DS blood platelets and cerebrospinal fluid; these deficits may be related to neuronal loss, and to dendrite and spine alterations leading to synapse loss. Very few data on neurotransmitters in mouse models for AD and DS are available. The aim of our study was to determine whether and how the levels of monamine transmitters and their metabolites were affected by APP or/and Dyrk1A overexpression in transgenic mice.
Results: Neurotransmitters expression was measured by electrochemical detection following by HPLC in hypothalamus, thalamus, hippocampus and striatum from 5 months old TgYAC hAPP (TgA) males mice, Tg mBACTgDyrk1A (TgD) male and female mice and wild type mice. We observed modifications in TgA, TgD mice and TgA/TgD mice of:
a) the noradrenergic system mainly in the hippocampus with a significant decrease in noradrenaline.
b) the dopamine system mainly in striatum with an increase in DOPAC and HVA and a decrease DA/DOPAC and DA/HVA suggesting an enhancement of dopamine activity. c) the serotonin system especially in the hippocampus and hypothalamus with a drastic 5-HT decrease and an important increase in the serotonine turn-over (5HIAA/5HT).
These results will be extended soon to the measurements of the COMT and MAO enzymes involved in these pathways.
Conclusion: Overexpression of APP or/and Dyrk1A genes involved in both AD and DS conditions induced modified expression of neurotransmitters in various brain areas. As some monoamines can be assayed in the human blood, their measurement might be useful to follow the progression of the disease and the effects of pharmacological intervention.
Fondation Jerôme Lejeune, AFRT (Associaiton française pour la Recherche sur la Trisomie 21)

EGCG (EpiGalloCatechine Gallate) might be beneficial for wake consolidation

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Background: Sleep fragmentation and consecutive daytime sleepiness are frequent in many pathologies including mental retardation from genetic origin (such as Trisomy 21: T21) and degenerative disease such as Alzheimer disease (AD). These disorders may have dramatical consequences on learning abilities. Our laboratory is working on transgenic mice for two genes of chromosome 21 (APP and Dyrk1A) in relation to brain plasticity and aging in T21 and AD.
Results: EGCG, a flavonoid found in green tea, has been shown to reverse the deleterious effect of Dyrk1A in transgenic mice overexpressing this gene (mBACtgDyrk1a mice: TgD;Guedj F. et al. 2009). We have investigated the effect of chronic treatment with EGCG on sleep parameters of wild type mice and TgD mice. In this preliminary study, we report about sleep parameters during 24 hours (light-dark period of 12 h) in wild type male C57/Bl6 mice treated with EGCG or placebo (sucrose). EGCG induces a significant increase of the time spent in wakefulness during the dark period with an enhancement of the mean duration of episodes. In parallel, total sleep (NREM + REM) was significantly reduced.
Conclusions: These results suggest that at least in wild type C57/Bl6 mice, EGCG has beneficial effects by consolidating wakefulness during the "active" period of the circadian rhythm. These results suggest that EGCG treatment may be beneficial also for cognitive functioning possibly through an increase of neuronal plasticity.
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Anti-apoE4 immunotherapy: a novel approach to the treatment of Alzheimer's disease (AD)

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Introduction: Previous studies revealed that the apoE4 gene is the most prevalent AD genetic risk factor. The apoE phenotype is detectable at an early stage, years before AD is diagnosed. Consistently, corresponding pathological phenotypes are observed in ApoE4 mice at a young age.
Methods: Our working hypothesis is that gain of toxic mechanisms play an important role in mediating the pathological effects of apoE4. Accordingly, we prepared anti-apoE4 mAbs which specifically recognize apoE4, in order to test the extent to which they can counteract the apoE4

phenotypes. The anti-apoE4 mAbs were injected to apoE targeted replacement (TR) mice in a preventive paradigm (10 weekly i.p injections of the mAbs, starting post-weaning) and in a treatment paradigm (3 i.p injections of the anti-apoE4 mAbs, prior to sacrifice at 4 months old). **Results**: Examination of naïve 4 months old apoE4 mice revealed distinct hippocampal pathologies, including tau hyperphosphorylation, Aβ neuronal accumulation, synaptic impairments as well as behavioral deficits. The anti-apoE4 preventive approach revealed that weekly i.p injections of the anti-apoE4 mAbs to 1 month old mice, for 3 months, prevented the tau hyperphosphorylation and partially reduced the Aβ neuronal accumulation in hippocampal neurons. In contrast, the excitatory marker VGluT1 decrease in the apoE4 mice was not affected by the injections. Preliminary results utilizing the treatment paradigm demonstrated that the apoE4 associated Aβ accumulation can be reversed by 3 weekly i.p injections of the anti-apoE4 mAbs, prior to sacrifice at 4 months old. The effects of treatment by the mAbs on tau, VGlut1 and other markers are currently being investigated.
Conclusion: i.p injected anti-apoE4 mAbs counteract the pathological effects of apoE4 in TR mice. This suggests a novel therapeutic approach for treatment of apoE4 carriers in AD and in other acute and chronic diseases.

The effect of STDP temporal window structure on the learning dynamics of single excitatory and inhibitory synapses

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Spike-Timing Dependent Plasticity (STDP) is characterized by a wide range of temporal learning patterns, depending on the studied network and the experimental conditions. These characteristic patterns represent the change in the measured post-synaptic potentials or currents as a function of the forced time interval (Δt) between pre- and postsynaptic spikes during the experiment. Long Term Potentiation (LTP) is marked by a positive sign of the characteristic function and Long Term Depression (LTD) by a negative sign. It is a common practice to define this function in segments of the time interval – typically in two segments, one for positive Δt (the causal branch) and the other for negative Δt (the acausal branch).
Here we suggest a model in which this pattern is constructed from a superposition of two separate processes one for the LTP and the other for the LTD. We approximate these two functional branches using a continuous non-segmented "probability like" function that captures the essential features of the STDP. We demonstrate how the various experimentally observed STDP temporal structures can be obtained by a gradual change of a single continuous parameter in our model. Analysis of the STDP dynamics reveals a critical point. Below this critical point the STDP dynamics is governed by a negative feedback and the synaptic weights are characterized by a unimodal distribution. Above this point, the stability of the STDP dynamics is governed by the synaptic weight dependence of the STDP rule. In the latter case there is a different parameter with a critical value, above which, a bimodal synaptic weight distribution exists. We show that the location of these critical points depends on general properties of the temporal structure of the STDP rule and not on its fine details. These results hold for both excitatory and inhibitory synapses. The symmetry in the learning dynamics of excitatory and inhibitory synapses is discussed.

Thrombin: a novel regulator of synaptic plasticity in the hippocampus

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Background: Thrombin, a serine protease involved in the coagulation cascade has been recently shown to affect neuronal function following blood brain barrier breakdown, therefore contributing to the stroke pathology. Several lines of evidence have shown that thrombin may exist in the brain parenchyma under normal physiological conditions, yet its role in normal brain functions and synaptic transmission has not been established. In an attempt to shed light on the physiological functions of thrombin and Proteases Activated Receptor 1 (PAR1) in the brain, we studied the effects of thrombin and a PAR1 agonist on long term potentiation (LTP) in mice hippocampal slices.
Results: Surprisingly, different concentrations of thrombin affect LTP through different molecular routes converging on PAR1. High thrombin concentrations induced a NMDA dependent, slow onset LTP, whereas low concentrations of Thrombin promoted a VGCCs, mGluRs dependent LTP through activated Protein C (aPC). Remarkably, aPC facilitated LTP by activating PAR-1 through an Endothelial Protein C Receptor (EPCR)-mediated mechanism which involves intracellular calcium stores.
Conclusions: These findings reveal a novel mechanism by which PAR-1 may regulate the threshold for synaptic plasticity in the hippocampus and provide additional insights into the role of this receptor in normal and pathological conditions.

Activity dependent neuroprotective protein (ADNP) as an erythropoiesis regulator

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The highly conserved Activity-Dependent Neuroprotective Protein (ADNP) is a member of a novel protein family, containing zinc-finger motifs and a homeodomain profile. During mouse embryogenesis, ADNP was identified as essential for brain development, and ADNP-knockout mice

exhibited marked growth retardation, defects in the closure of the cranial neural tube, and death at embryonic day ~9.5. At embryonic day 9, ADNP was shown to regulate >400 genes, encoding proteins associated with organogenesis, neurogenesis and heart development. ADNP was identified as a chromatin accessory protein, interacting with components of the SWI/SNF chromatin-remodeling complex, including Brg1. Previous studies have demonstrated that Brg1 is involved in erythropoiesis regulation, and is recruited to the β-globin locus by selective association with zinc-finger containing transcription factors. As ADNP belongs to the zinc-finger protein family, we postulated that Brg1 might mediate the effect of ADNP on erythroid development. Chromatin immunoprecipitation (ChIP) assays revealed, for the first time, recruitment of ADNP as well as Brg1 to the mouse β globin promoter in murine erythroleukemia (MEL) cells. However, MEL differentiated cells showed diminished binding ability on the third day after dimethylsulfoxide (DMSO) treatment compared to control cells that were not exposed to DMSO. These findings suggest that ADNP plays an important role regulating development, mediating its functions through transcriptional regulation of various systems involved in organogenesis, and specifically here, in erythropoiesis.

Gildor Chair, Adams Super Center, AMN, CFTAU, Allon Therapeutics (IG, Director, Founding Scientist)

A molecular signature in blood for early diagnosis of Parkinson's disease

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Background: Neurodegenerative diseases like Parkinson's disease (PD) and Alzheimer's disease (AD) are considered disorders of multifactorial origin, inevitably progressive and having a long preclinical period. Currently, the clinical diagnosis of PD can be made when motor symptoms occur, though the disease has originated several years earlier. Furthermore, at its initial stages PD may be confounded by other diseases, such as essential tremor, multiple system atrophy and progressive supranuclear palsy.

Results: The transcriptional expression of seven selected genes was examined in blood samples from 62 early stage PD patients and 64 healthy age-matched controls. Stepwise multivariate logistic regression analysis identified five genes as optimal predictors of PD. At a 0.5 cut-off the gene panel yielded a sensitivity and specificity in detecting PD of 90.3 and 89.1 respectively and the area under the receiving operating curve (ROC AUC) was 0.96. patient medication had no significant effect on the predictive probability (PP) of the classifier for PD risk The predictive ability of the model was validated in an independent cohort of 30 patients at advanced stage of PD, classifying correctly all cases as PD (100 % sensitivity). Notably, the nominal average value of the PP for PD (0.95 (SD=0.09)) in this cohort was higher than that of the early PD group (0.83 (SD=0.22)), suggesting a potential for the model to assess disease severity. Lastly, the gene panel fully discriminated between PD and Alzheimer's disease (n=29).

Conclusions: The findings provide evidence on the ability of a five-gene panel to diagnose early/mild PD, with a possible diagnostic value for detection of individuals at presymptomatic stages, who are good candidates for neuroprotective treatment.

Endocannabinoid-like entities as neuroprotectants after traumatic brain injury

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Background: Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. It involves two phases: 1.primary injury: irreversible, direct injury sustained at the moment of impact including the disruption of brain parenchyma with shearing of blood vessels and brain tissue, followed by a sequence of mechanisms which cause further brain damage, known as: 2.secondary injury, which includes increased cerebral edema and permeability of the BBB, axonal injury and neurodegeneration. In parallel, neuroprotective events also take place including the induction of the endocannabinoid (eCB) system, whose three main receptors are: CB1, CB2 and TRPV1. Levels of 2-arachidonoyl glycerol (2-AG), an eCB ligand, are elevated after TBI for at least 24 h. Moreover, treatment with 2AG after TBI was found to improve recovery, reduce edema, lesion volume, BBB permeability and neuronal death. Similar results were obtained after treatment with Arachydonoyl-Serine (Ara-S), an eCB-like compound belonging to the Fatty Acid-Amino Acids (FAAAs). This study was aimed to investigate the effect of two novel eCB-like compounds, belonging to the FAAAs, on functional outcome after TBI.

Results: Palmitoyl-Serine (Palm-S) and Oleoyl-Serine do not directly bind to eCB receptors. Yet, mice treated 1 h after TBI with these compounds displayed significant improvement of their neurological outcome. Interestingly, the effect of Palm-S was attenuated upon co-application with either CB1, CB2 or TRPV1 antagonists. Along the same line, preliminary

results reveal reduced effect of Palm-S on CB2-KO mice. In contrast, when CB2-KO mice were treated with Ara-S, the drug-mediated neuroprotection was further improved, which implies that CB2 may be interfering to the Ara-S-mediated neuroprotective mechanisms.
Conclusions: Taken together these findings suggest varied neuroprotective pathways mediated by indirect activation of the eCB receptors by those eCB-like compounds, following TBI.
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Spatial, temporal and mechanistic characterization of apoptotic death in the developing subventricular zone
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Background: We focused on developmental cell death in the neonatal subventricular zone (SVZ), a region that generates neurons and glia. While apoptosis is known to occur in the SVZ, there is a lack of knowledge regarding its temporal and spatial occurrence, the cell types affected, and underlying mechanisms.
Results: Apoptotic cells were identified using immunohistochemistry for cell death markers cleaved caspase 3 and phospho-H2AX, At p0, the highest proportion of dying cells, 0.4 %, was in the medial subregion (mSVZ). By p7, most apoptotic cells were in the dorsolateral SVZ subregion. Thus, the SVZ is a dynamic microenvironment, with a changing distribution of dying cells. Results showed that almost all dying cells at p0 and p7 are Ki67-, indicating that the apoptotic cells are postmitotic. NeuroD, a neuronal marker, was expressed in 69 % of the dying cells in the p0 mSVZ, while S100β, an astrocyte marker, and PDGFR alpha, an oligodendrocyte marker, were expressed by a minority of dying cells. Experiments also showed the BH3-only proapoptotic protein, Bim, was expressed by dying cells at p0, but not p7. Bim knockouts revealed protection from apoptosis at p0, but not p7. Lastly, we investigated extracellular regulators of apoptosis. Trks are neurotrophin receptors implicated in SVZ function. We found expression of TrkB receptors in the SVZ at p0 and p7. Injection of a Trk antagonist in the p0 mSVZ resulted in increased apoptotic cell number.
Conclusions: We identify the mSVZ and the dorsolateral SVZ as the primary sites of apoptosis in the SVZ at p0 and p7, respectively. Postmitotic neurons are the primary cell type to undergo cell death. Bim is expressed in the p0 mSVZ and its elimination offers transient apoptosis protection. TrkB is expressed in the p0 and p7 SVZ. Inhibition of Trks in the p0 mSVZ increases apoptotic cell death. Future studies will look at the cell types dying in the p7 SVZ, and the specific Trk involved in maintaining cell survival in the SVZ.
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Enhancement of neuronal growth and differentiation by the conjugation of β-NGF to maghemite nanoparticles
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The ability to control and manipulate neuronal growth has great implications in the tissue engineering field. Growth factors are critical components in nerve tissue development and repair. The nerve growth factor (β-NGF), a prototypical growth factor, functions as a signaling molecule and stimulates the growth, maintenance and survival of certain target neurons. In the present study, we describe a new approach to promote neuronal differentiation and growth, by using a NGF-nano-based tool. PC12 cells, a common model for primary neuronal cells, undergo cellular changes when exposed to β-NGF in vitro, i.e., cease proliferation, grow long neurites, and show changes in cellular composition associated with neuronal differentiation. We study the effect of β-NGF conjugated to maghemite (γ-Fe_2O_3) nanoparticles, fluorescently labeled, on the growth and differentiation of PC12 cells, compared to the free factor. We find that the stabilization of β-NGF by covalent conjugation to the maghemite nanoparticles significantly enhance PC12 neurites outgrowth, compared to free β-NGF at the same concentration. We also find an increase in the complexity of the branching tree and in the clustering behavior. We test several concentrations of nanoparticles and find the effect to be more significant at lower concentrations. Single cell imaging reveals particles accumulation in the soma (but not in the nucleus), in the growth cones and at branching points. We suggest that by covalently binding β-NGF to nanoparticles, β-NGF's half-life is extended and therefore has a stronger effect which leads to an increase in PC12 differentiation.

Regional differences in the representation of "change" within the Hippocampus
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Background: The link between the hippocampus and episodic memory is well known. The hippocampus however, is not a homogenous structure. Determining the manner in which different regions work in parallel and/or interact will provide a better understanding of how information is processed within this system. Given the importance of the hippocampus in navigation we provided an "episodic event" that included a "cognitive" manipulation (change in strategy/emotion/decision) while controlling for the trajectory and motor behavior of the rats.
Results: Using immediate early genes to identify individual cells

that differentiated between our task manipulations, we found heterogeneity both along the longitudinal axis (dorsal/septal vs. ventral/temporal) and among sub-regions of the hippocampus (DG, CA1, CA3). Similarly local field potential recordings show differences in theta frequency, correlation with running speed, changes in power and coherence along the longitudinal axis.
Conclusions: These data support and extend upon previous reports of regional differences in the hippocampal system. Our data indicate that both the dorsal and ventral regions of the hippocampus are involved in processing a navigation task. Furthermore there may be more integration and cooperation throughout the hippocampus with increased hippocampal task demands.

Optical probing of three-dimensional engineered neural-networks

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Background: Physiological and pharmacological studies of the mammalian brain in situ are inherently limited, due to light scattering as well as many other experimental difficulties, motivating the development of many in vitro preparations. These in vitro models are typically two-dimensional and thus provide only a limited similarity to natural physiology. Conversely, creating and working with three dimensional (3D), biologically relevant central nervous system (CNS) models also present major challenges, such as selecting a suitable 3D scaffold and developing fast 3D imaging systems.
Results: In this study we introduce and present the fundamental characteristics of a dense 3D neuronal network composed of rat primary cortical cells embedded in a hydrogel scaffold, and the 3D optical probing of the network using optogenetic probes. The network was transfected with viral agents for the calcium indicator GCaMP3 and for the light-gated channel Channelrhodopsin 2, facilitating the probing of a large population of neurons. We monitored the activity of large neuronal populations in our 3D network, using a fast custom-developed, temporal-focusing based imaging system with frame rates of up to 200 Hz. We will present the basic characteristics of network activity patterns and correlations between activity patterns of different cells in the network. Furthermore, we will present viability and immunohistological analysis of the forming networks.
Conclusions: This three-dimensional transparent neural environment allows optical monitoring and activation of the neural network. Combined with a fast custom-developed, temporal-focusing based imaging system, this tool opens new opportunities for large-scale neuronal interfacing and for applications of 3D engineered networks ranging from basic neuroscience to the screening of neuroactive substances.

Dietary modification of brain membrane phospholipid composition and signal transduction

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Brain microvascular pathology is a common feature of neurodegenerative disease and cognitive decline. In humans, poor folate status and elevated blood homocysteine are associated with increased risk for these conditions. In animal models, folate deficiency has been shown to cause brain microvascular damage and to decrease adult neurogenesis. These associations may be due in part to the role of folate and homocysteine metabolism in maintaining normal membrane phospholipid composition. Previous work has shown that folate deficiency can significantly lower the ratio of phospatidylcholine:
phsophatidylethanolamine in brain membranes, and that this change can be mitigated by the addition of methionine to diet. Methionine also mitigates the cognitive impairment induced by folate-deficiency, without lowering the concentration of homocysteine in blood. These findings are consistent with the hypothesis that diet-induced alterations in membrane-dependent signaling are important determinants of cognitive dysfunction. This study aims to identify transmembrane signaling pathways that are essential for neuronal and microvascular function, and which are disrupted by diet-induced changes in membrane composition. Here we focus on Notch protein, a trans-membrane regulator of neural and endothelial development and differentiation which has been implicated in both Alzheimer's and cerebrovascular disease. Work is underway to determine the effect of diet-induced changes in brain membrane composition on Notch signaling, by measuring changes in pathway activity and target gene-expression, in relation to diet, membrane composition and other biochemical, anatomical and behavioral outcomes. Identifying diet-sensitive signaling pathways in brain will assist in developing diet and drug-based interventions for the prevention and treatment of dementia.

The natural history of Alzheimer's disease: strategies for diagnosis and therapy

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Compelling evidence now shows that the Aβ-amyloid peptide is the central biochemical marker of Alzheimer's disease (AD), and is the most likely cause of the neurodegeneration manifest in synaptic dysfunction and eventual neuronal loss.
Our central interest lies in the mechanism through which Aβ undergoes toxic gain-of-function, inducing neuronal damage. This provides the most direct route for therapeutic intervention,

with least risk of therapeutic side-effects, since Aβ toxicity is unlikely to mimic any normal function. Various hypotheses have emerged to explain Aβ toxicity: redox chemistry associated with the Cu metal binding sites on Aβ, zinc-mediated oligomerization at glutamatergic synapses and lipid interactions associated with the α/β conformation of the hydrophobic C-terminus. Currently, we are purifying and characterizing the Aβ oligomeric species found in human AD brain and blood. The membrane associated fractions of Aβ may hold the key to understanding the complex relationship between the smaller pool of toxic oligomeric species the larger pool of fibrillar species locked into the amyloid plaques and congophilic angiopathy. Assays for monitoring the oligomeric species of Aβ in blood may be useful for the development of drugs which directly modulate the assembly of these oligomers. In vitro, PBT2, an 8-hydroxy-quinoline, has efficacy in reducing higher order Aβ oligomers. This drug is currently in clinical development.

The association between creativity and the 7R polymorphism in the dopamine receptor D4 gene (DRD4)

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Creativity can be defined as the ability to produce responses which are at the same time novel and appropriate. One approach for assessing creativity is measuring divergent thinking (DT) abilities which involve generating multiple novel and meaningful responses to open ended question. DT abilities have been shown to be associated with dopaminergic activity and may be impaired in attention deficit hyperactivity disorder (ADHD). Given that there is a strong association between the dopamine D4 receptor gene (DRD4) and ADHD, the current study examined the role of a repeat polymorphism in exon3 of the DRD4 (7R DRD4) in creativity in a group of healthy individuals (N=186). Scores on two DT tasks (Alternate Uses Task and a subset of the figural Torrance Tests for Creative Thinking) were used to assess different aspects of creativity (fluency, originality). Results showed that individuals carrying the DRD4-7R allele, as compared to non-carriers, scored significantly lower on tests of divergent thinking, and that this effect was evident in all measures of creativity including fluency and originality. The current results support a novel explanatory model of creativity, which centers upon the role of the dopaminergic system in divergent thinking.

The novel multi-target neuroprotective drug, M30 modulates the insulin signaling pathway in the brain of APP/PS1 double-transgenic Alzheimer's disease mice

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Background: Increasing evidence suggests that dysregulation of brain insulin receptor (InsR) and insulin signaling cascade are associated with the pathogenesis of Alzheimer's disease (AD). Our group has recently designed and synthesized a series of multifunctional non-toxic, brain permeable compounds for AD. One leading multi-target compound, M30 possesses the neuroprotective N-propargyl moiety of our anti-Parkinsonian drug, monoamine oxidase (MAO)-B inhibitor, rasagiline (Azilect®) and the antioxidant–iron chelating moiety of an 8-hydroxyquinoline derivative of the iron chelator, VK28. Positive outcomes for the neuroprotective effects of M30 were recently obtained in preclinical experimental studies, regarding pathological aspects relevant to ageing and AD. **Results**: We report a significant increase in brain insulin and InsR, transcript and protein, respectively and glycogen synthase kinase-3β phosphorylation in a double-transgenic (Tg) AD mouse model carrying mutations in the amyloid precursor protein (APP) and presenilin 1 (PS1) genes, systematically treated with M30 (1 mg/Kg for 9 months). In addition, we demonstrate that M30 up-regulated the levels of hypoxia-inducible factor (HIF)-1α and expression of its target genes involved in glycolysis, aldolase, enolase-1 and glucose transporter-1 (Glut-1), in the cortex of APP/PS1 mice, compared with vehicle-treated Tg mice. Treatment with M30 also lead to an increase in the hepatic protein expression levels of InsR and Glut-1 and lowered the increase in blood glucose levels following glucose tolerance test. **Conclusions**: Taken together, the findings suggest that the beneficial effects of M30 on central behavioral and pathological hallmarks of AD may be associated, at least in part, with the ability of this multifunctional iron chelating drug to regulate main brain glucose metabolism parameters.

EEG profile of dyslexic readers during a serial reaction time task.

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Background: Developmental dyslexia is largely characterized by a lack of accurate and fluent reading which persists into adulthood. Past research has investigated whether or not dyslexic readers (DRs) are impaired when performing tasks of implicit learning, such as serial reaction time (SRT) tasks. However, studies have revealed contradictory findings and no consensus has been reached on whether or not dyslexic

readers have a general deficit in implicit learning or if their difficulties are restricted to reading-related paradigms. Furthermore, the use of EEG has not been employed to understand the cognitive processing involved during implementation such tasks. This study used EEG with ERP methodology to compare the performance of dyslexic university students and control participants during an SRT task.
Results: DRs experienced a decrease in N170 amplitude over the course of the task, suggesting that they classified the target stimulus as "novel" for a longer duration than did controls. Both groups experienced a decrease in latency of the P2 component, but only controls exhibited a decrease in amplitude as well. This suggests that early processing of the target stimulus was still relatively effortful for DRs by the end of the task. While both groups showed a decrease in amplitude for the P3i component, only the controls showed an amplitude decrease for the P3ii component. This further implies that stimulus novelty had not worn off for the DRs as much as it had for the control group, thereby implying that less learning had occurred.
Conclusions: DRs have a specific problem with implicit learning when material is presented sequentially. They exhibit the ability to learn implicitly, but not in the same way or with the same efficiency as nondyslexic readers.
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Development of ApoE4 targeted therapy of Alzheimer's disease.
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Introduction: Apolipoprotein E4 (apoE4) is the most prevalent genetic risk factor of Alzheimer's Disease (AD) and at present there is no apoE4 targeted treatment. The apoE4 risk for AD may be due to either loss of "good" apoE3 allele(s) or to dominant negative effects of the "bad" apoE4 allele. We will presently address the hypothesis that the effects of apoE4 are mediated via gain of a cytotoxic effects. Accordingly, mAbs directed specifically against apoE4, which we have recently prepared, will be injected i.p. into apoE4 and apoE3 mice and the extent to which they can counteract the effects of apoE4 will be determined. The possibility that elevating the levels of apoE4 either exacerbates or diminishes the effects of apoE4 will be assessed utilizing the RXR ligand Bexarotene. The experiments will be performed utilizing young apoE4 and apoE3 targeted replacement mice and an unbiased approach in which the effects of apoE4 evolve spontaneously and are not manipulated via a hypothesis driven paradigm.
Results: Experiments uitilizing 4 months old targeted replacement apoE3 and apoE4 mice revealed that apoE4 triggers the accumulation of Abeta42 and hyperphosphorylated tau in hippocampal neurons and down regulates the levels of the presynaptic glutamate transporter, Vglut1. Weekly i.p. injection of anti apoE4 mAbs to one month old mice for three months prevented the accumulation of hyperphosphorylated tau in hippocampal neurons of the apoE4 mice and partially reduced the accumulation of neuronal Abeta 42. In contrast the apoE4 driven decrease in Vglut1 was not reversed by the anti apoE4 mAbs.
Conclusions: ApoE4 driven tau hyperphosphorylation of hippocampal neurons is prevented by i.p. injection of anti apoE4 mAbs. The extent to which such mAbs can also reverse the effects of apoE4 when applied following the appearance of the apoE4 phenotype and the degree to which up regulation of the levels of apoE4 by Bexarotene modulates the effects of apoE4 will be discussed.

Theta rhythm alterations during epileptogenesis: a novel biomarker for the prediction of seizures
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Background: Blood-brain barrier (BBB) dysfunction and the associated extravasation of serum albumin were demonstrated to underlie the induction of epileptogenesis. Here we explore the potential of electroencephalographic (EEG) features as biomarkers for epileptogenesis in animal models, aiming to develop a method for identifying at-risk patients.
Results: Mice were implanted with epidural electrodes and intraventricular pump infused either albumin, TGF-β, IL-6 (all shown to induce epileptogenesis) for one week. EEG was recorded continuously for 14 days. Mean of relative power in five frequency bands: θ (3-8 Hz), α(8-12 Hz), β (12-20 Hz), low (20-40) and high (30-100) γ, was calculated for every 60 s EEG segment. Linear regression of the means was calculated for day 2-4 post surgery. Mice showing seizures within the first 4 days after treatment were excluded from the analysis. Since θ was shown by previous studies to be decreased among epileptic animals, we used K-means algorithm to cluster groups of "θ slopes", and a statistical significant difference was revealed between epileptic and non-epileptic mice: θ power was unchanged for 13 out of 16 animals without epilepsy (slopes were within a tight range around zero), whereas among 10 out of 11 epileptic animals, θ slope was outside of this range. A significant inverse correlation was found between the rates of θ change and the day of first seizure. The change in θ was found to be inversely correlated with changes in power within the high γ band slope.
Conclusion: To our knowledge, this is the first study to identify a specific EEG pattern as a predictor for

epileptogenesis. The similar results obtained in the three animal models give hope that such a pattern may be found in other models of the disease, and could be translated to human studies.

