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ABSTRACTS

Abstracts of the German Congress on Parkinson's Disease and Movement Disorders (Deutscher Kongress für Parkinson und Bewegungsstörungen), 7–9 March 2019, Düsseldorf, Germany

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Abstract No.:
199

Authors:
Schramm, Axel; auf dem Brinke, Matthias; Ebke, Markus; Herrmann, Christoph; Huber, Martin; Mehnert, Sabine; Winterholler, Martin; van der Ven, Christian; Ndayisaba, Jean-Pierre; Reuter, Iris; Wissel, Jörg

Abstract Title:
Quantitative ultrasound in spasticity—inter-rater-reliability and muscular changes (Quantitative Sonographie bei Spastizität—Inter-Rater-Reliabilität und Muskelveränderungen)

Abstract Text:
Introduction: Spasticity is associated with secondary muscular changes (especially atrophy and increase of connective tissue) that might have implications for the efficacy of botulinum toxin (BTX) treatment. These changes could be visualized by ultrasound, nevertheless the reliability of this method and the degree and distribution of muscular alterations is not clear up to now.
Target: We therefore aimed to assess the inter-rater reliability of ultrasound in spasticity and to evaluated muscular changes in a quantitative way.
Methods: Patients with spastic hemiparesis due to intracerebral ischemia or bleeding (n = 14, age 56.6 years (20–76), duration of spasticity 8.5 years (3–19), duration of BTX treatment 4.3 years (1.8–7.5)) were examined by 5 neurologist using ultrasound. Assessed muscles at the upper limb included flexor carpi ulnaris (FCU), flexor dig. prof./superf. (index finger; FDP/FDS), extensor dig. com. (EDC) and at the lower limb medial gastrocnemius (MG) and tibialis anterior (TA) muscle. We assessed cross sectional area or a-p diameter and echogenicity using offline grey scale analysis and compared measurements of the affected side to the non-affected side.
Results: We found an excellent inter-rater reliability (ICC (2,5) 86–96%) concerning all parameters. At the upper limb we found a statistically significant increase in echogenicity on the affected side vs. the non-affected side (EDC 64 vs. 57, $p = 0.002$; FCU 71 vs. 56, $p < 0.001$; FDP 69 vs. 54, $p = 0.022$; FDS 65 vs. 52, $p = 0.003$) as well as a significant atrophy on the affected side (EDC 16.7 vs. 20.4, $p < 0.001$; FCU 8.2 vs. 10.6, $p = 0.002$; FDP 3.7 vs. 5.0, $p < 0.001$; FDS 5.5 vs. 7.9, $p = 0.001$). On the other hand, we did not find significant differences at the lower limb.
Conclusion: Ultrasound is an easy, quick and reliable method to examine muscular changes in spasticity which confirmed significant atrophy and hyperechogenicity at least at the upper spastic limb. Individual changes might have implications for botulinum toxin treatment concerning selection of muscles and efficacy. Nevertheless, larger and longitudinal studies are needed to assess the influence of duration of spasticity and BTX treatment on these muscular changes and to correlate them with efficacy of BTX treatment.

Abstract No.:
258

Authors:
Scheffels, Jannik; Kräling, Hannah; Kalbe, Elke; Kessler, Josef

Abstract Title:
Bidirectional conversions of DemTect, MoCA and MMSE in the context of Parkinson's disease screening (Bidirektionale Konversionen von DemTect, MoCA und MMST im Kontext des Parkinson-Screenings)

Abstract Text:
Introduction: For a comprehensive specification and quantification of neuropsychological deficits in Parkinson's disease as well as other neurological and psychiatric disorders, extensive neuropsychological assessment is needed. Due to its time intensiveness, this cannot be realised in every clinical setting. Therefore, screening instruments provide a first step. Because their selection differs between and sometimes even within clinics, a comparison of results in different screenings would be helpful for maintaining continuity and for follow-up studies.
Target: This study aimed at creating conversion tables for the German-speaking area including sum scores on one screening instrument as well as their equivalent sum scores on another one. For this purpose, the three mostly used screening instruments Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Dementia Detection Test (DemTect) were used.
Methods: In the Department of Neurology at the University Hospital of Cologne, 8240 patients suffering from neurological disorders including Parkinson's disease patients were examined between 2008 and 2017. MMSE and DemTect were conducted with 6287, MoCA and MMSE with 536 as well as MoCA and DemTect with 543 patients. Conversion scores using total scores on these screenings were then computed by using the equipercentile equating method implemented in R Statistical Software. This method has already been

used in English-speaking but not German-speaking countries with different patient populations (e.g. Parkinson's disease or Stroke) and smaller sample sizes. It assumes equivalence of two scores on different tests if their percentile rank is similar (e.g. if in the same cohort a score of 21 in the MMSE and a score of 26 in the MoCA is at the 45th percentile, these two scores would be considered as being equivalent).
Results: Total scores on the MMSE and MoCA ($r = 0.74$), DemTect and MoCA ($r = 0.70$) as well as DemTect and MMSE ($r = 0.67$) were highly correlated ($p < 0.01$, respectively). The calculated bidirectional conversion tables enable quick and easy comparisons between the three most frequently used screening instruments. Additionally, they are in agreement with those obtained in previous studies in English-speaking countries.
Conclusion: The results enable an enhanced longitudinal assessment of cognitive functions in different clinical settings, provide comparability as well as continuity, and offer more flexibility for determination of patient status. Additionally, communication between clinics is improved. An extension of the study might be the transfer of the method presented to other cognitive or affective screenings measuring for example executive dysfunctions or depressive symptoms that have a high prevalence in Parkinson's disease.

Abstract No.:
260

Author:
Schneider, Anja

Abstract Title:
Exosomes: novel biomarkers for the clinical diagnosis of neurodegenerative diseases (Exosomen: neue Biomarker für die Diagnostik neurodegenerativer Erkrankungen)

Abstract Text:
Introduction: Exosomes are vesicles of 40–120 nm diameter which are secreted by many cells. These extracellular vesicles can serve two major functions, (1) clearance of toxic or superfluous cellular content and (ii) to facilitate cell–cell communication by transfer of (signalling) proteins, lipids and RNA between cells. Exosomes from various origins are abundantly present in biofluids, including blood and are therefore accessible as biomarkers. Parkinson's disease is characterized by abnormal intraneuronal aggregation of alpha-Synuclein. Exosomes may transfer pathological alpha-Synuclein aggregates from diseased to so far unaffected neurons to induce misfolding and aggregate formation, thus contributing to propagation of disease pathology. We have previously shown that exosomes from cerebrospinal fluid of patients with alpha-Synuclein related neurodegeneration carry a pathogenic seed which can induce alpha-Synuclein aggregation in vitro.
Target: Here, we investigated the potential of plasma exosomes as a fluid biomarker to detect Parkinson's disease by quantifying exosome numbers and exosomal alpha-Synuclein content in 2 independent cohorts of patients with Parkinson's disease, Lewy body dementia and controls.
Methods: We first established and optimized standard operating procedures (SOPs) for the purification of plasma-derived exosomes by size exclusion chromatography. This purification methods results in preparations of superior purity, high reproducibility and and easy performance without expensive equipment, thus enabling this method to move to diagnostic routine. Exosomes were prepared from plasma and exosome numbers were quantified by nanoparticle tracking. Exosomal alpha-Synuclein content was quantified by a well-established electrochemiluminescence assay.
Results: We find that plasma exosomal alpha-Synuclein detects Parkinson's disease with high sensitivity and specificity. We could replicate these findings in an independent patient cohort.
Conclusion: Our results indicate that the quantification of plasma exosomal alpha-Synuclein may be a promising and easily accessible biomarker for the detection of Parkinson's diseases.

Abstract No.:
261

Authors:
Csoti, Ilona; Koleva-Alazeh, Natalia

Abstract Title:
Das "Trockene Auge" bei Parkinson-Syndromen und seine Folgen—Möglichkeiten der Therapie

Abstract Text:
Introduction: Patienten mit M. Parkinson (MP) und Progressiver supranukleärer Blickparese (PSP) leiden aufgrund des seltenen Lidschlags, der verminderten Tränenproduktion und der veränderten Zusammensetzung der Tränenflüssigkeit unter einer Keratokonjunktivitis sicca, auch "Trockenes Auge" (TA) genannt. Sie klagen über Brennen, Jucken und Rötungen der Augen, Trockenheits- und Fremdkörpergefühle. Die Lider können schwer und müde werden und auch zufallen. In Folge kann es zu Lidödemen, einer Lidrandentzündung (Blepharitis) und/oder einer Fehlstellung des Lidrandes (Ektropium) kommen. Paradoxerweise geht das TA auch manchmal einher mit einem ständigen Augentränen, ein Symptom, das Patienten bei dieser Krankheit aufgrund des Namens nicht erwarten. Das Augentränen entsteht durch eine Funktionsstörung der physiologischen Tränenableitung.
Target: MP und PSP Patienten leiden unter diffusen Sehstörungen, welche nur zum Teil behandelbar sind. Werden Symptome des trockenen Auges durch den behandelnden Neurologen im Rahmen der klinisch-neurologischen Untersuchung erfasst, kann eine Beratung der Patienten zu Möglichkeiten der Behandlung dieser Begleiterkrankung bereits frühzeitig im Krankheitsverlauf erfolgen. Schwerwiegende Folgen, wie schwerere Sehstörungen z.B. durch eine Keratitis, chronische Lidrandentzündungen, und/oder Lidfehlstellungen könnten verhindert werden.
Methods: Patienten mit MP und PSP werden im Aufnahmegespräch nach Sehstörungen befragt. Geeignet ist der Fragebogen zu nichtmotorischen Symptomen bei Parkinson (Nonmotor Symptoms Questionnaire/(NMSQuest). Berichten sie über Symptome eines Trockenen Auges kann das Ausmaß mit dem OSDI (Ocular Surface Disease Index) beurteilt werden.

Bereits während der stationären Behandlung wird mit einer Behandlung mit einem künstlichen Tränenersatzmittel, Salben oder Gelen begonnen. Liegt eine chronische Lidrandentzündung vor, erfolgt eine Beratung zur Lidrandpflege. Eine Vorstellung bei einem Augenarzt (Sicca Sprechstunde) wird regelhaft empfohlen.
Results: Durch konsequentes Erfragen und klinisches Erfassen von Symptomen des TA kann eine solches im Rahmen einer stationären Behandlung in einer Parkinson-Fachklinik klinisch sicher diagnostiziert werden. Der Schweregrad ist bei beiden Patientengruppen abhängig von der Dauer der Erkrankung, sofern nicht andere Risikofaktoren (z.B. Diabetes mellitus, Rheuma, Medikamente) hinzukommen. Rein theoretisch ist jedoch davon auszugehen, dass PSP Patienten ein höheres Gefährdungspotential aufweisen. Die Symptomatik hat in beiden Patientengruppen einen negativen Einfluss auf die Lebensqualität.

Häufig sind bereits bei der klinischen Untersuchung des äußeren Auges einschließlich Unter- und Oberlid Veränderungen der Konjunktiven und des Lidrandes zu objektivieren. Liegt ein Ektropium vor, befindet sich dieses bei MP Patienten häufig auf der von der Krankheit stärker betroffenen Seite. Der Leidensdruck wird durch die sensiblen Missempfindungen, die damit verbundenen Sehstörungen und die Folgen für den Lidrand bestimmt.

Conclusion: Durch den Beginn einer Behandlung mit einem künstlichen Tränenersatzmittel bereits während der stationären Behandlung kann eine Linderung der subjektiven Beschwerden erreicht werden. Bei einer PSP-Patientin konnte das spontane Zufallen der Augenlider (Lidheberapraxie) allein durch diese Behandlung deutlich gebessert werden. Eine konsequente Therapie mit künstlichen Tränenersatzmitteln, Wärme, Kortison/Cyclosporin/Operation (in schweren Fällen) und Augentraining führt zu einer signifikanten Besserung der Symptome und der möglichen Folgen des Trockenen Auges. Neben einer erhöhten neurologisch-diagnostischen Aufmerksamkeit ist eine enge Zusammenarbeit mit unseren ophthalmologischen Fachkollegen ist dafür zwingend erforderlich.

Abstract No.:
278

Authors:
Giehl, Kathrin; Ophey, Anja; Hammes, Jochen; Rehberg, Sarah; Reker, Paul; Eggers, Carsten; Lichtenstein, Thorsten; Maintz, David; Kalbe, Elke; van Eimeren, Thilo

Abstract Title:
Training of working memory in Parkinson's Disease: neural correlates of pure storage and manipulation (Arbeitsgedächtnistraining bei Parkinson: neuronale Korrelate der Speicherung und Manipulation von Information)

Abstract Text:
Introduction: Working memory (WM) describes a cognitive resource of limited capacity, which enables us to temporarily maintain and manipulate relevant information. Impairments of WM and especially its executive aspects (i.e. manipulation of information within WM) are early cognitive symptoms in Parkinson's Disease. Thus, maintaining high WM function is essential. Training of WM has been proven beneficial in non-PD populations, with positive effects also transferring to other cognitive abilities. Whether such training can also be beneficial for patients with PD and which effect such an intervention may have on the correlates of different aspects of WM in this cohort remains a weakly investigated question so far.
Target: This study aimed to investigate the neural correlates of different WM aspects (manipulation vs. maintenance) in a cohort of PD patients without cognitive impairment using a newly designed WM paradigm and functional magnetic resonance imaging (fMRI). Further, we aimed to evaluate the change of these correlates as a function of a computerized 5 week WM training.
Methods: 29 patients (13 female; mean age = 65y $\pm$ 10y) with idiopathic PD were recruited. All patients underwent an fMRI session on a 3T Philipps Ingenia while performing a newly designed WM paradigm before and after a 5 week WM training scheme. In order to disentangle pure WM storage from manipulation within WM, patients had to either memorize a sequence of letters or to memorize and reverse the letter order. After pre-processing, first and second level group analyses were performed for contrasts of interest (maintain > rest, manipulate > rest and manipulate > maintain) using SPM12. Results were considered significant on cluster-level when $p < 0.05$ (FWE-corrected).
Results: Pure maintenance in WM (maintain > rest) activated regions typically involved in WM such as vlPFC, dlPFC, OFC, anterior insula, premotor cortex, angular gyrus and cerebellum. Manipulating items within WM (manipulate > rest) required largely the same regions, however also relied on the striatum and left parietal lobe. This was even more apparent in the specific manipulate > maintain contrast, where also a strong activation of the precuneus was observed. As a function of training, PD patients showed increased activation in WM related areas, especially when manipulation of information was required.
Conclusion: Using this paradigm allowed us to successfully disentangle the differential regions involved in pure WM maintenance and WM manipulation and further allowed to estimate the functional change in these areas associated with WM training.

Abstract No.:
279

Authors:
Becker, Sara; Bäumer, Alena; Maetzler, Walter; Nußbaum, Susanne; Timmers, Maarten; van Nueten, Luc; Salvadore, Giacomo; Brockmann, Kathrin; Streffer, Johannes; Berg, Daniela; Liepelt-Scarfone, Inga

Abstract Title:
Association between non-motor symptoms and cognitive-driven activity of daily living impairment in Parkinson's Disease

Abstract Text:
Introduction: In Parkinson's Disease (PD), it is becoming increasingly evident that the frequency and severity of non-motor symptoms (NMS) considerably influences not only motor progression, but also the rate of cognitive decline. Behavioral symptoms that can indicate an early development of Parkinson's disease dementia (PDD) include depression, anxiety, sleep disturbances and hallucinations. These four symptoms can be summarized into a comprehensive DASH score. Moreover, there is evidence that mild activity of daily living (ADL) impairments primarily caused by cognitive dysfunction are also present in the prodromal stage of PDD. To date, the association of both risk factors has been sparsely investigated.
Target: Aim of the current research was to validate the DASH score in a large cohort of non-demented PD patients as well as to examine its association to other known risk factors for PDD, especially cognitive-driven ADL impairment. We hypothesized that higher DASH scores are associated to more impaired cognition and ADL function, especially in PD patients with mild cognitive impairment (PD-MCI), characterizing a risk group for PDD.
Methods: Data of 226 PD patients assessed with comprehensive non-motor, motor and neuropsychological assessments was analyzed. Patients were diagnosed with PD-MCI according to the Level-II recommendations of the Movement Disorder Task Force; patients who did not meet these criteria were classified as cognitively normal (PD-CN). Using the corresponding items of the PD NMS-Scale, the DASH-NMS score was constructed. Two sub-scores of the Functional Activities Questionnaire (FAQ) were constructed to primarily reflect both cognitive-driven (FAQC) and motor-driven ADL impairments (FAQM).
Results: Of all patients, 132 (58.4%) were characterized as PD-NC, and 94 (41.6%) as PD-MCI. Results showed that the DASH-NMS score was higher in the PD-MCI compared to the PD-NC group ($p = 0.037$). Higher values of the DASH-NMS score were correlated to worse neuropsychological test performance assessing attention/working memory ($p = 0.006$), visuo-spatial functions ($p = 0.005$), and language ($p = 0.050$). A linear regression with the DASH-NMS (dependent variable) and all variables significantly correlated to it (independent predictors), showed that the only statistically significant predictor of the DASH-NMS score was cognitive-driven ADL impairment ($p = 0.009$).
Conclusion: Our results show that the DASH-NMS score is related to the severity of cognitive impairment, and is primarily associated to cognitive-driven ADL impairment. Both factors may define a group of patients at risk for conversion to PDD; however, long-term studies are needed to evaluate the predictive value of the FAQ sub-score as well as the DASH-NMS score in terms of cognitive worsening and PDD development.

Abstract No.:
300

Authors:
Levin, Johannes; Maass, Sylvia; Schuberth, Madeleine; Giese, Armin; Mansmann, Ulrich; Bötzel, Kai; Huppertz, Hans-Jürgen; Ricard, Ingrid; Höglinger, Günter

Abstract Title:
Clinical and biomarker characteristics of patients with multiple system atrophy treated with epigallocatechin gallate for anti-aggregation of α-synuclein

Abstract Text:
Introduction: Intracellular α-synuclein aggregates are the pathological hallmark of multiple system atrophy (MSA). Inhibition of α-synuclein aggregation therefore appears to be a rational approach for developing a disease modifying treatment for MSA. Epigallocatechin gallate (EGCG) is an orally bioavailable small molecule that inhibits α-synuclein aggregation and shows efficacy in several in vitro and animal models of synucleinopathies. Due to rapid disease progression and lack of potent symptomatic treatments, there is a high and unmet need for a disease modifying therapy for MSA.
Target: To evaluate the safety and tolerability of epigallocatechin gallate (EGCG) in high doses (800–1200 mgs/day) and its efficacy to slow down disease progression in patients with MSA.
Methods: A double-blind placebo-controlled parallel-group phase III study including 92 participants meeting clinical criteria for MSA was conducted. Treatment with EGCG or placebo (randomized 1:1) was administered orally for 48 weeks followed by a 4-week washout phase. The primary endpoint was the change in motor symptoms assessed by the Unified MSA Rating Scale (UMSARS-ME) from baseline up to 52 weeks. In addition to the general study procedures, a subset of patients was examined by MRI.
Results: 127 participants were screened, 92 were randomized and 67 (72.8%) completed treatment. There was no statistically significant difference in UMSARS scores between EGCG (mean: 5.7; 95% confidence interval: 3.7–7.6) and placebo groups (6.6; 4.65–8.54) at the end of the study. Despite the negative clinical endpoint, we observed a significantly reduced loss in striatal volume in EGCG-treated MSA patients compared to controls. Significantly more liver toxicity was observed in the EGCG group.
Conclusion: Treatment with EGCG in high doses over 52 weeks did not slow the progression of MSA. Cases of hepatotoxicity in the EGCG group show that the limit of maximum tolerable EGCG doses has been reached. Reduced atrophy in MRI (exploratory endpoint) indicates that treatment approaches with more effective anti-aggregative compounds may be considered for future disease modifying studies in MSA.

Abstract No.:
301

Authors:
Huber, Sven; Altmann, Christian; Benz, Petra; Fleiner, Andreas; Wendler, Petra; Jost, Wolfgang

Abstract Title:
Effects of opicapone at different times of the evening (Effekte von Opicapon zu unterschiedlichen Zeiten des Abends)

Abstract Text:
Introduction: L-Dopa is still the gold standard in Parkinson therapy. Some approaches target on optimization of L-Dopa therapy, that is, a better and steadier effect and improved tolerance of the drug. One major progress was the introduction of COMT-inhibitors 2 decades ago. Opicapone, a peripheral, selective COMT-inhibitor, was approved in 2016. According to the manufacturer's recommendations, a simple single dose should be taken at bedtime, at least an hour before or after the L-Dopa dosage.
Target: In our clinical experience, patients often complain of how often their daily medication requires their attention at set times. The recommended later dosage of opicapone after L-Dopa intake is thus often seen as an additional burden by these patients. The purpose of our clinical observation was to determine whether (1) the patients sense a change or whether (2) any clinical differences can be documented when their opicapone intake is concurrent with their L-Dopa, as compared to delayed intake.
Methods: 16 patients were included in this clinical observation. Initially, opicapone was administered for 2 days under delayed intake as recommended. The subjects were requested to fill out a self-assessment questionnaire during this time period. In addition, on the second day an evaluation was completed by their physicians according to UPDRS parts 3&4. On the two subsequent days, L-Dopa was administered at the same time as opicapone, and the patients continued their self-reports, and finally on the fourth day the UPDRS evaluation was repeated.
Results: Comparing the categories of the self-assessment for the two conditions "concurrent intake" and "postponed intake", 75% of the patients reported having the same mood, while 25% reported an improvement in their mood state. The quality of sleep was described as identical by 62.5%, improved by 18.75% and as deteriorated by 18.75%. General mobility was rated as identical in 68.75%, and as improved in 31.25%. In one case under concurrent intake nausea was reported. In the category for dyskinesias there was no change. On average the score UPDRS III improved by 2.44 points and in IV by 0.43.
Conclusion: Our observations document that patients generally do not sense any significant differences under concurrent intake of L-Dopa and opicapone. Main obstacles are the short small sample size and the short duration of monitoring. Improvements in the UPDRS scores should be discussed with caution. On the other hand, the concurrent, simultaneous intake of both drugs would clearly increase the acceptance for many patients. A controlled study could prove very useful.

Abstract No.:
302

Authors:
Ophey, Anja; Giehl, Kathrin; Rehberg, Sarah; Hammes, Jochen; Reker, Paul; Eggers, Carsten; van Eimeren, Thilo; Kalbe, Elke

Abstract Title:
Computerized working memory training improves executive functions in patients with Parkinson's Disease (Digitales Arbeitsgedächtnistraining verbessert Exekutivfunktionen bei Patientinnen und Patienten mit Morbus Parkinson)

Abstract Text:
Introduction: Progressive cognitive impairments are a frequent and debilitating symptom of Parkinson's Disease (PD). Amongst the most common and earliest cognitive impairments in PD are dysfunctions of working memory, a capacity-limited memory system (visuospatial vs. numerical-verbal) that is responsible for the short-term storage and manipulation of information. Therefore, it is central to the execution of other cognitive processes. Previous studies with healthy young and elderly individuals and different patient groups, but not yet in PD, suggest that specific working memory training may lead to increased working memory performance. Moreover, transfer effects of the training to other cognitive domains have been described.
Target: The aim of this study was to investigate whether an adaptive computerized working memory training (CWMT) has an effect on cognition and motor impairment in patients with PD without cognitive impairment and to investigate predictors of training outcomes.

Methods: N = 75 patients with PD (46% women; age: M = 63.98, SD = 8.42; UPDRS: Md = 29, 10–53) without cognitive impairment (MoCA: M = 27.33, SD = 1.57) were included in this single-blind randomized controlled trial evaluating effects of a 5-week adaptive CWMT with selected tasks of the brain training program NeuroNation (Synaptikon GmbH, Berlin, Germany) against a passive control group. Patients were examined clinically and neuropsychologically including five cognitive domains (executive functions, memory, attention, visuospatial cognition, and language) at baseline, after training, and at 3-months follow-up. Training and experimental group were comparable regarding age, sex, education, global cognition and disease characteristics (disease duration; UPDRS; H&Y; LEDD).
Results: To examine the effects of the CWMT compared to the control group, multivariate analyses of variance (MANOVAs) were performed for each cognitive domain and motor impairment, with follow-up ANOVAs for each assessment separately in case of significance. The MANOVA yielded a significant time × group interaction for executive functions, Pillai's trace V = 0.19, F(5,68) = 3.13, p = 0.013, partial eta2 = 0.19, indicating a positive training effect in the CWMT group, especially in the subtests of semantic verbal fluency and logical reasoning. No other significant effects were found.
Conclusion: A 5-week specific CWMT may significantly improve executive functions in PD patients without cognitive impairment. Follow-up analyses are necessary to analyze whether long-term effects are also observable and whether CWMT may thus be an effective approach to prevent cognitive decline in patients with PD with (yet) no cognitive impairment in the long-term.

Abstract No.:
303

Authors:
Ophey, Anja; Eggers, Carsten; Dano, Richard; Timmermann, Lars; Kalbe, Elke

Abstract Title:
Health-related quality of life subdomains in patients with Parkinson's Disease: the role of gender (Subdomänen gesundheitsbezogener Lebensqualität bei Patient*Innen mit Morbus Parkinson: die Rolle des Geschlechts)

Abstract Text:
Introduction: In the context of Parkinson's disease (PD), numerous factors are conceived to contribute to decreased health-related quality of life (HrQoL) of patients with PD, with HrQoL being a more patient-based outcome than the traditional clinical evaluation that still focusses on a purely physical disease characterization. The most frequently used instrument to assess HrQoL in PD is the Parkinson's Disease Questionnaire 39 (PDQ-39). However, both the dimensionality of the eight PDQ-39 subscales and their summary score recently faced criticism. Furthermore, data on disease-related and (neuro-)psychological determinants and the role of gender on HrQoL in PD are inconclusive yet.
Target: In use of a large clinical database of the Cologne Parkinson Network, our aim was to reevaluate the PDQ-39 structure and to further explore determinants of HrQoL in PD.
Methods: 245 patients with PD (37.1% women; age: M = 69.64, SD = 8.43; H&Y: Md = 3.00, range 0–4; cognitive assessment with PANDA: M = 24.82, SD = 3.57) from the baseline database of the Cologne Parkinson Network were used to reevaluate the dimensionality of the PDQ-39 with a principal component analysis (PCA). Multiple regression analyses were then conducted to clarify general and domain-specific relationships between clinical, (neuro-)psychological, and sociodemographic variables, gender in particular, and HrQoL.
Results: The PCA identified three HrQoL domains: physical-functioning, cognition, and socioemotional HrQoL. Depressive symptoms were identified as the most important determinant of HrQoL across all models. Disease-related HrQoL determinants (UPDRS-III, H&Y stage, and LEDD) were less strong and consistent HrQoL determinants than nonmotor symptoms. Analyses did not reveal a global gender effect; however, female gender was a negative predictor for physical-functioning and socioemotional HrQoL, whereas male gender was a negative predictor for cognition HrQoL.
Conclusion: Our analyses suggest the consideration of a reevaluation of the PDQ-39. Instead of conceiving HrQoL as a unified construct, it seems more appropriate to consider different HrQoL domains. Only the full understanding of HrQoL, its determinants, and their interrelationships will allow the development of PD intervention strategies focusing on what matters the most for patients' HrQoL. Gender is one relevant variable that should be considered in this context.

Abstract No.:
304

Authors:
Tsoutsikas, Vasileios; Stolte, Frederik; Blaes, Franz

Abstract Title:
Chorea gravidarum by first pregnancy (Kinesiogene Dyskinesien bei Primipara)

Abstract Text:
Introduction: Choreatiform dyskinesias during pregnancy have been described by imperative, spontaneous and non-rhythmic movement disorders as Chorea gravidarum (CG). Hormonal etiologies like elevated estrogen levels or electrolyte disturbances have been discussed, but inflammatory rheumatic diseases are also associated with the entity.
Target: To describe a case of chorea gravidarum associated with surface-binding autoantibodies to basal ganglia neurons.
Methods: Clinical and immunological description of a chorea gravidarum.
Results: A 22-year-old female presented with a hyperkinetic-dyskinetic syndrome for several days, initially in the form of ballism and then as choreoathetosis. It started from the right side of the body and affected all segments of the extremities. In addition, the pathologic movements were partially provoked by distention of the extremities and could not be suppressed. Past medical history showed no streptococcal or other infection, tick bite, drug abuse or any distant journeys. CSF was normal, antineuronal, NMDA-Receptor-antibodies and other receptor antibodies were negative, but she had positive TPO and Thyreoglobulin antibodies, but normal TSH. MRI was also normal. After initial diagnosis of steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT), methylprednisolone was given, leading to transient improvement. Plasma exchange improved the symptoms markedly, but then, the patient worsened again and was re-admitted for intravenous immunoglobulins. However, the patient revealed to be pregnant (9th week) and therefore, the diagnosis of chorea gravidarum was suspected and immunotherapy was stopped. Immunological examination revealed surface-binding autoantibodies to cultured rat striatal neurons, but not hippocampal or cerebellar neurons.
Conclusion: We show here a patient with chorea gravidarum with autoantibodies against a striatal neuronal surface antigen, but without history of streptococcal infection or chorea minor. This observation supports the idea of an autoimmune process in chorea gravidarum.

Abstract No.:
305

Authors:
Sulzer, Patricia; Bäumer, Alena; Hoang, Huong Giang; Becker, Sara; Özbe, Dominik; Graessel, Elmar; Liepelt-Scarfone, Inga

Abstract Title:
Validation of the Erlangen test of activities of daily living in mild dementia and mild cognitive impairment in Parkinson's Disease (Validierung des ETAM bei Morbus Parkinson)

Abstract Text:
Introduction: Besides cognitive dysfunctions, problems in activities in daily living (ADL) are mandatory for the diagnosis of Parkinson's disease (PD) dementia (PDD). There is evidence that some PD patients with mild cognitive impairment (PD-MCI) already show mild difficulties in ADL, especially in instrumental ADL tasks, and might therefore be at higher risk for the development of PDD. In clinical practice, ADL functions are often assessed using questionnaires or interviews. However, self- and caregiver-reported ADL performance indicative for PDD is often confounded by motor dysfunctions and mood. Therefore, objective and time-economic performance-based measurements are needed to assess cognitive-related ADL functions in PD.
Target: The aim of this study was to evaluate the Erlangen Test of Activities of Daily Living in Mild Dementia and Mild Cognitive Impairment (ETAM) in a non-demented PD cohort.
Methods: Data of 21 PD patients with no cognitive impairment (PD-NC), 24 PD-MCI patients, and 17 healthy controls (HC) were analyzed. Apart from the ETAM, participants completed a comprehensive neuropsychological test battery and further ADL, mood, and motor measurements. A non-parametric test statistic was applied. Test reliability was calculated by means of interrater reliability (IRR, intraclass correlation), internal consistency (Cronbach's alpha), item-total correlation, and item difficulty. Construct validity was evaluated with the Spearman's rho correlation coefficient (rs).
Results: Analysis confirmed a very high IRR for the ETAM total score ($r = 0.96$). Item-total correlations indicated little redundancy amongst all items and item difficulty showed that most participants scored high on the ETAM subtests ($Pi > 90.98$). Correlation analysis revealed a significant association of the ETAM total score with self-rated ADL functions ($rs = -0.44$) and cognitive performance ($rs = 0.44$); however, mood ($rs = 0.05$), and motor function ($rs = -0.19$) did not interfere with the ETAM performance. A score of 27 was chosen as a cut-off to define affected ADL performance (lowest value in HC). No patients of the PD-NC group achieved a score below this cut-off compared to 26.1% of the PD-MCI group ($p = 0.012$).
Conclusion: The ETAM provides a good reliability and validity in PD. We were able to identify a subgroup of PD-MCI patients with pathological ADL dysfunctions, who we hypothesize will further progress towards PDD in the near future. To validate this assumption longitudinal investigations are needed to follow patients' cognitive progression, which are currently ongoing.

Abstract No.:
306

Authors:
Liepelt-Scarfone, Inga; Kalbe, Elke; Gräber, Susanne; Riedel, Oliver; Ringendahl, Hubert; Schmidt, Nele; Witt, Karsten; Roeske, Sandra

Abstract Title:
Guidelines for the neuropsychological assessment in Parkinson's disease

Abstract Text:
Introduction: Cognitive dysfunction is one of the most prevalent non-motor symptoms in Parkinson's disease (PD). Diagnosis of PD dementia (PDD) represents a key milestone in the course of PD, dramatically increasing the risk for nursing home placement and mortality. Presence of mild cognitive impairment (PD-MCI) is currently the best predictor for the development of PDD. Therefore, an early and valid diagnosis of both PD-MCI and PDD is of utmost importance for the treatment of PDD and, once available, PD-MCI, and for maintaining patients' quality of life. Diagnostic criteria for both PD-MCI and PDD have been suggested by the Movement Disorder Society. However, not all cognitive tests recommended by this international expert committee are available in the German language with proper standard values.
Target: Based on two systematic literature searches, evidence-based guidelines for the neuropsychological test assessment in PD are reported by the members of the focus group "Consensus guidelines for neuropsychological assessment" of the German Society for Parkinson and Movement Disorder.
Methods: Publications in English or German language were identified by a PubMed and PSI-Index database search according to predefined criteria. First, articles that presented guidelines (consensus papers or reviews) for the application of standardized neuropsychological assessments for diagnosis of cognitive impairment in PD were selected. Of those, only neuropsychological assessments in the German language with norm values referring either to a German, Austrian or Swiss population were considered. Second, articles comparing test performances of healthy controls vs. PD and/or different cognitive PD subtypes (e.g. no cognitive impairment, PD-MCI, PDD) with a sufficient sample size per group (≥ 20) were selected. Effect sizes for group differentiation were calculated.
Results: Within the first literature search, 2015 abstracts were reviewed and 1888 articles were excluded, resulting in 127 full-text articles reviewed for the identification of tests available in German with proper standard values. In total, 44 tests were identified, at least five for each cognitive domain. In the second search, 1716 articles were reviewed and 22 papers selected, all focusing on the comparison between healthy controls and PD patients. Highest effect sizes for group discrimination were revealed for tests assessing executive function, attention, and visuo-cognitive abilities. Based on the results of the two literature searches, consensus guidelines were defined by the authors, allowing for Level-II diagnosis for PD-MCI and PDD.
Conclusion: The presented guidelines may have the potential to standardize and improve the neuropsychological assessment of PD patients in German speaking countries.

Abstract No.:
307

Authors:
Ruck, Laura; Unger, Marcus; Spiegel, Jörg; Bürmann, Jan; Dillmann, Ulrich; Faßbender, Klaus; Reith, Wolfgang; Mühl-Benninghaus, Ruben; Yilmaz, Umut

Abstract Title:
Gastric motility in Parkinson's disease depends on the digestive phase and does not correlate with patient reported motor fluctuations (Magenmotilität bei M. Parkinson korreliert nicht mit Wirkungsfluktuationen)

Abstract Text:
Introduction: Altered gastric motility has frequently been reported as a non-motor symptom of Parkinson's disease (PD). It has been hypothesized that a disturbed gastric motility contributes to motor fluctuations in PD due to an erratic gastro-duodenal transport and an erratic absorption of anti-parkinsonian drugs.
Target: In this study we investigated whether patient reported fluctuations correlate with parameters of gastric motility visualized by real-time magnetic resonance imaging (MRI) of the stomach in different stages of digestion.
Methods: 36 subjects (16 PD patients, 20 controls) underwent real-time MRI of the stomach after a 12 h overnight fasting period. MRI was performed i) in the fasting state, ii) directly after a standardized test meal and iii) 4 h postprandially. Gastric motility indices for each point in time were calculated after determination of the amplitude and the velocity of gastric peristaltic waves.
Results: MRI showed an attenuated gastric contractility in PD patients compared to matched controls. The difference was most obvious (and statistically significant) in the early postprandial phase. MRI parameters of gastric motility did not correlate with patient reported motor fluctuations. Using an iron-containing capsule we were able to directly retrace retention of drugs in the stomach.
Conclusion: The results of this study are in accordance with previous reports on gastric motility in PD. In addition, our data show that the phase of digestion needs to be considered when investigating gastric motility in PD. Despite the theoretical plausibility, we did not find evidence for a correlation between MRI parameters of gastric motility and patient reported motor fluctuations. Higher level mechanisms of gastro-duodenal transport might have been missed by our investigations. We suggest multiple short-time MRIs to better track the whole gastro-duodenal phase in PD.

Abstract No.:
308

Authors:
Folkerts, Ann-Kristin; Dorn, Miriam E.; Roheger, Mandy; Maassen, Marco; Koerts, Janneke; Tucha, Oliver; Altgassen, Mareike; Sack, Alexander T.; Smit, Diede; Haarmann, Lena; Kalbe, Elke

Abstract Title:
Cognitive stimulation for individuals with Parkinson's disease dementia living in long-term care: preliminary data from a randomized crossover pilot study

Abstract Text:
Introduction: While the efficacy of cognitive stimulation (CS) has been demonstrated in patients with dementia, no study has included patients with Parkinson's disease dementia (PDD).
Target: For the first time, this randomized crossover pilot study examined the feasibility and potential effects of CS in PDD.
Methods: All residents of a PDD-specific long-term care unit in the Netherlands that were eligible for the study (n = 12) were randomly allocated to group A (n = 6) receiving CS (8 weeks, twice weekly for 60 min), or group B (n = 6) receiving usual care (control group, CG). The CG participated in CS afterwards, resulting in an experimental group (EG) consisting of n = 12. Pre- and post-assessments and a 6-week follow-up (FU) were conducted for cognition, depression, further neuropsychiatric symptoms, quality of life (QoL), and activities of daily living (ADL) outcomes.
Results: Between-group analysis with difference scores from pre- to posttest revealed a group difference for global cognition (CERAD total score) favoring the EG, with a moderate effect size and a p value just failing to reach statistical significance (p = 0.067, r = 0.43). A further statistical trend was observed for neuropsychiatric symptoms, again with a moderate effect size (p = 0.075, r = 0.42). Within-group analyses indicated improvement only in the EG with large effects also just failing to reach significance for global cognition (short-term, p = 0.060; r = 0.70) as well as for depression (long-term, p = 0.072; r = 0.61). ADL deteriorated significantly at FU in the EG (p = 0.014, r = 0.71).
Conclusion: Although our data are preliminary due to the small sample size, this study shows that CS is feasible and potentially effective for cognitive and non-cognitive outcomes in PDD patients. Randomized controlled trials with larger sample sizes are needed to confirm these promising results.