Modulation of synaptic plasticity in the hippocampus by sensory deprivation

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A fundamental feature of neural circuits is the capacity for plasticity in response to experience or learning. Primary sensory cortices display a 'critical period' (CP), an early postnatal epoch of enhanced plasticity during which large-scale changes in response selectivity can be induced by changes in sensory experience. Sensory input promotes maturation of cortical synapses, while sensory deprivation delays and prolongs CP. Later adult plasticity in sensory cortices is limited and depends on attention and behavioral outcome. In contrast, hippocampus is known to maintain its high capacity to undergo activity-dependent synaptic plasticity throughout life. While cortical efferents from all major sensory areas converge to the hippocampus via the perirhinal and postrhinal and then the entorhinal cortices, it is completely unknown whether sensory experience regulates synaptic plasticity in hippocampal networks.
We explored the effect of visual and somatosensory deprivation on synaptic dynamics in hippocampal networks by comparing synaptic local field potentials in hippocampal slices from control and sensory-deprived animals. Our data show that visual and whisker deprivation during the corresponding cortical CP alters short-term synaptic plasticity in several hippocampal pathways. Short-term facilitation in Schaffer Collateral synaptic connections was enhanced by both dark rearing and bilateral whisker trimming. Furthermore, whisker trimming increased synaptic facilitation in the medial temporoammonic and lateral perforant pathways, while it did not alter synaptic dynamics in the lateral temporoammonic and medial perforant pathways. These results demonstrate that sensory deprivation during cortical CP affects hippocampal synaptic processing by promoting short-term synaptic facilitation in a pathway-specific manner.

Cytoplasmic flow as a transport mechanism in nerve cells

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Two mechanisms are believed to participate in the movement of molecules inside the axon: thermal diffusion and axonal transport. Axonal transport is an active organized movement for material transportation within vesicles, but not necessarily for unbounded colloids or solutes. Thermal diffusion mixes all molecules by random collisions caused by the thermal energy. Diffusion is sufficient for material distribution in small cells, but it is impractical as means of transportation through axonal length scales. To the best of our knowledge, no driving force was ever suggested for the transport of axoplasmic molecules that are not attached to motor proteins. We suggest that a flow mechanism is central for the distribution of materials not carried by vesicles. In addition we describe how the active movement of organelles drags the surrounding fluid, thus inducing a cytoplasmic flow, similarly to observations in plant cells. The flow is predicted to depend mainly on the distribution of microtubules, the separation distance between organelles and a few physical properties of the axonal external layer.

The role of methyl donor nutrition in epigenetic mechanisms in the brain

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Recent work has shown that experience dependent, reversible epigenetic modification of neuronal DNA (i.e. DNA methylation) is required for the cellular changes that underlie cognitive function and learning and memory, including synaptic plasticity and possibly neurogenesis. Dietary factors such as high fat intake, folate deficiency and obesity can alter and disrupt DNA methylation in non-neural tissue. In light of the above, diet has been hypothesized to mediate brain function, development and aging through similar epigenetic mechanisms. Nevertheless, the extent to which this occurs remains largely hypothetical. We propose to address this hypothesis by examining the effect of dietary folate on brain DNA methylation and pathways of brain plasticity, using an animal model of folate-dependent cognitive impairment. Our aims are to identify molecular and epigenetic changes on neuronal processes responsive to dietary methyl donor availability (i.e. folate deficient (FD) diet) and determine whether Methionine (Met) supplementation, an essential amino acid whose metabolic salvage is a product of folate-dependent metabolism, would ameliorate FD effects. We observed changes in mRNA levels of TET1 and TET3, suggesting an alteration of DNA methylation/demethylation processes in FD rats. In addition, there was a pronounced change in genes related to neuronal plasticity (e.g. DCX, VEGF) all of which was restored by adding Met to the diet. Work is underway to determine the effect of diet-induced changes in total brain DNA methylation pattern. This result gives an initial insight into the effect of nutrition on gene expression related to neuronal plasticity and DNA methylation. An additional investigation is necessary to determine the

alteration in DNA methylation dynamics as a result of changes in nutrition and the effect of those on cognitive function.

Towards retinal stimulation with spatio-temporal patterns of ultrasound

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Background: Ultrasound (US) waves are commonly used in many medical applications, but have also been shown to stimulate neurons. These developments open new possibilities for non-invasive modulation of brain activity, however, for applications attempting to mimic physiological activation patterns, accurately controlled spatio-temporal patterns of excitation are required. Our study is aimed at demonstrating US spatio-temporal patterned stimulation of the retina.
Results: We approached the spatially-patterned US field problem by adapting methods from computer generated holography, addressing the generation of sparse and continuous patterns using Gerchberg-Saxton type algorithms. The algorithms were tested in simulations and resulting fields were measured using serial hydrophone scanning, concluding that US spatial distributions may be generated efficiently. Generalizations of the method, allowing propagation through composite media and geometrical constraints have been formulated, bringing the method closer to operation in a realistic environment. The US effect on the retina was studied in-vivo and in-vitro. In-vivo, full-field US pulse trains were transmitted to eyes of anesthetized rats, while measuring the evoked potentials (EPs) via subcutaneous electrodes. This US stimulation led to significant EPs with a power of ~25 % that of flash EPs and no damage was found to the stimulated retinas. In addition, responses to US stimulation of the eye were found in local field potentials measured from rat V1. In-vitro, isolated rat retinas were placed on multi-electrode-arrays and excited with either full-field or spatially-patterned US pulse-trains. Preliminary data show responses of the retinas to these stimuli.
Conclusions: Our results indicate that the retina is excitable by acoustic stimulation and that acoustic fields can flexibly patterned. Thus, vision restoration strategies based on US excitation of the retina may lead to non-invasive prosthetics.
InSightec LTD., Professor Ido Perlman

Ongoing activity in the Optic Tectum is correlated on a trial-by-trial basis with the pupil dilation response

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The peripheral sensory systems are constantly bombardment with stimuli, only a fraction of which induce behavioral responses. A major challenge in behavioral neuroscience is to predict which stimulus and when will be selected or in other words to identify the neural mechanisms that gate the sensory information. An emerging hypothesis is that the evolutionary role of the superior colliculus, and its avian homolog the Optic tecum (OT), is to sort stimuli based on saliency and send this information to the appropriate brain regions to direct orienting movements, attention and autonomic responses. We tested this hypothesis by recording the neural activity in the OT simultaneously with pupil dilation responses (PDRs), a behavioral indicator for stimulus perception. We presented long sequences of auditory stimuli and correlated on a trial-by-trial basis the fluctuations of the PDR with the neural activity in the OT. The main finding was that the PDR was correlated with the ongoing activity in the OT prior to stimulus presentation, but not with the neural response itself (post minus pre stimulus onset activity). Following this surprising finding, we characterized ongoing activity in the OT. We report that ongoing activity was highly variable and was characterized by spontaneous episodes of high activity. Using dual recordings we show that these episodes were correlated between the OT and the entopallium (E), the forebrain recipient of the tectofugal pathway. Moreover, during episodes of high ongoing activity the cross-correlations between spike trains in the OT and the E tended to increase. These results support the recently suggested hypothesis that the coupling between neural activity in the OT and the forebrain is dynamically controlled and plays a role in gating of sensory signals. The level of ongoing activity in the OT may reflect an internal state during which such coupling is increased.
The generous support of the Israel Science Foundation is gratefully acknowledged

Antidotal efficacy of MMB-4 compared to other oximes against nerve agents poisoning – in vitro and in vivo studies

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The bisquaternary oxime MMB-4 (methoxime) has been suggested as an efficacious oxime in the antidotal treatment against organophosphorus (OP) nerve agents. The in vitro reactivation of various OP-inhibited AChE by MMB-4, 2-PAM, TMB-4, Toxogonin, HI-6 and HLö-7 (pH=7.4, 23oC) was studied. The reactivation kinetics by oximes of AChE inhibited by sarin displayed superiority of MMB-4 compared to Toxogonin, TMB-4 and 2-PAM (kr=3.2, 0.17, 0.15 and 0.1×103, M-1 min-1, respectively). Further,

MMB-4 was found equipotent to TMB-4 but 25-fold faster than 2-PAM toward VX-inhibited AChE (kr=1.5×103, 3.5×103, 60 M-1 min-1, respectively). Non-aged soman-inhibited AChE could be reactivated only by HI-6, HLö-7 and MMB-4 (kr=9.2, 4.7, 0.9×103 M-1 min-1, respectively). The antidotal efficacy in rats of MMB-4 (M, 25 mg/kg, im) was compared to TMB-4 (T, 7.5 mg/kg, im) against sarin poisoning in conjunction with atropine (A, 3 mg/kg, im) and benactyzine (B, 1 mg/kg, im), following pretreatment (30 min) with pyridostigmine (Pyr, 0.1 mg/kg, im). The protection ratios (PR) obtained for MAB and TAB, 2.8 (2.3-3.3), 1.7 (1.5-2.0), respectively, indicate higher efficacy of MMB-4 vs. TMB-4. MMB-4 (M) was also used in combination with atropine (A) and caramiphen (C, 20 mg/kg, im) (MAC without pretreatment). The MAC mixture, provided higher survival rate than TAB against either 1.5 or 2xLD50 sarin (im). The PR of MAC with Pyr pretreatment against soman poisoning was higher than TAB, 2.9 (2.5-3.4) vs. 2.0 (1.7-2.4). However, in the absence of Pyr, MAC displayed similar antidotal efficacy to TAB against soman poisoning, PR: 1.6 (1.5-1.7), 1.4 (1.2-1.6), respectively. The efficacy of MAC and MAB mixtures against VX poisoning displayed remarkably high PR values 72(58-95) and 37(16-85), respectively, vs. TAB and TAC, PR: 25(19-33) and 29 (12-70). The antidotal data obtained with sarin and soman using MMB-4 instead of TMB-4 could be anticipated from the in vitro reactivation data.

New approaches to stroke recovery

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There is an urgent need to increase the effectiveness of rehabilitative therapies after stroke. Environmental enrichment (EE), a multimodal approach comprising physical, social and cognitive activity, is very promising as a strategy that is broadly deployable. There are very few, if any, pharmacological or non-pharmacological approaches to stroke recovery that have been shown in experimental studies to be as consistently effective as EE. Convincing evidence exists that EE improves cognitive reserve and functional activity and reduces anxiety-like behaviours in normal rodents and in different disease models. Multimodal stimulation promotes brain plasticity. Studies of brain plasticity have traditionally focused neuronal functions, in particular the roles of the synapse. However, astrocytes, microglia, different progenitors and vasculature are key elements in plasticity and are also profoundly influenced by EE. We now also begin to understand how to translate the positive effects of EE in experimental animal research to humans. The effects of multisensory stimulation constitute most likely important parts of the mechanisms underlying the beneficial effects of, for example, cardiovascular training and different cognitive challenges on functional recovery after stroke. Our work on environmental enrichment (EE) post stroke includes a meta-analysis demonstrating the effectiveness of EE in experimental stroke, and a pilot clinical trial of EE, which showed significant increases in overall, cognitive and social activity in patients exposed to an EE. Further, recent data from our population-based studies demonstrated that physical fitness is correlated with cognitive performance and mood. In ongoing studies, we are currently exploring the effects of a music and rhythm-based intervention in a cohort of stroke patients in chronic phase. These and other translational aspects of EE will be presented and further discussed.

Auditory responses and stimulus-specific adaptation in rat auditory cortex are preserved across wakefulness, NREM and REM sleep

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Sleep entails a disconnection from the external environment. By and large, sensory stimuli do not trigger behavior, are not consciously perceived, and do not induce plastic changes as is typically the case in wakefulness. It has been suggested that thalamic 'gating' may disrupt relay of sensory signals, but the extent of signal propagation along ascending sensory pathways in sleep remains unclear. In this study, neuronal responses in core auditory cortex were compared as freely moving WKY rats (n=6) spontaneously switched between wakefulness and sleep states. Local field potentials (LFPs), and single-unit activity (SUA, n=520) were recorded continuously along with EEG, EMG and video for determining vigilance states. In the first experiment, a wide battery of stimuli included tones, clicks and click-trains, complex environmental sounds and rat vocalizations, FM sweeps, and 'chirp AM' tones. Baseline neuronal activity showed robust differences between vigilance states (e.g. firing rate in NREM was 80.5 % of that in wakefulness, p<10-43). By contrast, both the selectivity and the magnitude of auditory-evoked responses were comparable across wakefulness, NREM and REM sleep (non-significant pair-wise differences <8 % between states), and this was confirmed separately for onset, offset, and sustained responses. In a second experiment, the processing of deviant tones was compared in sleep and wakefulness using an oddball paradigm. Robust stimulus-specific adaptation (SSA) was observed following

the onset of repetitive tones, whose strength (>15 %) was indistinguishable across vigilance states.
These results suggest that responses in core auditory cortex are preserved across sleep states, supporting the notion that neuronal activity in primary sensory cortices are primarily driven by external physical stimuli. During sleep, a functional disconnection within cortex may possibly prevent this activity to effectively drive high-order cortical regions.
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Role of the translational machinery in antioxidant-induced reversal of cocaine psychomotor sensitization
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It is well known that the use of cocaine cause various physiological changes in different organs, including the CNS. These changes caused severe damage and a variety of behavioral effects, and many studies are dedicated for investigating this phenomenon. In more recent studies, it has become evident that oxidative stress plays an important role in cocaine toxicity and cocaine induced addictive behaviors. Previously we have shown that the acute or chronic administration of cocaine induces massive oxidative stress in principle areas of the reward system such as the pre frontal cortex (PFC) and the nucleus accumbens (NAc). We found that the antioxidant Tempol abolished cocaine-induced elevation of oxidative stress in these areas both in vitro and following cocaine injection. Importantly, Tempol at a dose that does not affect the basal levels of locomotor activity, attenuated both the development and expression of cocaine-induced psychomotor sensitization and prevented the increase in oxidative stress following withdrawal. We also found that Tempol increases the phosphorylation of eukaryote elongation factor 2 (eEF2) in cocaine sensitized rats. However, the molecular mechanism by which Tempol acts remain poorly understood. We therefore hypothesized that antioxidants such as Tempol exerts their neuroprotective effects via activation of the translational machinery using eEF2 KI mice (D273A), in which the protein is present but defective.
We found an age dependent difference in cocaine psychomotor sensitization; while adolescent mice showed decreased in both the development and expression of sensitization compare to their littermates controls, adult mice showed a significant increase in sensitization. These results suggest that eEF2 indeed play an important role in the neuroadaptations that leads to cocaine sensitized response and currently we are exploring whether antioxidants such as Tempol acts via this molecular pathway.
National Institute for Psyochobiology in Israel (NIPI) and the Rosetrees Trust.

Regenerative response of optic nerve axons while using a specifically designed hydrogel
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Background: Regeneration of the CNS in mammals is limited by the generation of physical and chemical inhibitory barriers that are formed following injury and the absence of positive cues that elicit and guide repair. Hydrogels are considered to be good materials for CNS repair because of high oxygen and nutrient permeability and low interfacial tensions. Hyaluronic acid (HA) is a natural polymer used as a building block for hydrogel formation. This polymer is appealing for medical use owing to its similarity to the natural extracellular matrix (ECM) and to its biocompatible and biodegradable qualities. Peptide-based scaffolds represent another very important biocompatible material that can support cell growth.
Results: Hyaluronic acid (HA) based composite containing self assembled, small peptide nano-tubes (FmocFF) was selected for the *in vivo* study based on its net-like 3D structure. Cell culture analysis showed that the composite was non-toxic and allowed cell attachment. The right optic nerves (ONs) of adult rats were completely transected while sparing the vasculature and the meninges. The HA-FmocFF composite was implanted at the lesion site. The control group was implanted with 2 % unmixed HA. The HA-FmocFF composite was found to be non-toxic and biocompatible to the optic nerve, with no evidence of degeneration. Two months after injury, immunofluorescence analysis and MRI analysis were preformed. . In most ONs a small number of axons were found adjacent to the injury site. However, about a third of the ONs treated with the HA-FmocFF composite showed a more substantial regeneration towards the optic chiasm.
Conclusions: HA-FmocFF hydrogel appeared to contribute more to axonal regeneration than hyaluronic acid alone. Partial regeneration can be achieved with specifically designed hydrogels, which present the regenerating axons with a relatively clear pathway and net-like 3D scaffold to maintain their progress beyond the lesion site.

Neuronal electrical activity patterns depend on the axon morphology – analysing the Hodgkin Huxley cable model
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The Hodgkin Huxley model which was published in 1952, describes the mechanism and principles of electrical conduction of neuronal membranes. This model revolutionized our understanding of how the nervous system processes information. The model provides a mathematical depiction of the formation of the action potential, and its propagation along the axon. Using the Hodgkin Huxley model, we explore the axonal response to external current stimuli. We investigate the space clamp and cable models and present a novel detailed bifurcation analysis. In this study we focus on two borderline cases of electrical responses. In the first regime, a finite number of spikes are generated followed by constant voltage. We demonstrate that the number of action potentials is controllable and can be adjusted to any finite number. In the second regime, located between current stimuli that cause a train of action potentials and current stimuli that cause single spikes, spike series followed by failures are generated. We demonstrate the ability to control the number of action potentials before a failure. For specific current stimulus regimes, chaotic behavior was observed.
In addition, we examine the influence of axonal morphology, namely the axon radius and branching points, and the influence the temperature on activity patterns. The investigation of the electrical response for different axonal radii draws on a detailed non-linear analysis of the Hodgkin Huxley cable model. We find a strong correlation between the axonal radius and the activity pattern. These two borderline phenomena and the effect of morphology on the electrical response illustrate ways in which the pattern of axonal activity can be controlled, and suggest that this behavior may be instrumental in information coding. The study of the non-linear behavior of the neuronal electrical response may thus contribute to a better understanding of dynamical neuronal diseases such as epilepsy and Parkinson's.

Cell/gene therapy in a mice model of ALS delay the onset of symptoms and prolong lifespan

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Background: Neurotrophic factors (NTFs) preserve and protect motor neuron in ALS mice models. However, clinical studies administering NTFs in ALS patients have all failed. We have developed muscle progenitor cells (MPCs) population expressing BDNF, GDNF, VEGF or IGF-1. MPC populations, each expression one of the four NTFs, or a mixture of the four populations was transplanted into the hind legs of ALS (SOD1) mice model.
Results: We found that transplantation of the MPC mixture significantly delayed the onset of the symptoms by 30 days (143 vs. 113 in untreated mice). Moreover, the treatment prolonged the lifespan by 14 % (152 vs. 133 days in untreated mice). In contrast, transplantation of MPC alone or MPC overexpressing just one of the four NTFs did not elicit any improvement. We also found that the supernatant of a conditioned media mixture from MPC populations expressing the four NTFs increased, in motor neuron cell line (NSC-34), the phosphorylated AKT and BAD by 6-8 fold compared to MPC expressing a single NTF. We conjugated Qdot605 streptavidin to biotinylated GDNF and added it to the axon endings of primary motorneurons cultured in compartmental microfluidic devices, to study the possible axonal transport to the cell body. Strikingly, we observed that the Qdot-GDNF undergo highly directed axonal transport in the retrograde direction and accumulated in the cell body compartment.
Conclusion: We built a novel powerful strategy enabling the stable, long-term administration of a cocktail of the four NTFs factors. The constant release of the critical NTFs from the muscle fibers through the neuromuscular junction into the motor neuron system and the retrograde transport to the cell bodies in spinal cords, probably inhibit death pathways. We hope that our study will lead to a novel strategy to slow down the progress and alleviate the symptoms of ALS and extend the life expectancy and quality of affected patients.
The study was partially supported by Muscular Dystrophy Association (MDA), USA

Automated long-term tracking and analysis of social behavior in groups of mice

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Social interaction in a group of animals has been a difficult area of study since behavior develops over long periods of time, requires laborious time consuming manual annotation, and suffers from subjective scoring. We present a computer vision based method for tracking multiple mice over long periods of time (days) without mixing individual identities within the group. Our system computes the trajecotry of each individual and reconstructs high order statistical ethograms (e.g. relative posture, preferred locations, following, approaching, etc.). These correlates of social interaction can be used to study courtship, dominance and aggression, which may develop over the course of days and may not be observable in acute experiments. We show the applicability of our method in studying

how social hierarchy develops between a group of two males and two females over the course of 5 days.

Neural control of vascular reactions: the impact of emotion and attention

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Background: Recent evidence suggests that the brain is causally involved in the initiation and progress of cardiovascular diseases, by failing to regulate blood pressure responses to emotional events. This study examines the neural regions regulating blood pressure reactions to negative stimuli, and their possible modulation by attention. **Methods**: 24 healthy subjects (11 females; age=24.75± 2.49 years) participated in an affective perceptual load task that manipulated attention to negative/neutral distracting pictures. fMRI data was collected in a 3 T-Siemens scanner simultaneously to continuous recording of peripheral blood pressure. A parametric modulation analysis examined the impact of attention and emotion on the relation between neural activation and blood pressure reactivity in the task. **Results**: In attended conditions, distracting negative pictures resulted in behavioral interference, neural activation in an emotion-related network, and a positive correlation between peripheral vascular reactivity and activation in a cortico-limbic network. The effects were modulated by attention: behavioral and neural responses to highly-negative pictures were smaller or diminished in unattended conditions. **Conclusions**: These results emphasize the role of attention mechanisms in reactions to emotional information. Thus, the findings suggest that attention can serve as a therapeutic tool for decreasing abnormally enhanced vascular reactions to aversive stimuli, a main risk factor for cardiovascular diseases.

Early postnatal exposure to chlorpyrifos caused strain dependent changes in fear learning in adult mice.

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Background: CPF is the most widely used organophosphate pesticide in the world that can interact with brain acetylcholinesterase (AChE) activity. Human and animal studies indicate that CPF is a developmental neurotoxicant able to cause early cognitive and behavioral deficits at doses well below the threshold of systemic toxicity. However, the exact mechanisms of action underlying the developmental neurotoxicity by which CPF alter brain development are still unclear. In addition, less attention was paid to the potential risk of subtoxic dose of OPs during postnatal period and their persistent consequences on fear learning in adults. In this study, adult Balb/C and C57 mice pretreated with CPF during early prenatal period were tested on cued fear conditioning and on active avoidance learning task. Our objectives were (1) to investigate if repeated subthreshold exposure to CPF disrupts the expression of acetylcholinesterase splice variants (AChE-S and AChE-R) on pup brains during the critical postnatal period and (2) to determine if early prenatal exposure to CPF can alter fear learning in adulthood.
Results: A sub-toxic dose of CPF (1 mg/kg) was administered on post-natal day (PND) 4-10 to Balb/C and C57 mice. No signs of toxicity and weight changes were shown. In addition, no significant effect was observed on AChE-R and AChE-S transcript expression in pup brains treated with CPF compared to controls. However, adult Balb/C mice pretreated with CPF failed to learn cue fear conditioning and had a significant lower rate of learning in the active avoidance task. In contrast, C57 mice pretreated with CPF showed facilitated conditioned fear learning and no effect was found in the active avoidance test.
Conclusion: Early exposure to CPF induces persistent long term effects on fear learning in adult mice, nonetheless, no clear relation was found to the expression of acetylcholinesterase mRNA following injection in the immature brain.
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Time scale adaptation for evidence integration in human vision

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Background and Methods: Recent research in decision-making has focused on the process of evidence-integration and its neural substrate. Converging evidence from experimental psychology and neuroscience has revealed that observers accumulate sensory evidence to a response criterion. The time scale of this process is reported to go from about half a second to few seconds. In most studies that examined the integration range, the evidence stream was stationary. In such conditions the optimal strategy is to integrate for as long as the stimulus is available. In this study we examined evidence-integration with visual non-stationary evidence, subject to temporal uncertainty. 6 observers

were presented with 2 circles of fluctuating brightness. During each 5 sec trial, the brightness fluctuates randomly around a baseline (noise), except for a specific interval (t<<5 sec) of signal, in which one of the spots is brighter, and detection is required. In such a situation integrating for the whole interval is un-optimal, leading to an excessive integration of noise and resulting in elevated False Positives. Optimally, the observers should adapt the evidence integration time to the time-scale of the signals. To probe for the ability to adapt the integration time-scale, we carried out two types of sessions: i)with a predominance of long signals (900 ms), and ii) of short-signals (150 ms).
Results: For all observers, hit rates increased monotonically as a function of signal-strength and signal-duration. Critically, all participants showed time-scale adaptation of temporal integration to the characteristic signal duration: better accuracy (lower thresholds) in long predominance compared to short predominance sessions, on long signals, and vice versa for short signals.
Conclusions: This study demonstrates that human observers can successfully detect signals under conditions of temporal uncertainty by integrating for a time interval that is adapted to the environmental contingencies.

Differential inhibition of a-synuclein oligomeric and fibrillar assembly in Parkinson disease model by cinnamon extract

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Background: The oligomeriztion of a-synuclein into ordered assemblies is associated with the symptoms of Parkinson's disease. Yet, it is still debatable whether oligomers are formed as part of a multistep process towards amyloid fibril formation or alternatively as "off-pathway" aggregates.
Methods: 100 mM a-synuclein was incubated with decreasing amount of cinnamon extract precipitation (CEppt). The fibril formation was measured using spectroscopy and microscopy and oligomers were detected using blot analysis. The secondary structure of the protein was analyzed using CD. Brains of the Drosophila we studied using immunostaining and confocal microscopy.
Results: Here we probed the inhibition pattern of oligomeric and fibrillar forms of a-synuclein, using a natural substance, CEppt which was previously shown to effectively inhibit aggregation of b-amyloid polypeptide. We demonstrated that CEppt has a differential inhibitory effect on the formation of soluble and insoluble aggregates of a-synuclein in vitro. This inhibition pattern revokes the possibility of redirection to "off-pathway" oligomers. When administering to Drosophila fly model expressing mutant A53T a-synuclein in the nervous system, a significant curative effect on the behavioral symptoms of the flies and on a-synuclein aggregation in their brain observed.
Conclusions: We conclude that CEppt affect the process of aggregation of a-synuclein without changing its secondary structure and suggest that increasing amounts of CEppt slow this process by stabilizing the soluble oligomeric phase. When administered to Drosophila fly model, CEppt appears to have a curative effect on the defective flies.
General significance: Our results indicate that CEppt can be a potential therapeutic agent for Parkinson's disease.

Mutation in TECPR2 reveals a role for autophagy in hereditary spastic paraparesis

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We studied five individuals from three Jewish Bukharian families with an apparently autosomal recessive form of hereditary spastic paraparesis, accompanied by severe intellectual disability, fluctuating central hypoventilation, gastroesophageal reflux disease, wake apnea, areflexia and unique dysmorphic features. Exome sequencing identified one homozygous variant shared among all affected individuals and absent in controls, a 1 bp frame shifting deletion in TECPR2 leading to a premature stop codon and predicting significant degradation of the protein. TECPR2 has been reported as a positive regulator of autophagy. We thus examined the autophagy-related fate of two key autophagic proteins, SQSTM1 (p62) and MAP1LC3B (LC3) in skin fibroblasts of an affected individual , as compared to healthy control, and found that both protein levels were decreased, with a more pronounced decrease in the lipidated form of LC3 (LC3II). siRNA knockdown of TECPR2 showed similar changes, consistent with aberrant autophagy. Our results are strengthened by the fact that autophagy dysfunction has been implicated in a number of other neurodegenerative diseases. The discovered TECPR2 mutation implicates autophagy, a central intracellular mechanism in spastic paraparesis.

Conveying the impact of the input from the RMTg onto the VTA on cocaine addiction

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The reward system is of crucial significance in our everyday life since it mediates important behaviors for survival. It is well known that the rewarding effect and the feeling of euphoria depend on dopamine levels. Since the ventral tegmental area (VTA) is the major source for dopamine in the reward system and because initiation of drug addiction was demonstrated to occur in the VTA, its regulation is of great importance. Recently, focus was shed on the RMTg- a midbrain structure that exerts GABAergic input onto the VTA. Neuronal excitation in the RMTg was observed concurrent with foot shock, leading to the speculation that this area is involved in the processing of negative rewards.
We hypothesize that a temporal coupling between an infusion of cocaine and RMTg stimulation will strengthen the GABAergic tone on the VTA, which in turn will interfere with regular synaptic plasticity processes that occur with drug reception and partly mediate the formation of addiction. Furthermore, in accordance RMTg's role in the signaling of negative reward we expect future avoidance from the drug. Studying Sprague-Dawley rats, we used optogenetic and behavioral tools to probe the effects of activation of the RMTg while the rats were injected with cocaine. Since the borders of the RMTg are vaguely defined, we injected a nonspecific channel rhodopsin-containing virus that infected a broad area that included the RMTg. Contrary with our expectations, the stimulation enhanced the preference to the place the rats received the drug in the conditioned-place preference (CPP) protocol. Moreover, in a CPP to the stimulus itself rats preferred the place where they received the stimulus. Our results indicate that midbrain posterior areas, including the RMTg, provide important input to the VTA and exert a role in the reward system. However, in order to certainly define the impact of RMTg activation on the rewarding effect of cocaine we will next use further methods for obtaining specificity.
Israel Science Foundation (ISF) and Bretller Center at the School of Pharmacy.

Neural activity extraction from blurred light sheet microscopy images

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Background: Significant enhancement of data acquisition rate in functional neuronal microscopy may be obtained by using parallel optical excitation methods, such as multifocal multiphoton microscopy (MMM), selective plane illumination microscopy (SPIM), and temporal focusing (TF). However, since these methods usually detect the fluorescence signal using a camera, they are sensitive to tissue scattering effects, which blur the images, reduce the spatial resolution, and eventually limit the maximal imaging depth. Therefore, an efficient method for de-scattering of the acquired data is needed.
Methods: Here we present a simple algorithmic approach for data extraction from blurred images acquired by a dual two-photon laser scanning-TF microscope, which offers additional information regarding the cells' geometrical location. The algorithm uses a forward model of scattering and light propagation to predict the blurred images acquired by the camera and a regularized inverse solution to reconstruct the underlying activity.
Results: forward model results for increasing scattering depths show a gradual degradation of the blurred images quality. Separation between adjacent cells becomes challenging from depth of 200 μm and prevents direct analysis of the cells activity patterns. Simulations show that the use of this algorithm allows extraction of activity patterns for depths of more than 700 μm inside brain-like tissues, even in cases of severe noise.
Conclusions: We have tackled the major challenge of applying parallel excitation methods inside scattering biological media that rely on detection by a CCD. The framework we have developed enables to expand this work to study different tissue characteristics, different optical parameters, different noise models, and different inverting and regularization techniques. In addition, the algorithm can be implemented for investigating large-scale networks in vivo.