Abstract No.:
309

Authors:
Oehlwein, Christian; Mittmann, Katrin; Oehlwein, Marita; Baron, Johannes; Sarkisjan, Diana

Abstract Title:
Therapy overview of Parkinson patients with Opicapone: observation from real clinical practice

Abstract Text:
Introduction: Novel COMT-inhibitor Opicapone is already since 2016 on German market, however there is relatively little published experience effects of Opicapone therapy in Parkinson patients with motor fluctuations under real clinical conditions. With present observation we aim to fill this gap.
Target: To evaluate effect of Opicapone therapy on UPDRS and WOQ-9 in Parkinson patients with motor fluctuations under real clinical settings.
Methods: The effects of daily dose of 50 mg Opicapone in 57 patients (23 females, 34 males, mean age at diagnose 55 years, duration of disease 11 years) over 3 months have been measured by means of UPDRS (I–IV) and WOQ-9. The ensure stability of therapy effects, control data has been acquired in 20 patients for 12 months.
Results: After 3 months of the therapy, median UPDRS total score has improved from 44 to 33 after 3 months of the therapy, UPDRS I remained unchanged, UPDRS II reduced at baseline from 12 to 10, UPDS III—from 26 to 20, UPDRS IV—from 4 to 2 respectively. Further subgroup analysis revealed improvement of sleep disturbance (UPDRS IV Item 41) in 9 out of 19 patients in Opicapone therapy. Additionally, the number of patients with early morning dystonia (UPDRS IV Item 35) has also reduced from 46 to 22 within 3 months.

As measured by WOQ-9 Column A, condition of 43 patients out of 57 has improved by at least one point. The most prominent changes have been observed in categories muscle cramping, pain, any stiffness and tremor (40 to 16, 45 to 25, 55 to 36 and 24 at baseline to 12 control measurement respectively).

The Opicapone therapy effects were stable in 20 patients over at least 1 year, as measured by UPDRS and WOQ-9.

The most observed side effects were dyskinesia (6), sleep disorder (2), hallucination (2) and infection (2).
Conclusion: We have demonstrated that novel substance Opicapone offers effective tool in treating Parkinson patients with motor

fluctuations under routine clinical settings. The therapy effects are stable within at least 12 months and well tolerated. Our findings confirm previous result of pivotal clinical studies.

Abstract No.:
310

Authors:
Ruppert, Marina Christine; Greuel, Andrea; Tahmasian, Masoud; Aschenberg, Sophie; Maier, Franziska; Timmermann, Lars; Tittgemeyer, Marc; Drzezga, Alexander; Eggers, Carsten

Abstract Title:
Detection of nigro-striatal pathway disruption in Parkinson's Disease patients using a multimodal imaging approach (Detektion von Korrelaten der Degeneration nigro-striataler Bahnen bei Parkinson Patienten mittels multimodaler Bildgebung)

Abstract Text:
Introduction: Histopathological hallmarks of Parkinson's Disease (PD) include the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc). This neural degeneration is understood to lead to widespread disruptions along the nigro-striatal pathway, resulting in striatal dopamine depletion which consequently underlies the loss of motor control as seen in PD patients. In contrast to histopathological studies, functional imaging methods allow in vivo monitoring of functional correlates of cerebral pathologies and examination of neural pathway integrity.
Target: Assessment of nigro-striatal pathway integrity in PD patients using a multimodal imaging approach.
Methods: In the current study we combined 18F-Fluoro-L-Dopa positron emission tomography (F-Dopa PET), 18F-Fluorodeoxyglucose PET (FDG-PET) and functional MRI (fMRI) to characterize PD associated degeneration along the nigro-striatal pathway in a multimodal fashion. 42 mid-stage PD patients and 14 age-matched healthy controls (HC) underwent a multimodal imaging protocol and examination of clinical features. Between-group differences were analyzed using SPM12 and statistical correlation between imaging and non-imaging findings were computed using SPSS.
Results: Between-group analysis of metabolic activity measured by FDG-PET revealed a hypometabolic cluster in the midbrain in PD patients which comprised the caudal part of the bilateral SNc (FDR-corrected $p < 0.05$). Additionally, we found significantly reduced F-Dopa uptake in PD patients which was exclusively located in the bilateral posterior putamen (PP) (FDR-corrected $p < 0.001$). Interestingly, dopamine influx constant (Ki) values, quantifying bilateral putaminal dopamine synthesis, significantly correlated with nigral hypometabolism ($r = 0.46$, $p < 0.001$), revealing in vivo evidence for functional nigro-striatal pathway disruption in PD patients. ROI-to-ROI functional connectivity (FC) analysis also showed functional isolation of the SNc from the bilateral PP ($p < 0.01$). Of note, network alterations detected by all imaging methods significantly correlated with motor symptoms quantified by Unified Parkinson's disease rating scale (UPDRS) part III.
Conclusion: The present findings demonstrate that equivalents of histopathological changes in PD can be traced in vivo by multimodal imaging. It is hypothesized that PD pathology expands along distinct structural and functional pathways beyond the striatum into functional networks. Multimodal imaging is a promising approach for testing this hypothesis. The present results show that nigral metabolic deficits (FDG) and putaminal dopamine depletion (F-Dopa) are related to nigro-striatal pathway disruption (FC) in PD patients, suggesting that these methods may provide insight into network level changes.

Abstract No.:
311

Authors:
Marxreiter, Franz; Gassner, Heiko; Borozdina, Olga; Barth, Jens; Kohl, Zacharias; Schlachetzki, Johannes; Thun-Hohenstein, Caroline; Volc, Dieter; Eskofier, Björn; Winkler, Jürgen; Klucken, Jochen

Abstract Title:
Sensor-based gait analysis of individualized improvement during apomorphine titration in Parkinson's disease

Abstract Text:
Introduction: Mobile, sensor-based gait analysis in Parkinson's disease (PD) facilitates the objective measurement of gait parameters in cross-sectional studies. Besides becoming novel outcome measures for clinical studies, the application of gait parameters in personalized clinical decision support is limited.
Target: Therefore, the aim of this study was to evaluate whether the individual response of PD patients to dopaminergic treatment may be measured by sensor-based gait analysis.
Methods: Thirteen PD patients received apomorphine every 15 min to incrementally increase the bioavailable apomorphine dose. Motor performance (UPDRS III) was assessed 10 min after each apomorphine injection. Gait parameters were obtained after each UPDRS-III rating from a 2×10 m gait sequence, providing 41.2 ± 9.2 strides per patient and injection. Gait parameters and UPDRS-III ratings were compared cross-sectionally after apomorphine titration, and more importantly between consecutive injections for each patient individually. For the individual response the effect size Cohen's d for gait parameter changes was calculated based on the stride variations of each gait sequence after each injection.
Results: Cross-sectionally, apomorphine improved stride speed, length, gait velocity, maximum toe-clearance, and toe-off angle. Between injections, the effect size for individual changes in stride speed, length, and maximum toe clearance correlated to the motor improvement in each patient. In addition, significant changes of stride length between injections were significantly associated with UPDRS-III improvements.
Conclusion: In this study, we demonstrate that sensor-based gait analysis provides objective target outcome measure of gait performance, reflecting the effects of apomorphine-induced improvement of motor performance in PD. We show that using instrumented gait analysis to measure individual changes in the gait parameters stride speed, stride length, and maximum toe clearance may be a powerful assessment strategy for routine clinical care in individual PD patients. We propose clinically relevant instrumented gait parameters for clinical studies and personalized care.

Abstract No.:
312

Authors:
Palleis, Carla; Levin, Johannes; Bötzel, Kai; Danek, Adrian; Loosli, Sandra V.; Wlasich, Elisabeth; Brendel, Matthias; Rauchmann, Boris; Perneczky, Robert; Haass, Christian; Höglinger, Günter

Abstract Title:
Activity of cerebral networks, amyloid and microglia in corticobasal syndrome: a prospective biomarker study (Zerebrale Netzwerkdegeneration, Amyloid und Mikroglia bei Corticobasalem Syndrom: eine prospektive Biomarkerstudie)

Abstract Text:
Introduction: Corticobasal Syndrome (CBS) is a rare form of atypical Parkinsonism with heterogeneous phenotypes and poor prognosis. It is defined clinically on symptoms related to dysfunction of cortex and basal ganglia. The most frequent neuropathological diagnoses of

CBS patients are in 30% of the cases either the 3-repeat/4-repeat tauopathy Alzheimer's disease (AD), or the 4-repeat tauopathies Corticobasal Degeneration (CBD) and Progressive Supranuclear Palsy (PSP). Ante-mortem diagnosis of these entities is challenging. Biomarkers are needed to establish an early and reliable diagnosis of etiologic differentiation and to track disease progression. Microglia, the cerebral innate immune cells, have been shown to be dysfunctional in AD, CBD and PSP. However, the chronology of microglia dysfunction, cerebral atrophy and functional and structural connectivity remains unclear.

Target: The aim of this prospective cohort study is to analyse the topographical and temporal relationship between cerebral microglia activity changes, network degeneration and atrophy in context of CSF and blood biomarkers over 18 months disease course.

Methods: We aim to generate multimodal prospective imaging and fluid biomarker data in 30 CBS patients fulfilling either the Movement Disorders Society criteria for suggestive or possible PSP-CBS or the Armstrong Clinical Research criteria for possible or probable CBD-CBS. Patients will undergo comprehensive clinical, including cognitive, assessment. Biospecimens will be collected (blood and CSF) for the analysis of microglial function, like TREM2 in CSF. TSPO PET (18F-GE180) targets the 18 kDa translocator protein expressed in activated microglia in vivo. 18F-Flutemetamol PET is used to detect β-Amyloid depositions indicating possible underlying AD pathophysiology. MPRAGE, DTI, and RS-fMRI demonstrate regional atrophy, and structural and functional connectivity in the brain. Patients will be examined at baseline and at 18 months follow-up intervals. This CBS cohort is embedded in the interdisciplinary AD study "Activity of Cerebral Networks, Amyloid and Microglia in Aging and Alzheimer's Disease (ActiGliA)".

Results: We will show cross-sectional results from patients who completed baseline visits. In our cohort, we have identified less AD typical pathology in CSF and imaging than expected.

Conclusion: With this study, chronology of microglia dysfunction, cerebral atrophy and changes in functional and structural connectivity in CBS is explored in a multimodal manner. We aim to further understand the role of neuroinflammation in the pathogenesis of CBS and its pathological sub-forms, either AD-pathology or 4R-tauopathy.

Abstract No.:
313

Authors:
Klingelhoefer, Lisa; Hadjidimitriou, Stelios; Delopoulos, Anastasios; Karayiannis, Fotis; Grammalidis, Nikos; Stadtschnitzer, Michael; Bostanjopoulou, Sevasti; Chaudhuri, Kallol Ray; Hadjileontiadis, Leontios; Reichmann, Heinz; iPrognosis Consortium, on behalf of the

Abstract Title:
iPrognosis—early detection of Parkinson's disease via a smartphone application—proof of concept (iPrognosis—frühe Erkennung der Parkinsonerkrankung mittels Smartphone App—es ist möglich)

Abstract Text:

Introduction: Digital health tools that process densely sampled data streams arising from daily human-mobile interaction can objectify and monitor motor and non-motor symptoms unobtrusively and remotely which are suggestive of PD.

Target: In the i-PROGNOSIS project, we developed the "iPrognosis" Android smartphone application for unobtrusive data collection in the general population with the aim of evolving it into an early PD detection tool. Here we present evidence of clinically controlled application assessed data as proof of concept for remote assessment of PD symptoms by the iPrognosis application.

Methods: The iPrognosis application collects participants' behavioral data arising from the daily use of their smartphones over time in an unobtrusive way, since May 2017. The types of data, namely general usage data (GData), have been defined based on known motor and non-motor symptoms of PD and include features of voice, movement, location patterns and touchscreen-typing as well as NMS-related features such as mood characteristics. Currently this GData is clinically controlled based on a medical evaluation performed in participants by movement disorders specialists in Germany, Greece and United Kingdom. Hereby we provide proof of concept for single data types and the evaluation decision system of the application as a whole by comparison to medical evaluation as gold standard.

Results: 665 participants in total (574 healthy controls; 91 PD patients) downloaded the iPrognosis application and enrolled in the GData study. In total 35 participants (29 PD patients, 65.5% male, mean age 63.52 $\pm$ 6.67 and 6 healthy persons, 50.0% male, mean age 54.50 $\pm$ 12.69) underwent a medical evaluation by a movement disorders specialist. Mean UPDRS part III values as well as median Hoehn & Yahr stage have been significantly less in healthy persons (2.4 $\pm$ 3.58; 0, range 0–2) than in PD patients (18.97 $\pm$ 8.27; 2, range 1–3) ($p < 0.05$), respectively. In a first analysis, a bradykinesia index estimated based on touchscreen-typing pattern (hold time and flight time sequences), achieved a 70% discrimination accuracy between PD patients and controls based on "real-life" data and, within the "in-clinic" setting, correlated significantly with the UPDRS part III single item score ($r = 0.69$). Further analyses will be carried out in the upcoming weeks.

Conclusion: Smartphones offer the ability to remotely detect and monitor people's behavior unobtrusively over time. The comparison of application-derived behavioral patterns with corresponding medical evaluated motor symptoms of PD by movement disorders specialists seem to differentiate between healthy controls and PD patients and furthermore, correspond well concerning symptom severity. Therefore, the i-PROGNOSIS approach is promising regarding the potential for early PD detection.

Abstract No.:
314

Authors:
Kösters, Steffen; May, Caroline; Marcus, Katrin

Abstract Title:
Proteome analysis of human neuromelanin granules in the context of dementia with Lewy bodies

Abstract Text:

Introduction: Neuromelanin (NM) is a dark insoluble pigment, which forms so called Neuromelanin granules with lipids and proteins in the substantia nigra. It is widely debated if those granules are neuroprotective or neurodegenerative. For example, there is a loss of dopaminergic neurons containing NM during the course of dementia with Lewy bodies (DLB). DLB is known to be the second most frequent dementia following Alzheimer's disease.

Target: A proteome analysis of NM granules could allow deeper insight into the function of the NM granules in the pathogenesis of neurological disorders like DLB or Parkinson's disease.

Methods: NM granules were enriched from fresh frozen DLB and control tissue by laser microdissection. A tryptic digestion was performed afterwards. The samples were analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS). MaxQuant was used for the evaluation of the MS/MS spectra. A data synchronization was conducted with Gene Ontology for further analysis.

Results: Mass spectrometric analysis and subsequent evaluation of the data in this pilot study of four DLB and five control samples led to the identification of around 660 proteins. A significant differential study was performed to give a statement about over- and underrepresented proteins. 116 significantly (t-test < 0.05) differential proteins were identified: 72 proteins overrepresented and 44 proteins underrepresented in NM granules from DLB cases. Analysis revealed

that lysosomal associated proteins are significantly overrepresented and mitochondrial associated proteins are underrepresented in NM granules of DLB compared to healthy control cases. To affirm these results and increase the statistical significance, the study will be extended by 18 DLB and 13 control cases

Conclusion: The results of this pilot study support the hypothesis of the NM granules formation as described in the literature that NM granules are probably lysosome related organelle species. NM forms in the cytoplasm at physiological temperature and pH as a side product of dopamine synthesis and is incorporated by endosomes or lysosomes. Furthermore, 536 proteins were identified in all cases, which can be considered as biochemical essential composition of the NM granules.

Abstract No.:
315

Authors:
Wissel, Jörg; Hoonhorst, Maurits; Müngersdorf, Martina; Gallien, Philippe; Meier, Niklaus; Hefter, Harald; Koch, Manuel; Raymond, Romain; Fheodoroff, Klemens

Abstract Title:
First results from the early-bird study—a prospective, non-interventional study to assess effectiveness of abobotulinumtoxina (dysport) in post-stroke upper limb spasticity in relation to timing of treatment

Abstract Text:
Introduction: Recent studies of botulinum toxin for post-stroke spasticity indicate potential benefits of early treatment (i.e. first few months) in terms of developing hypertonicity, pain and passive function limitations.

Target: This non-interventional, longitudinal study aimed to assess the impact of disease duration on the effectiveness of abobotulinumtoxinA (AboBoNT-A) treatment for upper limb spasticity.

Methods: The early-BIRD study (NCT01840475) was conducted between Feb 2013 and Feb 2018 in 43 centres across Germany, France, Austria, Netherlands and Switzerland. Adult patients with post-stroke upper limb spasticity undergoing routine AboBoNT-A treatment were followed for up to 4 treatment cycles. Patients were categorized by time from stroke event to first BoNT-A treatment in the study (as defined by the 1st and 3rd quartiles time distribution) into early-, medium- and late-start groups. We hypothesised that the early-start group would show a larger benefit (decrease) as assessed by the modified Ashworth scale (MAS, primary endpoint) on elbow plus wrist flexors vs. the late-start group.

Results: Of the 303 patients enrolled, 292 (96.4%) received treatment and 186 (61.4%) completed the study (main reason for early discontinuation was lost to follow-up, n = 51). Patients in all groups showed a reduction in MAS scores from baseline over the consecutive injection visits (i.e. at end of each cycle). However, the primary analysis did not show a significant difference between early start vs. late start treatment (ANCOVA: difference in adjusted means of 0.15, p = 0.546) at last study visit.

Conclusion: Patients in all groups displayed a benefit from AboBoNT-A treatment, supporting the utility of treatment for patients at various disease stages. We did not, however, find evidence a significant benefit of early vs. late start of treatment in terms of MAS. Further analyses will evaluate goal attainment, quality of life and predictors of response.

Abstract No.:
316

Authors:
Pons, Laurent; Vilain, Claire; Picaut, Philippe

Abstract Title:
Outcomes of the first-in-human study with a recombinant botulinum toxin E (rBoNT-E): safety and pharmacodynamic profile of rBoNT-E compared with abobotulinumtoxinA (Dysport®)

Abstract Text:
Introduction: Naturally occurring botulinum toxin (BoNT) serotypes have different pharmacological features and are of aesthetic and therapeutic interest.

Target: We studied the safety and pharmacodynamic (PD) profiles of the first recombinant BoNT serotype E (rBoNT-E) versus abobotulinumtoxinA (aboBoNT-A; Dysport®) administered to the right extensor digitorum brevis (EDB) muscle of healthy males, by recording compound muscle action potential (CMAP).