Improving cell based therapy for Parkinson's disease

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Parkinson's disease is characterized by the progressive degeneration of midbrain dopamine neurons, resulting in motor dysfunction. While current therapies are limited, clinical trials have demonstrated that new dopamine neurones transplanted directly into the brain can structurally and functionally compensate for those lost in the disease. While providing proof-of-principle, these trials have also shown extensive variability amongst patients and exposed a number of caveats in the technology including limited tissue availability, poor cell survival and insufficient reinnervation of target tissues. These hurdles highlight the need for further research, and provide the foundation for our research. Our focus is on optimising donor material, improving graft survival and promoting integration of transplanted dopamine neurons.
In order to tackle these problems we rely heavily on knowledge of developmental biology. How are dopamine neurones normally born in the developing foetus and what regulates the growth and guidance of their axons to appropriate targets? Understanding these processes and exploiting them in a stem cell transplantation context could significantly improve this technology. We are additionally exploring the potential for bioengineered scaffolds to promote neural repair. Our research addresses a number of these issues and adopts diverse approaches to improve and advance the field of cell transplantation.

The fate of aversive emotional memories

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I will discuss two models that might explain post-traumatic behavior, and that rely on basic learning mechanisms. The first is failure of extinction, for which I will present behavioral and neural data that supports the idea that learning under uncertainty can lead to memories that are harder to extinguish, and that rely on synchrony between the primate amygdala and cingulate-cortex. The second is based on wider stimulus generalization, and I will present behavioral and neural data that shows wider generalization that is supported by the amygdala, for both secondary and primary reinforcers. This model is also validated on anxiety patients. These two models might suggest two complementing ways by which aversive memories are formed differently in the brain.

Get in touch: the role of oxytocin in social touch

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Social touch in humans and allogrooming in animals is an important part of everyday social interaction. In fact, several psychiatric disorders, among which are schizophrenia, social anxiety disorder and autism, are characterized by deficits in this particular behavior. Given the well known contribution of the neuropeptide oxytocin (OT) to social behavior, we examined its influence on social human touch. Using a within-subject crossover design, 30 male subjects performed a social touch task following the administration of placebo and OT one week apart. The task involved watching and rating the level of emotions expressed in photos presenting 2 men engaging in human grooming behavior (i.e hugging or touching hands in a friendly manner) vs. control photos that present 2 men engaging in conversation. The results showed that the participants spent more time gazing at photos presenting touch than at the control photos, following the administration of OT as compared to placebo. However, the emotional ratings of the pictures did not differ in the OT as compared to the placebo condition. Given that longer watching periods have been associated with increased reward, the current results may indicate that OT increased the rewarding effect of watching human social touch. It is suggested that the OT system may modulate human interest in social touch which is required for the formation and maintenance of social bonding.

Structural determinants of TDP-43 amyloidogenesis in ALS and its inhibition by small molecules

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Inclusion bodies of a novel protein, termed TAR DNA-binding protein (TDP-43), were recently shown to be a hallmark of neurons in most (95 %) patients of Amyotrophic lateral sclerosis (ALS). Moreover, TDP-43 pathology appears to be a contributing factor in FTLD-U and a secondary feature in additional neurodegenerative diseases including AD and PD. In these deposits TDP-43 is relatively insoluble, hyperphosphorylated and ubiquitinated. Since deletion of the TDP-43 encoding gene in mice, or of its Drosophila homolog, does not result in ALS-like deposits, it appears that a 'gain-of-function' mechanism rather than loss of its normal function is a very likely mechanism of pathogenesis in these TDP-43-associated diseases. The apparent similarity between TDP-43 aggregation and toxic amyloid depositions suggests that the molecular mechanism of formation of TDP-43 aggregates may be similar to the better characterized mechanism of amyloid formation by proteins such as Aβ and α-synuclein. We are in the process of identifying the minimal domain and specific residues necessary for the self assembly of TDP-43 into toxic amyloids. In preliminary experiments using various biophysical techniques, we found few nested peptides (~15 aa long) from TDP-43 that have amyloidogenic characteristics. Interestingly they harbor aromatic residues. We have previously shown that such amino acids are crucial for amyloid self assembly. We also test if available amyloid-inhibitors can inhibit TDP-43 aggregation and can serve as potential therapeutics for ALS. We began using NQTrp, a small novel molecule we have developed that is highly efficient in interfering with aggregation of Aβ and other amyloidogenic peptides both in vitro and in animal models. We fed transgenic flies expressing TDP-43 in their eyes with NQTrp. This resulted in significant amelioration of the neurodegenerative eye defects. This work should shed light on the mechanism of TDP-43 role in ALS and yield new candidate drugs.

Membrane-to-cytosol translocation of activated AKT kinase disrupts expression of Long-Term Potentiation

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Background: Serine/threonine kinase AKT/PKB plays a fundamental role in a wide variety of cellular functions, including protein synthesis, regulation of cell survival, metabolism and proliferation. In neuronal cells, AKT has been shown to be involved in neuronal cell development, axonal growth

and synaptic plasticity. Recently, a further downstream mechanism of AKT involvement in long-term depression (LTD) prevention and late phase long-term potentiation (LTP) has been revealed. Moreover, AKT is also known to be involved in early phase LTP; however no solid knowledge has been accumulated regarding the downstream effectors mediating AKT's effects on LTP. Here, we present our preliminary findings describing a mechanism of AKT's effect on LTP.

Results: Using different regimes for application of the AKT inhibitor A6730 (30 min drug exposure before high frequency stimulation (HFS), drug for 30 min before and 20 min after HFS, drug for 20 min 30 min after HFS), to acute hippocampal slices trained with the HFS paradigm, we observed that AKT regulates LTP expression without affecting its induction and maintenance. The effects of AKT inhibition was similar to that of PI3K inhibitors (worthmannin and LY294002). Further, we delivered an AKT activator in order to combine with inhibitors of various signaling pathways to prevent AKT - induced effect on LTP and to characterize a potential downstream mechanism of LTP regulation. Unexpectedly, SC79 (a novel activator of AKT), which also prevents AKT translocation to the plasma membrane, induced a significant decrease in basal synaptic activity and in expression of LTP.

Conclusions: We consider that translocation of AKT towards the plasma membrane is necessary for regulation of synaptic activity and LTP. Moreover, AKT related LTP expression is not dependent on downstream cytosolic factors, but is mediated via direct effects of AKT on post-synaptic density components and glutamate receptors.

Local brain activity in the retrosplenial region probes our own prior experience

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Background: A neural trace of our recent experiences is necessary for the sense of reality and continuity in our life. There is an ongoing debate whether the neural marking of prior experience is mediated by action perception or cognitive-memory systems. The current fMRI study aims to identify the neural trace of recently performed actions.

Prior to scanning, 26 subjects performed one of two short action sequences, both in a context of stealing an object from a room. Then in the scanner subjects passively viewed 36 short video clips, each describing one of the two action sequences, shown from a self-perspective point of view.

Results: To enhance sensitivity for repeated clip presentations we analyzed data from the initial 15 % of the experiments (1:36 min). A novel multivariate machine learning analysis was applied to classify which action sequence each subject performed prior to entering the scanner, based on the differential response to the two types of videos. This analysis achieved high cross validation accuracy (92 %), signifying a cluster in the Retrosplenial Region, as the most informative area for classification.

Conclusion: We show that it is possible to probe differences related to recently performed actions by using the proposed multivariate approach. This data driven analysis marked a relatively small cluster in the Retrosplenial Region as most indicative of the prior experience of the subject. The Retrosplenial Cortex has been shown to be consistently active during the recall of autobiographic episodic memories (especially recent ones), thus supporting the memory assumption regarding the neural mechanism that underlies our sense of self-experience recognition and the maintenance of the "autobiographical self".

An odor-dispensing device for the treatment of sleep apnea

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Obstructive sleep apnea (OSA) is a prevalent sleep disorder characterized by repetitive cessation or decreased amplitude of breathing lasting 10s or more. Clinical consequences cover a wide spectrum of cardiovascular, neurocognitive, and metabolic dysfunction. Current standard of care is continuous positive airway pressure (CPAP), which is effective butfsd characterized by low compliance due to encumbrance. Studies of olfactory processing during sleep suggest that pure olfactory and mildly trigeminal odorants do not arouse or wake, but nevertheless induce a sniff response. With this in mind we set out to test the hypothesis that odors can be used to "jump start" respiration during OSA without waking. We developed a computer-controlled touch-screen-interfaced home device that delivers pulses of odorants at either fixed intervals, or in response to apnea. Using an array of sensors, the device monitors and records nasal and oral respiration, heart rate, O2 saturation, and snoring. Overall activity is monitored by wrist-worn actigraph. The device obtains daily subjective measures of sleep quality through an interactive touch-screen, as well as an objective measure derived from a reaction time test. The device is placed in the participant's home for 2 weeks, recording data for 3 consecutive nights in each week, one week with odors and one week without (counter-balanced, participants uninformed to order). We used 5 odorants, which were delivered in pulses

of 15 s, both in a random order once every 13 minutes, and automatically in response to an apnea. We have studied 8 individuals of various OSA severity. Odor significantly improved reaction time during morning-after tests. Odor reduced apneic events and improved O2 saturation levels in some of the subjects. Sleep quality and activity reports suggested odors did not reduce number of wakes. Current effort is focused on improving the device, as well as replacing some of the odors for the sake of continued experimentation.
This work was supported by a grant from Johnson & Johnson

Avoiding a 'close talker': an EEG/ERP study of preferred interpersonal distance (part of a symposium on social behavior)

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Background: Despite the vast knowledge, both behavioral and neural, of the mechanisms defining space around a singular body, little is known about the neural mechanisms that encode space between bodies. Yet, the space between people creates and defines the social dynamics of our interactions with others. Although different between cultures, within each culture interpersonal distance is implicit but clearly felt, especially if one stands nearer or further than expected. To assess the neural dynamic of interpersonal distance preferences we used a revised version of the Comfortable Interpersonal Distance paradigm, in which participants imagine either a friend or stranger approaching (visualized on a computer screen) and are asked to stop the figure when feeling uncomfortable. Behavioral findings in 100 students indicated that preferred interpersonal distance is correlated with both measures of empathy and of social anxiety. We then used the same paradigm to explore how interpersonal distance modulates EEG suppression over sensory-motor cortex in the mu/alpha range. Analyzing the ERPs elicited by the same stimuli, we investigated how early in the perception time-course these factors affect perception.
Results: Mu suppression, a suggested marker of mirror neurons activity, was modulated by the type of figure approaching (friend or stranger). ERP differences between conditions were evident as early as about 300 ms, as demonstrated by a modulation of P3 by the same experimental factors.
Conclusions: Individual differences affect how comfortable we feel when being approached by a friend or stranger. These differences are determined early in perception, and modulate brain regions which have been shown to be engaged in understanding other people's actions and intentions. Future studies are planned to look at similar paradigms with individuals with difficulties in determining appropriate interpersonal distance, such as individuals with Asperger's syndrome.

Forgetting what was where: behavioral, neuropsychological and neuroimaging investigations

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An influential view of working memory (WM) proposes that objects are maintained in visual WM as an integrated unit. Therefore, when objects are forgotten they are lost as a whole, in their entirety. Here we investigate this claim by examining how object identity, location and - crucially - object-location associations are differentially susceptible to forgetting in healthy people, in patients with focal lesions of the medial temporal lobe (MTL) and in individuals with familial Alzheimer's disease. Our studies in healthy individuals demonstrate that when objects are rapidly forgotten they do not disappear completely from memory, but rather it is the links between identity and location that become vulnerable over time. When multiple items reside in memory for a few seconds, patients with focal MTL lesions were just as likely as controls to identify a previously presented item. However, contrary to some prevailing accounts of MTL function, they were significantly worse at localizing objects to their remembered locations. Crucially, this impairment was specifically associated with a systematic bias to misreport an object as having previously occupied the location of another object in memory. Our findings suggest that when objects are forgotten they do not vanish from memory but rather the links to their locations are gradually severed. Furthermore, MTL does not participate in retaining the identity of objects, but it is necessary for binding object identities to their correct locations. These results, supported with parallel fMRI findings, provide important evidence for the view that the MTL is not strictly involved in long-term declarative memory but also over far briefer retention intervals in binding object location-identity information. Assessing misbinding of object location and identity provides an important new way to diagnose individuals at risk of developing familial Alzheimer, tracking their progress and monitoring response to treatment.
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Functional and spatial correlation structure in the primary visual cortex of monkey

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Theoretical studies have shown that correlations in the trial to trial fluctuations of the neural responses to external stimuli may limit the information content that can be extracted from the neural responses. Here we use simultaneous recordings of large neural populations in the primary visual cortex of monkey to study these correlations and investigate their effect on the ability of the population response to reliably encode the orientation visual stimuli.

We find that most cell pairs show significant correlations. Analysis of the spectrum of the correlation matrix reveals a non-trivial correlation structure. However, analyzing the accuracy of the population vector and optimal linear readout we find that the considerable noise correlations do not limit their accuracy, in contrast to the theoretical prediction. Further analysis of the underlying structure of the correlations reveals that this non-trivial structure is spatial (i.e., structure that respects the physical position of the neurons) rather than functional (i.e., structure that respects the stimulus features which the neuron is most sensitive for).

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Epigenetic inheritance of a cocaine resistance phenotype

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A rat model was developed in order to delineate a heritable phenotype resulting from the self-administration of cocaine. Delayed acquisition and reduced maintenance of cocaine self-administration was observed in male, but not female, offspring of sires that self-administered cocaine. Previous work indicated that increased brain derived neurotrophic factor (BDNF) in the medial prefrontal cortex (mPFC) blunted the behavioral effects of cocaine. The current results showed enhanced mPFC BDNF mRNA and protein as well as increased association of acetylated histone H3 with BDNF promoters only in the male offspring of cocaine-experienced sires. Administration of a BDNF receptor antagonist (i.e. the TrkB receptor antagonist ANA-12) reversed the diminished self-administration of cocaine in male cocaine-sired rats, which suggests that enhanced BDNF expression in the mPFC reduced cocaine reinforcement in the male offspring of cocaine-experienced sires. In addition, the association of acetylated histone H3 with BDNF promoters was increased in the sperm of sires that self-administered cocaine. Collectively, these findings indicate that voluntary paternal ingestion of cocaine results in epigenetic reprograming of the germline resulting in profound effects on mPFC gene expression and resistance to cocaine reinforcement in male offspring.

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Reciprocal interactions between perceptual learning and adaptation in texture discrimination

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Background: Perceptual learning and adaptation are two instances of perceptual plasticity in the visual system. Although the two phenomena are intermixed during the learning process, the dynamics of the reciprocal interactions between them is unclear. Intensive training on a texture discrimination task (TDT) leads to performance deterioration which has been suggested to result from stimulus adaptation. This study explicitly examines adaptation in TDT by measuring (1) behavioral tilt aftereffects (TAE) and (2) Electroencephalographic (EEG) adaptation effects.

Results: (1) Intensive training in TDT with a target composed of three bars tilted 20° clockwise from the vertical axis caused a repulsive TAE, in which a near-vertical test bar appeared to be tilted counterclockwise. The TAE was much stronger at the trained location. (2) Analyzing EEG signals recorded during training revealed significant differences in amplitudes of early-vision event related potentials (ERP) components between the early and later phases of within session training. The amplitude of occipital N1 decreased in later training compared to early training, while the amplitude of posterior P2 increased. The rapid adaptive changes in the amplitudes of the early ERP components were significantly correlated with the psychophysical discrimination thresholds in the TDT task. Thus, more adaptation resulted in higher discrimination thresholds. Training the next day resulted in reduced adaptive changes in early ERP components.

Conclusions: Reciprocal interactions between perceptual learning and adaptation exist in TDT. While adaptation deteriorates performance in TDT, sleep dependent consolidation of perceptual learning seems to reduce adaptation effects.

Dominant and submissive mice respond differentially to distinct psychotropic agents

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Dominance and submissiveness are functional elements situated at opposite poles of the behavioral spectrum which are important to the establishment of social hierarchy and to the development of social interactions. Research in humans and animals suggests that extreme expressions of dominance and submissiveness may be involved in the etiology of behavioral disturbances. We previously demonstrated the inheritability of these traits by selective breeding based upon

the dominant-submissive relationships (DSR) food competition paradigm. Continued multigenerational selection yielded populations of mice with strong and stable features of dominance and submissiveness.
We found that these animals react differentially to stressogenic factors, antidepressants and mood stabilizing agents. The anxiolytic compound diazepam (1.5 mg/kg, i.p.) reduced anxiety-like behavior of submissive animals, but showed paradoxical, anxiogenic effects among dominant animals. In the Forced Swim test, the antidepressant paroxetine (1, 3 and 10 mg/kg, i.p.) markedly reduced immobility of submissive animals, demonstrating antidepressant-like effect. In contrast, when administered to dominant animals, paroxetine caused maladaptive, frenetic activity. The mood stabilizer lithium (0.4 %, p.o.) selectively influenced dominant mice, without affecting the behavior of submissive animals. In summary, we describe here two distinct animal populations possessing strong dominant and submissive phenotypes. We suggest that these animals hold potential as tools for studying the molecular basis and pharmacogenetics of dominant and submissive behavior.

Low intensity ultrasound can affect neurons through nanoscopic membrane vibrations

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Background: It is known that low intensity ultrasound (LIUS) can generate action potentials in excitable tissues, yet, to the best of our knowledge until now no rigorous explanation was given for this phenomenon. Hereby, we present a novel biophysical- biomechanical model for action potential generation by LIUS in a nerve cell membrane, based on the modified Hodgkin and Huxley (H&H) model of rat neural cortical cell. The model incorporates the dynamics of the intra-membrane cavitation (see the recent bilayer sonophore (BLS) model), with the bio-electric equations of the ions transports through different trans-membrane voltage gated channels (VGC). As the two leaflets' distance varies with the ultrasound pressure they mainly affect directly the membrane potential through changes in membrane capacitance; they also have a much weaker influence on the electric response of the membrane through modulation of the rate constants of each type of the VGC, that happen to be also sensitive to mechanical tension. **Results**: Model simulations show that action potential induction in neural cells by LIUS is mainly the result of Cl-ion flux out of the cell; and that the probability to induce action potential increases with pressure amplitude and pulse duration and decreases with frequency. Interestingly, the already known phenomenon of Compound action potentials (CAP) suppression by Ultrasound (US) at the peripheral myelinated axons can also be explained by incorporating this model with the cable theory equations.
Conclusions: The model provides a systematic means to investigate different manipulation modes of LIUS on excitable tissues, for many future therapeutic applications, using a noninvasive and targeted technology.
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Learning to avoid saccadic suppression

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Background: Humans naturally scan the visual scene by making fast, ballistic eye movements at about three times per sec. These saccades could potentially result in a smeared and jerky image of the world, but visual perception is clearly immune to such effects. One suggestion is that this perceptual constancy is accomplished by saccadic suppression: a sharp drop in visual sensitivity during a saccade. Saccadic suppression has repeatedly been demonstrated, but the neural mechanisms underlying it are less clear (e.g. at what level in the visual pathways does suppression occur). Specifically, it is unknown if saccadic suppression can be gated by higher level mechanisms such as selective attention.
Methods: Subjects performed a visual discrimination task while their eye movements were being recorded. Using a gaze-contingent paradigm, a visual stimulus (elliptic contour) was briefly presented during the execution of a horizontal saccade. In each trial, upon saccade completion, subjects reported the orientation of the ellipse (horizontal vs. vertical). Specificity to the location of the stimulus and the direction of the saccade were assessed by testing the degree of learning transfer to novel untrained conditions. **Results**: Performance was measured by the slope of the psychometric function (the percent of vertical choices as a function of the ellipse axes aspect-ratio). Preliminary results suggest that subjects improve considerably in this peri-saccadic discrimination task.
Conclusion: Perceptual learning is possible even when stimuli are presented only during a saccade. Thus, peri-saccadic visual information can be processed at will. This suggests that at least some of the behavioral suppression is caused by high-level cortical mechanisms. Further research and analysis would help us to better understand the nature of peri-saccadic learning and the mechanisms that allow it.

Compromised neuro-vascular coupling under blood-brain barrier dysfunction: a role in the pathogenesis of brain diseases?

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The brain uses more energy than any other organ of the body and relies almost exclusively on delivery of oxygen (O_2) and glucose through the vascular system. A regional increase in the metabolic demands of active neurons is supported by elevated blood flow, a phenomenon termed neuro-vascular coupling (NVC) or functional hyperemia. The blood-brain barrier (BBB) is the regulated interface between the peripheral circulation and the central nervous system (CNS). It's composed of endothelial cells which connected by tight junctions, and together with astrocytes, pericytes, neurons and the extracellular matrix, constitute the "neurovascular unit" that is essential for proper function of the CNS. Recent recordings in patients with sub-arachnoid hemorrhage demonstrated high incidence of BBB dysfunction together with impaired vascular response during neuronal activation. We thus hypothesized that BBB dysfunction predispose the brain to disturbed neuro-vascular coupling which may further contribute to cellular damage. BBB dysfunction was introduced with either photothrombosis or with exposure of the cortex to artificial "serum like" electrolytic solution containing physiological concentration of albumin, the most common blood protein. Neuro-vascular coupling was tested by imaging vessels diameter changes in the open-window method while corticographic recording of seizures-induced using 4-aminopyridine (4-AP). BBB integrity was estimated using angiography as previously reported. Our results show a pronounced and reversible dilation of cortical vessels during seizures in the healthy brain. In contrast, in the BBB dysfunctional brain (or in the brain exposed to artificial serum), vascular response to neuronal activation was significantly impaired, emphasizing the importance of intact BBB in the normal neuro-vascular coupling.

Beneficial effect of antibodies against beta secretase cleavage site of APP on Alzheimer's like pathology in triple-transgenic mice

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Background: Alzheimer's disease (AD) is characterized by the accumulation of senile plaques in the brain extracellular space and by intraneuronal accumulation of neurofibrillary tangles. Both active and passive immunization studies have shown that antibodies against amyloid-β peptides (AβPs) are effective in decreasing cerebral AβP levels, beta-amyloid (Aβ) accumulation, inflammatory adverse effects and attenuating cognitive deficits in animal models of AD.

Our lab previously described a novel approach to inhibit AβP production via antibodies against the β-secretase (BACE 1) cleavage site on the APP. These antibodies (BBS1) were found to block the β-secretase site on APP, interfere with APP-BACE interaction, exploiting their presence at the cell surface prior to their internalization to the early endosomes where BACE1 cleaves APP.

Results: Here, we investigate the effect of BBS1 on Aβ aggregation and on tau phosphorylation in triple transgenic mice model of AD (3× Tg-AD). The 3× Tg-AD mice harboring consequently, the concomitant manifestation of PS1M146V, APPSwe, and tauP301L transgenes were assigned into 2 groups. One group was immunized with the monoclonal antibody BBS1 and the second group was immunized with same dose of OK1, a non relevant antibody. For the immunization we used mini osmotic pumps adjusted intracerebroventricular (i.c.v) of right hemisphere, and pumping its content for one month. The experimental data demonstrated behavior improvement of treated mice, reduction in tau phosphorylation explained by significant reduction in GSK3β which phosphorylates tau, as well as significant decrease in plaques burden and reduced inflammation.

Conclusions: This data, showing that tau pathology was significantly reduced by BBS1 antibodies suggest a close interaction between tau and Aβ in the development of AD, and may serve as an efficient novel immunotherapy against both hallmarks of the disease.

The monoclonal antibody BBS1 is under a patent application licensed to NasVax. Ltd, Israel

Targeted delivery of membrane-impermeable cytotoxic compounds via TRP channels into specific cells

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We have previously demonstrated that the pore of the transient receptor potential channels, TRPV1 and TRPA1, is large enough to pass QX-314, a permanently charged derivative of lidocaine into neurons. Thus, activation of TRPV1 and TRPA1 channels applied with QX-314, allows selective entry of QX-314 into pain sensing neurons, producing inhibition of excitability while sparing non-painful sensory and motor neurons. Using this platform we were able to affect

other sensory modalities such as itch in which we demonstrated specific inhibition of activity of itch sensing neurons. Since TRP channels are expressed differentially among various types of cells, we are able to utilize this cell specific "machinery" and extend the platform not only to selectively silence specific neuronal populations but also to affect intracellular metabolic pathways. Here we present a proof of concept of this novel platform, by targeting charged chemotherapy agent, Adriamycin, into cancer cell-lines expressing large pore cation-non selective TRP channels. We demonstrated that mouse hepatocellular carcinoma cells (BNL1ME cell line) express functional TRPV2 channels. Activation of these channels by 2-Aminoethoxydiphenyl borate (2-APB) applied together with Adriamycin leads to selective entry of this charged chemotherapeutic agent into BNL1ME cells, facilitating Adriamycin-induced cell death.
This method for selective facilitated delivery of chemotherapeutic agents is expected to reduce their toxicity by decreasing concentrations, limiting side effects and ultimately leading to a better clinical readout. Moreover, these results enable implementation of this strategy on neuronal populations not only for killing specific cells but also for modulation of a pathway, in basic research and in neuronal based pathologies.
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Single-trial decoding of intention from EEG
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Brain Computer Interface applications require single-trial decoding of brain activity. Electroencephalography (EEG) holds promise for such applications, since it is non-invasive and has high temporal resolution. However, due to low signal-to-noise ratio, classification of intentions on single-trial EEG with high accuracy has been a challenge. In this work we consider a task, where the subjects had to press a right (left) hand button rapidly and accurately in response to a right (left) arrow cue. Our goal was to examine if single-trial data from this experiment contained sufficient information to infer the type of intended movement. If so, could we design a classifier that would work well across different subjects? Does the EEG *dynamics* provide important information for this task? We have studied a classifier based on Fisher Linear Discriminant (FLD) applied to the pooled EEG data from all subjects. Our first finding is that the performance of FLD classifier that takes as input a single time-point EEG activity vector is relatively poor with classification error of 30 % at the optimal time. Next, we have constructed a classifier that uses the time course of the EEG traces. In addition, we performed dimensionality reduction on the electrode array by using only the top 15-20 most informative electrodes. This method yielded a classification success rate of 87 %, ranging from 80 % performance in 'poor' subjects to 95 % for the 'best' subject. For the task studied here, we show that single-trial EEG data contains sufficient information to perform an accurate binary classification of intended movement. Interestingly, it was not necessary to build a separate classifier for each subject. On the other hand, information about the EEG dynamics was crucial for good performance. These results may bear important implications for Brain-Computer Interface applications, as well as for understanding the nature of the EEG signaling of movement preparation.

Effector and regulatory T cells play distinct but beneficial roles in recovery from central nervous system trauma
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Background: Spinal cord injury (SCI) results in immune activation and immune cell entry into the injured tissue. While macrophages are major players during wound healing of the injured CNS, the role of T cells is still debatable. Studies have found that autoreactive T lymphocytes impair recovery of locomotor function and contribute to tissue injury. On the other hand, CNS-specific autoimmune T cells were shown to promote neuronal survival and functional recovery from acute and chronic neurodegenerative conditions. Part of the controversy draws from a general overview of the T cell response, disregarding the specific subsets of T cells, the dynamics of the healing response and the location. In our work, we dissected the CD4+ T cell response in order to understand this intricate network of events.
Results: Here, we demonstrated that recovery from SCI is dependent on the fine-tuned crosstalk between T cells and macrophages. In particular, we found that both effector and regulatory T (Treg) cells have important roles in the recovery process. Mice deficient in Th1 cells showed impaired recovery, which was correlated with a reduced recruitment of M2 macrophages at the injured site. Consequently, we found that an impaired M2 response led to deficiency in Treg cells, involved in the later phase of remyelination.
Conclusions: The results described here demonstrate the intricate interactions between the innate and the adaptive immune system, following spinal cord injury. The optimized action of this network was found to work at two levels; first, by controlling the local inflammation and thus decreasing the secondary degeneration, and second, by promoting the critical step of white matter remyelination, thereby reducing the functional deficit in the CNS and promoting

regeneration. This physiological response can be fine-tuned to improve recovery, as a therapeutic approach for CNS trauma.

Attention shifts the location of fixation toward attended stimuli in a

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Background: The "Posner Cueing Task" is a task often used to estimate spatial attention effects. During the task subjects view two stimuli (boxes, letters, etc.) and are cued by an arrow to attend to one of the stimuli, while fixating on a central cue, and respond to target stimuli. Traditionally, any difference between subjects' behavioral or neuronal response to a given stimulus when it is attended versus when it is unattended, is interpreted as an attentional effect. This is based on the assumption that the stimulus had an equal low-order impact on the visual system in both conditions. Our work examined this assumption.
Results: Subjects performed a Posner Cueing Task while having their eye movements monitored. The results showed a significant bias of subjects' fixation toward the attended location, so that attended stimuli fell closer to the fovea then unattended stimuli.
Conclusions: Given that the visual system is characterized by a computational gain to central stimuli, our results suggest that effects of cueing may result in part from a fixational bias leading to greater proximity of attended stimuli to the center of the retina, rather than a top-down "endogenous" attentional benefit.