Methods: 28 healthy males were randomised (3:1) in this double-blind, placebo-controlled single ascending dose study (sequential cohorts; up to 3.6 ng rBoNT-E). 24 further subjects were randomised (6/treatment arm) to receive a double-blind injection of aboBoNT-A 20, 40 or 70U, or placebo. Data from active treatment groups only (rBoNT-E and aboBoNT-A) are described.

Results: All rBoNT-E doses were well tolerated. Most treatment-emergent adverse events (TEAEs) were evaluated as unrelated to study treatment; no severe TEAEs or serious AEs were reported, none led to study withdrawal or death. No unexpected treatment-related toxicities were identified with rBoNT-E versus aboBoNT-A.

Onset of action (15% inhibition of CMAP): Day 1 or 2 with rBoNT-E; Day 1 to 7 with aboBoNT-A. Maximal CMAP inhibition: ~ 50% for 0.04 ng rBoNT-E and 20 U aboBoNT-A; ~ 70% for 0.2 ng rBoNT-E and 40 and 70 U aboBoNT-A; ~ 90% for 0.9 and 3.6 ng rBoNT-E. Maximal effect was reached ~ 1 week post-injection for rBoNT-E and 2–6 weeks for aboBoNT-A. Inhibition lasted ~ 7 weeks for 0.9 and 3.6 ng of rBoNT-E, persisting until 26 weeks post-injection for aboBoNT-A subjects.

Conclusion: A comparatively good safety profile of single intramuscular doses of rBoNT-E was demonstrated up to 3.6 ng. rBoNT-E has faster onset of effect, greater peak effect and shorter duration of action versus aboBoNT-A, when injected in EDB muscles of healthy males. The PD profile of rBoNT-E addresses new and different patient needs both in therapeutics and in aesthetics.

Abstract No.:
317

Authors:
Koschel, Jiri; Jost, Wolfgang

Abstract Title:
Entacapone induced diarrhea can lead to severe electrolyte imbalance (Entacaponinduzierte Diarrhoe kann zu lebensbedrohlichen Elektrolytengleisungen führen)

Abstract Text:
Introduction: Entacapone as adjunct to Levodopa has been shown to be an effective strategy in treatment of Parkinson patients experiencing motor fluctuations. Diarrhoea, a non-dopaminergic side effect of entacapone can lead to severe electrolyte imbalance and deterioration of quality of life, if the drug is not withdrawn or replaced.

Target: We want to demonstrate that entacapone-induced diarrhea sometimes lasts for weeks until the drug is discontinued, which can lead to life threatening hypokalemia, even though it is a well-known side effect of entacapone (as well of tolcapone).

Methods: In this report, we present three patients with Parkinson's disease (PD), who suffered from diarrhea caused by entacapone for several weeks, despite of medical consultation. In all three cases, diarrhea stopped within 2 days after discontinuing entacapone.
Results: In one case, the PD (m, 69 y) patient developed a tetraparesis after approximately 3 weeks of entacapone-induced diarrhea, caused by hypokalemia of 1.3 mmol/l (3.5–5.1 mmol/l). The second PD patient (m, 75 y) had chronic renal insufficiency with creatinine of 4.14 mg/dl (0.72–1.18 mg/dl). He experienced diarrhea 5–6 times per day for about 6 months. After entacapone withdrawal, diarrhea stopped, creatinine decreased to 3.24 mg/dl, and potassium increased from 3.7 to 4.4 mmol/l. The substitution of potassium (1200 mg per day had to be reduced). The third PD patient (f, 79 y) had severe orthostatic hypotension, which worsened because of chronic diarrhea. She wasn't able to stand up, because after orthostasis she always lost consciousness. Level of potassium was 2.1 mmol/l.
Conclusion: In vitro, entacapone induces Cl^--secretion in PD rat colon tissue by elevating intracellular cAMP levels, resulting in secretory diarrhea. This may be one of the mechanisms by which entacapone induces diarrhea. So far, diarrhea was not observed under treatment with opicapone. All three patients reported experienced a reduced quality of life for weeks and a deterioration of their PD-symptoms. For two of them, hypokalemia became even life-threatening. To reduce motor fluctuations, all three patients were treated with the COMT inhibitor opicapone. So far, none of them suffered from chronic diarrhea again.

Abstract No.:
318

Authors:
Jost, Wolfgang; Francisco, Gerard E.; Bandari, Daniel S.; Bavikatte, Ganesh; Munin, Michael C.; Tang, Simon Fuk Tan; Largent, Joan; Zuzek, Aleksej; Patel, Anand; Esquenazi, Alberto

Abstract Title:
Individualized onabotulinumtoxinA treatment for Spasticity Resulted in High Patient and Clinician Satisfaction: ASPIRE (Hohe Patientenzufriedenheit durch individualisierte Behandlung der Spastik mit OnabotulinumtoxinA)

Abstract Text:
Introduction: OnabotulinumtoxinA treatment for patients with spasticity is variable and dependent on numerous factors.
Target: Explore real-world onabotulinumtoxinA utilization and effectiveness in patients with spasticity over 2 years from the Adult Spasticity International Registry (ASPIRE) study.
Methods: Multicenter, international, prospective, observational registry (NCT01930786), examining adult patients with spasticity across multiple etiologies treated with onabotulinumtoxinA at their clinician's discretion. Assessments include utilization (each visit) and clinician (next visit)/patient (5 ± 1 weeks post-treatment) satisfaction.
Results: Patients (N = 730) were on average 54 years old, 52% female, and 77% Caucasian, with 37% naïve to botulinum toxins for spasticity. At baseline, 73% of patients presented with upper limb (UL) spasticity, 85% with lower limb (LL) spasticity, and 57% with both. In Germany, 30 patients were enrolled, were on average 56 years old, 53% male, and 100% Caucasian, with 37% naïve to botulinum toxins for spasticity. At baseline, 77% of German patients presented with UL spasticity, 70% with LL spasticity, and 50% with both. In the total population, the most commonly treated UL presentation was clenched fist (52%). Across all clenched fist treatment sessions (N = 1505), percentage injected and dose (mode) injected into each muscle were as follows: flexor digitorum superficialis (86%, 50 U), flexor digitorum profundus (80%, 50 U), flexor pollicis longus (25%, 20U), flexor pollicis brevis (9%, 25 U), other (6%, 20 U). In the total population, the most commonly treated LL presentation was equinovarus foot (59%). Across all equinovarus foot treatment sessions (N = 1609), percentage injected and dose (mode) injected were as follows: gastrocnemius (79%, 100U), soleus (70%, 100 U), tibialis posterior (48%, 50 U), flexor digitorum longus (21%, 50 U), flexor hallucis longus (8%, 50 U) and other muscle (13%, 50 U). EMG was frequently used to localize the muscles to treat clenched fist (> 44%) and equinovarus foot (> 40%). Overall, $\geq$ 93% of clinicians and $\geq$ 85% of patients reported being satisfied/extremely satisfied that onabotulinumtoxinA helped manage spasticity. 261 patients (36%) reported 831 adverse events (AEs); 23 AEs in 20 patients (3%) were considered treatment-related. 94 patients (13%) reported 195 serious AEs; 3 serious AEs in 2 patients (0.3%) were considered treatment-related. No new safety signals were identified.
Conclusion: ASPIRE provides valuable, real-world data on dosing, injection guidance, and muscle targeting over 2 years, that may help guide clinical strategies. ASPIRE captured the individualized nature of onabotulinumtoxinA utilization for spasticity, while demonstrating consistently high satisfaction. These results add to the body of evidence on the safety and effectiveness of onabotulinumtoxinA for the treatment of spasticity.

Abstract No.:
324

Authors:
Muthuraman, Muthuraman; Bange, Manuel; Koirala, Nabin; Pintea, Bogdan; Glaser, Martin; Groppa, Sergiu

Abstract Title:
Effective deep brain stimulation co-modulate cross-frequency coupling of narrowband gamma frequencies to the stimulation frequency in a cortical-subcortical network (Effektive tiefe Hirnstimulation co-moduliert Kreuz-Frequenz Kopplung…)

Abstract Text:
Introduction: The disruption of pathological signals in the cortico-basal ganglia-network has been hypothesised as a mechanism of action of deep brain stimulation (DBS). The induced decrease of pathologically prolonged beta bursts within the sub-thalamic nucleus (STN) through DBS could therefore permit the preferential processing of physiological activity. Similarly, a modulation of physiological and pathological oscillations of other distinct frequencies, e.g. in the gamma range, occurs. However, a comprehensive model for DBS modulating gamma oscillations is still missing. Besides considering gamma as physiologic and pro-kinetic, it has been suggested that finely tuned gamma oscillations between 60 and 90 Hz reflect dynamic processing, possibly by inducing local inhibition or facilitation. Most studies investigating gamma focused on oscillations within the STN, motor cortex (M1), supplementary motor area (SMA), and the pallidum. Only a limited number of studies examined more than two regions at the same time. Furthermore, elements of the BG-thalamo-cortical network like the premotor (PMC) or prefrontal cortices (PFC) and the sub-cortical network of cerebellum (CB), brain stem (BS) have been neglected to date.
Target: We hypothesised that clinically effective high-frequency-DBS of the STN modifies beta and gamma oscillations in wide cortical-subcortical network of interconnected regions. We aimed to reveal that network during resting state EEG recordings.
Methods: We recorded resting state high-density 256-channels EEG of 31 PD-patients during DBS at the clinically most effective frequency (i.e. 130 Hz or 160 Hz). We compared spectral power and cross-frequency coupling (frequency to power) of cortical and sub-cortical regions using a beamformer algorithm for coherent sources. Two clinically ineffective frequencies have been tested as control conditions.

Results: We demonstrated that clinically effective STN-DBS alters oscillatory activity in a wide-spread network of cortical and subcortical regions. A reduction of beta and increase of gamma power is attested in the cortical (M1, SMA, PMC, PFC) and sub-cortical network nodes (STN, CB, BS). Additionally, we found increased cross-frequency coupling of narrowband gamma frequencies to the stimulation frequency in the same nodes of the cortico-subcortical network. No such dynamics were revealed within control regions (i.e. posterior parietal cortex). Furthermore, stimulating at lower or higher frequencies did not significantly alter the networks' source power spectra or cross-frequency coupling.
Conclusion: We were able to show a modulation of beta- and gamma-power and cross-frequency coupling during DBS with HD-EEG in a cortical-sub cortical network. DBS does not exclusively influence motor-function but also the physiological processing related to facilitation and dynamic adaptation, in line with the proposed function of gamma oscillations.

Abstract No.:
325

Authors:
Reuter, Iris; Mai, Natascha; Kaps, Manfred

Abstract Title:
Failure of long-term botulinum toxin treatment for spasticity and dystonia in patients with MSA-P and CBD (Versagen der Therapie mit Botulinumtoxin bezüglich Spastizität und Dystonie bei Patienten mit MSA und CBD)

Abstract Text:
Introduction: Multiple system atrophy (MSA) and corticobasal dystonia (CBD) are progressive movement disorders without any available causal treatment. MSA is characterised by an association of autonomic failure and motor symptoms. The clinical hallmark of corticobasal degeneration is the so-called alien limb syndrome. Patients are not able to perform voluntary movements with the limb and even do not consider the limb as belonging to them. Besides the core symptoms in both conditions patients develop often spasticity and dystonia of their upper limbs. Additionally, patients with MSA often suffer from blepharospasm and cervical dystonia.
Target: The aim of the study was to evaluate the benefit of botulinum Toxin injections for spasticity and dystonia of the upper limbs in patients with MSA-P and CBD.
Methods: 6 Patients with MSA-P and 4 patients with CBD were followed up for 7.8 years. Patients fulfilled the consenus criteria for MSA and CBD respectively. 4 of 6 patients with MSA-P showed blepharospasm and 2 showed cervical dystonia. 1 patient with CBD showed blepharospasm. In MSA-P and CBD patients showing blepharospasm treatment with BoNT was initiated. Patients received low dosages of BoNT (50,1Units) and responded well. Despite controversial reports in the literature we treated cervical dystonia in patients with MSA-P with BoNT (200 Units). Patients had no dysphagia and responded sufficiently.

When patients showed dystonic posturing and/or spasticity of an upper limb, BoNT -treatment was initiated. Treatment interval was 3 months. Prior to treatment with BoNT, 6 weeks and 12 weeks after treatment patients were asked regarding hand function. Spasticity was assessed using the modified Ashworth score (MAS). Hand function was assessed by using the Jebsen hand function scale.
Results: MSA-P-patients were on average 61.6 years old. 4.1 years after diagnosis of MSA-P patients developed dystonic posturing of the more affected upper limb followed by spasticity. 8–12 months later dystonic posturing and spasticity occurred in the other arm. Patients were unable to manage everyday life and became dependent on their carers. Patients with CBD were on average 59.6 years old and showed increased muscle tone of the more affected hand on average 3.2 years after diagnosis. The second hand developed spasticity about 12 months later. They were not able to open their hands and showed fists on both sides.

When patients developed dystonic posturing of the arms, BoNT treatment was applied with 3-month interval between injections. On average 350 Units were injected.

MSA-P and CBD-patients responded well to BoNT-treatment regarding spasticity with a decrease of MAS by 2.1 points, but significant functional improvement was observed in 2 patients only. Patients improved in subscores of the Jebsen hand function scale. They were able to feed themselves and to grip objects.

However, response to BoNT-treatment decreased after three injections. There was no response to BoNT after the 4th injection. In one patient with CBD Botulinumtoxin treatment failed already after 3 injections. There was still response to injections for blepharospasm and to cervical dystonia. BoNT dosage was increased up to 700 Units without response and BoNT type A was switched to BoNT type B without improvement of response.
Conclusion: Treatment of upper limb spasticity and dystonia with BoNT provides only short-term relief and is not suitable for long-term treatment. Systemic spasmolytic therapy did not show much benefit either. Thus, botulinumtoxin is worth considering for treatment of spasticity and dystonia in MSA-P and CBD, but patients should be informed that treatment success might be short-term only. The reason for treatment failure remains unclear so far, antibodies to Botulinumtoxin can be excluded since patients with blepharospasm and cervical dystonia still responded to BoNt for these conditions.

Abstract No.:
326

Author:
Reuter, Iris

Abstract Title:
Loss of functional decline in young adult patients with cerebral palsy is reversible (Die funktionelle Verschlechterung bei jungen erwachsenen Patienten mit kindlicher Zerebralparese ist reversibel)

Abstract Text:
Introduction: Patients with cerebral palsy (CP) receive special care by multiprofessional teams in childhood. When young adult patients are transferred to movement disorder clinics for adults, we often observe a drop of functional performance. Consecutively, patients are more impaired in everyday life.
Target: We conducted an observational study in 10 patients with CP and functional loss in mobility, especially in walking, balance, strength and endurance. Aim of the study was to investigate if functional deficits can be improved by modification of botulinum treatment on its own and if further improvement can be achieved by an additional intensive physiotherapy programme.
Methods: 10 young adult patients with CP were assessed for BoNT-treatment. BoNT-treatment was modified if necessary. After the second treatment with the modified BoNT-3 pattern, patients underwent a physiotherapy programme tailored to their individual needs 5x/week for 1 h over a period of 6 months. Prior to the change to BoNT-treatment, before, immediately after and 12 months after the physiotherapy intervention the following assessments (suitable to perform in an outpatient clinic) were conducted: Modified Ashworth score, 10-m walking test, 6-min walking test, climbing a flight of stairs, chair-raising test with one leg, chair-raising test with both legs 10x, one leg stand (20 s) and tandem stand. Paired t-Test was used for statistical analysis.
Results: 10 Patients (mean 24.5 y) showed MAS of the lower limbs of 2.7 prior to treatment with botulinum toxin. There was a tendency for the MAS to decline over the study period but this was not significant. After reduction of dosage of BoNT-treatment, especially in

proximal leg muscles, performance in chair raising test increased and balance improved slightly. At the end of the 6 months of intensive physiotherapy treatment, time for the 10-m walking test decreased significantly, distance on the 6-min walking test improved. Time for the one leg stand improved. Prior to the intervention 4 patients were able to climb a flight of stairs without support; afterwards, 9 of 10 patients managed the task. Before the intervention 2 patients managed to raise from a chair with one leg, 5 with two legs without support of the arms, afterwards 5 with one leg and 8 with both legs 10 × without arm support. The assessments 12 months after the intervention showed a slight loss of strength in the chair raising test; there was no decline in walking speed and balance.

Conclusion: In conclusion loss of function in young adult patients seems to be multifactorial. Our study shows that botulinum treatment has to be reviewed regarding dosage and pattern. After modification of botulinum toxin treatment strength and balance increased slightly. Significant functional improvement was observed after 6 months of intensive physiotherapy treatment. Apart of a mild decline in strength patients were able to keep the regained functions with 2 sessions of supervised physiotherapy per week and additional home exercises. The study shows that young adult patients with cerebral palsy are able to regain lost functions.

Abstract No.:
327

Authors:
Gladow, Till; Gaßner, Heiko; Ullrich, Martin; Hannink, Julius; Roth, Nils; Marxreiter, Franz; Kuederle, Arne; Kohl, Zacharias; Winkler, Jürgen; Eskofier, Björn; Klucken, Jochen

Abstract Title:
Sensor-based gait analysis distinguishes fallers from non-fallers in Parkinson's disease under clinical and real-life conditions (Sensorbasierte Ganganalyse unterscheidet stürzende von nicht stürzenden Parkinson Patienten unter klinischen und…)

Abstract Text:
Introduction: Gait impairments and reduced mobility are major risk factors for falls in Parkinson's disease (PD) and substantially influence the quality of life in PD patients. Recurrent falls are associated with disease progression where the frequency of falls (FoF) can vary between once a year to several times a day. Therefore, the assessment of gait-related fall risk under clinical and real-life conditions is crucial for clinical routine care and an important target for clinical trials. Shuffling of gait, freezing episodes, decreased step length and increased step time variability are known predictors for falls. Gait analysis with wearable sensors is a promising approach to assess gait impairments on large cohorts in clinical routine and especially in long term observation under real-life conditions in patient's home environments.

Target: To distinguish PD fallers from non-fallers by assessing gait parameters with wearable sensors under clinical and real-life conditions is the goal of this project. Comparing standardized gait tests in clinical environments with home-monitoring recordings, equivalent walking bouts have to be defined and extracted from sensor data.

Methods: Gait parameters and fall events of PD patients are measured routinely at the movement disorder outpatient unit at the University Clinic Erlangen. Gait parameters were captured under clinical conditions by a mobile gait analysis system while patients performed a standardized 4 × 10-Meter-Test (4×0MT) and the 2-Min-Walking-Test (2MWT). Measuring gait parameters in real-life scenarios, a long-term gait monitoring system was used and gait bouts were automatically selected and analyzed from daily activities. The number of falls per year was assessed by the Erlanger Frequency of Falls Questionnaire (erFoF).