Effects of isoflurane on sensory integration of different synaptic pathways in auditory cortex

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Background: Sensory awareness involves comparison of cortically-generated predictions with incoming sensory information. An example of this in core auditory cortex (A1) is modulation of auditory responses by input from extrastriate visual cortex. Evidence suggests that upon anesthetic-induced loss of consciousness, ascending sensory pathways are relatively unaffected, but descending pathways are disrupted, leading to a failure of the prediction process. We investigated the laminar profile of synaptic activity in A1 to determine the effect of isoflurane (ISO) on visual versus auditory evoked local field potentials (LFP) in rats chronically implanted with electrode arrays in A1, and in thalamo-cortical (TC) mouse A1 brain slices. Current source density (CSD) of the columnar response was estimated and analyzed for changes in profile and magnitude.
Results: Auditory stimuli *in vivo* elicited early current sinks in middle layers that spread to supragranular (SG) and infragranular (IG) layers. Visual stimuli elicited longer latency sinks in IG layers followed by sinks in SG layers. ISO dose-dependently decreased the responses, with a greater effect on visual (V) versus auditory (A) responses [0.4 %: V-71 %, A-15 %; 0.8 %: V-96 %, A-20 %; 1.6 %: V-114 %, A-42 %]. In slices, TC afferents stimuli elicited an early sink in middle layers, whereas cortico-cortical (CC) stimuli elicited early superficial sinks. ISO suppressed TC and CC responses to a similar extent [0.25MAC: TC-94 %, CC-108 %; 0.5MAC: TC-52 %, CC-81 %; 1MAC: TC-60 %, CC-66 %]. High and intermediate ISO levels decreased paired pulse depression (PPD) following TC stimulation but increased PPD following CC stimulation.
Conclusions: ISO decreased TC responses *in vitro* and auditory responses *in vivo* similarly. The greater suppression by ISO of visual responses in A1 versus CC responses *in vitro* suggests additional cortical mechanisms of anesthetic disruption of multimodal processing, such as the visual cortical responses.
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Behavioral and neural correlates of emotional Intelligence: an event-related potentials (ERP) study

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Background: The present study aimed to identify potential behavioral and neural correlates of Emotional Intelligence (EI) by using scalp-recorded Event-Related Potentials (ERPs). We identified ERP correlates of emotional processing by comparing ERPs elicited in trials using pleasant, neutral and unpleasant pictures. These emotional picture effects were then compared across groups with low and high EI levels.
Results: Behavioral results revealed a significant valence×EI group interaction effect since valence ratings were lower for unpleasant pictures and higher for pleasant pictures in the high compared with the low EI group. The groups did not differ with respect to neutral picture ratings. The ERP results indicated that high EI participants exhibited significantly greater mean amplitudes of the early attentive P2 (195–285 ms post-

stimulus) ERP component in response to emotional and neutral pictures, at posterior-parietal as well as at frontal scalp locations.

Conclusions: The present study is the first to demonstrate ERP correlates of EI in response to visual emotional stimuli. It also underscores the usefulness of the ERP methodology as a sensitive measure for the study of emotional processing in the research field of emotional intelligence.

Coupling sound to movement – design and assessment of learned auditory-proprioceptive integration

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Background: Sensory integration plays an important role in the perceiving our own body. Proprioceptive knowledge regarding, e.g., the movement of one's own arm, arises from distinct sources that are combined together - somatic information originated in sense receptors within body tissues, and visual information that comes from viewing the arm. Not much research has been done on auditory-proprioceptive integration, despite the clear relation of sound to body movement. In this study we hypothesize that auditory information can be integrated into proprioception by means of an artificially designed system. Our objective is to investigate sound-body perceptual interaction and suggest possible application for physical therapy. In the experiments presented, sound is synthesized in real-time according to movement parameters captured by a sensor attached to the arm. Specifically, we couple the dimensions of arm elevation and auditory pitch.

Results: We operationalize our hypothesis using a motor task, in which subjects lift their arms towards a target point. Continuous sonification of arm elevation angle is present, or not (control condition), during movement trajectory. First, we show that after a short learning period with a fixed angle-to-pitch mapping, sonification improves accuracy in the motor task, compared to control. Second, we distort the learned mapping without informing participants. Mean hand positions are significantly affected by the mapping manipulation, while most subjects do not report awareness of it.

Conclusions: Auditory pitch can be integrated into body perception rapidly and efficiently. Distorting the learned movement-to-sound mapping results in a complex auditory-somatic competition. We propose that such distortions could be applied to amplify the range of movement in motor neuro-rehabilitation. We demonstrate how advanced interface technology can be used for the design of novel experimental scenarios and application in cognitive science.

Semantic influence on episodic encoding: evidence from fMRI repetition suppression

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It has long been acknowledged that congruency with semantic knowledge has a robust positive effect on episodic memory encoding. Although recent empirical work highlights possible brain systems involved in this process, the mechanisms underlying superior episodic encoding of semantically-congruent items remain largely unknown. In the current study, we attempt to examine one possible structural account of the effect: According to our hypothesis, items presented in a congruent context result in enhanced excitation in the semantic network (compared with items presented in an incongruent context), which subsequently leads to enhanced episodic encoding. To examine the first part of the semantic excitation proposal, we scanned participants using fMRI in a repetition suppression paradigm that was aimed at studying the amount of semantic-related suppression caused by congruent and incongruent items. Participants were presented with congruent (e.g., "Yellow Banana") or incongruent (e.g., "Blue Banana") noun-adjective pairs which were later followed by a presentation of the noun alone (e.g., "Banana"), while performing an incidental encoding task which did not require attending to the congruency status of the items. Initial results provide support for our hypothesis concerning the superior semantic status of congruent items: Congruent items elicited a stronger suppression of the concept ("Banana") than did incongruent items. These differences in levels of suppression were observed mainly in brain regions known to be involved in semantic processing, including left inferior frontal and left temporal regions. These results provide evidence that congruent and incongruent items result in differing amount of excitation of concepts in the semantic network. Additional studies currently conducted in our laboratory examine the relationship between the level of suppression of items presented in a congruent context and the successful episodic memory for these items.

Synaptic activity of the Abelson family of non-receptor tyrosine kinases

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Background: The Abelson family of non-receptor tyrosine kinases is best characterized in cancer, and also possesses important physiological roles in neural development as well as the regulation of synaptic structure and function, mediated via interaction with the F-actin cytoskeleton, signaling

adaptors, and scaffolding proteins. In the hippocampus, Abl kinases modulate neurotransmitter release, affect paired pulse facilitation/depression related short-term synaptic plasticity, co-localize with PSD-95 and regulate its clustering. In the prefrontal cortex, Arg, an isoform of Abl kinase family, orchestrates spine maturation and cocaine-induced plasticity. An important role of Abl kinases in Ab production and signaling has been also shown. Despite the accumulating evidence, not much is known about their direct involvement in the regulation of synaptic activity/plasticity processes. Hence, to investigate the role of Abl kinases in synaptic transmission, we recorded spontaneous miniature excitatory postsynaptic currents (mEPSCs) in the presence of TTX and PTX from primary hippocampal neurons after 14-16 days in culture.

Results: We found that acute treatment of cultured rat hippocampal neurons with STI571 (imatinib mesylate /Gleevec), a selective irreversible Abl kinase activity blocker, significantly increased mEPSC amplitudes comparing to control with no effect on interepisode intervals distribution of mEPSCs. Moreover, a new Abl kinase specific activator DPH produced an opposite effect from significant reduction to complete elimination of mEPSCs in a drug dose and exposure time dependence manner.

Conclusions: We suggest that Abl kinases may be involved in regulation of basal synaptic activity of excitatory neurotransmission in hippocampal neurons, having potential implications on the processes of learning and memory formation.

The role of microglia and signaling via their CX3C receptor-1 in hippocampal and olfactory bulb plasticity

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Background: Recent studies suggest that microglia are involved in hippocampal-related behavioral and neural plasticity and that the number of microglia is increased following exposure to environmental enrichment (EE). CX3CR1 is a receptor which in the brain is exclusively expressed by microglia, binds the neuronally-derived CX3CL chemokine, and mediates tonic inhibition exerted by neurons over microglial activation. To examine the role of microglia activation and CX3CR1 signaling in plasticity, we exposed heterozygous CX3CR1-GFP mice (CX3CR1+/-) and mice with homozygous expression of GFP in which the CX3CR1 gene is functionally deleted (CX3CR1-/-) to either EE or to odor enrichment (OE) and assessed memory, neurogenesis and microglia status in the hippocampus and olfactory bulb(OB).

Results: Non-enriched CX3CR1-/- mice displayed better hippocampal spatial memory and olfactory recognition than CX3CR1+/- controls. In CX3CR1+/- mice, EE improved spatial memory and neurogenesis and OE improved olfactory recognition and neurogenesis, however neither EE nor OE further improved memory functioning in CX3CR1-/- mice. Consistently with the behavioral findings, the number of microglia in the hippocampus of non-enriched CX3CR1-/- mice was greater than in CX3CR1+/- mice and their soma size was increased, suggesting mild activation status. Furthermore, following EE the number and soma size of hippocampal microglia in CX3CR1+/- was significantly increased, whereas no further microglial changes were found in the hippocampus of CX3CR1-/- mice. In contrast, the number and morphology of microglia in the OB of CX3CR1+/- OE-exposed mice was not different than controls.

Conclusions: These results imply that microglia activation status and microglial interactions with neurons via the CX3CR1 play an important role in memory and neurogenesis. Furthermore, the effects of EE on microglia and the possible role of these cells in enrichment-associated neurobehavioral functioning is region-specific.

Modulation of auditory cortex during action execution

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Background: The notion of a corollary discharge that is sent by the motor cortex to sensory regions prior to voluntary action has long been suggested to modulate neural activity in sensory cortices. Most physiological data demonstrate reduction but some suggest enhancement of activity in sensory cortex. The aim of the current study was to further examine the putative role of a corollary discharge in modulation of auditory cortex during keyboard playing.

Results: Healthy subjects (N=15) played short musical sequences on an MR compatible piano keyboard with either their right or left hand while auditory feedback was provided. Identical auditory feedback was subsequently replayed to the subjects during passive listening. The functional MRI signal in auditory cortex (superior temporal gyrus; STG) was enhanced during playing compared to passive listening of identical auditory sequences. Control experiments exclude habituation as a possible explanation for the reduced activity during listening. Importantly, enhancement was lateralized. The signal in left STG was stronger during playing with the right (contra-lateral) hand than during playing with the left (ipsi-lateral) hand. Symmetrically, the signal in right STG was stronger during playing with the left hand compared with playing with the right hand. Similar laterality effects were obtained when identical auditory feedback during left and right hand playing was

provided – excluding the possibility that the laterality effects are due to octave differences between the two hands during normal playing.

Conclusions: Our results show that a) performing an action enhances neural activity in the sensory cortices relevant to the perception of action consequences and b) this enhancement is lateralized. Taken together, these data support the notion of a corollary discharge from motor cortex enhancing activity more strongly in ipsilateral sensory cortex, suggesting a more low-level source of the corollary discharge.

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Wiring the brain for function

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The brain must be wired correctly in order to function. Brain wiring forms through a series of highly orchestrated molecular, cellular and activity-dependent events. Axonal connections between the two sides of the nervous system are known as commissural projections. The development of these connections is regulated by a number of different mechanisms including the formation of midline tissue called the commissural plate, the guidance of commissural axons by midline glial and neuronal populations, and the expression of specific axonal guidance molecules. There are three commissural projections in the forebrain of placental mammals; the corpus callosum, the hippocampal commissure and the anterior commissure, all of which function to integrate information between the two hemispheres. Recent data from our laboratory indicates that the correct patterning and formation of the commissural plate provides an essential substrate for commissure formation in the telencephalon. As commissural axons arrive at the midline they must navigate through an environment of both attractive and repulsive molecular axon guidance cues. These molecular cues are expressed by midline glial populations and are critical for commissure formation. As such, midline glia are associated with commissural projections throughout the nervous system of all bilaterally symmetrical animals and the molecules they express are highly conserved. A family of transcription factors called the Nuclear Factor One (Nfi) genes regulate the development of these glia and are thus indirectly crucial for commissure formation. After crossing the midline, callosal axons must find their target in the contralateral hemisphere, and both molecular and activity dependent cues are likely involved in their targeting. Overall, the formation of the corpus callosum provides an excellent model system for understanding how the brain becomes wired up during development.

Abnormal neuronal differentiation and mitochondrial dysfunction in hair follicle-derived induced pluripotent stem cells of schizophrenia patients

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Background: Schizophrenia is currently conceptualized as a neurodevelopmental disorder, involving dysfunction of dopaminergic and glutamatergic systems. Accumulating evidence suggests mitochondria as an additional pathological factor in schizophrenia. An attractive model to study neurodevelopmental related processes in schizophrenia is reprogramming of somatic cells into induced pluripotent stem cells (iPSC) and differentiating them into different neuronal lineages.

Results iPSC from 3 schizophrenia patients and from 2 controls were reprogrammed from hair follicle keratinocytes, due to their accessibility and common neuroectodermal origin with neurons. iPSC were differentiated into Pax6+/Nestin+ neural precursors and then further differentiated into b3-Tubulin+/TH+/DAT+ dopaminergic neural cells. In addition, iPSC were differentiated through embryonic bodies into β3-Tubulin+/TBR1+ glutamatergic neural cells. Schizophrenia-derived dopaminergic cells showed severely impaired ability to differentiate, whereas glutamatergic cells were unable to maturate. Mitochondrial respiration and its sensitivity to dopamine-induced inhibition were impaired in schizophrenia-derived keratinocytes and iPSC. Moreover, we observed dissipation of mitochondrial membrane potential (Δym) and perturbations in mitochondrial network structure and connectivity in dopaminergic and in glutamatergic neural cells and along the differentiation process.

Conclusions: Mitochondrial dysfunction in Schizophrenia was highly correlated with the extent of differentiation impairment in both neural lineages. Our data unravel perturbations in neural differentiation and mitochondria function, which are possibly interconnected and may be of relevance to early neurodevelopmental processes in schizophrenia.

NARSAD, Chief Scientist of the Israeli Ministry of Health

Chromatin remodeling – a novel strategy to control excessive alcohol drinking

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Background: Alteration in gene expression is a central feature underlying neuroadaptations that result from chronic

drug and alcohol use. One means of controlling gene expression is the remodeling of chromatin structure. Specifically, chromatin condensation and decondensation block or allow, respectively, the accessibility of gene promoters to the transcriptional machinery. **Results**: Here, we report that changing the level of chromatin condensation by affecting DNA methylation or histone acetylation limits excessive alcohol drinking and seeking behaviors in rodents. Specifically, we show that inhibiting the activity of DNA methyltransferase prevents excessive alcohol drinking. Similarly, we show that systemic treatment with several histone deacetylase (HDAC) inhibitors reduces binge-like alcohol drinking. We further report that systemic administration of the FDA-approved HDAC inhibitor, SAHA, inhibits the motivation of rats to seek alcohol. Importantly, the actions of the chromatin modifiers are specific for alcohol, as no changes in saccharin or sucrose intake were observed.
Conclusion: Together, our findings demonstrate that DNA methylation and histone acetylation control the level of excessive alcohol drinking and seeking behaviors in preclinical rodent models. Our study therefore highlights the possibility that HDAC and DNMT inhibitors can be used to treat alcohol abuse disorders. Finally, a molecular mechanism underlying epigenetic changes induced by alcohol exposure will also be described.
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Changes in frequency and duration of insight following exposure to unaware clues
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Background: Insight is a problem solving process, in which the solution happens suddenly after unique characteristic stages such as incubation and reconstuction that do not occur in incremental process. Insight involves unconscious thought processes. We suggest that unaware hints might have an effect on two parameters: 1.The length of time required to achieve a solution 2.The group frequency of achieving insight.
Results: Participants solved the "10 coin" puzzle. 17 subjects were exposed to an unaware visual hint. The hint was displayed in a sequence of three screens: 1. The initial setup of the puzzle (a triangle). Duration of exposure was for 1 second. 2.The hint screen: the 10-coin triangle with the 7 central coins painted gray, emphasizing the invariant factors in the puzzle, for 30 milliseconds. 3. A "noise" image (masking), for 250 milliseconds. The sequence was repeated three times in a row. Afterwards, the subject was asked to solve the puzzle. After solving, all subjects were tested and found to be unaware to the hint. In the control group, 16 subjects solved the puzzle without being exposed to the hint. The time unstill solution was measured for both groups. After solving, each subject was asked in which of the 2 manners he solved the puzzle: incremental or by insight. In the "hint" group the average time until insight was 1.41 minutes (sterr=0.23 min). In the control group (without a hint) the average time was 2.97 minutes (sterr=0.46), Results were significant, $p=0.0045$. 13 subjects reported an insight solution in the hint group and 4 reported an incremental solution. In the control group, 9 reported an incremental solution and 7 reported an insight solution ($p=0.0799$).
Conclusions: A "supportive" unaware hint might speed up insight processes and within a group might increase the probability to achieve insight. We suggest that the information inherent in the hint is integrated in the problem's representation and influence reconstuction.

Neuronal D-serine and glycine release through Asc-1 transporter regulates NMDAR-dependent synaptic activity
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Background: D-Serine and glycine are co-agonists of NMDA receptors (NMDAR), but their relative contributions for NMDAR-dependent processes are unclear. D-Serine was initially thought to originate from astrocytes, but recent studies show a preferential neuronal localization of the D-serine biosynthetic enzyme. We have shown that neuronal D-serine is released through alanine-serine-cysteine transporter-1 (Asc-1) but the physiological importance of this pathway was not evaluated.
Results: We now report that the Asc-1 mediates release of both D-serine and glycine from neurons, and this modulates NMDAR synaptic activity. Asc-1 antiporter activity is enhanced by D-isoleucine (D-ile), which releases D-serine and glycine from neurons but not astrocytes in primary neuronal cultures and hippocampal slices. We show that D-ile enhances the long-term potentiation (LTP) at hippocampal CA1 by stimulating Asc-1-mediated D-serine release. D-Ile effects on synaptic plasticity are abolished by enzymatically depleting D-serine or by employing serine racemase knockout (SR-KO) mice, confirming its specificity and supporting the notion that LTP depends mostly on D-serine release. On the other hand, our data also disclose a role of glycine in activating synaptic NMDARs. Although enzymatic depletion of D-serine also drastically decreases the isolated NMDAR synaptic potentials, these responses are still enhanced by D-ile. Furthermore, the NMDAR synaptic potentials are preserved in adult SR-KO mice and can be enhanced by D-ile as well, indicating that glycine overlaps with D-serine at synaptic NMDARs.

Conclusions: Altogether, our results disclose a novel role of Asc-1 in regulating NMDAR-dependent synaptic activity by mediating concurrent non-vesicular release of D-serine and glycine. Our data also highlight an important role of neuron-derived D-serine and glycine, and challenge recent models that suggest astrocytic D-serine as the sole responsible for activating synaptic NMDARs.

CaMKII is differentially regulated in striatum and cortex

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CaMKII is involved in ischemic/excitotoxic cell damage. Striatum is more sensitive than cortex to ischemia/excitotoxicity. Whether this is due to differences in perfusion or intrinsic factors is unknown. We investigated changes in CaMKII activation in striatum and cortex following MCA (middle cerebral artery) occlusion in vivo and excitotoxic stimulation of microslices in vitro. Phosphorylation changes in Thr286-αCaMKII, Thr253-αCaMKII, Ser831-GluA1 and Ser1303-GluN2B were measured by western blotting in: microslices of striatum and cortex from Sprague Dawley (SD) rats after stimulation with 100 μM AMPA, 100 μM NMDA + 50 mM glycine, or 2.5 mM glutamate + 50 mM glycine; and micropunch homogenates of striatum and cortex after varying periods of MCA occlusion and reperfusion. Autophosphorylation of Thr253-aCaMKII induced by in vivo ischemia occurred more rapidly, to higher stoichiometry, and lasted longer in striatum than in cortex whereas the changes in Thr286-αCaMKII autophosphorylation were equal between the regions. In vivo ischemia also induced more rapid, larger and longer lasting increases in phosphorylation of Ser831-GluA1 and Ser1303-GluN2B by CaMKII in striatum than in cortex. These phosphorylation changes were mimicked in vitro following excitotoxic stimulation of microslices. These results show that there are intrinsic differences between striatum and cortex in the regulation of CaMKII and implicate tissue differences in Thr253-αCaMKII phosphorylation in the differential sensitivities of striatum and cortex to ischemia/excitotoxicity.

Learning to recognize degraded objects is associated with a greater match to the objects' template patterns in lateral occipital cortex

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One feature of visual processing in the ventral stream is that cortical responses gradually depart from the physical aspects of the visual stimulus and become correlated with perceptual experience. Thus, the object-related lateral occipital complex (LOC) is typically more invariant to parameter changes (e.g. contrast, viewpoint, etc.) than early retinotopic areas. Here, we use a complementary approach to highlight changes in brain activity that result solely from a perceptual state shift. We focus on LOC and early visual cortex (EVC) and compare their fMRI responses to degraded object images, prior to, and following perceptual learning that renders initially unrecognized objects, identifiable. Using three complementary analyses, we find that in LOC, learned recognition is associated with a change in the multi-voxel response pattern to degraded object images, such that the response becomes significantly more correlated with the pattern evoked by the intact version of the same image. This provides further evidence that the coding in LOC reflects the Gestalt, perceptual level of representation of visual objects.
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Amalgamating positional and directional signals by hippocampal place cells

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Most theories of navigation rely on the concept of a mental map-and-compass. Hippocampal place cells are neurons thought to be important for the neural implementation of the mental map; these neurons fire when the animal traverses a specific location in the environment (the 'place field'). Head-direction cells are neurons found outside the hippocampus, whose activity encodes the animal's head orientation, hence implementing a neural compass. The prevailing view posits that head-direction cells do not encode the animal's position, while place cells do not encode the head-direction. However, little work has been done to date to investigate in detail the possible head-directional tuning of hippocampal place-cells. Here we addressed this by recording the activity of single neurons in the hippocampus of two evolutionarily distant bat species, the Egyptian fruit bat and the big brown bat, which crawled in 3 different arenas. We found that a large proportion of hippocampal neurons, in both bat species, showed a conjunctive tuning to the animal's position in space (place field) and to its head direction. The head-direction tuning was significant even after controlling for the behavioral coupling between position and head-direction. Surprisingly, some hippocampal neurons preserved their head directional tuning outside of the neuron's place field – suggesting that the 'spontaneous' spikes outside of the place-field are not noise, but in fact carry head-direction information. These findings suggest that hippocampal neurons can provide the brain's navigational system with both map information and compass information, and are therefore ideally suited to serve as the hub of spatial representation in the brain.

Specific cognitive and anatomical alterations in post-traumatic patients highlight the importance of intra-hemispheric connectivity for associative memory

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Background: Memory deficits are a common complaint reported by patients with post-traumatic stress disorder (PTSD). Despite their vivid trauma-related memory, studies confirmed memory impairment for non-trauma related stimuli when compared to controls; specifically in associative memory (Guez et al., 2011). Studies in healthy individuals showed hemispheric memory asymmetry with left prefrontal lateralization of encoding and right prefrontal lateralization of episodic retrieval, suggesting a role for inter-hemispheric communication in memory-related tasks (Gazzaniga, 2000; Ringo, Don, Demeter, & Simard, 1994). Since brain magnetic resonance imaging (bMRI) in PTSD patients suggested volume alterations in various regions, including white matter changes, we aimed to test the relationship between cognitive memory deficits and volume of the white matter corpus callosum (CC) in PTSD patients.

Methods: We probed for specific alterations in associative memory in PTSD and measured the volume of sub portions within the CC employing bMRI.

Results: Our results highlight a reduction in CC white matter volume in PTSD as compared to controls that was correlated to lower associative performance.

Conclusion: We propose that CC volume reduction is a potential substrate for the associative memory deficits found in PTSD. *Supported by The German Science Foundation (DFG, Trilateral Program).*

The effect of number of distractors on perception of items within the subitizing range

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Background: The brain is tuned to perceive quantities. This basic ability exists not only among human adults but also in some form among infants and animals. Kaufman et al. (1949) named the perception of a small number of items "subitizing" (meaning "sudden" in Latin) to reflect the notion of one's sudden perception of small numbers. We (Goldfarb & Treisman, submitted) recently suggested that perceiving the quantity in a subset (e.g., perceiving "2" when two plates and one cup are displayed on a table) is qualitatively different from perceiving the total number of items (e.g., perceiving "3" in the previous example). We suggested that the number of items in the subset is perceived via an attentional path and it is effortful. The aim of the present study was to explore an important aspect of this theoretical notion in which the number of distractors effects the perception of subset items even within the subitizing range.

Results: According to the assumptions, we found that in a jumbled distractors display, RT for counting subset target items within the subitizing range was faster when there were few distractors in comparison to many distractors. However, when distractors were organized in a specific pattern, allowing quantity pop-out (in contrast to effortful subset counting), there was no difference in RT for counting subset target items between few and many distractors.

Conclusions: The results indicate that when distractors are disorganized, and subset counting is required, serial effortful counting is required even for items in the subitizing range. This serial counting doesn't occur when distractors appear in an organized manner and pop-out counting can be performed. It seems that for different arrangements of distractors different cognitive processes are require in order to count target items in the subitizing range.

Local electrical stimulations of the ventral prelimbic cortex ameliorates depressive-like behavioral traits in a genetic rat model for major depression

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Background: Approximately 25 % of all patients suffering from Major Depressive Disorder (MDD) fail to respond to traditional antidepressant pharmacotherapy, thus raising the need for novel therapeutic alternatives. One approach that is highly effective in treating drug-resistant MDD is electroconvulsive therapy (ECT), however such extensive and wide-spread brain stimulation often induces severe side effects which may outweigh the therapeutic benefit. It has been suggested that repeated local stimulations of specific brain circuits may achieve a similar therapeutic effect while minimizing the associated side effects, thereby offering a novel

therapeutic approach for MDD. The current study investigated how local subconvulsive electrical stimulations (SCES) affect depressive-like behaviors in a genetic rat model for MDD. Methods: an extracellular stimulating electrode was unilaterally implanted in the left ventral prelimbic cortex (vPLC) of Depressive Rat Line (DRL) rats. These rats have been selectively bred in our lab to express depressive-like behavioral traits, which are resistant to Desipramine treatment but not to ECT. DRL rats received 10 sessions of SCES or sham stimulations, after which depressive-like behaviors were quantified.
Results: compared with sham stimulations, repeated SCES of the vPLC in DRL rats increased sucrose preference and swimming duration in the Forced Swimming Test.
Discussion: we show that the vPLC can be locally stimulated to ameliorate genetically-induced depressive-like behavioral traits in rats.

Tapping into the brain: An ultra-high resolution investigation of the sensory-motor system using 7-Tesla fMRI

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Advances in magnetic resonance technology now allow us to probe the functional architecture of the human brain at increasing spatial resolutions. High field scanners make it possible to image brain activity at sub-millimeter voxel sizes permitting noninvasive imaging of functional structures such as ocular dominance columns (Yacoub et al., 2007) or auditory tonotopic maps (Formisano et al., 2003). These ultra-high resolution scans also allow segregation of different depths of the cortical sheet, providing a glimpse at differential neural activity corresponding to activity within different cortical layers (Zimmermann et al., 2011). Though the functional architecture of the visual cortex has been extensively explored (Grill-Spector and Malach, 2004), the functional organization of the sensory-motor cortex is still under debate. For example, though a general somatotopic organization of the motor cortex has been well documented (Penfield and Boldrey, 1937), the existence of somatotopic maps representing single digits has been a topic of dispute (Sanes et al., 1995). However, previous investigations of finger somatotopy may have been hindered by the spatial resolution of the imaging devices employed. Here we investigated the functional architecture of the sensimotor cortex using 7- tesla fMRI. Several experiments were conducted including: high resolution (1.3 mm) and super high resolution (0.75 mm) mapping of motor somatotopy, somatosensory finger mapping, and high resolution resting state scans. Thirteen subjects participated in part or all of the experiments. The results revealed representations for single digits within the motor cortex, with high selectivity for specific finger movements. Sampling of different cortical depths, functional connectivity, and inter-hemispheric relationships between finger regions were examined. These findings shed new light on the functional organization of the motor cortex during both activity and rest.
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An atypical form of neuronal cell death in neuronopathic Gaucher disease

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Background: Gaucher disease (GD) is the most common lysosomal storage disorder. This metabolic disorder is caused by mutations in the gene encoding glucocerebrosidase and as a result, glucosylceramide (GlcCer) accumulates within the cell. Type 2 and 3, the most severe forms of the disease, are characterized by neurological impairment and neuronal cell death. However, the molecular mechanisms leading from GlcCer accumulation to neurodegeneration and/or neuronal cell death are as-yet unknown.
Results: We have recently characterized severe neuronal loss in several brain areas in a murine model of neuronopathic GD (nGD). Although profound cell death was detected by both Nissl and FluoroJade B-staining, no TUNEL-positive cells were observed in the affected brain areas. Moreover, cell death was not accompanied by elevation in caspase 8 and 9 activities and only a slight increase in caspase 3 was detected in the latest stage of the disease, suggesting that neuronal cell death in nGD is caspase-independent. However, although there is no up-regulation of caspase 8 activity in nGD mice, RIP1 Kinase, the substrate of caspase 8, appears to undergo cleavage in nGD mice brain possibly by an alternative protease, and its cleavage correlates with disease progression. Moreover, RIP1 Kinase undergoes cleavage in brains from GD type 2 human

patients in the same manner as in nGD mice. RIPK1 cleavage was not common to all lysosomal storage disorders, suggesting a specific cleavage mechanism in which GlcCer is involved rather than a general lysosomal-related mechanism. Neuronal ultrastructure as detected by transmission electron microscopy revealed markers of both apoptosis and necrosis in nGD brains.