Results: 97 PD patients (Hoehn&Yahr 1-3) were included in this cross-sectional study and were separated into fallers (n = 36) and non-fallers (n = 61) obtained by the erFoF. Group comparison of fallers vs. non-fallers showed significant differences in both clinical test conditions (4×10MT and 2MWT) for the mean values of the gait parameters Toe-off angle (4×10MT $p = 0.035$; $d = 0.45$; 2MWT $p = 0.039$; $d = 0.44$), Heel-strike angle (4×10MT $p = 0.015$; $d = 0.52$; 2MWT $p = 0.026$; $d = 0.47$), maximum Toe-clearance (4×10MT $p = 0.027$; $d = 0.47$; 2MWT $p = 0.037$; $d = 0.44$) and landing Impact-intensity (4×10MT $p = 0.006$; $d = 0.58$; 2MWT $p = 0.009$; $d = 0.56$). Comparable results could be found in first recordings under real-life conditions, but more data of participants are necessary for comprehensive analysis.

Conclusion: Sensor-based gait analysis under clinical and real-life conditions has the potential to distinguish fallers from non-fallers in specific parameters. More home-monitoring data has to be recorded in multicenter studies, to sufficiently compare clinical and real-life conditions.

Abstract No.:
328

Authors:
Bergmann, Jeannine; Hösl, Matthias; Amberger, Tamara; Lutz, Lisa; Jahn, Klaus

Abstract Title:
Ratio of body sway to limits of stability—An indicator for fall risk and fear of falling?

Abstract Text:
Introduction: Postural instability is a major component in Parkinson's Disease (PD) which predisposes individuals to falls and shows limited response to drug treatment. Falls often induce fear of falling, but also individuals without a history of falls show fear of falling and activity avoidance.

Individuals with PD have altered center of pressure fluctuations during standing and reduced postural stability margins. A recent study showed that they sway markedly more as a percentage of their limits of stability (LOS) compared to healthy subjects (Menant et al., 2011). This may indicate a higher risk of falling.

Target: To determine whether the ratio of body sway to LOS during standing correlates with fall risk and fear of falling in PD.

Methods: Subjects with idiopathic PD (Hoehn & Yahr 1-4, on medication) were included. Two posturographic measurements were performed using a force plate (Kistler): static standing with eyes open (sway path, velocity, area, and amplitudes), and the LOS (maximum excursion). The ratio of the maximal sway amplitude to the LOS (sway-to-LOS ratio) was calculated in the anterior–posterior (AP) and the medio-lateral (ML) planes. The posturographic data of the PD subjects were compared to normative data of 50 healthy subjects (aged 30–80, 10 subjects per age decade).

Balance, risk of falls, and the fear of falling were assessed with the Timed up and Go test, the Berg Balance Scale, the reported number of falls within the last 12 months, and the Falls Efficacy Scale.

Results: We included 15 individuals with PD (3 females, age 69 ± 12, duration of PD 7 ± 7 years, median UPDRS 29 IQR 30). All sway parameters were significantly larger in PD subjects than in the healthy control group, while the LOS were significantly smaller. This resulted in significantly higher sway-to-LOS ratios in both planes in individuals with PD.

There were moderate to high correlations of the sway-to-LOS ratio in AP with all clinical scales and the number of falls ($rSp > 0.5$, $p < 0.045$). This was not the case in the ML plane.

Conclusion: Individuals with PD approach their LOS during static standing more than healthy controls. In the AP plane, this correlates with an increased risk of losing balance and falling, and also with

higher fear of falling. The sway-to-LOS ratio AP seems to be indicative for the individual risk and fear of falling and could be used to assess fall risk in PD subjects.

Abstract No.:
329

Authors:
Greuel, Andrea; Präger, Lea; Kordys, Elena; Apetz, Nadine; Tittgemeyer, Marc; Timmermann, Lars; Drzezga, Alexander; Endepols, Heike; Eggers, Carsten

Abstract Title:
Cerebellar glucose metabolism in PD increases contralaterally to putaminal dopamine depletion (Cerebellärer Glucosemetabolismus ist bei Morbus Parkinson kontralateral zu putaminalem Dopaminmangel erhöht)

Abstract Text:
Introduction: In Parkinson's disease (PD), relative hypermetabolism of the cerebellum is hypothesized to represent a compensatory mechanism to balance striatal dysfunction. A recent study used positron emission tomography (PET) imaging in a hemiparkinsonian rat model and found evidence supporting this theory: lesion severity was associated with contralesional cerebellar hypermetabolism and motor symptoms (Kordys et al., EJNMMI Research, 2017). While relatively increased cerebellar metabolism has previously been demonstrated in PD patients, existing studies did not account for laterality of this observation.
Target: To test whether striatal dopamine depletion and cerebellar glucose metabolism in PD patients are lateralized in correlation with each other, and if the degree of laterality in limb motor scores is reflected in the cerebellum.
Methods: PET imaging with [18F]Fluorodeoxyglucose (FDG) and [18F]-Fluoro-L-Dopa (F-Dopa) was performed in 42 mid-stage PD patients. Analysis: 1) Dopamine influx constants (Ki) were calculated, and the degree of laterality in the posterior putamen estimated by dividing Ki-left/Ki-right: values < 1 represented more advanced dopamine depletion on the left, values > 1 indicated that the right putamen was more affected. Corresponding values were created by dividing left/right measurements of 2) limb motor scores from the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) and 3) FDG uptake in the anterior cerebellum (lobules 3–5, anatomical VOIs corresponding to findings in rats). Based on the rat model, a positive correlation between laterality values of all three measures was hypothesized.
Results: Laterality values for putaminal F-Dopa correlated positively with those for limb UPDRS-III scores ($r = 0.496$, $p = 0.001$) and cerebellar FDG ($r = 0.407$, $p = 0.007$). An association was also found between FDG and UPDRS-III lateralization ($r = 0.380$, $p = 0.013$).
Conclusion: Clinically left-dominant parkinsonism is associated with right-hemispheric dopamine depletion, and vice versa. The presented approach to assess laterality enabled detection of this fact in a group with mixed left- and right-dominant parkinsonism, even when patients with symmetrical symptoms were included. More importantly, applying the same concept to cerebellar FDG uptake allowed translation of findings from a hemiparkinsonian rat model to human subjects. To our knowledge, this is the first time that the aspect of laterality has been evaluated in PD-associated changes in cerebellar metabolism. Future studies should investigate whether this might represent compensation for impaired dopamine-mediated motor functions.

Abstract No.:
330

Authors:
Kohl, Zacharias; List, Julia; Klucken, Jochen; Winkler, Jürgen; Gassner, Heiko

Abstract Title:
Standardized gait assessments correlate with clinical rating scores and fear of falling in hereditary spastic paraplegia (Ganganalyse korreliert mit klinischen Skalen und Sturzangst bei hereditärer spastischer Spinalparalyse)

Abstract Text:
Introduction: Impairment of gait represents the major clinical symptom in hereditary spastic paraplegia (HSP) and often associates with increased fear of falling and reduced quality of life. However, so far comprehensive studies addressing standardized assessment of gait in HSP patients, including the commonly used Spastic Paraplegia Rating Scale (SPRS) with objective standardized measures are missing.
Target: The aim of this study was to correlate easy-to-perform functional gait measures with clinical rating (SPRS) in patients with "pure" HSP, as well as self-rated questionnaires for fear of falling and quality of life.
Methods: 22 patients with a "pure" HSP and 22 age- and gender-matched healthy control persons were included in an observational single-center study. Clinical evaluation was performed including the SPRS by experienced movement disorder specialists. Study participants rated their fear of falling by using the Falls Efficacy Scale International (FES-I), and quality of life by the SF-12 questionnaire, respectively. Standardized gait measurements included the assessment of gait speed and step length from a 10-meter walk test, the Timed up and go test (TUG), and the maximum walking distance from the 2-min walking test. Participants were instructed to walk in self-selected walking speed for the 10 m-walk, and at maximum speed as far as possible for the 2-min walk test. Correlation analysis between functional gait measures and clinical rating as well as self-rating questionnaires war performed using Spearman's rank correlation (r).
Results: Standardized functional gait measures correlated strongly with SPRS total score, as well as SPRS subscores "Functional" and "Spasticity and Weakness". More importantly, standardized gait parameters correlated with fear of falling and the physical component of the quality of life assessment. Interestingly, both self-rated measures also showed strong correlations to the clinical rating (SPRS).
Conclusion: Standardized functional gait measures reflect motor impairment, fear of falling as well quality of life in HSP patients. Gait analysis supports the clinical workup by more objective, standardized parameters. Fear of falling and quality of life should be considered as important self-reported markers for gait impairments in HSP patients.

Abstract No.:
331

Authors:
Mendonca, Nuno; Bateman, Randall J.; Boxer, Adam L.; Braunstein, Joel B.; Claassen, Daniel; Holtzman, David M.; Kerwin, Diana; Rendenbach-Mueller, Beatrice; Soares, Holly
Presenter:
Höglinger, Günter

Abstract Title:
ARISE Study: study design and baseline characteristics for a phase 2 trial of the Anti-Tau Antibody ABBV-8E12 in Progressive Supranuclear Palsy

Abstract Text:
Introduction: ABBV-8E12 is a humanized anti-tau monoclonal antibody being developed for the treatment of PSP and early Alzheimer's disease (AD). A phase 1 double-blind, placebo-controlled, single ascending dose study on the safety, tolerability, and pharmacokinetics of ABBV-8E12 in PSP patients (NCT02494024) was recently completed. The phase 1 results showed that ABBV-8E12, when administered as a single dose up to 50 mg/kg, exhibited an acceptable safety and tolerability profile to support repeat-dose testing in larger cohorts of patients with tauopathies.
Target: This double-blind, placebo-controlled phase 2 study (M15-562 ARISE study, NCT02985879) assesses the safety and efficacy of ABBV-8E12 treatment in patients with progressive supranuclear palsy (PSP) for 52 weeks.
Methods: Male and female patients, at least 40 years of age, are being enrolled at approximately 40 global study sites. Prior to enrollment, patients will have had symptoms for less than 5 years and meet the NINDS-PSP criteria for possible or probable PSP. Patients will be randomized to one of two ABBV-8E12 dose arms or placebo.
Results: The primary efficacy outcome is the change from baseline to week 52 in Progressive Supranuclear Palsy Rating Scale total score. Key secondary endpoints include the Schwab and England Activities of Daily Living Scale, the Unified Parkinson's Disease Rating Scale Part II, the Clinical Global Impression of Severity and Change, the PSP-Quality of Life subscale scores, and the Visual Analog scale. Table 1 includes baseline characteristics for the first 233 enrolled patients.
Conclusion: The current study is ongoing and designed to evaluate the 52-week safety and efficacy of ABBV-8E12 in PSP patients. In addition to the ongoing phase 2 study in PSP patients, a phase 2 study evaluating ABBV-8E12 in early AD patients is also currently ongoing (NCT02880956).

Abstract No.:
332

Authors:
Oehlwein, Christian; Mittmann, Katrin; Oehlwein, Marita; Baron, Johannes; Sarkisjan, Diana

Abstract Title:
Does duration of Parkinson disease affect outcomes of Opicapone Therapy?—Retrospective subgroup analysis

Abstract Text:
Introduction: With progression of Parkinson Disease, therapy scheme becomes more complex. However, the question remains open whether early application of Opicapone in the patients with motor fluctuations could be advantageous.
Target: To evaluate effect of disease duration on outcomes of Opicapone therapy, we have compared changes of UPDRS and WOQ-9 scores in two groups of patients with below and above 10 years of Parkinson disease diagnosis.
Methods: For this comparison, the data from patients with below and above 10 years of Parkinson disease diagnosis (30 and 27, respectively) has been used. The patients in the first group had motor fluctuation for 2.1 years and in the second group for 6.4 years in average respectively. We measured UPDRS (I-IV) and WOQ-9 at baseline and after 3 months of Opicapone therapy (50 mg daily) under routine clinical setting.
Results: In both groups we have seen similar improvements. Namely, median of UPDRS total score after 3 months has improved from 42 to 31.5 in patients below and from 52 to 40 above 10 years of the diagnosis respectively. UPDRS I remained unchanged (from 1 to 1 in both groups respectively), UPDRS II in ON changed from 11 to 9 and 11.5 to 9.5, UPDRS II OFF—from 16 to 11 and from 21 to 16, UPDRS III—from 26 to 19 and from 33 to 25, and finally, UPDRS IV—from 4 to 2 in both groups respectively. Further subgroup analysis revealed reduction of number of patients with sleep disturbance (UPDRS IV Item 41) in 3 out of 7 and 3 out of 8 patients above and below 10 years of diagnosis respectively. Additionally, the number of patients with early morning dystonia (UPDRS IV Item 35) has also reduced from 25 to 10 and from 18 to 9 of both groups within 3 months.

However, the most prominent differences we have observed in WOQ-9 scores. 25 patients out of 30 with below 10 years old diagnosis improved by at least 1 point and 5 remained unchanged. In the other group—18 out of 27 improved, 7 remained unchanged and 2 worsened.
Conclusion: Both groups of patients have demonstrated improvement of UPDRS scores under Opicapone Therapy within 3 months. However, the group of patients with shorter duration had better WOQ-9 scores.

Abstract No.:
333

Authors:
Oehlwein, Christian; Mittmann, Katrin; Oehlwein, Marita; Baron, Johannes; Sarkisjan, Diana

Abstract Title:
Does previous COMT-inhibitor affect outcomes of Opicapone Therapy: retrospective subgroup analysis?

Abstract Text:
Introduction: COMT-inhibitors have proved their efficacy in Parkinson patients with motor fluctuations. However, the newest COMT-inhibitor Opicapone due to higher affinity offers significantly longer action time. Nevertheless, there is relatively little known whether previous COMT-inhibitors affects efficacy of the new one.
Target: The main goal of the study was to investigate possible effects of previous use of COMT-inhibitors before starting Opicapone therapy. To this end, we compared efficacy of Opicapone in previous Entacapone or Tolcapone with COMT-naive patients. To evaluate this effect, we have compared changes of UPDRS and WOQ-9 scores in both groups of patients.
Methods: For this comparison, we used data acquired from 23 patients with previous COMT-inhibitor and 34 COMT-naïve patients. We measured UPDRS (I-IV) and WOQ-9 at baseline and after 3 months of Opicapone therapy (50 mg daily) under routine clinical setting.
Results: Generally, we observed somewhat better efficacy in COMT-naïve patients. For instance, the group with previous COMT-inhibitor, median UPDSR total score improved from 41 to 32, in the other group—from 46.5 to 34 respectively within 3 months. UPDRS I remained unchanged (from 1 to 1 in both groups respectively), UPDRS II in ON changed from 12 to 10 and 13 to 10, UPDRS II OFF—from 18 to 13 and from 19 to 14, UPDRS III—from 24 to 18 and from 28.5 to 21, and finally, UPDRS IV—from 4 to 2 in both

groups respectively. As measured by UPDRS IV Item 41, reduction of patients with sleep disturbance reduced by 80% (4 out of 5) with previous COMT-inhibitor and 50% (5 out 10) by COMT-naive. In addition, the number of patients with early morning dystonia (UPDRS IV Item 35) has also reduced by 63.5% (16 to 6) and by 54.8% (24 to 13) of both groups within 3 months respectively.

However, noticeable difference was observed in WOQ-9 scores. 41.2% (14 out of 34) of all COMT-naïve patients have improved by at least 3 points, whereas in previous COMT-group only 34.8% (8 out of 23) of patients.

Conclusion: Our data demonstrates that switch from previous COMT-inhibitor to Opicapone could still improve clinical outcome of the new therapy. However, since COMT-naïve patients in some parameters were way better, Opicapone could be considered as first choice.

Abstract No.:
334

Authors:
Marxreiter, Franz; Cosma-Grigorov, Alexandra; Gaßner, Heiko; Meixner, Holger; Kohl, Zacharias; Neurath, Markus F; Wirtz, Stefan; Winkler, Jürgen

Abstract Title:
Gastrointestinal microbiome in Parkinson's disease in a Bavarian cohort

Abstract Text:
Introduction: Accumulating evidence suggests that alpha-synucleinopathy within the enteric nervous system (ENS) may be one of the initial sites for the premotor onset of Parkinson's disease (PD). Altered gut microbiota may contribute to, or trigger the pathological process of alpha-synuclein aggregation in the ENS. Altered abundances of Prevotellaceae, Lactobacillaceae, and Enterococcaceae have previously been observed in different North European study populations.

Target: Our goal was to evaluate, whether gut microbiota are similarly altered in a Bavarian PD cohort and whether altered gut microbiota are evident already early in the course of PD. We assessed changes in the gut microbiome in different disease stages and hypothesized that the microbiome of PD patients is altered already at an early disease stage. Furthermore, we tested whether initial changes persist at intermediate and late disease stages.

Methods: Between November 2016 and June 2018, 176 subjects were screened. Of these, 102 (71 patients, 31 controls) were enrolled. Motor symptoms were measured using part III of the Unified Parkinson's Disease Rating Scale (UPDRS III) and disease staging followed the modified Hoehn & Yahr scale (H&Y). Severity of non-motor symptoms was assessed using the Non-Motor Symptoms Scale (NMS). The degree of constipation was assessed using the Wexner constipation score. Participants collected fecal samples in a DNA stabilizing solution (Stool Collection Tubes with Stool DNA Stabilizer; Stratec®, Stratec Molecular, Berlin, Germany). Total DNA was extracted from the samples. Polymerase chain reaction amplification and pyrosequencing of the V3 and V4 regions of the bacterial 16S ribosomal RNA gene was performed and used for taxonomic assignment.

Results: We analyzed the microbiome of 71 PD patients (mean age: 65.2 ± 10.2; 45.1% females) and 31 controls (mean age: 64.3 ± 8.9; 45.2% females). Our results indicate that there is no change in alpha- or beta-diversity in the gut microbiome between groups. However, abundances of individual bacterial families, such as Lactobacillaceae, Sutterellaceae, and Enterobactericeace differ between disease stages and controls. On the genus level, abundances of Citrobacter and Lactobacillus were significantly altered, particularly at H&Y IV.

Conclusion: Distinct bacterial families are altered at early PD stages. Thus, the pattern of specific bacterial families may contribute to an altered micromilieu, favoring alpha-synuclein aggregation early in the course of PD. At later stages, alterations in other bacterial families may rather be related to non-motor symptoms like constipation. Overall, the gut microbiome signature may result in distinct inflammatory events, driving the course of the disease.

Abstract No.:
335

Authors:
Altmann, Christian; Trubelja, Kristian; Emmans, David; Jost, Wolfgang

Abstract Title:
Progression of cognitive impairment in Parkinson's disease (Fortschreiten kognitiver Einschränkungen bei Morbus Parkinson)

Abstract Text:
Introduction: Cognitive impairment and dementia are common non-motor symptoms in Parkinson's disease. Thus, patients often express concern about the nature of cognitive deficits they could face in the course of Parkinson's disease and the rate of cognitive decline.

Target: To elucidate the typical progression of cognitive decline in Parkinson's disease and its variation, we retrospectively surveyed neuropsychological data obtained at the Parkinson-Klinik Wolfach, Germany in the years 1996–2015.