Conclusion: Together, our results suggest an atypical form of neuronal cell death in neuronopathic Gaucher disease.

Cognitive impairments in young ApoE4 targeted replacement mice

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Introduction: ApoE4 is the most prevalent genetic risk factor of Alzheimer disease.

The pathological effects of ApoE4 start decades before the onset of the disease. We have recently shown, utilizing 4 months old ApoE3 and ApoE4 targeted replacement mice, that ApoE4 is associated with distinct hippocampal pathology (e.g Tau hyperphosphorylation and the accumulation of Aβ42 in hippocampal neurons as well as and lower levels of the presynaptic glutamatergic transporter Vglut). In the present study we examined the extent to which the pathological effects of ApoE4 are associated with cognitive impairments. This was performed by subjecting 4 months old ApoE3 and ApoE4 male mice to in battery of cognitive tests and assessing the extent to which the performance is affected by the ApoE genotype.

Results: Morris water maze revealed that ApoE3 mice performed better than the corresponding ApoE4 mice both in learning and memory tasks. Further studies utilizing the object recognition test. This revealed that the ApoE4 mice were impaired relative to the ApoE3 mice in their ability to distinguish between old and new objects and this was associated with decrease exploration. Control experiments revealed that the velocity and locomotion of ApoE4 was similar to those of ApoE3 mice. Fear conditioning experiments which were performed on the same mice used in the object recognition test revealed a decrease in the freezing time of the ApoE4 mice relative to the ApoE3 mice. This effect however was not statistically significant. Lastly, the ability of the mice to nest was assessed. This revealed that at the age of 4 months, both ApoE3 and ApoE4 build nests but the ApoE4 mice do so less efficiently.This effect was age dependent and was much more pronounced in 1 year old ApoE4 mice.

Conclusions: The results show that male ApoE4 mice are cognitive impaired at the age of 4 months. The extent to which these cognitive deficits are related to the neuropathological effects will be discussed.

Towards using MFB stimulation for studying the hippocampal space code in flying bats

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In recent years, we introduced the bat as a new mammalian model for studying neural codes for space in the hippocampus. We characterized the functional properties of space-mapping cells in 2-D and 3-D environments, using a custom neural-telemetry recording device for freely-flying bats. However, the repertoire of possible 3-D behavioral tasks for bat hippocampal experiments is currently limited by the experimenter's ability to manually reward fast-flying bats; therefore, it is desirable to develop a rapid, potent, long-lasting motivator for training – such as electrical stimulation of the medial forebrain bundle (MFB). Indeed, past work in rats showed that MFB stimulation, which releases dopamine, allows training of rats on highly complex tasks. Here we set out to create methodology for MFB stimulation in bats. For this purpose, we developed a lightweight, wireless neural stimulator, which is head-mounted on the bat and is remotely triggered to deliver programmable electrical stimulation via up to 7 independent electrodes. We also characterized anatomically the VTA-MFB dopaminergic pathway in the bat. We found that MFB stimulation shaped the bat's behavior very effectively in two-alternative forced choice flight experiments. In future work we plan to incorporate MFB stimulation into hippocampal recording experiments, in order to train bats on complex tasks (such as repeatedly flying through a defined 3-D volume), as well as to prolong recordings by using the long-lasting effectiveness of MFB stimulation. To allow this combination of stimulation and recordings, we are now developing a "Neuro-Logger" – wireless device that will include a 7-channel wireless stimulator, as well as a high-quality headstage and amplifier for 16-channel neural recordings of spikes, which will store up to 2 hours of wideband neural data on a flash memory on-board the animal. This unique device will weigh <6 gr, including battery, and will be the first of its kind in the world.

Effects of picture repetition on oscillatory MEG gamma band activity in patients with schizophrenia

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Background: Cognitive dysfunctions represent a core feature of schizophrenia and a predictor for disability and long-term

outcome. Impaired learning due to reduced cortical plasticity may constitute one possible mechanism for the cognitive deficits. In the current study, we aimed to explore whether experience-dependent modifications of cortical networks are disturbed in patients with schizophrenia.

Methods: To address this issue, we employed magnetoencephalography (MEG) during a repetition priming paradigm in a sample of chronic patients with schizophrenia, and in a group of healthy controls. Repetition priming refers to the change in speed and accuracy in processing a stimulus following prior exposure to the same stimulus and is thought to be a form of implicit learning. Recent neuroimaging studies have shown that behavioral priming is typically associated with a decrease of neural activity (repetition suppression) which has been related to the sharpening of the underlying neural network. In the experiment, pictures of everyday objects were presented three times and repeated either consecutively or with 5-15 different intervening stimuli. The participants' task was to decide whether the object was natural or man-made. MEG signals were analyzed for spectral changes in oscillatory activity in the frequency range of 25-200 Hz.

Results: Compared to healthy controls, schizophrenia patients showed a reduced behavioral priming effect and significantly reduced repetition suppression of gamma-band activity over parieto-occipital sensors. These effects were more pronounced for repetitions that were temporally separated.

Conclusions: These results suggest that schizophrenia is associated with aberrant learning-dependent modifications of neural oscillations which could be involved in cognitive dysfunctions of the disorder.

CB1 receptor deficiency affects maternal behavior and alters the dam's hippocampal oxytocin receptor and BDNF expression

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Maternal care is the newborns' first experience of social interaction, which affects their development and social competence throughout life. For the first time, we investigated the involvement of the endocannabinoid system (ECS) in mother-infant interaction in mice. We recently found that postpartum blocking of the CB1R endocannabinoid receptor impaired maternal behavior. In this study, we examined the impact of complete deletion of the CB1R (CB1R KO) on hippocampal expression of oxytocin receptor (OXTR), brain-derived neurotrophic factor (BDNF), and stress-mediating factors in dams as well as nulliparous (NP) mice. The impact of CB1R deficiency upon maternal care was assessed by time to retrieve pups, as well as the pups' ultrasonic vocalization and body weight.

On postpartum day 8, wild type (WT) dams displayed elevated levels of CB1R and OXTR in the hippocampus compared to NP mice. In contrast, CB1R KO dams showed no such elevation of OXTR expressionin comparison to NP mice. Furthermore, CB1R KO dams exhibited lower hippocampal OXTR and higher corticotropin-releasing hormone (CRH) mRNA levels when compared to NP mice. These effects were not seen among WT dams in comparison to NP mice. Serum oxytocin levels in NP CB1R KO were higher than in NP WT, but no difference was found between CB1R and WT dams. Hippocampal BDNF mRNA levels of CB1R KO mice were lower than those of WT mice, among both dams and NP animals.

Thus, it appears that the blocking of endocannabinoid signaling by CB1R deletion alters expression of genes involved in hippocampal regulation of the stress response, leading to deleterious effects upon maternal behavior.

Cell-targeted holographic retinal photo-stimulation in vivo

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Background: Degenerative diseases of the outer retina lead to photoreceptor loss and eventually cause blindness. However, the retinal ganglion cells (RGCs) are relatively preserved. Artificial photo-stimulation of these functional cells could be the key to developing retinal neuroprosthetic devices, which will restore patients' vision. A successful retinal prosthesis should induce activity patterns which will enable downstream circuits to correctly interpret the artificially generated stimulus as the intended image. In previous work, we demonstrated patterned photo-stimulation of RGCs *in-vitro*, using optogenetic and photo-thermal mechanisms.

Methods: The research presented here constitutes a first step in advancing towards *in-vivo* retinal stimulation. We have constructed a system which integrates precise spatiotemporal holographic photo-stimulation with high resolution fundus imaging. This system allows one to target the projected pattern at specific locations in order to excite desired RGCs.

Results: The system was utilized to acquire both brightfield and fluorescence fundus images of mice and rats *in-vivo*. In addition, holographic patterns were projected onto the rodents' retinas and imaged. The optical parameters of the holographic photo-stimulation system have been characterized. The

system's imaging resolution allows one to identify single RGCs for stimulation. The stimulation spot diameter is sufficient for cellular targeting using patterned photostimulation *in-vivo*.

Conclusions: Our system enables single-cell resolved patterned holographic photo-stimulation of RGCs. In addition, it could prove to be a basic tool for non-invasive *in-vivo* small animal retinal imaging in a wide array of vision applications, including the tracking of fluorescently tagged cells and the expression of gene-therapy and optogenetic vectors. Furthermore, functional calcium imaging may be performed using this system in order to translate the aforementioned research to an *in vivo* setup.

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Genetic approaches to understanding the etiology of mood disorders

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Background: Within the mood disorders, depression is moderately heritable whereas bipolar disorder is highly heritable. This suggests that differing approaches may be of use in attempting to identify genetic contributors to these conditions. Genetic linkage analysis and fine mapping association studies of bipolar disorder has led to the identification of several potential candidate loci and susceptibility genes, while genome wide association studies have also led to the identification of several potential susceptible genes. A second approach, used more frequently in studies of depression, is to examine the effect of polymorphic variation in previously implicated candidate genes on biomarkers associated with illness.

Results: Linkage studies of bipolar disorder have implicated a locus on chromosome 15q25-26 and fine mapping association studies have identified the sialyltransferase gene ST8SIA2 as a putative bipolar susceptibility gene. Resequencing analysis of the sialyltransferase gene and one of its targets, NCAM1, have given insights into the genetic variation that may underpin susceptibility for bipolar disorder. International collaborative genome wide association studies have have led to the characterisation of candidates such as neurocan (NCAN), calcium channels (CACNA1C) and ODZ. Finally, biomarker traits associated with depression such as EEG activity and neurocognitive measures, have been examined for the impact of polymorphic variation in genes such as brain derived neurotrophic factor (BDNF).

Conclusions: Our understanding of the genetic contributors to the mood disorders is still developing, with no genes of major effect having been identified. However, using complementary approaches, progress has been made in identifying a number of genes which contribute to the risk of developing depression or bipolar disorder.

National Health and Medical Research Council, Australia; Australian Research Council.

Harnessing immune cells to the benefit of the central nervous system: no longer 'if' but 'how'

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Introduction: The central nervous system (CNS) tissues, including the brain, the eye and the spinal cord, are immune-privileged, secluded from the circulation by a complex of barriers and equipped with their own myeloid cell population, the resident microglia. Based on the classical perspective of immune-brain interactions and on the contribution of such interactions to the progression of Multiple Sclerosis, an autoimmune inflammatory disease of the CNS, circulating immune cells were traditionally viewed as an enemy of the nervous system. However, over the past two decades, we demonstrated the pivotal role of monocyte-derived macrophages and adaptive immune cells in CNS repair and functional plasticity including neurogenesis, cognition, and coping with mental stress. The biggest eniga has been how the immmune cells get excess to the traumatized CNS, given its unique structure, and where is the site of their activity in the healthy CNS.

Results: We have identifies the unique routes through which immune cells infiltrate to the traumatized CNS that does not necessitate break down of barriers but rather activation of a physiological route of entry the choroid plexus epithelium that we identified as a site that orchestrates the fate of the infiltrating cells to drive a risk-free benefit for their repairing effect. In the healthy CNS we identified how the same site, the choroid plexus epithelium, as a site whereby adaptive immunity controls in a remote way CNS plasticity, and how such immunity from essential becomes detrimental with aging.

Conclusions: Taken together, these recent advances reveal a dramatic therapeutic opportunity for controlled harnessing immune cells for repair of the damaged CNS following acute insults, and for modulating the aging, distressed and neurodegenerative conditions, and in psychiatric disorders.

The role of sexually dimorphic hypothalamic neurons in regulation of maternal responses

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The hypothalamus plays a critical role in coordinating expression of reproductive behaviors and physiological responses with environmental cues. Its close anatomical and physiological relationship with the pituitary gland provides an effective means for coordinating diverse homeostatic processes through neuroendocrine regulation of hormone secretion. The hypothalamus contains sexual dimorphic areas which are different in morphology, density, gene expression and neuronal projections. One of the sexually dimorphic neuronal populations in the hypothalamus is tyrosine hydroxylase expressing (TH-ir) neurons whose number is greater in female than in male mice. The role of the sexual dimorphism of these TH-ir neurons is still unknown. In this work we used 6-hydroxydopamine (6-OHDA) to "masculinize" the number of a specific TH-ir neuronal population in the hypothalamus of adult female mice. 6-OHDA is a neurotoxin known to selectively ablate dopaminergic and noradrenergic neurons. Our results indicate that TH-ir lesioned females exhibit lower maternal behavior. This suggests that the sexually dimorphic TH-ir neuronal population in adult mice is involved in regulation of sexually dimorphic parental behavior.

The role of attention in the resolution of verbal conflicts while processing metaphorical language among adults with ADHD and without it

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Background: Conventional metaphors are expressions that lost their metaphoricity due to repeated use. In order to understand conventional metaphors like 'time is money' people must make an appropriate abstraction of the vehicle ("money") and inhibit its literal meaning. Therefore, we assume that in early stage of processing, there is a competition between the literal and the metaphorical meanings. Thus, we offer to refer to this competition as a conflict resolution task. Attention deficit/hyperactivity disorder (ADHD) is a chronic disorder of childhood onset that persists into adolescence and adulthood. Individuals with ADHD often demonstrate difficulty with 'executive attention' that is manifested in a difficulty to resolve conflicts between stimuli and/or responses. In the current study we addressed the question whether adults with ADHD are less efficient in processing conventional metaphors and resolving conflicts between their literal and metaphoric meaning.

Results: We found that participants with ADHD resolved conflicts between meanings slower than controls. The difference between the groups became more pronounced as a function of the conflict complexity. We also found a significant correlation between the executive attention score (measured by a location-direction Strooplike task) and the efficiency of the conflict resolution in a metaphorical processing task.

Conclusions: The study suggests that attentional functions modulate high level language processing, though participants with ADHD may show intact structural language but inefficient processing of figurative language. The study emphasizes the connections between the attentional networks and language processing, and offers to use sensitive and specific language evaluation tools, to assess abilities and difficulties of participants with attention disorders.

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A BBB disrupter is also a potent alpha-Synuclein aggregation Inhibitor: a novel dual mechanism of mannitol for the treatment of Parkinson's disease

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Misfolding and aggregation of α-synuclein (α-syn) is the hallmark of Parkinson's disease (PD). No disease modifying treatment is available for PD. Osmolytes, such as polyols, are small molecules which accumulate under stress conditions and stabilize protein structure, acting as 'chemical chaperones'. Thus, they may reduce protein misfolding and aggregation in neurodegenerative diseases. The polyol Mannitol is one such compound. It is a non-metablolized FDA-approved osmotic diuretic agent that also has BBB disrupting properties. We examined the ability of Mannitol to interfere with the aggregation of α-syn in vitro and in vivo. Low concentrations of Mannitol (450 and 225 mM) inhibited the in vitro formation of α-syn fibrils. High concentrations (900 mM) significantly decreased formation of tetramers and high molecular weight oligomers, and shifted the secondary structure from a-helical to a different structure, suggesting alternative potential pathways for aggregation. Feeding α-syn expressing Drosophila, which serve as an established model for PD, with 75 mM Mannitol dramatically corrected their behavioral defects and reduced the amount of a-syn aggregates in their brains. Daily injection (IP) of 1 g/kg Mannitol to mThy1-human α-syn transgenic mice caused a significant decrease of α-syn accumulation in several brain regions, suggesting that Mannitol promotes α-syn clearance from the cell bodies. Mannitol appears to have a general neuroprotective effect in the transgenic treated

mice, which includes the dopaminergic system. No adverse effects were observed in control Mannitol-treated flies or mice. We therefore suggest Mannitol as a basis for a dual mechanism therapeutic agent for the treatment of PD – a BBB disruptor that will also serve by itself as a chemical chaperone correcting the pathogenic misfolding of α-syn.
Parkinson' Disease Foundation

Cannabinoid and glucocorticoid receptors in the amygdala modulate the stress- induced impairment of LTP in the hippocampal-accumbens pathway

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Background: Exposure to acute stress results in release of glucocorticoids which are potent modulators of both learning and plasticity, and these effects are presumably mediated by the basolateral amygdala (BLA). Since high densities of cannabinoid CB1 receptors are expressed in the BLA, and our previous data suggest that cannabinoid receptor agonists in the BLA can prevent the effects of stress on learning and memory, the present experiment investigated whether cannabinoid receptor activation and glucocorticoid receptor (GR) blockade in the BLA can alleviate the effects of acute stress on plasticity in the ventral subiculum (vSub)-nucleus accumbens shell (NAcS) pathway.
Results: We examined: (a) whether intra- BLA microinjections of Ru-486 (RU), a GR antagonist, or WIN55,212-2 (WIN), a CB1/2 receptor agonist, can reverse the effects of acute stress on plasticity in the vSub-NAcS pathway, and (b) whether RU and WIN can normalize the stress-induced alterations in the levels of phosphorylated cAMP response element-binding protein (pCREB) in the NAcS. Both bilateral and contralateral BLA administration of RU or WIN reversed the impairing effects of stress on vSub-NAcS LTP. Administering RU or WIN bilaterally into the BLA with no stress exposure also impaired LTP. Further, exposure to stress or WIN-only significantly reduced pCREB levels in the NAcS compared with the vehicle group and this effect was normalized in rats exposed to both stress and intra-BLA WIN.
Conclusions: The results suggest that the preventing effects of intra-BLA WIN and RU on vSub- NAcS plasticity are not necessarily mediated through a direct pathway from the BLA to the NAc, and that CREB activation in the NAcS is involved in the preventing effects of WIN. RU and WIN reverse the effects of stress on plasticity and hence could represent a therapeutic target for the treatment of stress-induced cognitive impairments.
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Elevation of Nrf2 in Astrocyte mediates neuroprotection in stroke in an IL-10-dependent manner

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Background: Oxidative stress plays an important role in the pathogenesis of different brain insults such as stroke. Astroglia are the main glial cells that play a fundamental role in maintaining the homeostasis of the CNS and are important for protection, and aid the brain in the functional recovery from injuries. It was shown that the brain can be prepared to withstand an oxidative stress insult by a process known as preconditioning. We investigated whether preconditioning to mild oxidative stress and glucose deprivation (OSGD) of astroglia can lead to better cell survival and to neuroprotective features.
Results: We discovered in our work selective changes in astroglia activity when preconditioned to mild vs. severe oxidative stress. Interestingly, we discovered significant increase in levels of the anti-inflammatory cytokine IL-10 vs. pro-inflammatory cytokine IL-1β, in mild vs. severe oxidative stress, respectively. We discovered that preconditioning astroglia to mild OSGD increases survival to second insult through activation of Nrf-2 pathway. Furthermore, we discovered that preconditioned astroglia are neuroprotective in an IL-10-dependent manner. By using tert-Butylhydroquinone (tBHQ), a known specific activator of Nrf-2, we suggest that Nrf-2 can enhance IL-10 expression.
Conclusion: We demonstrated that preconditioning astroglia to mild oxidative stress increase cell survival through elevation of Nrf2 and increase neuroprotection through secretion of IL-10. Further studies of Nrf-2 mediated cellular pathways in astroglia through IL-10 may provide useful insights into the development of therapeutic intervention following oxidative stress insults, such as ischemic stroke and other neurological insults.

Giving the brain a helping hand: manipulating empathy through motor action

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Background: Viewing motor actions performed by another person causes automatic activation of motor brain circuits involved in producing the same actions. Different theories suggest that empathy relies on this kind of motor resonance between self and other. However, support for these theories is usually limited to correlational data, not allowing to infer

causality. If one could experimentally manipulate motor resonance, it would be possible to test its causal connection to empathy. Continuous muscle contraction elicits far reaching cognitive effects that can last up to several minutes after the motor manipulation. These effects are attributed to the spreading of Mu-rhythm desynchronization over central and frontal brain areas. Interestingly, during action observation, motor resonance is thought to be indexed by similar Mu rhythm desynchronization. It is possible then, that the muscle contraction paradigm can also affect motor resonance.

Hypothesizing that such modulation can indeed occur, we explored the possibility of affecting empathic ability by activating the motor system. Participants rated the valence and arousal of their reaction to emotional facial expressions and completed a test of emotion recognition after continuously squeezing a ball or after rest.

Results: Preliminary data suggests that contracting both hands or only the left hand results in enhanced emotion recognition compared to rest, with both-hands contraction yielding the larger effect.

Conclusions: These data are a first step in establishing a paradigm that can manipulate motor resonance. This has the potential of providing an easy, yet powerful technique to investigate the long hypothesized causal role of motor resonance in empathy.

Incubation of craving and fear: behavioral and neuronal mechanisms

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Using a rat model of drug relapse and craving, we previously found time-dependent increases in cue-induced cocaine seeking after withdrawal from the drug, suggesting that cocaine craving incubates over time (Grimm et al. Nature 2001). In this lecture, I will summarize results from studies on the generality of this incubation phenomenon to other drug and non-drug rewards and to fear conditioning in a rat model of delayed-onset PTSD. I will then summarize results from a series of studies on the neuronal mechanisms of incubation of drug craving. These include recent studies on the role of Toll-like receptor 4 (an innate immune system pattern recognition receptor) in incubation of heroin craving, and the role of orbitofrontal cortex neuronal ensembles in this incubation. *Supported by NIDA*

Neurobiology of Schizophrenia

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There is widespread agreement that cortical interneurons are pathological in schizophrenia. We have shown that this pathology occurs in multiple regions, involves multiple interneuron types and impacts GABA receptor levels. Interneurons require growth factors for their differentiation and survival and we find promoter-specific reductions in cortical BDNF in people with schizophrenia and an unexpected increase in the truncated BDNF receptor, trkB, changes which are strongly correlated with interneuron demise. We have evidence that interneurons are displaced and found in the white matter [previously termed interstitial white matter neurons (IWMNs)]. Our observation challenges the long-held interpretation that these IWMNs are subplate neurons and suggests instead that they are derived from the ventral telencephalon. This is important as the ventral telencephalon produces neurons capable of migration to areas of cortical injury in adulthood and we have evidence that cortical injury and neuroimmune activation occurs in a subset of people with schizophrenia (~40 %). We suggest that increased IWMN density found in people with schizophrenia may represent new neurons being recruited to the damaged cortex in an attempt to rebuild. Our working model is that people with schizophrenia will have altered interneuron development due to multiple factors that reflect the heterogeneous nature of the illness, such as genetic variation in interneuron growth factors or variations in hormone responsiveness. For example, some patients carry risk variants in the schizophrenia susceptibility gene neuregulin (NRG1) which changes expression levels of NRG1 and alters the development and maturation of cortical interneurons, while others exhibit worse symptoms when estrogen signalling is low and low estrogen is known to impair neuronal maturation and survival. We have begun to test the extent to which stimulation of estrogen receptor alpha (ERa) can bring about clinical improvement.

The modulatory effect of Munc13-1 and PKC on neuronal network activity

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Background: Neuronal neurotransmitter release is a tightly regulated process controlled by complex protein machinery at the synapse. Munc13-1 is an active zone protein regulating the priming process of synaptic vesicles into a fusion competent state. Diacylglycerol (DAG) and phorbol esters potently potentiate synaptic transmitter release by activating protein kinase C (PKC) and Munc13 in parallel pathways. Here, we used microelectrode arrays (MEAs) to elucidate the effect of Munc13-1 overexpression on the activity of cortical neuronal networks and its relative role in the phorbol ester potentiation of cortical transmission.

Results: In networks grown on MEA plates the activity converges into a synchronized mode of spiking activity (network burst) separated by periods of reduced activity. Cortical networks overexpressing Munc13-1 showed enhanced network activity with increased network burst rate and reduced inter-burst interval. The recurring bursting activity reduced the network synchronization and led to a significant decrease in the number of spikes in each burst. While phorbol-ester 12,13-dibutyrate (PDBu) dramatically increased the network firing rate and disrupted the network synchronization, the PKC blocker Gö6983 only partially reduced the potentiation. As Munc13-1 overexpression caused similar effects as PDBu after PKC inhibition by Gö6983, it is reasonable to assume that the remaining effects of PDBu are attributed to the activation of Munc13-1 by PDBu.
Conclusions: This work demonstrates how manipulation of Munc13-1 expression levels in the cellular level affects the neuronal network activity. Although Munc13-1 supports increased transmitter release in the cellular level it alters neuronal network activity by inducing smaller bursts at a higher frequency; possibly as a result of insufficient vesicle replenishment. Our data suggest a role for both PKC and Munc13-1 in PDBu potentiation of cortical network activity.

The role of perceptual load in driving: eliminating interference of irrelevant task during driving
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Drivers' attention can be modulated by relevant and irrelevant stimuli (RS, IS) presented inside and outside the vehicle. Those IS (e.g., Smartphones, billboards) tend to impose costs such as high information load on drivers, interrupting the primary purpose of safe driving, the detection and/or recognition of critical events. Perceptual load theory (Lavie, 1995) describes the processing of IS, suggesting that the extent to which IS can be ignored depends on how the processing of RS is affected by perceptual load. Thus, under high attentional load perceptual resources are fully occupied so there is no capacity left for processing IS, and the effect of IS can be eliminated. The current study examined whether drivers are capable of ignoring visual irrelevant tasks under conditions of high perceptual load. The author used driving simulation video scenarios in which, while following a lead vehicle (LV), participants responded to the LV's braking lights, and detected color changing billboards. Participants had to ignore the color changing billboards, defined as low prioritized change detection task (CDT; irrelevant task) to the main driving task, and to assign high priority to the braking task (BT; relevant task). Perceptual load was manipulated by road curvature: (1) curve road (complicated) produced high perceptual load, (2) straight road produced low perceptual load. Single (BT or CDT) and dual tasks (both tasks simultaneously) were used. Response times (RTs) to LV and accuracy rates to color changing billboards were compared according to the perceptual load (curve vs. straight). As expected, accuracy for CDT deteriorated under high perceptual load. Hence, the interference effect by the IS task was undermined under high perceptual load, whereas under low perceptual load it was practically unimpaired. The data suggest that high perceptual load may assist drivers to ignore IS task to the driving primary task, thus drivers may focus more attention on RS (e.g., hazards).
A final course project: Introduction to Traffic Safety, Prof. D. Shinar and Mrs. I. Oppenheim

From a visual to a symbolic object in algebra and geometry: ERP study with mathematically excelling male adolescents
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Background: In this study we performed a comparative analysis of brain activity associated with transition from visual objects to symbolic objects in algebra and geometry. Algebraic tasks required translation from graphical to symbolic representation of a function whereas tasks in geometry required transition from a geometrical object to symbolic representation of its property. We focused on brain activation associated with solving advanced mathematical tasks by adolescents excelling in mathematics who differ in their general giftedness level.
Results: Geometry and Algebra Tests were designed of batteries of short choice-reaction tasks. 32 right-handed male-students who excel in mathematics were chosen for comparative data analysis. We found that non gifted (NG) participants had higher brain activity than their gifted (G) counterparts. This difference was significant in the first stage of the task, 300-400 ms post stimulus at parieto-middle areas of the cortex. Moreover, higher brain activity was found during the geometry test as compared to the algebra test. In addition laterality differences for found between the different types of tests.
Conclusions: The finding are consistent with the neural efficiency hypothesis of intelligence, stating that brighter individuals display lower (more efficient) brain activation while performing cognitive tasks (for review see Neubauer & Fink, 2009). These differences seem to stem from the different visual-spatial strategies of processing in the introduction stage.). In addition, we can argue that geometric tasks increase the participants' working memory load by keeping the visual geometric object in working memory until the problem is solved.

Depressive disorders and cognitive impairment may share similar molecular mechanisms

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Background: Age-related cognitive impairment is a devastating disorder of unclear etiology developing over a period of years. Memory deficit is one of the strongest manifestations of this disorder. Depression and apathy are common comorbidities presenting with cognitive impairments. We developed animals with strong dominant and submissive phenotypes, of which submissiveness is an essential element of depressive conditions, and antidepressant drugs from different classes and generations tend to reduce submissive behavior. In this study we attempt to find functional substrates common to the development of cognitive impairments related to submissive behavior, an important element of depressive conditions, and to aging.
Results: Use of the Morris water maze and new object recognition paradigms showed that although young (3 months) submissive animals' performance was similar to dominant and wt mice, it markedly declined with advanced age (9 months), in comparison to their dominant and wt counterparts. Despite the absence of cognitive dissimilarity at the early stage of life, electrophysiological study revealed significant differences in short- and long-term synaptic plasticity between dominant and submissive animals: acute hippocampal slices taken from submissive mice failed to develop paired pulse facilitation in the CA1 region upon stimulation of Shaffer collaterals, in contrast to dominant counterparts. Moreover, upon application of primed burst (PB) stimulation paradigm, we observed strong sustained LTP in submissive mice, which declined within an hour among slices from dominant mice. In addition, qPCR analysis revealed that IGF-1 (deficit of which is associated with cognitive impairment and dementia) mRNA levels were significantly lower among submissive animals in comparison to dominant and wt mice.
Conclusions: This study further demonstrates that depressive-like state may accelerate cognitive impairments.

The role of Dlgap2 (SAPAP2) in PSD zone; possible implication to synapse formation

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Disks Large-Associated Protein (Dlgap) family is one of the less studied components of the PSD zone. It was proposed to mediate the translocation of the scaffolding protein PSD95 from the cytosol to the membrane and its communication with sub-synaptic molecules. Impaired expression of Dlgap members was reported in fragile X syndrome and in mental disorders. We have shown abnormal Dlgap2 expression associated with maladaptation to trauma in PTSD-like rats. The aim of this study was to identify a role for Dlgap2 in PSD zone and in synaptogenesis by its silencing in Sprague-Dawley rat hippocampal primary culture. Time-dependent morphological changes of cultures, which included increased neurits length and number, with no change in cell size, were associated with bell a shape-like change in mRNA and protein levels of Dlgap2. Additional members of PSD, such as PSD95, Neuroligin (NLG) 1 and 2 and NMDA receptor subunits NR2A and NR2B showed parallel changes in their mRNA levels, which were highly correlated with those of Dlgap2. Silencing of Dlgap2 using shRNA technique, which resulted in 73 % reduction in Dlgap2 mRNA and 62 % of its protein levels was associated with a significant reduction in PSD95 mRNA levels (35 %). A tendency towards significant reduction was also observed in two additional PSD zone proteins CAMK2 and NR2B, while not in NLG1, NLG2 and NR2A. Concomitantly, synaptogenesis, measured by co-localization of synapsin1 and PSD95, pre and post-synaptic markers, respectively, was reduced by 42 % in Dlgap2 silenced cultures. The data suggest a role for Dlgap2 in synaptogenesis and in the modulation of mRNAs of the PSD members. The latter may be through the interaction of Dlgap2 as well as other members of the PSD with the mRNA binding protein FMRP. We believe that if verified such a mechanism may be of relevance to impaired postsynaptic function in mental disorders.

The compositional representation of trajectory in the motor cortex: An fMRI study

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Human actions are highly stereotypical despite the large number of degrees of freedom available at the anatomical, kinematic, and neural control levels. These redundancies may be simplified by the construction of elementary control building blocks (primitives). Despite the appeal of this theory, the neural substrates of primitives are still unknown. Of a particular interest are the primitives underlying curved trajectories: while could be composed of a superposition of straight strokes, curved trajectories have recently shown to be composed of parabolic elements (Polyakov et al., 2009). We used a task developed by Hocherman and Wise (1991), where subjects are required to reach 3 targets employing curved and straight trajectories. Using classification methods of fMRI signals, we examined the neural substrates of primitives by searching for cortical areas that show

sensitivity to trajectory shape irrespectively of its position in space (e.g. generalization). The differential representation of straight and curved trajectories was examined within regions of interest and across the whole brain. Classification analysis showed generalization of trajectory shape across space in premotor dorsal (PMD) and caudal parietal cortex. While in primary motor cortex (M1) classification rates for trajectories were higher than chance, generalization was not found. This result suggests that movement shape is represented in PMD and its specification in space is represented in M1. Whole brain comparison between straight and curved trajectories revealed increased activation for curved trajectories in motor and visual cortices. Yet, classification analysis in M1 and PMD showed higher classification rates for the straight trajectories. These results suggest that the neural representation of curved trajectories may correspond to the superposition of multiple elements. Our results provide insights into the dynamic compositional organization of movements along the cortical motor hierarchy.

Ladostigil prevents aging-related changes in microglia: brain region-dependence and correlation with cognition

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Background: We have shown that ladostigil, a drug that inhibits cholinesterase and monoamine oxidase, prevents aging-related cognitive decline. Although ladostigil attenuates reactive microgliosis in some brain regions the correlation with cognitive performance is not consistent. In the present study we correlate morphological changes in non-reactive (ramified) microglia with cognitive performance.
Methods: Wistar rats were randomized to receive ladostigil 1 mg/kg or 8.5 mg/kg from 16 months of age for 6 months. There were non-treated age-matched and adult control rats. Tests of cognition: spatial - Morris water maze and object location; non-spatial: object recognition. Immunohistochemical tests included complement 3 receptor (C3R) using OX42 clone and a polyclonal antibody to ionized calcium-binding adapter molecule 1 (Iba1).
Results: Microglial process ramification: In hippocampal CA1 region, Iba-1 demonstrated aging-related de-ramification of microglia that was prevented by ladostigil and correlated with spatial cognition but not with object recognition. In peri-rhinal cortex, ramification correlated with object recognition but not with spatial cognition. In parietal cortex, microglial process ramification was increased by aging and by ladostigil but did not correlate with cognition. However, in the parietal cortex, aging-related increase in C3R-positive bulbous tips was prevented by ladostigil and correlated with spatial- but not with non-spatial cognition.
Conclusions: Although it is widely assumed that aging-related microglial activation in all brain regions contributes to cognitive decline, the present study shows that aging-related changes in non-reactive microglia are brain-region dependent and closely correlate with behavior. Ladostigil prevents these changes keeping the relation to cognition similar to that of adult rats.

Lost in translation: failure of the NMDA antagonists clinical trials in TBI and stroke

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For more than two decades the intensive research effort on the role of NMDA receptors (NMDAR) in traumatic brain injury (TBI) and cerebral ischemia (stroke) was led by observations from *in-vitro* and *in-vivo* studies that overstimulation of these receptors plays a major role in brain pathologies. NMDA-mediated glutamate toxicity is considered responsible, at least in part, for the devastating neurological and psychiatric sequelae of head trauma and stroke.
In view of this concept studies in animal models have demonstrated that indeed, NMDAR antagonists improve outcome after TBI and stroke. These findings led to some large scale placebo-controlled clinical trials with NMDAR antagonists. However, all these trials have demonstrated either no benefit or even deleterious effects suggesting that NMDAR inhibition is either irrelevant or even harmful for TBI and stroke outcome. Critical review of the reports on these clinical trials suggest that in the translational phase not enough attention was paid to the pre-clinical findings that NMDAR antagonists lose efficacy if administered more than 30–60 min post-injury. The discrepancy between the animal and human studies in the treatment protocol on one hand, and on the final outcome on the other, prompted us to investigate the temporal changes of the NMDAR after brain insult in animal models of TBI and stroke, using ^{3}H-MK-801 autoradiography. We found desensitization and loss of functional NMDAR, which persists for weeks. After showing the long lasting hypo-functional state of NMDAR we propose a paradigm shift towards targeting stimulation, rather than inhibition of NMDAR as a therapeutic substrate for TBI and stroke, and believe that the road is now cleared for clinical trials based on this approach.
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The perceptual consequences of action: preferential binding with vision

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Acting on the environment creates perceptual consequences—moving an object changes its visual appearance, and potentially creates an auditory event. In order to examine the relative impact on auditory and visual events, we had observers make a voluntary action to initiate each trial, and subsequently make an audiovisual temporal order judgment. The first stimulus could appear immediately after the action, or be delayed by 500 ms. The visual event was perceived sooner (i.e., the auditory event had to be presented sooner to achieve a point of subjective simultaneity) when the action immediately preceded the first stimulus. Manipulations of relative spatial arrangement had no effect on this shift in perceived onset of the visual event. There is some indication that the action must be voluntary to produce this effect. Results are discussed in terms of the impact of action on perception.

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Prenatal stress differentially disrupts the normal course of development of hippocampal neuronal markers in the male and female rat offspring

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Background: Stress during pregnancy increases the prevalence of anxiety, learning deficits and depression in humans and experimental animals, which may be sex-specific. There are hardly any studies that examined the effect of prenatal stress on brain histology that can underlie these behavioural changes and none has examined whether these differ according to the age and sex of the offspring. In the present study, we analysed the developmental course of hippocampal neuronal markers which were correlated with learning and memory, in control and prenatally-stressed male and female rats at pre-puberty and adulthood.
Results: Pre-pubertal control females had a higher intensity of staining of GluR1 and nNOS markers and a higher count of activated neurons (measured by c-Fos) in the hippocampus, but lower staining intensity of DCX (a marker of neurogenesis) in the hippocampal sub-granular zone than their male siblings. Prenatal stress selectively reduced the intensity of GluR1 and nNOS in females, but not in males. An increase in the number of c-Fos$^+$ neurons was seen in both sexes but to a much higher degree in males. A reduction in DCX intensity was only seen in males. At adulthood, most of the sex differences in these neuronal markers (except for c-Fos$^+$ neuronal count) were no longer evident. Prenatal stress increased the number of GluR1 and nNOS positive neurons in both sexes in contrast to what was seen at pre-puberty. An enduring reduction in DCX intensity in adult males and an increase in c-Fos$^+$ cell counts in both sexes were also evident at adulthood.
Conclusions: The present data provide evidence for sex and age specific effects of prenatal stress on hippocampal neuronal markers supporting the need for further exploration of the effect of this early life event not only at adulthood but also earlier in development in both sexes.

Location-specific adaptation of auditory responses in the human EEG

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Background: To probe the representation of sound location in the human brain it is essential to find a neural index of spatial sensitivity. Early studies have found attenuation of the N1-P2 vertex response following repetition of sounds from the same location. However, these studies reported the peak to peak N1-P2 amplitude, but not each component's amplitude separately. In recent years the question of whether N1 and P2 reflect the same or different processes has become subject to debate. Furthermore, previous studies were conducted in very unnatural conditions, some manipulating sound source difference by changing Inter-aural Intensity Differences (IID), and mainly using pure tones, which are relatively hard to localize. Here we presented pairs of complex tones from 3 speakers in free field and measured the N1 and P2 responses. We compared the degree of attenuation to the second stimulus when preceded by a sound in the same location, 30° apart, or 60° apart.
Results: In line with previous studies we found overall attenuation of the N1 and P2 responses to the second stimulus compared to the first in all conditions. In addition, we found that the amplitude of the second sound P2, but not N1, was positively correlated with the distance between the locations of the first and second sounds.
Conclusions: These findings indicate that P2 reflects activity based on spatially selective neurons, with a resolution of at least 30° within hemispace. Furthermore, the discrepancies between our findings and previous research support the notion that N1 and P2 represent different processes, which might be affected differently by complexity of stimuli and by different manipulations of sound source perception.

Synapsin IIa function is regulated by an ATP binding site

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The synapsins are neuron-specific proteins mostly known for their capability to cluster synaptic vesicles and to control vesicle movement between adjacent en-passant synapses. Early studies revealed various sites that were suggested to

regulate the activity of synapsin I, the first synapsin to be described. Although synapsin IIa was recently shown to be the dominant member of this family, at least in small glutamatergic synapses, its regulation has not been studied in any detail to date. All members of the synapsin family bind ATP at a well-conserved site in their central "C" domain. Intriguingly, ATP binding is differentially regulated by calcium ions, suggesting a physiological function. Nevertheless, the significance of ATP binding has not been investigated in the context of neurotransmission. To study this question, we measured the rescue of synaptic depression in autaptic neurons lacking all synapsins by the over expression of either exogenous wild type synapsin IIa or synapsin IIa carrying a mutation (K270A) which prevents ATP binding. We found that K270A-synapsin IIa only partially rescues synaptic depression. All results support a role for ATP in regulating synapsin activity in synapses in-vivo.

Elucidating the role of environmental enrichment in mitigating Alzheimer's disease pathology through microRNAs regulation

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Introduction: Exposure to enriched environment (EE) has been shown to have protective effect in mice as well as in human subjects, by slowing disease progression and reducing AD-like cognitive impairment. We were interested in studying the molecular consequences of the exposure of WT C57B mice to EE on the one hand, and of AD pathology in 3xTgAD mice model on the other hand.

Results: Measuring the proteins levels in the hippocampi of WT C57B mice that were exposed to EE, we have found that EE increases the level of expression of proteins that are positively involved in synaptic transmission like synaptophysin and reduces the level of negative regulatory proteins such as tomosyn. As opposed to EE, old 3xTgAD mice showed significantly higher expression levels of Tomosyn in all of the hippocampal sub-areas compared to control mice. To study the molecular regulators responsible for the changes in synaptic proteins we studied the expression levels of microRNAs in C57B WT mice that were exposed to EE and in mice model of AD as compared to their control mice. We found several important microRNAs which were substantially upregulated in 3xTgAD mice compared to their age-matched WT C57B control group. These microRNAs were highly concentrated in the synaptic fraction of the brain, and are predicted to down-regulate essential synaptic proteins. MicroRNAs that were inversely-regulated in mice model of AD or following EE affected not only synaptic proteins and modulators, but also molecular factors that are associated with AD pathology and may contribute to the rescue effect of EE on AD pathology.

Conclusions: By modulation of the expression levels of microRNAs, EE can enhance the expression of proteins that mitigate AD pathology as well as many key-players in the synaptic transmission machinery. Moreover, EE also influences survival factors and neurofactors that are essential for neuronal viability, thus preventing the neuronal loss attributed to AD pathology.

Bilateral and multisensory integration in striatal microcircuits

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The basal ganglia are involved in various motor and reward-related functions, however, their role in sensory processing remains unclear. The striatum is the input layer of basal ganglia, receiving excitatory inputs from most cortical areas and from both hemispheres. In this study we aimed to answer how striatal neurons integrate bilateral and multisensory sensory input. To answer this question we obtained *in vivo*whole-cell patch-clamp recordings from neurons in the dorsolateral striatum and in cortical layer V of the barrel field (BF) in anesthetized mice. We recorded the evoked responses to ipsi- and contralateral whisker stimulation using air-puff, and responses to simultaneous whisker and visual stimulus (delivered as light flashes in front of the contralateral eye). Recorded neurons were stained with neurobiotin and the different types of striatal neurons were identified by their morphological and electrophysiological properties. Our results show that all recorded striatal neurons respond to bilateral whisker stimulation, responding faster to contra- than ipsilateral stimulation. Around 35 % of neurons respond to visual stimulation too, showing that neurons in the dorsolateral striatum integrate inputs from different sensory modalities. Striatal MSNs have slower onset slopes compared with those in cortical neurons. Furthermore, slopes were significantly slower for D2 than D1 MSNs. D1 MSNs responded with larger amplitudes and longer delays between ipsi- and contralateral responses. These results suggest different functional roles in bilateral sensory integration by the direct and the indirect pathways. Our results

show that individual striatal neurons perform bilateral and multimodal sensory integration of cortical inputs.
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Measuring the intricacy of a stimulus
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Intuitively we can distinguish an intricate image or sound from simple ones. However, characterizing intricacy of stimuli in a measurable manner remains a challenge.
We propose that perceptual variance can be taken as a measure of stimulus intricacy. The more variance - the more intricate the stimulus. For this property to be a property of the stimulus it needs to be consistent regardless of the question asked. Thus, we set out to test the initial hypothesis that perceptual variance is stimulus-specific. We obtained 3 different data sets of odor ratings applied by ~50 subjects to ~20 odorants, containing ~250 different perceptual questions in total. We found that the relative amount of variance associated with a given odor is highly consistent, regardless of the descriptors applied. When we simulated the mean variances for two sets of 20 randomly selected descriptors we got spearman correlations greater than $r=0.8$ across the two sets. When we used sets of 30 descriptors we got spearman correlations greater than $r=0.86$ across the two sets, indicating the highly consistent ordering of the variance of the stimuli. Thus we conclude that a property of intrinsic perceptual variability can be reliably assigned to a stimulus, and we propose to take this as a measure of stimulus intricacy. Lastly we propose this measure as a tool to directly investigate logical aspects of processing of stimuli.

Selective increase in the association of the beta2 adrenergic receptor, beta Arrestin-1 and p53 with Mdm2 in the ventral hippocampus four weeks after underwater trauma
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Although activation of the sympathetic nervous system is a critical stress response aimed at maintaining homeostasis, its prolonged activity is harmful in the long run. A recent study showed that chronic infusion of mice with a b2 adrenergic receptor (b2AR) analogue causes long-term DNA damage in a pathway which involves b Arresin-1-mediated activation of Mdm2 and subsequent degradation of the tumor suppressor protein p53. The objective of the present study was to test whether a single acute stress, which manifests long lasting changes in behavior, affects the interaction of Mdm2 with p53, b2AR, and b Arrestin-1 in the dorsal and ventral hippocampal CA1. Adult rats were subject to underwater trauma, a brief forceful submersion under water. A month later, behavioral tests were conducted and immediately followed by biochemical analysis. Elevated plus maze tests confirmed that a month after trauma the animals present heightened levels of anxiety. An examination of the CA1 hippocampal areas of the same rats showed that underwater trauma caused a significant increase in the association of Mdm2 with b2AR, b Arrestin-1, and p53 in the ventral but not dorsal CA1. Our results provide support for the idea that stress-related events may result in biochemical changes restricted to the ventral 'emotion-related' parts of the hippocampus.

Mismatched microRNA/acetylcholinesterase interaction as a diagnostic predictor of anxiety disorders
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MicroRNAs (miRs) may modulate entire pathway(s) by simultaneously interacting with conserved sequence motifs in multiple mRNA targets. Therefore, single-base mismatches preventing the miR-based repression of one mRNA target might lead to elevated levels of this target while exacerbating silencing of its other targets, resulting in bidirectional modulations affecting the entire pathway. Here, we report a primate-specific miR which impairs cholinergic signaling by interacting with the 3'-untranslated region of acetylcholinesterase (AChE) mRNA, increasing the risk of chronic and acquired anxiety-related diseases. We further provide surface plasmon resonance (SPR) evidence that a single nucleotide mismatch in the AChE target site for this miR weakens its AChE interaction by 15-fold. Also, in transfected cells, this mismatch led to greater miR-mediated suppression of another of its targets, the anxiety regulator Rho GTPase CDC42. Furthermore, 76/372 healthy young carriers of this SNP in the HERITAGE cohort (average age: 34 years) showed higher trait anxiety, systolic and diastolic blood pressure and inflammation ($p<0.001$). Our findings present a multi-leveled approach for studying the physiological impact of specific miR-target interactions. At

the translational level prognostic SNP genotyping for evaluating the risk of anxiety-related diseases in mismatch carriers is important because these specific risks may be minimized by changes in life style and prophylactic treatment.

Compartmentalization of voltage-gated Ca2+ channels in the membrane of rat anterior pituitary cells

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Introduction: Voltage-gated Ca^{2+} influx (VGCI) through Ca^{2+} channels plays a key role in the secretion of pituitary hormones. It is well established that L-type Ca^{2+} channels are involved in this VGCI. Whether non-L-type Ca2 channels contribute to this VGCI is unknown. In this study we examined: 1. whether non-L-type Ca^{2+} channels exist in the membrane of pituitary cells. 2. Whether Ca^{2+} channels are segregated among different membrane compartments in the membrane of pituitary cells.
Results: Whole-cell recordings and the use of specific Ca^{2+} channel toxin blockers revealed a fraction of non-L-type VGCI that might reach ~46 %. Western blotting identified immunblots for; α_{1C}, α_{1D}, α_{1A}, α_{1B} and α_{1E} subunits, corresponding to $Ca_v1.2$, $Ca_v1.3$, $Ca_v2.1$, $Ca_v2.2$, and $Ca_v2.3$ channels. Additionally, RT-PCR identified transcripts for α_{1C}, α_{1D}, α_{1A} and α_{1B} subunits. Transcripts for α_{1E} were non-specific and transcripts for α_{1S} were not detected at all. Taken together these results clearly demonstrate the co-existence of L-type ($Ca_v1.2$ and $Ca_v1.3$) and non L-type ($Ca_v2.1$, $Ca_v2.2$ and $Ca_v2.3$) Ca2+ channels in the membrane of anterior pituitary cells. Whether these channels are segregated among different membrane compartments was further investigated in flotation assays, demonstrating that $Ca_v1.2$ and $Ca_v2.1$ channels were mostly localized in light Nycodenz gradients fractions, i.e., in lipid raft domains. $Ca_v1.3$ channels were distributed among both light and heavy gradient fractions, i.e., among raft and nonraft domains whereas $Ca_v2.2$ and $Ca_v2.3$ channels mostly among nonraft domains.
Summary: We demonstrate here multiple pathways for VGCI through L-type and non-L-type Ca^{2+} channels in the membrane of native anterior pituitary cells. Compartmentalizations of these channels among raft and nonraft membrane domains suggest differential regulation by signaling pathways of VGCI in pituitary cells. *Supported by the Israel Science Foundation (ISF) Grant no. 1325/08 to I.N.*

Radiocarbon analysis of neurogenesis in the adult human brain

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Background: Much of the impetus in regenerative medicine is fuelled by the prospect of promoting cell replacement, or blocking unwanted cell production. Without knowing, however, if a specific cell type is renewed in the healthy or pathological situation, it remains uncertain whether it may be realistic and rational to modulate this process. Despite the importance of this information, remarkably little is known about the age of cells in many regions of the adult human brain and body, particularly neuronal replacement in the brain. This is largely due to difficulties in studying this process in humans.
Methods: Using recently established methodology, which integrates biomedical approaches with recent developments in nuclear physics, it is possible to establish the turnover of cells in human tissues. By measuring 14C derived from nuclear bomb tests in DNA it is possible to retrospectively establish the birth date of cells. This principle can be applied to neurons isolated from the adult human brain and neurogenesis in health and pathology in humans assessed.
Results: Previously we reported no evidence for the long term stable integration of newborn neurons in the adult human cortex. More recently we show that contrary to expectation, 14C concentrations in olfactory bulb neurons correspond to atmospheric levels at the time of birth of the individuals, establishing that there is very limited, if any, postnatal neurogenesis. Thus identifying a fundamental difference in the plasticity of the human brain compared to other mammals. Unpublished work on adult human hippocampal neurogenesis will also be discussed.

Neuropsychological subtypes among adults with and without ADHD

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Background: Attention deficit hyperactivity disorder (ADHD) is a prevalent developmental disorder, defined by behavioral symptoms of inattention, and/or hyperactivity and impulsivity which affects approximately 10 % of children and 4 % of the adult population. ADHD has lately been

conceptualized as a heterogeneous syndrome with multiple underlying cognitive mechanisms. In a recent study, Fair and colleagues (2012) applied a community detection algorithm to identify neuropsychological subtypes among children with ADHD and typically developing children. In the present study, we follow the four functions of attention model (Tsal et al., 2005) as a framework for ADHD, and by using graph theory and community detection, we explored whether data-driven attentional subtypes could improve discrimination of adults with/without ADHD.
Methods: 151 adult ADHD participants and 123 controls performed four visual attention tasks assessing performance of the sustained, selective, orienting and executive functions. Four summarizing measures from these four tasks were used as an input to the Newman's community structure in networks algorithm.
Results: Five subgroups were identified by Newman's algorithm. Each subgroup consisted of a similar number of ADHD and controls. In each of those subgroups an SVM classification algorithm was utilized which classified a novel participant as either ADHD or control, with an average of 66 % accuracy, 76 % sensitivity and 58 % specificity. Interestingly, different levels of correct classification were obtained in each of the clusters, ranging from 52 % to 82 %.
Conclusions: Multiple attentional profiles exist among adults with and without ADHD. This research demonstrated (a) how a graph theory approach can enrich the theoretical framework of ADHD by revealing the nature of the relations between the four functions of attention (b) how discrimination of ADHD and control participants can benefit from an identifying profile category.

Rescue of neurons from undergoing hallmark tau-induced Alzheimer's disease cell-pathologies by the antimitotic drug paclitaxel

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Through the use of live confocal imaging and electron-microscopy, we documented that mutant-human-tau (mt-human-tau) induces hallmark Alzheimer's disease (AD) cell pathologies in cultured Aplysia neurons. These included: swelling of axonal segments, translocation of tau and microtubules (MT) to submembrane domains, reduction in the number of MTs along the axon, the reversal of the MT polar orientation, impaired organelle transport, accumulation of macro-autophagosomes and lysosomes, compromised neurite morphology and degeneration. When expressed presynaptically these structural changes are associated with reduced EPSP amplitude, faster homosynaptic habituation and the reduced ability to undergo 5HT induced facilitation. The development of these neuronal cell pathologies are rescued by the incubation of neurons expressing mutant-human-tau in 5 nM paclitaxel. Higher paclitaxel concentrations (100nM) do not prevent the unfolding of the pathology. Our results demonstrate that MT-stabilizing (antimitotic) reagents may serve to slow down or prevent the development of tauopathies.
The C. Smith and Prof. J. Elkes laboratory for collaborative research in psychobiology

A cognitive trap: chemistry defines the biology of amyloid proteins, not human language

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Amyloid proteins, whether tau, Abeta, PrPSc, huntingtin (>35Q), alpha-synuclein are considered to play a pathogenic role in a swathe of neurodegenerative conditions. "When Bad is Good" is the title of an editorial accompanying a recent publication showing that we could reverse paralysis and inhibit inflammation in a model in mice of multiple sclerosis, termed experimental autoimmune encephalomyelitis (EAE). Our previous experiments established that amyloidogenic peptides from the small heat shock protein, HspB5, and from Amyloid β fibrils, characteristic of Alzheimer's disease, were therapeutic in EAE, which models aspects of neuroinflammation in multiple sclerosis. To understand the molecular basis for the therapeutic effect, a set of amyloidogenic hexameric peptides, including those from the major prion protein, tau, Amyloid β, HspB5, amylin, serum amyloid P and insulin B chain, were shown to be anti-inflammatory, capable of reducing serological levels of IL-6, and of attenuating paralysis in EAE. Loss of function experiments emphasize the protective role of amyloids: Remarkably, the clinical signs and inflammation of EAE are exacerbated in knockout mice for various amyloid proteins including HspB5, amyloid-β A4, the major prion protein, serum amyloid P, and tau compared to wild type animals. Genetic deletion of molecules that bind amyloid including Apolipoprotein E is known also to exacerbate EAE. We need to reconsider whether amyloid molecules are good or bad. Daniel Kahneman, 2002 Nobel Laureate, wrote "A reliable way of making people believe in falsehoods is frequent repetition, because familiarity is not easily distinguished from truth." (Kahneman Thinking, Fast and Slow). We need to question whether amyloid proteins and hexameric derivatives are not just always 'bad', ie pathological, but might also be protective and physiological. We need to think about this in terms of chemistry not language.

Properties of cultured neuronal networks taken from down syndrome mice

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Down Syndrome (DS) is a chromosomal condition in humans characterized by cognitive impairment. Two murine models for DS exist: Ts65Dn with an extra small chromosome including about 50 % of the ortholog genes of DS, and TC1 which has an extra human 21 chromosome and about 92 % of the DS genes. We have used patterned neuronal cultures from WT and DS littermates to determine the differences in properties of normal and DS neurons. Using one-dimensional cultures we measured the speed of propagation of the network activity. This is sensitive to both synaptic strength and the number of connections per neuron. Our results indicate that the velocities of WT were 50 % higher than Ts65Dn cultures (Ts65Dn: 105±10 mm/sec, 5 cultures, 119 network bursts, control: 153±6 mm/sec, 14 cultures, 315 network bursts) and 25 % higher than TC1 cultures (TC1 132±3 mm/sec, 19 cultures, 890 network bursts, control: 166±5 mm/sec, 13 cultures, 428 network bursts). Imaging of [Ca2+]i variations in populations of cultured neurons provides a reliable measure of network activity. We imaged [Ca2+]i in populations of neurons, and observed that WT was higher by about 50 % than DS (Ts65Dn 0.59± 0.02, TC1 0.52±0.02, WT 1±0.03 (normalized intensity: absolute amplitude divided by baseline)) This result was reproduced in two-dimensional cultures. Higher resolution measurements showed that in both DS and WT almost all neurons fire in each synchronization burst, and therefore it may be that different fluorescence level indicates that DS neurons fire fewer action potentials in a burst. We also found a significant change in spike afterhyperpolarization (AHP): at 5 ms after a spike, AHP amplitude was: TS65Dn -2v± 0.6v (8 cells), WT -9.4v±2.5v (11 cells). This difference may underlie the difference in bursting properties between the control and DS cultures. We conclude that neurons in DS generate networks with different properties than controls.. These results encourage a continuation of the exploration of differences between WT and DS, which may contribute to the understanding of the disease process.

Reading with sounds: sensory substitution selectively activates the visual word form area in the blind

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Using a visual-to-auditory sensory substitution algorithm, congenitally fully-blind adults were taught to read and recognize complex images using "soundscapes"-sounds topographically representing images. fMRI was used to examine key questions regarding the Visual Word Form Area (VWFA): its selectivity for letters over other visual categories without visual experience, its feature-tolerance for reading in a novel sensory modality and its plasticity for scripts learned in adulthood. The blind activated the VWFA specifically and selectively during the processing of letters soundscapes relative to of both textures and visually-complex object categories, and relative to mental-imagery and semantic-content controls. Further, VWFA recruitment for reading soundscapes emerged following two hours of training in a blind adult on a novel script. Therefore, the VWFA shows category-selectivity regardless of input sensory modality, visual experience and long-term familiarity or expertise with the script. The VWFA may perform a flexible task-specific rather than sensory-specific computation, possibly linking letter shapes to phonology.

Sweet neurobiology: new insights into the importance of glycosylation in Alzheimer's disease

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Neurodegenerative diseases are associated with pathogenic oligomers of misfolded proteins that aggregate and cause loss of neurons in the brain. One process which can be affected in neurodegenerative disorders is post-translational protein modification, known to be derailed during aging. Protein modifications e.g. phosphorylation, acetylation, glycosylation and oxidation are critical to normal function of many proteins. We focus on protein glycosylation. The majority of proteins synthesized in the rough ER undergo glycosylation, an enzyme-directed site-specific process. Protein glycosylation also occurs in the cytoplasm and nucleus as an O-GlcNAc modification, which, interestingly, competes

with phosphorylation of the same amino acids. We explore the role of glycosylaition in Alzheimer's disease (AD). The hallmarks of AD are Aβ plaques and neurofibrillary tangles of hyper-phosphorylated tau protein. Several reports indicated vast alterations in protein glycosylation in the brain of AD patients, while others demonstrated changes in glycosylation of specific proteins related to AD pathology in the disease state, such as tau and APP, the Aβ precursor.