Methods: Many of the patients in the surveyed period were repeatedly admitted to our clinic and we were thus able to compile re-test data for 58 patients (male: 39) obtained at varying time intervals. Mean age at the time of initial diagnosis was 65.7 years (SD: 8.3), first neuropsychological testing occurred on average at an age of 71.8 years (SD: 6.7). Only patients with idiopathic Parkinson syndrome were included in the analysis, patients with secondary forms or atypical Parkinsonian syndromes were not analyzed. Neuropsychological testing was conducted with the NAI (Nürnberger Alters-Inventar). This battery provides sub-tests that examine cognitive processing speed, executive function, working memory and verbal/visual memory functions. To evaluate cognitive decline and to compare across sub-tests, we normalized test raw scores with respect to the first time measurement of our patient sample. As a result, we obtained z-scores that allow for comparison of decline rates between sub-test scores.

Results: The re-test time span varied across patients from below 1 year up to about 12 years (mean: 3.2 years). Most patients were seen twice, but some patients were tested up to 8 times. The steepest rates of cognitive decline were observed for the NAI sub-tests Stroop-Color Naming (Farbworttest-Farben benennen: $z = 0.41$/year, SEM: 0.15) and the Figures Test/Visual Memory (Figurentest: $z = -0.25$/year, SEM: 0.10), that exceeded the rates due to normal aging by far (about $z = 0.03$/year and $z = 0.02$/year, respectively). Intermediate rates of decline were found for Stroop-Word Reading (Farbworttest-Wörter lesen), Number Trail Making (Zahlenverbindungstest), Maze Test (Labyrinthtest), Digit Span (Zahlen nachsprechen), and Word List (Wortliste). Stroop-Interference (Farbworttest-Interferenz) and Pictures Test (Bildertest) showed no or only very little deterioration over time in our sample.

Conclusion: In sum, this study evaluated cognitive decline in a sample of patients with idiopathic Parkinson's disease. Our data suggest that the cognitive capacities for cognitive processing speed and purely visual memory were particularly prone to decline in Parkinson's disease.

Abstract No.:
336

Authors:
Grimm, Max-Joseph; Respondek, Gesine; Piot, Ines; Arzberger, Thomas; Giese, Armin; Roeber, Sigrun; Höglinger, Günter

Abstract Title:
Simplifying the application of MDS-PSP criteria through multiple allocation extinction (MAX) rules (Vereinfachung der Anwendung der MDS-PSP Kriterien durch "Multiple Allocation Extinction" (MAX) Regeln)

Abstract Text:
Introduction: New diagnostic criteria of the progressive supranuclear paresis (MDS-PSP Criteria) had been introduced by the movement disorder society (Höglinger et al., 2017). Using these criteria, a major part of the patients can be allocated to more than one PSP predominance type and certainty level.
Target: We aimed to make the MDS-PSP Criteria more applicable for clinical use by developing rules for multiple allocation extinction (MAX rules).
Methods: A chart review of 195 autopsy confirmed patients with symptoms for diagnosing PSP by using MDS-Criteria was created. The patients were allocated to PSP-predominance types and diagnostic certainty according to the MDS-Criteria. By analyzing the progression of the phenotypes and diagnostic certainties, the following MAX rules were created:

- MAX 1 (diagnostic certainty): prob. > poss. > s.o.
- MAX 2 (phenotypic hierarchy): PSP-RS > PSP-OM/PI > all other phenotypes
- MAX 3 (temporal order): 1st > 2nd > 3rd diagnosis…
- MAX 4 (MAX hierarchy): MAX 1 > MAX 2 > MAX 3

Results: By application of the MAX rules, the number of diagnostic allocations per patient can be reduced from 5.26 to 1.06 diagnoses per patient. At the end of record only 22 (11%) instead of 159 (82%) patients show more than one diagnosis, while the number of patients without diagnoses stay at 11 patients before and after applying MAX rules.
Conclusion: By applying the MAX rules, the number of diagnostic allocations per patients can be reduced, which tremendously clarifies the applicability of the MDS-PSP Criteria in clinical practice.

Abstract No.:
337

Authors:
Paschen, Steffen; Helmers, Ann-Kristin; Volkmann, Jens; Deuschl, Günther; Berg, Daniela; Zeuner, Kirsten

Abstract Title:
Bilateral stimulation of the internal pallidum in Wilson's disease

Abstract Text:
Introduction: Wilson's disease (WD) is a rare autosomal recessive disease with a mutation of the ATP7B gene and subsequent copper accumulation and toxicity in multiple organs, mainly affecting the liver, the central nervous system, the eyes and other organs.

Treatment of neurologic symptoms in WD such as dystonia and tremor can be challenging. Deep brain stimulation (DBS) of the globus pallidus internus (GPi) may be beneficial in medically refractory patients.

Target: We aimed at evaluating the safety and efficacy of bilateral GPi DBS in a patient with a predominantly mobile, severe generalized secondary dystonia due to WD.
Methods: This is a report of a 49 year old patient with an 18 year history of a dystonic movement disorder that affected primarily the neck. Initially, Botulinum toxin treatment was effective. However, during the past 8 years the movement disorder changed to a generalized dystonic, choreo- and ballistic-like involuntary movement. He was sufficiently treated with penicillamine up to 2400 mg with adequate decoppering. There was no further improvement with Trientine up to 2400 mg and zinc. The MRI showed no progression. Botulinum toxin and anticholinergics were ineffective. Therefore deep brain stimulation was considered a possible therapeutic approach. The primary endpoint was the change of dystonic symptoms on the Burke-Fahn-Marsden scale—movement scale (BFMDRS-M) 6 month post bilateral GPI DBS. As secondary endpoints, the Abnormal Involuntary Movement Scale (AIMS) and the Blepharospasm Disability Index (BSDI) were evaluated.
Results: The evaluation of the primary endpoint showed a 32% reduction of dystonic symptoms on the BFMDRS—movement scale (pre-op: 39.5 points, 6 month post GPi DBS: 27 points; absolute reduction: 12.5 points). The AIMS was reduced by 31% (pre: 29, post: 20; reduction: 9 points) and the BSDI by 33% (pre: 9; post: 6; reduction: 3 points).
Conclusion: Bilateral stimulation of the GPi was safe and efficient in a patient with a severe, generalized secondary dystonia in Wilson's disease. GPi DBS in dystonia due to WD should be considered in selected patients.

Abstract No.:
338

Authors:
Zella, M. A. Samis; May, Caroline; Müller, Thomas; Ahrens, Maike; Tönges, Lars; Gold, Ralf; Marcus, Katrin; Woitalla, Dirk

Abstract Title:
Landscape of pain in Parkinson's Disease: impact of gender differences (Topographie des Schmerzes bei M. Parkinson: Bedeutung von Geschlechtsunterschieden)

Abstract Text:
Introduction: Pain as a symptom of Parkinson's disease (PD) was mentioned in the first essay on PD, in 1817, where James Parkinson described pain stemming from "rheumatism" as a common feature of the disease. Few systematic studies have been carried out and there are still no guidelines on pain therapy in PD. Additionally, within the studies that do exist, gender-specific differences in pain perception are often the focus, though no consistent results have to date been obtained. Therefore, an analysis centred on pain is essential to better understand its physiopathology as well as its relationship to gender.
Target: The first main aim of our study was therefore to map pain in the largest PD study group to date, with the second being the analysis of the impact of different pain therapies in PD. The third and main aim was to correlate the obtained results with gender.
Methods: A structured questionnaire with questions focusing on pain was sent to PD patients, with a subsequent statistical analysis correlating the data on pain features and pain therapy with gender. All patients included in the analysis belonged to the Deutsche Parkinson Vereinigung e.V. (DVP), a support organisation that encompasses around 23,000 PD patients and aims to improve the quality of life of PD patients and their relatives in Germany.
Results: The study included 1204 female and 1610 male PD patients. Spinal-paravertebral pain emerged as the dominant form of pain. A significant dependency was further demonstrated between gender and pain localisation, pain intensity (p-value < 0.05), and pain as impairment to quality of life (p-value < 0.05). Nonsteroidal anti-inflammatory drugs (NSAIDs) were the painkillers most frequently used by the patients. Aside from non-opioid analgesics (p-value < 0.05), there was no demonstrated significant dependency between pain treatments and gender.

Conclusion: Patients with PD appear to be predisposed to the development of pain, and clinicians should bear in mind that pain per se can be a symptom of PD. As clearly demonstrated, pain in PD involves mostly muscular and spinal structures. In view of this form of pain, the most frequently used painkillers are NSAIDs. This study found that gender influenced pain perception in the PD patients tested, but did not impact the approach to pain therapy. In conclusion, the results herein provide an initial attempt at understanding the pathophysiological mechanisms of pain, as relate to gender, which can be used for the development of appropriate therapeutic strategies.

Abstract No.:
339

Authors:
Janocha, Laura; Wüllner, Ullrich; Weismueller, Tobias; Kaut, Oliver

Abstract Title:
Transcutaneous vagus nerve stimulation (tVNS) in patients with Parkinson's disease and delayed gastric emptying (Transkutane Nervus Vagus Stimulation bei Patienten mit idiopathischem Parkinson-Syndrom und Gastroparese)

Abstract Text:
Introduction: Gastrointestinal dysfunction and symptoms in Parkinson diseased patients are often overlooked by both doctors and patients themselves because motor symptoms may appear more dominantly. At least 30% of Parkinson patients complain about gastrointestinal symptoms when specifically questioned. Delayed gastric emptying, a state in which the digestive step of stomach emptying is pathologically slower is estimated to be even more common in Parkinson's disease (PD) with a prevalence of 70%. Gastroparesis is the combination of cardinal gastrointestinal symptoms and delayed gastric emptying.

Understanding gastroparesis and its consequences may not only be relevant to reduce suffering and improve quality of life but may also play an essential role for therapy effectiveness with oral medication such as L-Dopa, as the pathology may explain response fluctuations. Since no long-term medication for gastroparesis and its symptoms exists, new therapy possibilities need to be investigated.
Target: The primary goal of the study was to test if tVNS improves gastrointestinal symptoms in PD. The secondary goal was to measure changes of the gastrointestinal motility using the 13C-octanoic acid breath test.
Methods: We evaluated a randomized group of 19 patients with Parkinson's disease in a double blinded study. 9 patients (2 male/7 female; aged 67.2 ± 6.3 years; disease duration 3.5 ± 3.7 years) used a sham-device (GammaCore®) to stimulate the vagal nerve and 10 patients (4 male/6 female; aged 69.6 ± 4.6 years; disease duration 4.8 ± 4.7 years) were randomized to a verum-device over the course of 4 weeks with four stimulations per day. Symptoms were rated with the Gastrointestinal Symptom Rating Scale (GSRS) whereas gastrointestinal motility was measured with the 13C-octanoic acid breath test.
Results: The verum-group showed an improvement in the overall sum of the Gastrointestinal Symptom Rating Scale (3.0 ± 4.1; $p = 0.048$) comparing before and after treatment, which was not seen in the sham-group (1.8 ± 3.5; $p = 0.161$). In the 13C-octanoic acid breath test however, no significant changes in either one of the groups were detectable. Not all individuals applied the full number of stimulations but the number of stimulations was not correlated with the outcome values.
Conclusion: tVNS may be a promising non-invasive therapy option to improve symptoms caused by gastric delayed emptying in PD. It was well tolerated but nevertheless treatment adherence was low. A larger patient sample size will need to be evaluated in future studies and reasons for patient non-compliance need to be investigated.

Abstract No.:
340

Authors:
Jensen, Dennis; Gassner, Heiko; Spital, Laura; Raulet, Paula; Bohlen, Stefan; Muratori, Lisa; Eskofier, Björn; Klucken, Jochen; Winkler, Jürgen; Reilmann, Ralf; Kohl, Zacharias

Abstract Title:
Mobile sensor-based gait analysis provides objective motor assessment in Huntington's disease (Mobile sensor-basierte Ganganalyse zur objektiven Bewegungsanalyse bei der Huntington Erkrankung)

Abstract Text:
Introduction: Impaired gait plays an important role for quality of life in patients with Huntington's disease (HD). Measuring gait parameters in patients with HD is essential (1) for an unbiased and objective assessment of motor deficits, (2) to monitor disease progression and (3) to detect potential beneficial effects of interventions.
Target: In order to establish a mobile, objective gait analysis system to allow a rater and time independent assessment of gait, this study aimed to identify specific features of gait in patients with HD compared to healthy controls. Moreover, gait parameters were correlated to clinical scores such as the UDHRS Total Motor Score (TMS) and Total Functional Capacity (TFC).
Methods: Patients with manifest HD at two German sites (Erlangen, Muenster; $n = 43$) were included and received standardized clinical assessments during their annual Enroll-HD visit. In addition, these patients and a cohort of age- and gender matched healthy controls performed defined gait tasks in self-selected speed consisting of a 4×10 m walk, the 2-Min-Walk-Test, and the Timed Up and Go Test (TUG). Gait data were recorded by inertial sensors (accelerometers and gyroscopes) laterally attached to the heel of shoes. Machine learning algorithms were applied to calculate spatio-temporal gait parameters.
Results: Specific gait parameters such as stride length and gait velocity were severely reduced. Furthermore, stride and stance time were significantly increased in patients with HD compared to healthy controls. Gait variability was significantly higher in HD subjects and showed strong correlations to TMS and TFC. The objective gait measurements reflected disease stage according to TFC. In contrast, correlations of functional measures (e.g. TUG) to clinical scores were notably weaker.
Conclusion: Mobile gait analysis objectively supports the identification of specific features of motor impairment in HD and complements clinical scores. Higher variability of gait was identified as sensitive biomarker for motor impairment in HD patients. Gait measurements may possibly serve as additional endpoints in future clinical studies and support monitoring of disease progression. Moreover, there is urgent need for further validation of these initial findings, including longitudinal assessments over the disease course.

Abstract No.:
341

Authors:
Cerinza Sick, Cristina; Chehroudi, Shirin; Altmann, Christian; Jost, Wolfgang

Abstract Title:
Clock Drawing Test vs Montreal Cognitive Assessment—How comparable are these two cognitive tests in Parkinson patients?

Abstract Text:
Introduction: The Montreal Cognitive Assessment (MoCA) is accepted as efficient for diagnosis of cognitive deficits in Parkinson's disease. The sensitivity is superior to the Mini-Mental State Examination (MMSE), especially for mild cognitive impairments. Another widely used test is the CLOX—also known as clock drawing test (CDT), as a fast clinical test to evaluate cognitive function in patients with Parkinson's disease. The test consists of two assignments: first, the patient is instructed to draw a clock showing a given time on an empty piece of paper; for example 11:10 AM (Command clock). The second task is for the patient to draw the same time (11:10 AM) into the outline of an already drawn clock (Copy clock).
Target: The purpose of our study was to evaluate the comparability of the CDT and the MOCA, and if the CDT is sufficient enough as screening tool for cognitive impairments.
Methods: We examined 106 (male 55) patients with Parkinson's disease; MoCA and CDT scores were obtained. We computed the correlation between CDT and MoCA test scores. Since both tests are employed in dementia screening, we hypothesized good comparability.
Results: The average age of patients was 72.28 (SD 9.62, 34–84 y), with 8.66 years since their initial diagnosis of Parkinson's disease. Overall, our results showed a significant negative correlation between MoCA und CDT ($r = -0.547$).
Conclusion: Our data suggest that the CDT is a fairly valid test, with at least moderate comparability with the more time-demanding MoCA test battery. The CDT might not be sufficient to replace the MoCA, but its results could provide useful information to judge cognitive functional disabilities. Larger sample sizes may be necessary to determine if the test is useful for the dementia screening process in general.

Abstract No.:
342

Authors:
Pfister, Franz M. J.; von Schumann, Anna; Bemetz, Josef; Thomas, Janek; Ceballos-Baumann, Andres; Bischl, Bernd; Fietzek, Urban

Abstract Title:
Recognition of subjects with early-stage Parkinson from free-living unilateral wrist-sensor data using a hierarchical machine learning model

Abstract Text:
Introduction: Diagnosis of Parkinson's disease is mostly clinically driven, and often established without confirmatory testing. This is because confirmatory tests are time consuming (e.g. sniffin sticks®), expensive (e.g. nuclide imaging), performed only in few specialized centers (e.g. skin biopsy), or lack clinical specificity (e.g. MRI, sleep lab). A widely available, inexpensive, objective and interpretable clinical test to confirm diagnosis of PD is a clinical need to get diagnostic certainty about the diagnosis, to save costs, and to initiate effective dopaminergic treatment.
Target: We aimed to develop an objective data-driven approach for the diagnosis of early-stage PD using motion data captured from the subject's wrist in a free-living setup using a hierarchical machine learning model.
Methods: We recorded 3D-accelerometer and gyroscope data from N = 25 PD patients with early stage disease, defined as disease duration < 2 years, and N = 25 healthy controls. Both groups were recorded in free-living setups. Recordings were captured using the Microsoft Band 2 with a sampling rate of 62.5 Hz and stored for offline analyses. Diagnosis of PD was certified by expert evaluation and by UK BB criteria. Sensor data was preprocessed and engineered features were subjected to a hierarchical machine learning model that (i) recognized the activity "walking" and (ii) classified extracted sensor-data windows during those walking-episodes to a PD/non-PD group using Random Forests/XGBoost.
Results: The PD group consisted of 12 males and 13 females, the average age was 70.5 years, the median Hoehn & Yahr stage 2. The healthy controls were on average 64 years old (7 men, 18 women).

The employed Activity Recognition layer to detect walking episodes showed an accuracy of 0.925/AUC of 0.958. The subsequent PD recognition layer classified 22 of 25 PD patients as PD positive, and 21 of 25 HC as PD negative. Thus, specificity was 0.85; sensitivity rate was 0.84. The positive predictive value was 0.88, and the negative predictive value was 0.84. Overall diagnostic accuracy was 0.86.
Conclusion: We demonstrate the feasibility of diagnosis of PD using motion data and machine learning algorithms. We were able to achieve similar clinimetric results in terms of specificity and sensitivity as established confirmatory tests, such as nuclide imaging techniques. The results require confirmation in larger cohorts, but provide substantial evidence already for translation to further clinical usage.

Abstract No.:
343

Authors:
Drexel, Simon; Klietz, Martin; Kollewe, Katja; Paracka, Lejla; Kutschenko, Anna; Schulte-Sutum, Annika; Kopp, Bruno; Lange, Florian; Wegner, Florian; Dressler, Dirk

Abstract Title:
Dystonia treated with botulinum toxin: quality of life and caregiver burden (Dystonie behandelt mit Botulinum Toxin: Lebensqualität und Caregiver Burden)

Abstract Text:
Introduction: Dystonia is a common chronic movement disorder producing abnormal postures and pain. Health related Quality of Life (HrQoL) may be reduced, but may be improved by Botulinum Toxin (BT) therapy.
Target: We wanted to study how BT therapy of dystonia affects patients and the caregivers.
Methods: For this, all patients were assessed with the Burke-Fahn-Marsden Scale (BFM movement 0–120, BM impairment 0–30) for their dystonia, with the Montreal Cognitive Assessment (MoCA 0–30) for cognitive functioning, with the Beck Depression Index (BDI 0–63) for mood and with the WHO short form 36 (SF-36 0–100) for HrQoL. Primary caregivers were examined with the Caregiver Burden Inventory (CBI 0–88) for caregiver burden, the BDI and the SF-36.
Results: So far, 100 patients were tested (age 64.2 ± 11.5 years, 74% females, 26% males). 56% suffered from cervical dystonia, 15% from blepharospasm. Dystonia severity was mild to moderate (BFM movement 12.1 ± 13.7, min 0.5/max 72, BFM impairment 2.5 ± 4.1, min 0/max 29). Cognitive functioning was normal (MoCA 25.3 ± 3.2), so was mood (BDI 11.2 ± 8.8) and HrQol (SF-36 49.7 ± 10.9). Also, 85 caregivers were recruited (age 62.1 ± 13.8 years, 66% males, 34% females). Caregiver burden was

normal in most patients (CBI 8.1 ± 9.7, min 0/max 48), and so was mood (BDI 5.8 ± 5.7, min 0/max 23) and HrQol (SF-36 55.2 ± 9.7). **Conclusion:** Dystonia patients suffer from mildly reduced HrQoL even under BT therapy. Caregiver burden could not be detected. Further analysis will explore caregiver burden in specific dystonia manifestations such as generalised dystonia.