Using an in silico approach we found that many glycosylation-related enzymes exhibit different expression profile in brains of AD patients as compared with healthy subjects. We next studied the effect of enhancing or reducing expression of the glycosylation-related genes in transgenic Drosophila over-expressing human tau, which serve as an established AD model. We identified key glycosylation enzymes, both augementing and ameliorating tauopathy symptoms using the Drosophila eye neurodegeneration as a model. For example, over-expression of CG6370, the Drosophila homologe of human RPN2, partially ameliorated the defective eye phenotype caused by tau over-expression. As expected, silencing CG6370 increased neurodegeneration. The effct of leading enzymes on tau pathology will be further evluated behaviorally and biochmically.

Evidence for impaired social behavior associated with decreased BDNF in DISC1 muted mice, a genetic model for Schizophrenia

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Background: Schizophrenia (SCZ) is a prevalent psychiatric disease affecting approximately 1 % of the population. Evidence indicates that polygenic factors combined with a variety of environmental insults influence neurodevelopment that enhances the vulnerability to develop SCZ. Disrupted in Schizophrenia 1 (DISC1) is considered the most prominent candidate gene for SCZ. The disease is associated with complex of neurotransmitter

disregulation, predominantly increased dopamine, decreased GABA and glutamate resulting in low glutamate–decarboxylase 67 (GAD67) and altered availability of brain neurotrophic factors mainly BDNF. We have used male and female transgenic mice expressing a mutant DISC1 gene (acting as a dominant negative DISC1 mutant). Mice (wild type compared to DISC1) were tested in several behavioral procedures. Behavior was videotaped and analyzed using the Noldus system and software.

Results: Our results in the open field test indicate that DISC1 mice showed lower locomotor activity accompanied by increased anxiety. In the novel object recognition test DISC1 mice revealed a lower cognitive score, and in social preference test impaired sociability compared to wild type mice. Biochemical analysis of prefrontal cortex and hippocampus reveaedl a significant decrease in BDNF in the DISC mice compared to controls. Surprisingly, DISC1 mice showed higher levels of GAD 67 and pERK. In addition we found a marked decrease in the expression of canabinoid-1 CB1 receptors in DISC-1frontal cortex of females and hippocampus of males.

Conclusions: DISC1 mice show disrupted behavioral pattern associated with increased anxiety and impaired cognitive and social behavior. These modifications paralleled a decrease in brain BDNF and alterations in pERK and CB1 brain expression. Our .results show for the first time a possible link between DISC1 and the cannabinoid system.

Sparse decoding and blind extraction of representational structure from human spike trains

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Background: Brain–machine interfaces (BMIs) rely on decoding the activity of neuronal populations from multiple electrodes. The implantation procedures, however, guarantee an anatomical distance between recording sites rather than a physiological task-relevance of recorded neurons. Therefore, selection of task-relevant neurons is critical to decoder performance. Nevertheless, it is typically performed heuristically.

Results: We describe two new methods for analyzing neural spike trains. The first algorithm decodes/classifies volitional actions from multiple spike trains, by automatically selecting relevant neurons. The method uses a sparseness constraint during the classification to simultaneously optimize neuronal weights and select the relevant neuronal features. The new method was tested against a range of existing methods using simulations and recordings of the activity of 1592 neurons in 23 neurosurgical patients who performed motor or speech tasks. The parameter estimation algorithm is orders of magnitude faster than existing methods and achieves significantly higher accuracies for both simulations and human data.

As a second step, we employ the classifier and its error structure (confusion matrices) to deduce the natural organization of features represented in the population-level neural code. The method was employed to extract the representation of vowels in the neuronal population code. Using activity of 716 neurons from 11 neurosurgical patients, our method has

shown that the neuronal representation of vowels matches that of the international phonetic alphabet (IPA) chart, representing the highest point of the tongue during articulation.

Conclusions: The highly effective performance of sparse decoders and the ability to discover hidden structures in the representation of population-level neural firing patterns could contribute to both BMI systems and basic neuroscience research.

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Impaired holistic processing in congenital prosopagnosia and its possible amelioration

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Background: Congenital prosopagnosia (CP) is a face processing deficit that is often accompanied by impaired holistic processing even for non-face stimuli that was suggested to account for the difficulty in face perception. Here we further investigate this intriguing observation by examining 8 CP individuals and their controls on two tasks involving holistic processing of non-face stimuli.

Results: We first, applied a classic Garner interference task in which participants were asked to judge the width of visually presented rectangles while ignoring their task irrelevant height. As expected, controls were affected by changes in the irrelevant dimension hence exhibiting Garner interference. In contrast, the CP group demonstrated no interference, attesting to their impaired holistic processing. We then used a variation of the Navon task in which participants were presented with a large arrow made of small arrows. The small and large arrows could either point to the same (congruent) or different directions (incongruent). Participants were asked to attend to the global or local shape in separate blocks. The critical modification was the addition of an auditory, warning cue, which preceded the arrow in half of the trials and was shown to enhance global processing in normal participants (Weinbach & Henik, 2011; 2012). As expected, the CP group differed from controls in the no-warning trials and showed a local processing bias. However, similarly to controls, they benefited from the warning cue such that during the local task, global interference was greater in warning compared to no-warning trials.

Conclusions: Together, the results highlight the holistic impairment in CP and underlie it as a possible mechanism for the impairment in face perception. The enhancement in global processing obtained in these individuals, following the warning cue, could serve as a potential rehabilitation mechanism which may ameliorate, at least to some extent, the face processing deficit.

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Ongoing excitation and inhibition are not balanced across brain states

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The prominent feedback connections between excitatory and inhibitory neurons in the mammalian cortex suggest that the cortex operates at a balanced state in which inhibition modulates the magnitude of excitation. We recorded intracellularly the ongoing excitatory and inhibitory inputs onto cortical neurons across distinct brain states, induced by altering the depth of anesthesia. While the magnitude of inhibition increased under the deeper-state, the magnitude of excitation was not state-dependent. Importantly, these results were recapitulated using different anesthetics, indicating that state-dependent changes in the balance between excitation and inhibition are mediated upstream to the cortex. That excitation was indifferent to the state-dependent changes in inhibition, suggests that ongoing cortical activity is not at a balanced state but rather operates as expected from feedforward mechanisms.

Motor coding in the human supplemental motor area

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Background: The neural code in the motor system was intensively studied using animal models, in which recordings are made after a long training period. It is largely unknown how these studies reflect the naive coding in the human motor system, where such a prolonged training is not present. Using deep electrodes, we study the activity characteristics of human neurons in the supplemental motor area (SMA), a brain region known to participate in movement planning and execution.

Results: Many human neurons exhibit very narrow sensitivity to movement direction, as compared to parallel neurons in the SMA and primary motor area (M1) of rhesus monkeys. These narrow direction tuning curves yield significantly lower signal correlations between pairs of cells with close preferred directions. When the full activity profile of human SMA neurons is used to infer movement direction from spike counts, the decoding accuracy is inferior to that obtained with the similar full activity of monkey neurons. This difference is largely due to a sharp decline in decoding accuracy after movement onset, which was not observed in monkey SMA or M1.
Conclusions: Coding of movement direction in SMA neurons in naive human subjects differs significantly from the parallel coding in monkeys: in humans, the tuning curves are narrower, the signal correlations are weaker, and the decoding accuracy is lower. These differences could be due to effect of training, or due to inter species differences. Also, human SMA neurons operated in a "launch and forget" mode when coding movement direction, and may be rapidly switching to code other aspects of movement such as movement speed.

Synchronized rhythmic neuronal activity encodes the novelty value of a stimulus during social recognition

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Background: The ability of an animal to recognize familiar individuals is critical for mammalian social behavior. Most mammals rely primarily on olfactory cues for social recognition. A meeting between two unfamiliar rats or mice usually starts with a period of intensive olfactory investigation, which precedes further social interactions. We used the social recognition paradigm, which is known to depend on brain activity of both oxytocin and vasopressin, to explore the electrophysiological changes in the brain of behaving rats during the acquisition of social memory. By combining video recordings with wireless data acquisition, we could monitor neuronal activity in several brain areas, including the main and accessory olfactory bulbs, the medial amygdala and the lateral septum, in behaving rats.
Results: A power-spectrum analysis of the recorded LFP signals revealed a peak around 8 Hz (theta rhythm) which was most prominent during investigation of a novel animal and gradually declined during repeated investigations of the same stimulus. Accordingly, the strength of the theta rhythm in these brain areas correlates with the time of investigation, which serves as a measure for the social recognition memory. These changes in neuronal activity are social stimulus-specific and do not occur during object recognition. Moreover, they are not limited to episodes of actual investigation hence seem to represent an internal state of the animal during social behavior.
Conclusions: We conclude that social investigation behavior evokes synchronized neuronal activity in a dispersed neuronal network known to be modulated by neurohypophysial hormones, the magnitude of which is proportional to the novelty of the social stimulus.

Stimulus asynchronicity during pair associate learning modulates ERP correlates of episodic cued recall

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The time course and distribution of brain processes supporting associative retrieval have yet to be well characterized. We investigated one important aspect of associative memory: the ability to remember connections between stimuli experienced asynchronously. We hypothesized that variations in the temporal structure of stimulus presentation would affect the nature of the associative binding of the stimuli, in turn affecting processes required for retrieval. Young adult participants studied pairs of object pictures which were presented either simultaneously or sequentially, by making semantic judgments about the relationships between the depicted objects. At retrieval, one pair member was presented, and participants were asked to recall the pair-associated item. EEG was recorded while subjects performed the recall task, allowing us to track the temporal dynamics of the retrieval processes. The results indicated that there are two activation patterns associated with retrieval success. An early retrieval success effect was observed in both tasks, maximal in frontal channels at ~350 msec post cue presentation. A later retrieval success effect was maximal in posterior channels at ~800 msec, but was only apparent in the asynchronous condition. This indicates that episodic retrieval of asynchronous association involves additional processes beyond those needed for retrieval of synchronous events.

Acute stress effect on perception and the involvement of attentional load. A behavioral- EEG study

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Background: For optimal performance in a stimuli saturated world it is essential to have attentional selectivity to relevant information. Perceptual load (PL) is created by

processing relevant information while ignoring irrelevant stimuli. Under low PL attentional resources are available allowing irrelevant information to be processed and interfere; however, under high PL this interference is eliminated. Factors such as stress modulate attentional selectivity. It is suggested that acute stress and PL consume the same attentional resources and together enhance attentional selectivity under optimal conditions. We aimed to test the interactions between acute stress and attentional load using the emotional cognitive load paradigm and electroencephalography (EEG) measurements.

Results: 29 healthy students were recruited of which 11 performed the Trier social stress test (TSST) before the task. During the task a target letter was presented along with 1 (low load) or 5 (high load) distracting letters, in the absence or presence of a picture. Subjects were asked to respond to the target letter by pressing a computer keyboard and their response time (RT) was measured. In the control group, heightened PL or the presence of a picture increased RTs. However, in the stress group only under low PL, RTs increased due to picture presence. EEG results were consistent with the behavioral results and revealed virtually no significant differences in electrical brain activity in the absence or presence of a picture, under high PL conditions. In the control group, high load condition evoked increased activity in both hemispheres in the Cuneus, middle temporal gyrus, inferior parietal lobule, and posterior cingulate while stress evoked increased activity in additional areas.

Conclusions: Stress enhance attentional selectivity but only when attentional resources are limited. We suggest that high PL and stress consume the same attentional resources and the same neurophysiological processes.

The breath-prints of Alzheimer's and Parkinson's diseases: a pilot study

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Background: The prevalence of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) is expected to increase as the population ages. To date, the ante-mortem diagnosis of AD and PD still relies mostly on clinical symptoms and is thus associated with highly variable sensitivity and specificity, depending on the proficiency of the treating physician. Breath testing based on the analysis of volatile organic compounds (VOCs) is currently attracting much research interest as a possible fast and non-invasive alternative diagnostic method for various diseases. The objective of this research is to identify VOC patterns in the exhaled breath of patients using nanomaterial-based-sensors and to assess whether there are specific breath-prints to AD and PD that could be utilized to identify the diseases.

Results: Alveolar breath was collected from 57 volunteers (AD and PD patients and healthy controls) and analyzed using sensors based on organically functionalized carbon nanotubes or gold nanoparticles. Discriminant factor analysis was applied to detect statistically significant differences between study groups and classification success was estimated using cross-validation. The sensors could clearly distinguish both AD and PD from healthy states, as well as AD from PD (classification accuracy: 85 %, 78 % and 84 %, respectively). The chemical composition of the breath samples was studied using gas chromatography/mass spectrometry; the analysis showed statistically significant differences in the average abundance of several VOCs in the breath of AD, PD and healthy subjects, thus supporting the breath-prints observed with the sensors.

Conclusions: The results of this pilot study point to specific breath-prints of AD and PD that could have future potential to aid diagnosis, especially in non-specialist settings. Further studies to evaluate the usefulness of these breath-prints in clinical practice are underway.

Synchronization between grid cells in the medial entorhinal cortex

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Grid cells are an exclusive category of excitatory neurons of the medial etorhinal cortex (MEC). These cells are thought to participate in formation of a cognitive map underlying spatial navigation. Grid cells fire with a spatially reproducible hexagonal pattern, when the animal is foraging in an open field. The hexagonal pattern of each cell can be characterized by a typical spatial frequency, orientation and spatial phase. Previous studies have shown that the relative spatial phase between two grid cells in the MEC is preserved between environments. One explanation for this phenomenon is that the connectivity between cells affects the spatial phase between pairs of grid cells. Indeed, many models share the tenet that grid cells closer in phase are also more strongly interconnected. In order to check this assumption, we analyzed a database of grid cells available publically (Sargolini, Fyhn et al. 2006). We compared pairs of grid cells, and classified those cells, which have a similar spatial

frequency, as belonging to the same module. We then measured the spatial phase difference between pairs of grid cells belonging to the same module. In addition, we compared the temporal cross-correlations at short windows between the same pairs of grid cells. We found that pairs of neurons which are similar in spatial phase have a tendency to be temporally correlated to each other. Moreover, there was a functional relation, such that the smaller the spatial phase difference was, the larger was the temporal correlation. All in all, our results demonstrate that spatial relations between grid cell fields may be explained by synchronization between highly interconnected cells in this network.

Dysfunction in DJ-1 protein linked to Parkinson's disease accelerates microglia neurotoxicity

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Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting more than 1 % of individuals over 55-year-old and more than 3 % of those over age 75. Activation of glial cells in the CNS is the first defense mechanism against pathological abnormalities that occur in neurodegenerative diseases. Recently, we and others have discovered that microglia dysfunction may lead to stress conditions resulting in neuronal death. DJ-1, an oxidative stress sensor that localizes to the mitochondria when the cell is exposed to oxidative stress, was linked to PD. We postulate that DJ-1 dysfunction may affect microglia cell activity in PD.
Methods: DJ-1 mutations are loss of function mutations. In order to address the role of DJ-1 in microglia activity we down-regulated the DJ-1 expression using shRNA approach. Microglial cell line was transfected with shRNA against DJ-1 or with non target shRNA used as control, and cell activity was evaluated by gene expression, protein levels, reactive oxygen species production and neurotoxicity.
Results and conclusions: We found that down-regulation of the DJ-1 gene increases microglial pro-inflammatory cytokines IL-1β and IL-6 levels, as measured by ELISA. Furthermore, DJ-1 impairment results in increased microglia production of reactive oxygen species (ROS) levels and accelerated microglia neurotoxicity in rotenone models of PD. We suggest that dysfunction in DJ-1 protein in microglia may accelerate neuronal death in PD. Further studies of DJ-1-mediated cellular pathways in microglia may provide useful insights into the development of PD providing future avenues for therapeutic intervention.
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Mouse model of empathy reveals differences in neural activity underlying recollection of 'witnessed' vs. 'experienced' trauma

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The DSM IV criteria for diagnosing post traumatic stress disorder (PTSD) include both personal experience and witnessing a traumatic event. However, physiological differences between recalling 'experienced' and 'witnessed' trauma are not well understood, and their investigation using animal models is a challenge. Recent observational fear learning protocols indicate that mice exhibit freezing following witnessing other mice receiving foot shocks, and that freezing duration is related to familiarity between these mice. Still, the neural substrates of long term representations of 'witnessed' trauma in rodents remain obscure. The current study compared behavioral and neural responses in three groups of mice: mice subjected to foot shocks (Shocked); mice that observed a cage-mate being shocked (Observer); and cage-mate pairs that were not shocked (Naive). In a context test two weeks after the manipulation, a gradient in freezing duration was evident; Observer mice freeze significantly longer than Naive mice but significantly shorter than Shocked mice. Furthermore, when compared with Naive mice, Observer mice spend significantly more time directing their attention to their Shocked cage-mates. Neural activity during the context test, assessed by immediate early genes expression, differed between the groups in the lateral septum, bed nucleus of the stria terminalis, basolateral/central amygdala and paraventricular nucleus of the hypothalamus but not in the hippocampus, medial amygdala or prefrontal cortex.
The findings suggest that the although the behavioral manifestation of recalling 'experienced' and 'witnessed' trauma may appear similar, they may be mediated by activity in discrete neuronal circuits. Characterizing these neural differences may provide opportunities for better targeted interventions in PTSD patients.

A New multispectral combinatoric tracing technique enables mass neuronal mapping and reveals two level circuit rearrangement during development

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The fundamental aspect of neural organization is that each neuron's axon projects specifically to particular regions but not to others. Due to the remoteness of neuronal somata from their targets and the convolution of the projections of neighboring neurons, it has been difficult to map the projections of many different nearby neurons in the same preparation. Therefore, we have developed a novel strategy allowing us to map the precise projections of neuronal cells to their targets. We injected the tracer Wheat Germ Agglutinin (WGA) conjugated to 4 spectrally distinct colors in 4 proximate points in the neurons target area. The concentrated dyes diffusely dispersed from the injection points and created an area in which each small region contains different combinations of the 4 colors, determined by the distance of this region form each injection point. Neurons innervating this area took up the WGA with the unique color combination and transported it to the cell body in vesicles. Thus, many neuronal somata distanced from the injection point contain a distinct combination of colors which can be matched to the original injection site. This enables us to reconstruct the axonal arbor distribution in the target area of that neuron. We named this technique Neuronal Positioning System (NPS) due to the ability to detect a neuron's position by its distance from known reference points. Using this approach we were able to map projections of dorsal root ganglion (DRG) neurons to the skin preparation of a rodent hind paw and map projections of the submandibular (SM) ganglion cells to their large peripheral end organ, the SM gland. Moreover, application of NPS in a Brainbow mouse demonstrated that neurons in the SM ganglion, which are innervated by the same axon, occupy proximate areas in the gland. Thus, this approach enables us, for the first time, to show the relation between the developments of two levels in the same neuronal circuit.

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Astrocytic P2Y1 receptors induce the spread of calcium waves from astrocytes to neurons

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ATP released by astrocytes mediates the spread of Ca2+ waves through the astrocytic network. It was shown in the hippocampus that ATP affects also the excitability of CA1 pyramidal cells (PCs) by activating P2Y1 receptors. However, recent evidence suggests that PCs do not express P2Y1 receptors. We therefore hypothesized that the PCs respond to astrocytic P2Y1 receptor activation via other signaling pathways. Application of the P2Y1 receptor selective agonist ADPβS to rat hippocampal slices led to a significant increase in cytosolic Ca2+ concentration (Cai) both in astrocytes and in PCs, monitored optically with the Ca2+ indicator Fluo-4. This effect was seen also in presence of blockers of excitability or of fast synaptic transmission. The evoked increase in Cai was due, at least in astrocytes, to Ca2+ release from the endoplasmic reticulum (ER), as it was abolished by ER depletion. Intriguingly, elimination of astrocytes, by preincubation of slices with the gliotoxin L-AA, prevented the ADPβS-induced Cai elevations in PCs. However, L-AA application did not prevent Cai elevation in PCs induced by caffeine or mGluR activation. The ADPβS-induced Cai elevation in PCs, but not in astrocytes, was blocked by MCPG, a mGluR antagonist. We conclude that extracellular ATP mediates the spread of intracellular Ca2+ waves from astrocytes to PCs by activating astrocytic P2Y1 receptors, causing Ca2+ release from astrocytic ER. This, in turn, causes the release of astrocytic glutamate, which activates mGluRs in PCs, causing Ca2+ release from its ER. This cascade may participate in astrocytic-neuronal signaling in a variety of physiological and pathophysiological processes. Supported by ERC (AB), ISF (YY), and the Henri J. and Erna D. Leir Chair for Research in Neurodegenerative Diseases (YY).

Representation of three-dimensional space in the hippocampus of freely flying bats

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Place cells are neurons in the mammalian hippocampus which are active in a restricted region of the environment; this activity region is termed the 'place field'. Place cells are considered pivotal elements in the brain circuitry underlying spatial memory and navigation, and are typically studied in one-dimensional (1D) or two-dimensional (2D) environments. Little is known, however, on how these neurons encode three-dimensional (3D) space. This question is important, because most animals, on air, water or land, navigate in 3D environments. Here, we used a tetrode-based microdrive and a custom, lightweight multichannel neural telemetry system, and conducted the first electrophysiological recordings from the hippocampus of a freely flying mammal, the Egyptian fruit bat. Experiments were conducted in two different 3D enclosures, a 6×5×3 meters rectangular cuboid enclosure and a 3×3×3 meters cube, and revealed that the 3D firing fields of single hippocampal neurons were strongly tuned to all three dimensions of the environment. In both experimental setups, the 3D firing fields represented each dimension with the same precision (same size of place field in the x, y and z-dimensions), and were isotropically tuned in all directions. Individual place-fields from different neurons occurred in different locations in the room, and the firing locations across the neuronal population spanned the flight-room, representing uniformly the entire available environment. The firing fields of individual neurons were stable throughout the recording session, thus providing accurate and reliable representation

of the bat's position in 3D space during flight – including altitude (z-height). Finally, the neural activity of almost all hippocampal place-cells did not show theta modulation during flight, which argues against a temporal phase-code for 3D position. Taken together, these results suggest that the mammalian hippocampus represents 3D space by a uniform and isotropic rate-code.

Brain angiotensin receptor type 2 mediates nueroprotection after traumatic brain injury

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Background: HA is a preconditioning model achieved by long term exposure to mild heat (34±1C°) for a period of 4 weeks. This model has been found to suggest cross tolerance against various novel stressors including traumatic brain injury (TBI). In efforts to characterize the mechanisms underlying HA mediated nueroprotection, we have previously found up regulation of hypoxia inducible factor 1α (HIF-1α), brain derived neurotrophic factor (BDNF) alongside with reduced apoptosis. However upstream signals or receptors responsible to described alternations are currently unknown. One candidate receptor that is capable to trigger such effects was also found to mediate nueroprotection in brain ischemia. is angiotensin receptor type 2 (ATR2). **Aims**: In the current study we have used ATR2 antagonist to explore ATR2 role in HA phenotype establishment. Other perspective of this study was to evaluate the implication of ATR2 pharmacological activation in control (normothermic) mice.
Results: We have found that ATR2 blockage did not affect post injury recovery or cognitive function of the control group, however HA benefits were abolished after the treatment. Moreover, ATR2 activation in control mice dramatically improved functional recovery and cognitive memory in a dose-response manner.
Conclusions: We conclude that ATR2 has a role in adapting HA neuroprotective phenotype and most importantly, may be a novel drug target to treat TBI victims.

The Hoffman Leadership and Responsibility Program , the Hebrew University of Jerusalem

The dopamine D4 receptor gene shows a gender sensitive association with cognitive empathy: Evidence from two independent samples

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Increasing evidence point to a role of dopaminergic pathways in modulating social behavior. Specifically, a polymorphic region in the third exon of the Dopamine D4 receptor (DRD4) has been associated with a host of social behaviors in an environment sensitive manner. Empathy is thought to be an important motivator of prosocial behaviors and is multi-faceted, combining cognitive empathy (CE) and emotional empathy (EE). In the current study we analyzed the association between DRD4 and the two empathy facets, and it's contingency on gender as a meaningful predictor of empathy. A large sample of adult participants (477 participants) was inventoried for general empathy, CE and EE and genotyped for the DRD4 exon 3 polymorphism. Women scored higher than men on all empathy measures and no main effect of genotype was observed. Importantly, a significant interaction between genotype and gender emerged specifically for CE, with women carriers of the 7R-allele scoring higher than non-carriers, whereas in men 7R-carriers scored lower than -7R. Notably, these findings were replicated in an independently recruited sample (121 participants). The current report shows that the DRD4 exon3 polymorphism is associated with cognitive empathy and the direction of the association is gender sensitive.

Non-invasive detection of brain microvascular dysfunction by near infrared spectroscopy

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Structural and functional disturbances of the brain's microcirculation are common in aging. However their contribution to cognitive impairment is uncertain. We have developed an innovative non-invasive near infrared spectroscopy (NIRS) system to address this question, allowing us to obtain quantitative, absolute measurements of oxygen-bound [HbO], oxygen-free [Hb] and total brain hemoglobin concentration [HbT], hemoglobin oxygen saturation (StO2%), blood volume and vascular reactivity at rest and in response to transient physiological challenges in rat models of Vascular Cognitive Impairment (VCI). NIRS measurements in the Spontaneous Hypertensive Rat model of VCI reveal significant decrease of cortical [HbT] without change in StO2% and a tendency for attenuated response to hypercapnia challenge compared to

normotensive controls. In folate-deficiency (FD) induced VCI, Hallacoglu et al. observed decreased hemoglobin concentration [HbT] and cerebral blood volume, decreased StO2%, and impaired vascular reactivity. Our goal is to validate the hypothesis that FD causes brain vascular rarefaction and concurrent reduction in CBV and StO2% and determine whether Methionine supplementation, an essential amino acid whose metabolic salvage is a product of folate-dependent metabolism, would ameliorate FD effect on NIRS. We have found that [HbT], [HbO] and StO2% were reduced by FD diet but were not restored by Methionine. [Hb] was unaffected by FD and by Methionine. There was a significantly more profound cerebrovascular reactivity in the control group as oppose to FD. This was restored by Methionine to control levels. Together, these findings are consistent with the hypothesis that reduced [HbT] reflects capillary rarefaction and reduced brain perfusion. Ultimately, this will advance the validation of absolute NIRS for non-invasive monitoring of cerebral microvascular health in humans.

Transcranial magnetic stimulation enhances blood-brain barrier permeability

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Transcranial magnetic stimulation (TMS) is a non-invasive method that uses electromagnetic field generation to induce low –level electric currents in the cerebral cortex. This induction is produced by passing high-level electric currents through an electromagnetic coil placed adjacent to the scalp. The blood-brain barrier (BBB) is a complex structure designed to maintain a stable extracellular environment by limiting the penetration of intravascular hydrophilic molecules into the brain. While an intact BBB is essential for proper brain functions, it also limits the delivery of chemotherapeutics and the effective treatment of primary and metastatic brain tumors. Thus, a strategy to increase the efficiency of drug delivery to the brain should induce a transient, preferably local increase in BBB permeability to allow better administration of chemotherapy in the chosen time and place. Using a novel approach for analyzing BBB permeability in-vivo, we present here that the application of TMS can result in increased BBB permeability in anesthetized rats. Before, following and post stimulation the rat is injected intravenously with a BBB-impermeable fluorescent tracer, (e.g. sodium-fluorescein, MW=376 Da), and cortical surface images are acquired at 5/s simultaneously. Offline image analysis is performed using home-made MATLAB algorithms in order to quantify BBB permeability. Our results indicate that repetitive TMS (rTMS) at low frequency (1 Hz) is more efficient in increasing BBB permeability compared to stimulation at 10Hz, and that this increase lasts for about an hour after the stimulation. We also similarly measured rTMS induced BBB permeability to various seizure-inducing factors (e.g. Penicillin) and chemotherapeutics. These findings suggest that rTMS may be used as a new, non-invasive approach to produce controlled and transient BBB opening for the more efficient delivery of drugs into the brain.

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MRI multiparametric hemodynamic characterization of the normal brain

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Introduction: Blood oxygenation level dependent (BOLD) imaging under either hypercapnia or hyperoxia, and dynamic susceptibility contrast (DSC) imaging have been used to study vascular properties in healthy subjects and in patients. These techniques enable a comprehensive characterization of the structure and function of the brain's vascular system. The aim of this study is to characterize brain tissue vascularity and regional differences in healthy subjects using multiparametric hemodynamic MRI methods.

Methods: 21 healthy subjects were included in this. MRI protocol was performed on a 3 T MRI scanner and included: DSC, BOLD hypercapnia and hyperoxia challenges. Signal recovery, maximum signal change, cerebral blood volume and flow maps were calculated from the DSC images and areas under curve maps were calculated from the DSC and BOLD images. Unsupervised k-mean classification was performed based on these three methods. The obtained clusters were later identified as dura&blood vessels, gray matter and white matter. Hemodynamic values were measured in the identified brain tissues; vascular territories; arteries and veins.

Results: Significant differences emerged between all tissue types for most hemodynamic parameters, supporting the grading vascularity of the tissues (BVD>GM>WM). Significant differences between vascular territories were detected only for the DSC parameters, with delayed start time and prolonged transfer time in the posterior cerebral artery compared to other territories. The DSC start time of the vein was significantly delayed by 1.3 sec relative to that of the arteries.