Abstract No.:
344

Authors:
Gandor, Florin; Tesch, Manfred; Neuhauser, Hannelore; Gruber, Doreen; Heinze, Hans-Jochen; Ebersbach, Georg; Lempert, Thomas

Abstract Title:
Fixation suppression the easy way—when nothing else matters (Fixationssuppression des VOR einfach getestet)

Abstract Text:
Introduction: Fixation suppression of the vestibulo-ocular reflex (FS-VOR) is a reliable clinical feature to test for cerebellar function, and its disturbance indicative of cerebellar pathology. It can therefore serve as a valuable clinical test for identifying a subtle cerebellar syndrome, when other cerebellar symptoms such as ataxia, dysarthria, dysmetria or dysdiadochokinesia are not yet prominent enough. In movement disorders, it can serve as an additional feature to differentiate patients with idiopathic Parkinson's disease from those with atypical Parkinsonian Syndromes such as multiple system atrophy. The gold standard to test for FS-VOR is utilizing a video-nystagmography system and an electronic rotary chair. However, such devices are expensive, need expertise in interpreting results, and are time and personnel consuming. We here describe a bedside test that allows for fast, easy to interpret and reliable assessment of the FS-VOR that enables video documentation of the test.
Target: Validation of a simple bedside test to objectify the fixation suppression of the vestibulo-ocular reflex in patients with cerebellar syndrome.
Methods: Methods: the vestibulo-ocular reflex and its fixation suppression were assessed in 20 healthy subjects (mean age 56 ± 15, 14 women) and 19 patients with a cerebellar syndrome (mean age 70 ± 11, 10 women). The most exact method utilizing video-nystagmography during a defined rotation speed on a swivel chair was compared to a simple self-made bedside test using the video function of a smart phone and asking the patient to fix their gaze on the lens whilst being rotated on the swivel chair with a defined speed. Videos were assessed by blinded raters and dichotomously rated as normal or pathological FS-hVOR. Results were compared to the video-nystagmography data and reliability calculated. Furthermore, inter-rater reliability was measured.
Results: VNG in healthy controls showed a sufficient suppression of the horizontal VOR with a reduction of nystagmus counts of 95.0% ± 7.2 (mean ± SD), whereas in patients with cerebellar syndrome, reduction of horizontal nystagmus counts was only 26.3% ± 25.1. Video analysis by blinded raters showed an excellent inter-rater reliability of 0.85 (0.76–0.93). Comparison of VNG results to the video ratings showed a very high reliability of 0.91 (0.84–0.96). Sensitivity of the video analysis was 0.92 (0.83–0.96), its specificity 0.99 (0.93–1.00).
Conclusion: The smart phone bedside test is an easily performed, reliable, highly sensitive and specific, and inexpensive alternative to video-nystagmography for assessing the fixation suppression of the vestibulo-ocular reflex.

Abstract No.:
345

Authors:
Stock, Lena; Krüger-Zechlin, Charlotte; Deeb, Zain; Timmermann, Lars; Waldthaler, Josefine

Abstract Title:
Mild Cognitive Impairment changes natural reading performance in Parkinson's disease (Mild Cognitive Impairment beeinflusst die Leseleistung bei M. Parkinson)

Abstract Text:
Introduction: There is high need for extending the focus on eye movement deficits in idiopathic Parkinson's disease (PD) as they occur across all disease stages and might have an impact on daily activities such as reading. From an eye movement perspective, reading consists of serial fixations as well as forwards and regressive saccades. Since PD saccades are known to be hypometric and tend to show a prolonged latency in cognitively impaired PD patients, those factors may contribute to reading performance.
Target: To our knowledge, this is the first study characterizing eye movements during natural reading in correlation to cognitive status in PD.
Methods: For this halftime preliminary analysis of a larger trial, eye movements of 38 PD patients in ON medication state (13 treated with DBS, DBS OFF) were recorded during mute reading of one of the International Reading Speed Texts (IReST) using a video-based eye tracker (Eyelink 1000 plus, SR research). Motor and cognitive functions were assessed with MDS-UPDRS III and a comprehensive neuropsychological test battery. Mild Cognitive Impairment (PD-MCI) was diagnosed according to the MDS task force criteria level 2.
Results: 14 patients were diagnosed with PD-MCI (age 63.8(10.0), disease duration 9.0(6.4), years of education (YoE) 13.8, UPDRS III 26.0), 24 were cognitively normal (age 62.0(6.3), disease duration 8.6(5.0), YoE 13.2, UPDRS III 29.8). Patients with PD-MCI read fewer words per minute [175.8(48.8) vs. 235.7(53.1), $p < 0.01$] due to an increased number of fixations ($p < 0.05$) and regressive saccades per word ($p < 0.05$). Further, the number of progressive saccades and the mean amplitude of regressions tended to be higher in PD-MCI, while mean fixation duration and mean amplitude of progressive saccades did not differ between the groups.
Conclusion: This study shows a correlation between MCI and certain characteristics of eye movements while reading in PD.

As such, it might be necessary to consider MCI as another individual influencing factor in the assessment of reading performance of PD and HC in further research.

Abstract No.:
346

Authors:
Respondek, Gesine; Klockgether, Thomas; Spottke, Annika; Höglinger, Günter

Abstract Title:
German prospective studies on PSP: ProPSP and DESCRIBE-PSP

Abstract Text:
Introduction: Progressive Supranuclear Palsy (PSP) is an adult-onset neurodegenerative disorder with distinct cerebral tau pathology. It's classical clinical manifestation is termed Richardson-Syndrome. In recent years, retrospective clinico-pathological studies have demonstrated a striking clinical heterogeneity of PSP with a spectrum spanning from movement disorders to fronto-temporal dementias. Prospective studies on these "atypical" PSP-variants are widely lacking. Clinical research into treatment of this rare disorder has been limited due to delay in clinical diagnosis and lack of natural history

data on "atypical" PSP-variants. To improve early clinical diagnosis of PSP and increase diagnostic sensitivity, new criteria for the clinical diagnosis of PSP were recently developed based on retrospective clinico-pathological data and literature review (MDS-PSP-criteria, Höglinger et al. 2017).
Target: Our aim was to conduct prospective observational studies on PSP to

- validate prospectively the new criteria for the clinical diagnosis of PSP,
- develop new markers for diagnosis, prognosis, and progression, and
- generate natural history data on Richardson-Syndrome and atypical PSP-variants.

Methods: Inclusion criteria for both observational studies is a clinical diagnosis of probable PSP, possible PSP or suggestive of PSP according to the MDS-PSP criteria for the clinical diagnosis of PSP. For assessment of the natural disease course, patient's history, standardized neurological examination, PSP-specific clinical scales, parkinsonism-specific clinical scales and generic rating scales are collected prospectively every 6 months and documented on a central database. In addition, prospective MRI, functional imaging, and biomarker are collected. The ProPSP database is coordinated at the "Münchner Studienzentrum" at the Technical University in Munich and the DESCRIBE-PSP database is coordinated at the German Center of Neurodegenerative Diseases (DZNE) in Bonn.
Results: Two German networks to recruit and prospectively follow-up patients with PSP were set up, which include the ProPSP network (26 centers) and the DESCRIBE-PSP network (10 centers). For ProPSP, N = 60 patients have been recruited, starting in 05/2018, and biomaterial has been collected from N = 38 patients (status as in October 2018). For DESCRIBE-PSP, N = 164 patients have been recruited, starting in 12/2015. Biomaterial was collected from N = 129 patients (status as in October 2018).
Conclusion: We have successfully initiated ProPSP and DESCRIBE-PSP, which are the first prospective observational studies on PSP in Germany. The natural history data generated in these cohorts will improve early clinical diagnosis and understanding of disease progression in Richardson-Syndrome and all the more in patients with atypical PSP-variants.

Abstract No.:
347

Authors:
Stammel, Oliver; Urban, Peter Paul; Bachmann, Nina

Abstract Title:
Focal Chorea as unusual phenotype of Fragile X Spectrum Disorders (FXSD) (Fragiles X-Syndrom mit fokaler Chorea der Hand)

Abstract Text:
Introduction: Das Fragile-X Tremor-Ataxie Syndrom ist eine seltene neurodegenerative Erkrankung, die X-chromosomal vererbt wird und auf einer Verlängerung eines CGG-Triplettrepeats in Exon 1 im Gen FMR1 beruht. Die Erkrankung ist gekennzeichnet durch einen späten Erkrankungsbeginn und progressiven Verlauf der klinischen Hauptsymptome Intentionstremor und Ataxie (1). In Abgrenzung zu anderen Differentialdiagnosen zeigen sich typische neuroradiologische Veränderungen (2). Molekulargenetische Untersuchungen des FMR1 Gens sind notwendig, um die Diagnose zu bestätigen. Der Schweregrad der klinischen und neuropathologischen Befunde korreliert mit der Größe der CGG-Expansion.

Wir berichten den Fall eines 72 jährigen Mannes mit einer progredienten fokalen Chorea-Athetose der Hand in Abwesenheit eines Intentionstremor und relevanten Ataxie als klinische Variante im Rahmen des Fragilen X-Syndroms, unserer Kenntnis nach wurde eine fokale Chorea im Rahmen der Fragilen X Spektrumerkrankung noch nicht beschrieben.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disease caused by an expansion of 55–200 CGG repeats located in the FMR1 gene. FXTAS was first reported in 2001 by Hagermann et al. (1) who reported on five patients with fragile X premutation. The typical clinical neurological features of FXTAS include progressive intention tremor, gait ataxia, mild hypokinetic signs, autonomic and cognitive dysfunction and neuropathy beginning after the age of 50.

To the best of our knowledge, this is the first report of a focal chorea extending the phenotypic pattern of Fragile X Spectrum Disease (FXSD) almost without showing the name-giving clinical features intention tremor und ataxia.
Target: Nach unserer Kenntnis wurde eine fokale Chorea im Rahmen der Fragilen X Spektrumerkrankung noch nicht beschrieben.
Methods: Case report (MRT, Liquor, Serologie, genetische Molekulardiagnostik etc.).
Results: Positives MCP-Zeichen) + CSS-Zeichen im MRT.

Positive FA für Fragiles X Syndrom (Stammbaum).

Bei unserem Patienten erfolgte nach Abschluss der stationären Behandlung eine molekulargenetische Diagnostik mit dem Nachweis eines Praemutationsallel und Expansion von 85 ± 3 CGG-Wiederholungen bei unauffälligem Methylierungsmuster.
Conclusion: Nach unserer Kenntnis ist dies der erste Fall einer Fragilen X Praemutation mit fokaler hyperkinetischer Bewegungsstörung im Sinne einer Chorea in Abwesenheit der bisher nach Jaquemont (2) gültigen klinischen Kardinalsymtome. Neben den klassischem Tremor/Ataxie–Komplex finden sich vereinzelt Fallberichte anderen Bewegungsstörungen wie Oro-Mandibulärer Dystonie (7), tardiven Dykinesien (8) oder Parkinsonsymptomatik im Rahmen des FXS, eine fokale Chorea ist unserer Kenntnis bisher nicht beschrieben.

Der weitestgehende Ausschluss anderer symptomatischer oder neurodegenerativer Ursachen, die typischen kernspintomographischen Befunde mit einer Leukencephalopathie sowie flächenhaften T2-FLAIR-Hyperdensitäten bds. im Crus cerebelli mit Fortsetzung in den medialen Pedunculus (MCP-Zeichen) und des Corpus callosum splenium (CSS-Zeichen) sowie die molekulargenetische Testung mit dem Nachweis eines Praemutationsallel mit einer Expansion von 85 ± 3 Triplettwiederholungen im FMR1-Gen stützen die Annahme einer fokalen Chorea als phänotypische Variante im Rahmen der Fragilen X Spektrumerkrankung.

Abstract No.:
348

Authors:
Hammes, Jochen; Meier, Michelle; Drzezga, Alexander; Dratsch, Thomas; Kobe, Carsten; Pinto dos Santos, Daniel; van Eimeren, Thilo

Abstract Title:
Automated interpretation of FP-CIT-SPECT images based on artificial intelligence

Abstract Text:
Introduction: With FP-CIT-SPECT, we can visualize the integrity of nigro-striatal dopaminergic synapses in vivo. Although it is currently the gold-standard imaging method for the diagnosis of Parkinsonism it is susceptible to inter-rater variability and quantitative threshold-values are not well established. Automated image processing by artificial intelligence (AI) holds the potential to drastically simplify and standardize FP-CIT-SPECT reading.
Target: Our objective is to develop an AI-based approach to automatically rate FIP-CIT-SPECT data.
Methods: 460 FP-CIT-SPECT datasets that had been acquired on a Picker Prism 3000 and reconstructed with an OSEM algorithm were

retrospectively selected and expert ratings regarding presence of pathology were obtained and classified in three categories (healthy, pathologic, undetermined). Cranio-caudal maximum intensity projections (MIPs) were calculated from the unprocessed image data to provide two-dimensional input images. A Google-Tensorflow® AI-environment was set up and the openly available pretrained "Inception-Net" for automated image classification was retrained with the FP-CIT MIPs after removal of the last training layer. Classification performance was cross-validated by a leave-n-out approach.
Results: Initial classification performance for automated detection of pathological scans was in a range from 65 to 75%. The application of other pre-trained image classification networks, classification of MIPs derived from spatially normalized data and alternative tree-classifier-driven approaches are currently being explored.
Conclusion: Although the classification performance of anatomically unprocessed data needs further improvement, we provide a proof of principle, that AI-based image processing in FP-CIT SPECT is possible. Improved image preprocessing and alternative approaches will likely have a significant impact on the classifications performance so that AI-based automated image rating of FP-CIT-SPECT might be supportive in a future clinical setting.

Abstract No.:
349

Authors:
Steinhardt, Julia; Münte, Thomas F.; Schmid, Sebastian M.; Wilms, Britta; Brüggemann, Norbert

Abstract Title:
Body mass gain in Parkinson's disease following deep brain stimulation: a systematic meta-analysis (Gewichtszunahme bei Patienten mit Morbus Parkinson nach tiefer Hirnstimulation: eine systematische Meta-Analyse)

Abstract Text:
Introduction: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a well-established therapy in advanced Parkinson's disease (PD) for managing severe motor complications. However, a remarkable body mass gain may occur after STN DBS, which at least partly counteract the positive effects of motor improvement.
Target: To investigate the extent and time course of body mass gain after STN DBS in PD patients.
Methods: For this systematic meta-analysis, a computerized search for relevant articles was performed in MEDLINE, Cochrane Library, Clinical Trials, and Livivio against a priori inclusion and exclusion criteria. Body mass and body mass index (BMI) were considered as main outcome parameters and effect size was calculated using Cohen's d.
Results: Following application of these criteria, 38 out of 154 studies remained and were included in the meta-analysis yielding a total sample size of 979 PD patients with STN DBS with a mean age across studies of 59.0 ± 7.5 years (range 54.9–66.0 years). A follow-up assessment of each patient was performed between 1 and 60 months after surgery. Considering the longest follow-up time for each study, body mass and BMI showed a mean increase across studies of 5.7 kg ($p < 0.0001$; $d = 0.64$) and 1.8 kg/m2 ($p < 0.0001$; $d = 0.78$). We analyzed the time course of body mass gain after surgery and detected a continuous increase ranging from 2.9 kg ($d = 0.69$) at 3 months, 3.9 kg ($d = 0.21$) at 6 months, 6.4 kg ($d = 0.72$) at 12 months, and 6.1 kg ($d = 1.02$) above 12 months of stimulation.
Conclusion: Our meta-analysis clearly demonstrates a massive body mass gain following STN DBS. Recent research identified possible mechanisms that drive this body mass gain, such as improvement of resting tremor and dyskinesias, changes of energy expenditure during rest, changes in eating behavior and food intake, as well as alterations in hypothalamic adipokine release. In light of these findings and considering the negative health implications of obesity we recommend the development of tailored therapies to prevent obesity and associated metabolic disorders following STN DBS surgery.

Abstract No.:
350

Authors:
Frank, Anika; Peikert, Kevin; Hermann, Andreas

Abstract Title:
Evaluation of the Movement Disorders Society Criteria for the clinical diagnosis of Progressive Supranuclear Palsy in clinical practice

Abstract Text:
Introduction: The Movement Disorders Society (MDS) Criteria for the clinical diagnosis of progressive supranuclear palsy (PSP) were recently published. Only few data exist yet on their usability and practicability in a classical movement disorder clinical setting, none for retrospective analysis.
Target: (1) To evaluate whether the new criteria are suited to retrospectively assign PSP patients to the respective clinical predominance types and whether and how the new classification differs compared to specialist diagnosis prior to the new criteria. (2) To analyse the application of the midbrain-to-pons ratio as supportive diagnosis feature in daily practice.
Methods: Single center retrospective analysis of case files of movement disorders specialist care. First contact clinical phenotypes were analysed. Furthermore, the midbrain-to-pons ratio was retrospectively measured in the midsagittal plane of conventional MRI (according to Massey et al., 2013).
Results: We identified 80 patients with the clinical diagnosis of PSP from 2006 to 2018 (male/female 52/28, age at diagnosis: mean 70, range 51–87). It was possible to assign PSP (clinical predominance type) diagnosis according to the MDS criteria in 57/80 cases. Lack of subgroup allocation was the main difference in former expert opinion classification. However, the new criteria might overemphasize postural instability and thus classify most cases as PSP-RS even though clinically fitting better in other categories. This was most obvious in PSP-CBS, PSP-SL and PSP-PGF.

cMRI were rated pathological/suggestive for PSP by neuroradiologists in 17/71 cases, however cMRI midbrain-to-pons ratio was pathological in 40/62 if measured by a blinded movement disorder specialist.
Conclusion: The MDS-PSP criteria do work well also in retrospective allocation to PSP subgroups. However PSP-RS might be overestimated by the current criteria. Midbrain-to-pons ratio quantification in cMRI is not regularly implemented in daily use by neuroradiologists. Thus, the MRI supportive diagnosis feature is often missed.