Conclusions: Multimodal vascular characterization of several brain areas was performed; reference values were obtained from the healthy brain; and differences between vascular territories and between veins and arteries were detected. Findings

from this study may have clinical importance in patients with cerebrovascular diseases such as stroke and carotid stenosis.
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Stereo-fusion acquisition and preservation: effects of peripheral fusion locks

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We studied the efficiency and stability of the oculomotor mechanism to create stereo fusion undertaken with, or without zero-disparity fusion locks. We were motivated by optometric experience showing that peripheral locking devices improve the stability of binocular vision. Eight normal-sighted participants were trained to elicit free-fusion stereo images embedded in RDS stereo pairs. Stimuli were static Landolt-C rings or"E" targets (2 deg diameter), displayed in one of four directions. In phase 1 we tested stimuli with crossed or uncrossed horizontal disparity of 1 Pixel (1.7 arc-minutes). In a second phase the same participants were presented with identical stimuli, but horizontal disparities of 3 5or7Pixels (5.2,8.6, and 12 arc-minutes). The peripheral locks were white rectangular frames, symmetrically superimposed on target area Small Frame:17.5× 9 deg. Large Frame: 25.5×13 deg. We measured reaction-times for Landolt-C gap or letter E direction detection. Binocular eye-movements were recorded (EyeLink1000 system) during trials and ITI's. With 1-Pixel horizontal disparity displays (Phase1), presence of both peripheral locks significantly enhanced stereo-fusion efficiency. In all experimental conditions the task of uncrossed fusion was more difficult than crossed fusion. Fusion locks significantly improved performance with uncrossed fusion targets, which was found extremely difficult without fusion locks. Contrary to Phase1 with 3,5or7-Pixels horizontal disparity in Phase2 the effect of peripheral locks was reversed and interfered with the stereo fusion process. In both phases, detection with crossed fusion was more efficient and easier than uncrossed fusion. We also observed4 of the participants to have reversed fusion directions: targets they perceived recessed were perceived by the others as in front. Our results support the role of remote peripheral zero-disparity images as trigger of a sustained Vergence fusion-lock mechanism during stereopsis.

Primary oligodendrocyte death does not elicit anti-CNS immunity

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Anti-myelin immunity is commonly thought to drive multiple sclerosis, yet the initial trigger of this autoreactivity remains elusive. One of the proposed factors for initiating this disease is the primary death of oligodendrocytes. To specifically test such oligodendrocyte death as a trigger for anti-CNS immunity, we inducibly killed oligodendrocytes in an in vivo mouse model. Strong microglia-macrophage activation followed oligodendrocyte death, and myelin components in draining lymph nodes made CNS antigens available to lymphocytes. However, even conditions favoring autoimmunity—bystander activation, removal of regulatory T cells, presence of myelin-reactive T cells and application of demyelinating antibodies—did not result in the development of CNS inflammation after oligodendrocyte death. In addition, this lack of reactivity was not mediated by enhanced myelin-specific tolerance. Thus, in contrast with previously reported impairments of oligodendrocyte physiology, diffuse oligodendrocyte death alone or in conjunction with immune activation does not trigger anti-CNS immunity.

General ability vs. expertise in mathematics: An ERP study with school students who answer geometry questions

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Background: Research has been conducted on (a) neural foundation of mathematical cognition (e.g. Dehaene et al., 2003), (б) Human intelligence including individual differences in general intelligence (e.g. Deary et al., 2010), and (c) Mathematical giftedness (e.g., Grabner et al., 2009). However, differences between giftedness and expertise have not been addressed in brain research. We integrated 4 groups of adolescents (43 participants), divided according to general giftedness (G) and mathematical expertise (E). The study uses ERP methodology to shed light on the temporal characteristics of geometric reasoning.
Results: There were no main effects of G and E factor on the accuracy measure. There was significant main effect of E factor on the RT measure: RT(E)<RT(NE). The mean activity in these time frames was significantly lower in S1 than in S2. This finding suggests that the introduction stage demanded fewer cognitive resources than the verification stage. Electrophysiological data revealed also that both G and E factors caused different patterns of brain activity in later time epochs (starting from 300 ms after stimuli presentation) of the process of geometric problem solving. The findings demonstrated that both in anterior and posterior parts of the brain, differences between two subsequent stages of problem-solving are significantly less prominent in the G-E group. The more significant difference was found between the G-E and NG-NE groups.
Conclusion: G factor does not influence problem solving performance. E factors reflects participants expertise which is mainly expressed in RT. We hypothesise that G factor and E

factor are of different neuro-cognitive nature. We hypothesize that G-E students start solving the task at S1 while for NG-NE students main activity starts only at S2.

The Interaction between Alertness and Executive Control

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Background: There is growing interest in how attentional networks interact in order to achieve adaptive behavior. An example is the interaction between executive control—a system that deals with goal achievement—and alertness—a subcortical-based mechanism that modulates the level of arousal. Specifically, studies have revealed an increased cognitive conflict (i.e., congruency) following presentation of alerting cues. This interaction reflects a modulation of higher brain regions (i.e., prefrontal cortex) by a lower subcortical system. However, the mechanisms underlying this effect are unclear.
Results: In a series of studies we found that increased congruency, following alerting signals, was limited to conflict tasks in which spatial attention was required. When no spatial distractors were present, the effects of alerting and congruency were additive.
Conclusion: We suggest that alerting does not actively inhibit executive control as was previously suggested, but rather disrupts conflict resolution by allocating attention to irrelevant competing stimuli in the periphery.

Attenuation of Alzheimer associated cerebral and behavioral deficits by novel multi-target iron chelating compounds in animal model of aging

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Background: Aging of the brain appears to be the main risk factor for Alzheimer's disease (AD) and thus, investigating the pathological brain changes occurring in aging is of crucial importance to treat cognitive diseases. Recently, we have synthesized multi-target non-toxic, brain permeable iron-chelators, M30 and its stable derivative VAR, possessing the N-propargyl moiety of the anti-Parkinsonian drug/monoamine oxidase (MAO)-B inhibitor, rasagiline and the antioxidant-iron chelator moiety of 8-hydroxyquinoline derivative, VK28, as drug candidates for age-related neurodegenerative diseases. The main objectives of this study were to investigate the neuroprotective effects of the novel multifunctional compounds, M30 and VAR in aged rodents. M30 (1 and 5 mg/kg) or vehicle were systemically administered for 6 months to aged mice (15 month-old), and VAR (1 mg/kg) or vehicle were systemically administered for 6 months to aged rats (20 month-old). Behavioral and cognitive tests were performed 4 weeks before the end of treatments.
Results: M30 and VAR treated-aged mice and rats, respectively, exerted significant neuroprotective effects on neuropsychiatry functions and cognitive age-related impairments, accompanied by a marked decrease in cerebral amyloid precursor protein and beta amyloid deposition. Both compounds increased the levels of hippocampal brain-derived neurotrophic factor and its upstream regulator cAMP responsive element binding protein in aged mice and rats. Additionally, M30 and VAR caused a significant selective inhibition of brain MAO-A and -B activities, and markedly regulated cerebral iron accumulation and iron homeostatic-related genes in aged-treated animals.
Conclusions: Our results demonstrated that our novel compounds, M30 and VAR, prevented memory impairments and beta amyloid deposition, and thus may provide a potential therapeutic strategy for age-related neurodegenerative disease, such as AD.

Cannabinoids modulation of the effects of trauma and situational reminders on behavior and synaptic plasticity in a rat model of PTSD

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Background: The formation of a fear memory following a traumatic event is an important mechanism for the subsequent development of anxiety disorders, such as post-traumatic stress disorder (PTSD). The consequences of exposure to trauma are affected not only by aspects of the event itself, but also by the frequency and severity of trauma reminders. There is a growing body of data pointing to a therapeutic potential of cannabinoids for treatment of PTSD. Here we aimed to test the hypothesis that exposure to a single traumatic event followed by discrete reminders of the event would have a profound impact on the neuronal networks implicated in emotional disorders in rats, and to explore whether early intervention using cannabinoid activation would prevent the effects of exposure to trauma and reminders on behavior and plasticity.
Results: Rats were exposed to a single shock (1.5 mA, 10 sec) followed by exposure to two contextual 1-minute reminders of the shock on days 3 and 5 after the trauma. WIN55,212-2 (0.5 mg/kg) or vehicle were injected i.p. 2 hrs after trauma exposure. One week after the initial trauma, we examined the rats' ability to extinguish the initial trauma using an avoidance procedure and measured plasticity in the hippocampal-accumbens pathway. We found that shock exposure resulted in the blockade of extinction, hence rats demonstrated persistent avoidance from the trauma context. The agonist WIN prevented this

effect. Shocked rats exposed to reminders also demonstrated impaired LTP in the hippocampal-accumbens pathway and this impairment was prevented by the cannabinoid agonist WIN55,212-2.

Conclusions: These results strongly support the notion that cannabinoid activation in proximity to trauma can prevent the subsequent development of anxiety disorders and PTSD in particular.

Stimulating the brain through the nose

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In animals, electrical stimulation of the olfactory epithelium induces responses at the olfactory bulb. Whether these responses reflect an olfactory percept remains unclear. Electrical stimulation of the human olfactory epithelium has generated mixed results, ranging from diverse olfactory sensations (Uziel et al., 1973), to no sensation at all (Straschill et al, 1983, Ishimaru et al, 1997). We set out to test the hypothesis that modern methods would allow us to generate odor perception by electrical stimulation. We used endoscopic guidance to place a pure silver stimulating-electrode on the ventral surface of the middle turbinate. Stimulation was generated using a battery-powered electronic stimulator, driven by an electro-optically isolated function generator. Different electrical stimulus parameters were tested. At high currents, those stimuli generated tactile sensations, pain, and visual phosphenes, but failed to generate olfactory percepts.

Whether or not an odor percept is generated, electrical stimulation of the olfactory mucosa may nevertheless induce brain activation. To test for this, we repeated the stimulation procedure concurrent with EEG. The EEG signals were recorded continuously by using a Biosemi Active II system with 64 Ag-AgCl pin-type active electrodes mounted on an elastic cap according to the extended 10–20 system, and from two additional reference electrodes placed at the right and left mastoids. Recordings were sampled at 256 Hz. To date, we have failed to identify an EEG response to stimulation. This result may reflect either a failure to activate the brain, or a brain activation pattern that does not influence EEG. To address this, we will present data of a repeat of this method, concurrent with fMRI. If we can successfully drive brain activation through electrical stimulation in the nose, this may provide a novel means of treatment for a host of neurological diseases treated through brain stimulation.

Psycho-semantics of odor space

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Several standard references describe the space of odors according to different sets of descriptors. We propose our own set of descriptors based on a quantitative semantic analysis of 20 subject's free descriptions of 11 odors. The subjects generated 7800 responses, which were merged and categorized, resulting in a compact set of 109 relevant descriptors. We compared our set of descriptors to the commonly used set described by Dravnieks [Atlas of odor character profiles] in terms of their predictive power reliability and information content. We found that our semantically selected set of descriptors outperformed Dravnieks in every measure: The Cronbach's Alpha of the new questionnaire is 0.895 against 0.683 of the Dravnieks questionnaire, and the correlation of the new Questionnaire with the Euclidean distances between every 2 odors is 0.670 against correlation of 0.416 of Dravnieks questionnaire. Furthermore, as opposed to Dravnieks' descriptors, the descriptors arrived at through our selection process were relatively free of comparisons to familiar objects. I.e. the selected descriptors tended to be of attributes (e.g., "warm"; "heavy") rather than comparisons (e.g., "like an orange; "like a banana"). This result supports a theory of perception where features are decided before identification is made. A similar theory is well established in Vision, and we suggest a similar process in olfaction.

Specific morphological features of a synaptic spine predict its life-time in vivo

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The persistence of synapses, manifested as the stability of spines, is believed to underlie our ability to store memories for long periods of time. Therefore, to understand how memories are maintained, it is important to study spine turnover in the living brain. In recent years, chronic spine imaging in living mice has opened the door to studying many individual spines over extended periods of time. Previous studies have demonstrated that the persistence of a spine is positively correlated with both its age and its size: the larger and the older a spine is, the longer it will survive. However, because spine age and spine size are positively correlated, it has been unclear whether spine turnover

depends on the age of the spine, its size or both. The goal of this study is to quantitatively characterize the dependence of spine turnover on spine age, spine size and two additional morphological characteristics of the spine. For this purpose, we chronically imaged of more than 1,800 spines in the auditory cortex of mice in vivo. We demonstrate substantial turnover that is correlated with (1) spine size and (2) spine age. Moreover, we observe that spine size is correlated with spine age, in line with previous studies. To study the relative contribution of the two factors to the turnover, we use logistic regression and show that the life-time of a spine independently depends on both its size and its age. We extend the model to incorporate the contribution of additional morphological features, the ellipticity of the spine and its distance from the dendrite to spine turnover. We show that spine turnover also depends on ellipticity such that the more elongated a spine is the less stable it is. By contrast, we found no dependence of life-time on the distance of the spine's center of mass from the dendrite. In conclusion, these results demonstrate that the survival of spines in vivo depend both on their age, their size and on specific morphological characteristics.

Stimulus-specific adaptation in a model of primary auditory cortex

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In the primary auditory cortex (A1) of cats and rats, neurons decrease their responses to frequently-presented stimuli but not to rare stimuli. This phenomenon, called stimulus-specific adaptation (SSA), originates in the cortex and may underlie short-term sensory memory and deviance detection. To investigate possible mechanisms of SSA, we employed a neural network previously used to reproduce several other A1 response properties, including frequency tuning, forward masking, lateral inhibition, and hyper-sensitive locking suppression (Loebel et al. 2007). This network has synaptic depression, which gives rise to population spikes (PSs). Our model exhibits SSA: rare stimuli elicit a PS but frequent stimuli do not. In contrast to a model based on adaptation of excitation in narrow frequency bands (analyzed in Taaseh et al. 2011), our model shows clear preference to deviance, i.e. a contrast with regularity of the background as opposed to rarity in an irrgeular background – in line with previous experimental results (Taaseh et al. 2011). SSA in our model strongly depends on stimulus and network parameters (input amplitude, inter-stimulus interval, time-constants of synapse recovery etc.) through their control of PS responses. We identified several regimes of PS generation and, through analytical treatment of an analogous mean-field model, demarcated the regions in parameter space that allow SSA. Our results compare with experimental data and provide predictions that will be tested by electrophysiological recordings in rats.

Using next generation sequencing to elucidate the role of hypocretin neuronal networks

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The mechanism that regulates sleep and metabolism is conserved in all vertebrates. The hypothalamic hypocretin/orexin (HCRT) neurons, integrate internal and external inputs to regulate feeding and sleep behavior and loss of HCRT neurons cause the sleep and metabolism disorder narcolepsy. However, the molecular identity of HCRT neurons and the mechanism of narcolepsy are poorly understood. In zebrafish, the HCRT neurons encompass only ~16 cells and their brain location and function are conserved in mammals. Furthermore, genetic ablation of HCRT neurons altered sleep and locomotor response to external stimuli in zebrafish larvae. To identify the genes that co-localized in HCRT neurons and potentially involved in regulation of sleep and metabolism, we have developed a novel protocol to specifically isolate mRNA from only 300 EGFP-labeled HCRT neurons and to sequence the whole transcriptome. A transgenic hcrt: EGFP line was used for FAC sorting and isolation of the whole population of HCRT neurons.. In order to prepare the library for next generation sequencing (RNA-seq), we used a unique method, which enables cDNA synthesis and amplification from ultra low amounts of RNA. We have further sequenced the entire transcriptome of the neurons and used bioinformatics and in vivo techniques to determine the list of putative candidate genes, which may be involved in sleep and metabolism regulation, and narcolepsy. Zebrafish is a unique model empowering to specifically isolate the entire HCRT neuron population. Using the advantages of zebrafish as genetic transparent model organism, this transcriptome will be tested in live animal and the mechanism of narcolepsy may be clarified. It will also open the opportunity to untie the complex neuronal networks that regulate sleep and metabolism.

Legacy Heritage biomedical program of the Israel Science Foundation

Novel new multi target anti Alzheimer drugs with neuroprotective and neurorestorative activities

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The role of iron and oxidative stress in Alzheimer's Disease (AD) lead us to develop non-toxic, lipophilic propargylamine, brain permeable multifunctional compounds with iron chelation, cholinesterase (ChE) and monoamine oxidase (MAO) inhibitory moieties properties for AD. We investigated the neuroprotective and neurorestorative effects of M30, HLA20 and M30P in transgenic APP/PS1 (Tg) mice model of AD. These studies include regulation of Ab aggregation and plaque areas, holo-APP expression levels and APP-processing mechanisms and cognitive abilities, since the 5' untranslated region of APP mRNA has a functional iron-responsive element. Comprehensive behavioral batteries determined at 10 month of age revealed that transgenic APPswe/PS1 mice given M30 during that period were protected from cognitive impairments in a verity of tasks of spatial learning and memory retention, working memory, learning abilities, anxiety level, and memory for the novel food and nesting behavior. Non treated transgenic mice remained impaired in all of these cognitive tasks/domains. M30 markedly reduced the levels of holo- APP and β-CTF in the frontal cortex, hippocampus and parietal cortex of APP/PS1 treated mice compared to non-treated animals. Coordinately, the levels of cerebral amyloidogenic Aβ peptide in soluble and insoluble fractions and the number of Aβ plaques and dimeric Aβ contents in the frontal cortex, hippocampus and parietal cortex were decreased in M30-Tg mice as compared to non-treated animals. Regarding aspects of cell signaling pathways associated with Alzheimer's disease (AD) pathology, M30 activated HIF, induce cell cycle arrest at G0/G1, enhanced the levels of BDNF, GDNF VEGF, phospho-AKT and phospho- glycogen synthase kinase (GSK)-3b and attenuated Tau phosphorylation. Our findings provide support for long-term M30 therapy as primary strategy for treatment of AD.

Continuous flash suppression modulates cortical activity in early visual cortex

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Background: A salient visual stimulus can be rendered invisible by presenting it to one eye while flashing a mask to the other eye. This compelling phenomenon, called continuous flash suppression (CFS), has been proposed as an ideal way of studying awareness as it can make a stimulus imperceptible for extended periods of time. Previous studies have reported robust suppression of cortical activity in higher visual areas during CFS, but the role of primary visual cortex (V1) is still controversial.In this study, we resolve this dispute and also begin characterizing the computational processes underlying CFS.
Results: Early visual cortical activity was measured with functional magnetic resonance imaging while human subjects viewed stimuli composed of target and mask, presented to the same or different eyes. Stimulus-evoked responses in early visual cortex were smaller when target and mask were in different eyes compared to the same eye, not only for the lowest contrast target rendered invisible by CFS, but also for higher contrast targets which were visible even when presented to the eye opposite the mask.
Conclusions: We infer that CFS works by modulating the gain of neural responses, akin to reducing target contrast.
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Zebrafish as a model for monocarboxyl transporter 8-deficiency

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Allan Herndon Dudley syndrome (AHDS) is a severe psychomotor retardation characterized by neurological impairments and abnormal thyroid hormone (TH) levels. Mutations in the TH transporter, monocarboxylate transporter 8 (MCT8), are associated with AHDS. MCT8-knockout mice exhibit impaired TH levels; however, they lack neurological defects. Here, the zebrafish mct8 (Slc16a2) gene and promoter were isolated, and a Tg(mct8:EGFP) transgenic line was used to show that, similar to humans, mct8 is primarily expressed in the nervous and vascular systems. Knockdown and rescue experiments showed that MCT8 is a crucial regulator during embryonic development. This study establishes the first vertebrate model for MCT8-deficiency that exhibits a neurological phenotype.
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Prereproductive stress in female rats affects CRF type 1 receptor expression in brain and oocytes, and alters behavior in offspring

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We have previously shown in rats that stress to the dam well before she becomes pregnant (preconceptual stress, PRS) impacts her future offspring's behavior. The offspring's emotional and social behavior is altered in complex ways that differ in males and females, and persist into their adulthood.

Here we investigate whether the transgenerational stress-induced changes is mediated by alterations in mRNA expression of CRF type 1 receptor 1 (CRF1) in brain and oocytes. Stress is well known to affect the expression of CRF1 in brain in cortical regions, hippocampus, amygdala, brainstem and cerebellum. In the ovary, CRF1 expression is dependent upon the ovulatory stage and is believed to contribute to reproductive success. We examined CRF1 expression in several brain regions of PRS and control female rats and their adult offspring. In addition, we examined CRF1 expression in oocytes of PRS and control rats, and in the brains of their offspring at birth. We found an increase in CRF1 in PRS females, as well as in the brain of their female offspring at birth and in offspring exposed to psychological stress in adulthood. In addition, we found a 20-fold increase in CRF1 mRNA in the oocytes of female PRS rats, which did not correlate with litter size or birth weight. These findings indicate that (1) CRF1 expression changes both centrally and peripherally in response to unpredictable stress; (2) both behavioral alterations and CRF1 expression changes are transmitted across generations; (3) CRF1 expression in the oocyte may play a role unrelated to reproductive success, and may mediate the offspring's response to stressful situations. While the exact molecular mechanism of this finding remains to be clarified, this may suggest an epigenetic mode of inheritance whereby stress effects are transmitted across generations.

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Vision to touch substitution in the real world

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Sensory substitution is an approach that uses one sense (e.g., touch) for gathering environmental information usually gathered by another sense (e.g., vision). In most vision to touch/hearing substitution devices (VTSD/VHSD) the sensor and stimulator are attached to different body organs, and light intensity is translated to tactile/acoustic vibrations. Here we examined the efficiency of a VTSD attached only to the hand and which translates light intensity to tactile pressure directly. Therefore, a stationary stimulus creates a constant pressure and sensory adaptation. To activate mechanoreceptors of the fingers, thus, the subject must move the hand much like during natural touch. Six blindfolded participants were asked to recognize a 2D black shape in the first stage (1.5 hours) and a 3D colored object in the second stage (1.5 hours). In each trial they were presented with 5 objects of ~15*15 cm size from a distance of ~1 meter. The participants succeeded in recognizing 2D and 3D shapes in less than 30s in 86 % and 95 % of the trials, respectively. Comparing these results with previous passive and active touch VTSDs reveals remarkable and moderate improvements, respectively. Our results also indicate better performance in speed and accuracy of an active-touch VTSD when compared with a VHSD (vOICe). We analyzed sensor (hand) movement and its interactions with the object as well as participants' reports and behavior. We recognize three major factors that may account for the observed improved performance: (i) Capturing ~25 % of the object size in each snapshot, (ii) attaining externalization of the sensed data, and (iii) developing an ability to identify local features (e.g., orientations, curvatures, vertex, corners). We conclude that using motion-dependent tactile sensation and having motion and sensation on the same organ can improve perception via a VTSD significantly, and that this improvement depends critically on the participant's active strategy.

Enhancement of addictive behaviors and neurochemical markers associated with drug addiction in two distinct animal models of depression

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Major depressive disorder (MDD) is one of the world's greatest health problems, and it is often accompanied by a comorbid substance abuse disorder (SUD). A few mechanisms have been suggested for this phenomenon, however the full set of features, especially whether or not there is a causal basis for this comorbidity, are not completely understood. In the following study, we have investigated the effects of depressive-inducing manipulations on different features of drug addiction. For this purpose, we employed two distinct animal models representing either environmental or genetically induced depression: the commonly used chronic mild stress (CMS) model; and a genetic model developed in our lab based on selective breeding for a depressive-like phenotype. Our results indicate that induction of a depression like state using either CMS or selective breeding strengthened a preference of heroin over a natural reward in a conditioned place preference paradigm. Moreover, CMS increased rates of relapse to cocaine seeking behavior in the self administration (SA) paradigm, while genetically depressed-like animals from our selective breeding model displayed higher rates of lever presses during acquisition and maintenance of cocaine self administration, and tended to display higher relapse rates than control animals. The results in both environmental and genetic models for depression clearly indicate that induction of a depressive-like state in rats enhances different behavioral features of drug addiction.

In addition, we found that CMS followed by heroin CPP of cocaine SA caused several alterations in the protein levels of

Brain-Derived Neurotrophic Factor (BDNF) and of the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor subunit GluA1 in reward related brain regions. These changes might shed light on the mechanism by which depression-like states enhanced addictive behaviors.

The neural mechanisms of selective attention at a 'cocktail party'

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Background: The ability to focus on and understand one talker in a noisy social environment is a critical social-cognitive capacity, whose underlying neuronal mechanisms are unclear. We investigated the manner in which speech streams are represented in brain activity and that way that selective attention governs the brain's representation of speech using a 'Cocktail Party' Paradigm, using direct electrocorticography recordings (ECoG) from the cortical surface in surgical epilepsy patients. Participants attended to long segments of natural speech while ignoring other concurrently presented speech by another speaker.
Results: We find that brain activity dynamically tracks speech streams using both low frequency phase and high frequency amplitude fluctuations, and that optimal speech encoding likely combines the two. In and near low level auditory cortices, attention 'modulates' the representation by enhancing cortical tracking of attended speech streams, but ignored speech remains represented. In higher order regions involved in speech processing and attentional control, such as inferior frontal cortex inferior partial lobule, the representation appears to become more 'selective,' in that that there is detectable tracking only of attended by not of ignored speech. This selectivity itself seems to sharpen as a sentence unfolds.
Conclusions: Our results provide an empirical basis for the idea that selective attention in a 'Cocktail Party' setting relies on an interplay between bottom-up sensory responses and top-down control, resulting in a dynamic and selective neural representation of attended speech, particularly in higher-order regions. This pattern of results provide a compelling example of 'Active Sensing', a process in which the brain dynamically shapes its internal representation of stimuli, and particularly those of natural and continuous stimuli, according to environmental and contextual demands.

Maternal administration of citalopram induces sex-dependent changes in behaviour, CRH-mRNA and that of its receptors in prenatally stressed and control rats

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Rationale: An increasing number of pregnant women with depression are being treated with antidepressant drugs but it is not clear whether any benefits of treatment outweigh the potential adverse effects on the offspring.
Objectives: To compare the early and long-term effects of prenatal citalopram in prenatally-stressed (PS) and control rats of both sexes.
Methods: Pregnant rats were administered citalopram (10 mg/kg/day) in their drinking fluid from day 7 of gestation until after their pups were weaned. Half of them were subjected to once-daily varied stress from day 14-21 of gestation. Offspring behaviour and gene expression of the CRH family in the amygdala was evaluated in adulthood.
Results: PS rats showed anxiety in the elevated plus maze, depressive-like behaviour in the forced swim test, and sex dependent alterations in CRH signalling in amygdala. Citalopram prevented anxiety of stressed mothers and in their female offspring, but not the depressive-like behaviour in both sexes. Citalopram had little effect on CRH signalling in PS males but reduced the expression of CRH, and its binding protein, CRHR1 and CRHR2 in PS females. Citalopram treatment of control mothers induced depressive-like behaviour in the offspring of both sexes.
Conclusion: Although citalopram can prevent anxiety in stressed rat mothers it does not normalize behaviour of their offspring. Blockade of the 5HT transporter by citalopram during development could lead to reduced activation of post-synaptic 5HT receptors resulting in changes in CRH signalling in the amygdala and depressive-like behaviour in adulthood.

Noise and the perceptual filling-in effect

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Background: It was shown that collinear flankers increased the reports of a target present (false alarms, FA), an effect that is attributed to filling-in of the target location due to increased activity induced by the flankers. A filling-in effect is characterized by high FA and a high percent correct, leading to low decision criterion, which indicates high reports of a target present. However, according to the standard notion, FA is attributed to noise in the system. We hypothesized that if the reports for FA are due to noise, then different levels of external noise implemented in the filling-in task should modulate the filling-in effect.
Method: Here we investigated the effect of manipulation on the filling-in effect by external noise that was added to the Gabor target, presented between two collinear Gabor flankers in differing target-flanker separations. The target was masked by white noise with differing levels of contrast.
Results: The results show that raising the levels of the noise modulate the filling-in effect; increasing FA at low noise levels,

but decreasing the filling-in effect for higher noise levels. The visual sensitivity (d') decreases with increasing noise, indicating a masking effect of the noise on the target alone.
Conclusions: The results indicate that the filling-in effect is not due to noise induced by flankers on the target location, rather, it can be inferred to stem from real lateral excitation on the target by the lateral flankers.

Characteristics of photo-absorber induced neuro-thermal stimulation (PAINTS)
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Background: Low power IR pulses can directly stimulate neurons using thermal transients resulting from the laser's energy absorption. Here we present the characteristics of a novel physical method for optical neural stimulation which relies on the absorption of focused laser beams by exogenous micron-scale photo-absorbers introduced in the vicinity of target cells. To induce highly localized thermal transients, a CW laser or a femtosecond IR laser were focused onto the particles and pulsed for periods ranging from 50 μs to 5 msec.
Results: Focused laser pulses absorbed by carbon-based photo-absorbers, led to rapid (milliseconds timescale) thermal transients with a well-defined and highly-localized dynamics which was visualized using temperature sensitive dyes, and matched theoretical predictions. Using calcium sensitive dye imaging, we observed that the thermal transients repeatedly excited neurons in the close vicinity of the absorbers, when pulse power/energy exceeded a certain threshold. The threshold activation energy decreased as a strong function of pulse duration (from a couple of micro joules to ~hundred nano joules) and the threshold behavior for short pulses was found to be highly dependent on laser properties. The overall behavior matched a quantitative model's prediction.
Conclusion: Photo-absorber induced neural-thermal stimulation (PAINTS) introduced here resulted in high spatiotemporal activation of neurons. The observed differences between CW and pulsed lasers suggest that the observed phenomenon potentially combines both photothermal and photo-mechanical effects. PAINTS can be combined with advanced microdisplay systems to achieve parallel control of a large number of neurons and thus lead the way to the development of new minimally intrusive optically based neuro- prosthetics.
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