Abstract No.:
351

Authors:
Jaeger, Hagen; Stadtschnitzer, Michael; Dias, Sofia; Hadjileontiadis, Leontios

Abstract Title:
i-PROGNOSIS: development of a speech enhancement algorithm for the intervention of Parkinson's disease (i-PROGNOSIS: Entwicklung eines Sprachverständlichkeitsverbesserungs-Algorithmus zur Intervention bei der Parkinson-Erkrankung)

Abstract Text:
Introduction: Parkinson's disease is a disease of the nervous system that manifests itself through motor dysfunctions as a result of neurodegenerative processes. Since Parkinson's disease cannot be cured,

it is important to initiate appropriate medication and intervention measures early in order to attenuate the course of the disease and improve the patient's quality of life.
Target: i-PROGNOSIS is a Horizon 2020 EU project, which covers the exploration of non-invasive disease treatment through an application by guiding appropriate intervention actions. These will be implemented to work on an ambulatory and unobserved basis with the aid of mobile devices. The i-PROGNOSIS app will, besides a personalized game suite in which patients can playfully train and improve their motor skills, and a gait rhythm insurance training, offer a functionality for sharing voice messages optimized in intelligibility.
Methods: A voice message is recorded within the i-PROGNOSIS app, which is then optimized in real time by applying block-oriented signal processing strategies to increase speech intelligibility. For the implementation, common methods in the area of single-channel noise reduction and dynamic compression are implemented, such that the processed voice message yield good intelligibility. To achieve this, the 'Speech Transmission Index' (STI) is used as an objective measure, working on blind estimates of modulation depths, to estimate the speech intelligibility of the de-noised and to adjust its spectral weighting to the estimation result accordingly. The optimized voice message can be shared and transmitted directly after recording by using various messenger apps, such as WhatsApp or Facebook Chat. Additional options such as sending via MMS, email, or sharing in a cloud will also be possible.
Results: The current prototypical implementation of the speech enhancement algorithm delivered promising results in internal hearing tests. A self-generated, English-language data set was used for subjective evaluation, which was collected from one of the medical project partners (King's College London). It contains 30 min of spoken language as well as 30 min of spontaneous language.
Conclusion: By using suitable signal processing measures and an objective speech intelligibility estimation, an automated speech enhancement algorithm for Parkinson's disease patients can be implemented. The proposed algorithm will be part of the i-PROGNOSIS app, to make speech-based communication via mobile devices easier for Parkinson's patients.

Abstract No.:
352

Authors:
Wihan, Jeanette; Grosch, Janina; Kalinichenko, Liubov S.; Müller, Christian; Winkler, Jürgen; Kohl, Zacharias

Abstract Title:
Layer-specific axonal degeneration of serotonergic fibers in the prefrontal cortex of transgenic A53T alpha-synuclein mice

Abstract Text:
Introduction: Aggregation of α-synuclein (α-syn) plays an important role in the pathogenesis of Parkinson's disease (PD). Intriguingly, axonal pathology precedes cell loss in the substantia nigra indicating a dying back axonopathy of nigrostriatal projections. Although the dopaminergic system has attracted major attention in PD, a substantial body of evidence suggests the involvement of further neurotransmitter systems, particularly, the serotonergic system. The prefrontal cortex (PFC), one of the major target fields of raphe nuclei (RN), is linked to important emotional and cognitive functions. Thus, alterations within the prefrontal serotonergic system may be crucial for neuropsychiatric symptoms in PD.
Target: Within the scope of this project, we investigated the impact of human α-syn overexpression on serotonergic projections into the PFC of aged A53T α-syn expressing mice (A53T mice).
Methods: We systematically assessed the prefrontal serotonergic system in A53T mice compared to non-transgenic littermates. First, a detailed layer-specific analysis of the serotonergic fiber innervation and axonal morphology was undertaken using confocal microscopy. In addition, we determined prefrontal 5-HT levels via HPLC and assessed the expression of tryptophan hydroxylase 2 in the murine RN via quantitative RT-PCR. Finally, the expression of synaptic proteins as well as vesicle packaging and axonal transport proteins was quantified performing western blot analysis.
Results: We identified a layer-specific reduction of the serotonergic input to the PFC layers II and V/VI of A53T mice, sparing layer I. While residual axons were characterized by enlarged varicosities, prefrontal 5-HT levels were not affected. However, we detected a transcriptional upregulation of tryptophan hydroxylase 2 in the RN of aged A53T mice, indicating an increased serotonin biosynthesis. In line, A53T mice showed an elevated expression of the anterograde vesicle transport protein kinesin family member 1a (Kif1a) and the vesicle packaging protein vesicular monoamine transporter 2 (vMAT2).
Conclusion: We provide evidence for a profound layer-specific axonal degeneration of prefrontal serotonergic projections in A53T mice probably paralleled by compensatory mechanisms such as increased 5-HT synthesis, vesicle packaging and axonal transport capacity. These compensatory mechanisms within the monoaminergic neurotransmitter systems may contribute particularly to the temporal characteristics of the premotor phase in PD.

Abstract No.:
353

Authors:
Martini, Max; Utz, Kathrin; Mrochen, Anne; Klucken, Jochen; Renner, Bertold; Winkler, Jürgen; Marxreiter, Franz

Abstract Title:
Multisensory deficit of hedonic perception in Parkinson's Disease

Abstract Text:
Introduction: We recently demonstrated that hedonic perception of odors (hedonic olfaction) is impaired in Parkinson's Disease (PD). In particular, reduced perception of odor pleasantness correlated significantly with anhedonia as assessed by the Snaith-Hamilton-Pleasure-Scale (SHAPS) but not with depression as assessed by the Zung Self-Rating Depression Scale (SDS) and the Beck Depression Inventory II (BDI-II). However, hyposmia, a very common feature in PD confounds these results, limiting the assessment of odor pleasantness as surrogate for anhedonia in PD.
Target: To further evaluate whether hedonic perception is per se altered in PD, we conducted a study analyzing the hedonic perception in three sensory systems. We hypothesized, that the hedonic perception of odors, images and sounds in PD patients generally differs from healthy controls.
Methods: After routine clinical assessment, the olfactory (Sniffin ID test), visual (visual acuity determination), and acoustic (hearing threshold) systems were tested. In addition, cognitive performance was examined using the Montreal Cognitive Assessment. Participants fulfilling the inclusion criteria subsequently performed testing for hedonic perception. For hedonic odor perception, 22 different sniffing sticks were evaluated with regard to hedonic ("how pleasant or unpleasant is the scent?") perception on a scale from -4 (extremely unpleasant) to +4 (extremely pleasant). Accordingly, 22 different pictures (taken from the International Affective Picture System), and 22 different noises (from the International Affective Digitized Sounds-2 library) with neutral, pleasant as well as unpleasant sounds needed to be evaluated. Depressive Symptoms were assessed using the BDI-II, anhedonia using the SHAPS.
Results: In total, 62 participants (30 PD patients and 32 controls) were enrolled. Groups did not differ in demographical characteristics

like age, gender, cognitive function, hearing threshold, visual function and anhedonia ratings. As expected, PD patients scored significant lower in the Sniffin ID test and had higher BDI-II ratings compared to controls. We observed a significantly reduced range of hedonic odor perception, confirming our previous results. Importantly, also the range of hedonic perception for sounds and pictures was significantly reduced in PD.
Conclusion: Our findings indicate that hedonic perception is reduced across the three sensory systems tested. This global anhedonic perception for sensory stimuli may be related to a common functional deficit when judging hedonic stimuli in PD. Further studies may provide insights into the involvement of i.e. basal ganglia-prefrontal circuits.

Abstract No.:
354

Authors:
Badr, Mohammad; Hünig, Thomas; Koprich, James; Brotchie, Jonathan; Volkmann, Jens; Lutz, Manfred; Ip, Chi Wang

Abstract Title:
Neuroprotection in the AAV1/2-A53T-alpha-Synuclein Parkinson's disease mouse model employing a CD28 superagonist (Neuroprotektion im AAV1/2-A53T-alpha-Synuclein-Mausmodell der Parkinson-Krankheit mittels CD28-Superagonist)

Abstract Text:
Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease with still no cure available. The prominent feature of PD is the loss of dopaminergic neurons (DNs) at the Substantia nigra (SN). Genetic and environmental insults affecting the SNCA gene encoding the alpha-Synuclein (alpha-Syn) protein result into an aberrant form of the protein with higher propensity towards oligomerization becoming part of insoluble inclusions called Lewy Bodies (LBs). LBs impart cytotoxicity leading to neurodegeneration, activate resident microglia and escape to the periphery where they get captured by dendritic cells and presented to naïve T cells. Proliferating effector T lymphocytes invade the brain releasing proinflammatory cytokines and performing a cytotoxic effect on neurons.
Target: Objective: In this study, we examine the hypothesis that the expansion of regulatory T cells (Tregs) could exert an anti-inflammatory effect that averts neurodegeneration in the AAV1/2-A53T-alpha-Syn mouse model for PD.
Methods: Mice brains were transfected by a unilateral stereotaxic injection at the SN region with a chimeric Adeno-Associated Viral vector of serotypes 1 and 2 (AAV1/2) carrying the A53T-mutated human SNCA gene encoding the readily aggregating aberrant alpha-Syn (AAV1/2-A53T-alpha-Syn. One week after injection, mice were treated with the CD28 superagonistic antibody (CD28SA), known to significantly expand the Treg population. Mice were then analyzed by behavioral analysis using the Rotarod performance test and the Cylinder test. The impact of CD28SA on the immune system was examined by flow cytometry. The integrity of the nigrostriatal system was assessed by stereological quantification of Tyrosine-hydroxylase (TH)-stained DNs in SN and optical density measurements of TH-stained striatum. Potential changes in levels of neurotrophic factors were quantified by ELISA.
Results: We observed an expansion of Tregs by FACS analyses 3 days after CD28SA treatment, demonstrating target engagement. CD28SA treatment of AAV1/2-A53T-alpha-Syn mice provided neuroprotection evident through elevated numbers of DNs in the SN and higher optical density of TH-staining in the striatum, in CD28SA-treated mice compared to PBS-treated control mice, and that was reflected in an enhanced performance in behavioral studies. Additionally, brain infiltration of proinflammatory activated T lymphocytes (CD4 + CD69 + and CD8 + CD69 + cells), that were obvious in PBS-treated AAV1/2-A53T-alpha-Syn control mice, was augmented in PD mice receiving CD28SA. CD28SA treatment led to an increase of GDNF and BDNF in some brain structures that was not observed in untreated mice.
Conclusion: In the AAV1/2-A53T-alpha-Syn PD mouse model, CD28SA suppresses proinflammation as evident by reduction of CD4 + CD69 + and CD8 + CD69 + cells and is neuroprotective on SN cells.

Abstract No.:
355

Authors:
Karikari, Akua Afriyie; Gehmeyr, Mona; Ribechini, Eliana; Volkmann, Jens; Brotchie, Jonathan M.; Koprich, James B.; Lutz, Manfred B.; Ip, Chi W.

Abstract Title:
CD4 + T-lymphocytes exacerbate neurodegeneration in a new A53T-alpha synuclein expressing mouse model for Parkinson's disease (CD4 + T-Lymphozyten verschlimmern Neurodegeneration in einem neuen A53T-alpha-Synuclein-exprimierenden Mausmodell für die…)

Abstract Text:
Introduction: The consequence of the adaptive arm of the immune system on the progression of Parkinson's disease (PD) remains unresolved. Our research focuses on the contribution of the adaptive immune system in a novel PD mouse model that is based on an AAV1/2 mediated overexpression of mutated human A53T α-synuclein (aSyn). This model was selected because it better reflects the molecular pathology of the human disease than the commonly used neurotoxin mediated models for PD.
Target: To determine the role of lymphocytes in neurodegeneration and the subset of T-lymphocytes that is more detrimental in the A53T-aSyn based model for PD.
Methods: Bone marrow transplantation was performed by preparation of bone marrow cells from wild type (wt), CD8 +, CD4 + and B-cell knock out mice and cell suspension was injected i.v. into 8-week old male RAG-$1^{-/-}$ mice, which lack mature lymphocytes. AAV1/2-A53T-aSyn or AAV1/2 empty vector (EV) at a concentration of 5.1 × 106^12 gp/ml were unilaterally injected into right substantia nigra (SN) of these mice at 13 weeks old in addition to injection in wt C57BL/6 mice that served as controls. Immunohistochemistry was done to determine lymphocyte infiltration in the SN. FACS analysis was implemented to ascertain the phenotype of immune cells in the brain. Integrity of the dopaminergic nigrostriatal system was assessed by quantifying striatal dopaminergic (DA) terminals and dopamine and by stereological analysis of dopaminergic SN cells.
Results: Immunohistological stainings showed an increase of CD8 + and CD4 + cells numbers in the SN of A53T aSyn injected wt and RAG-$1^{-/-}$ mice which received wt bone marrow (RAG-$1^{-/-}$ wt BM). FACS analysis using CD69 as activation marker showed a high activation of CD8 + and CD4 + T-cells in the brain after A53T-aSyn injection. Stereological analysis showed a reduction in the number of DA cells in the SN of wt and RAG-$1^{-/-}$ wt BM mice as compared to controls. However, there was a rescue of DA cells in RAG-$1^{-/-}$ A53T aSyn mice. Mice which received only CD4 + and both CD4 + and CD8 + had significantly decreased numbers of DA cells in relation to control groups 10 weeks after AAV injection There was however, no significant loss of dopaminergic cells in the mice which received only CD8 + cells when compared to controls. With respect to striatal dopamine levels and terminal loss, there was a significant decrease in all groups that received A53T-aSyn.

Conclusion: CD4 + lymphocytes augment neuronal cell loss in the AAV1/2-A53T-aSyn mouse model for PD.

Abstract No.:
356

Authors:
Rauschenberger, Lisa; Knorr, Susanne; Al-Zuraiqi, Yaser; Volkmann, Jens; Ip, Chi Wang

Abstract Title:
Abnormal plasticity, stress-dependent dopaminergic and glutamatergic dysregulation in the striatum of a DYT12 mouse model (Abnormale Plastizität, dopaminerge und glutamaterge Dysregulation im Striatum eines DYT12 Mausmodels)

Abstract Text:
Introduction: A loss-of function mutation affecting the α3 isoform of the Na +/K + -ATPase (ATP1α3) and exposure to a stressful event underlie the development of Rapid-Onset Dystonia-Parkinsonism (DYT12). After stress exposure, patients develop permanent generalized dystonia and parkinsonism. The mutation as well as the phenotype can be pharmacologically mimicked through perfusion of ouabain, a selective ATP1α3-blocker, into the striatum and cerebellum of wild type (wt) mice followed by mild motor stress.
Target: Understanding the role of the striatum in DYT12 pathogenesis by study of structural and metabolic changes in a phenotypic mouse model.
Methods: Ouabain or NaCl as control were chronically perfused into the striatum and cerebellum of wt mice. Animals were repeatedly subjected to mild physical stress. The phenotype was characterized by a tail suspension test (TST) using a newly developed scoring system from 0 to 8 points with evaluation of dystonia-like movements (DLM) in front limbs, hind limbs and trunk. DLM were also assessed in a modified Dystonia Rating Scale (DRS). The striatal neuronal population was analyzed via Golgi-Cox staining and immunohistochemistry. HPLC and rtPCR were used to study changes in monoamine activity and receptor expression.
Results: Ouabain-perfused, stressed mice presented a significantly more pronounced dystonic phenotype than unstressed animals (after 24 h: DRS: $3.0 + 0.18$ vs $1.56 + 0.21$, $p < 0.0001$; TST: 4.91 ± 0.33 vs 3.33 ± 0.46, $p < 0.01$). Analysis of the structural integrity of the striatum revealed dendritic spine reduction of medium spiny neurons as well as loss of interneurons independent of stress. In unstressed mice, HPLC analysis showed a significant reduction of striatal dopamine (DA) in ouabain compared to vehicle treated animals while stress led to a hyperdopaminergic environment in ouabain mice. Ouabain-perfused, non-stressed animals showed a significant upregulation of DA receptor 4 (DRD4) and significant downregulation of NMDA- and AMPA-receptors. In contrast, ouabain-perfused mice subjected to stress showed a statistically non-significant downregulation of DRD4 and upregulation of NMDA- and AMPA-receptors.
Conclusion: We created a pharmacological mouse model with DYT12-like phenotype after exposure to mild physical stress. Structural changes of the striatum independent of stress and symptom manifestation suggest that abnormal synaptic plasticity may be considered an endophenotype to DYT12. Changes in dopaminergic and glutamatergic neurotransmission seem to act as compensatory mechanisms capable of counteracting the development of a dystonic phenotype in DYT12 until stress exposure. These mechanisms might entail modulation of the output of the direct and indirect pathway as well as modulation of the corticostriatal input.

Abstract No.:
357

Authors:
Sixel-Döring, Friederike; von Eckardstein, Kajetan; Malinova, Vesna; Pinter, Anabel; Dragaescu, Cristina; Rohde, Veit; Trenkwalder, Claudia

Abstract Title:
Subthalamic lead placement in Parkinson's disease: Do we need microstimulation? (Subthalamische Elektrodenplatzierung bei M. Parkinson: Brauchen wir die Mikrostimulation?)

Abstract Text:
Introduction: Intraoperative microstimulation (MS) for determination of definite lead placement in deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD) requires the patient being awake and cooperative in the medication-off state during surgery. Due to the potential physical discomfort and emotional stress implied by the awake procedure, patients may decide against DBS, although they would clearly benefit.
Target: To assess the importance of microstimulation for clinical outcome in subthalamic lead placement with regard to the question whether or not patients may be operated in general anesthesia when implanting conventional ring electrodes.
Methods: We retrospectively evaluated microelectrode recordings (MER) and intraoperative MS with regard to the overall and side-specific postoperative motor outcome assessed with the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS 3) after 1 year to determine the number of hemispheres in which the results of MS overruled those of MER.
Results: 134 definite leads in 67 patients with a follow-up of 7 to 18 months were available. The overall surgical index, calculated as the relation of the preoperative improvement on UPDRS 3 achieved with L-Dopa to the improvement achieved with stimulation, was determined at 0.99 ± 0.24. Side specific surgical indices averaged at 1.04 ± 0.45. In 72% of patients' hemispheres the results of MS on clinical symptoms confirmed the trajectory suggested as optimal by MER. In 28% of patients' hemispheres however, MS overruled MER results in the choice of the final trajectory selection, with favored effects in 8% and adverse effects in 20%.
Conclusion: Using MER and MS in the awake and cooperative patient led to optimal motor outcome in this cohort of PD patients receiving conventional ring electrodes for STN DBS. As MS overruled MER results concerning final trajectory selection in 28% of patients' hemispheres, the placement of DBS leads in general anesthesia without the possibility of trajectory confirmation by clinical testing cannot be safely advocated. With the advent of directional leads, MS may become less important, as postoperative corrections of the electrical field become possible.

Abstract No.:
358

Authors:
Iankova, Vassilena; Respondek, Gesine; Aiba, Ikuko; Boxer, Adam; Golbe, Lawrence; Grossman, Murray; Josephs, Keith; Lang, Anthony; Litvan, Irene; Stamelou, Maria; Höglinger, Günter

Abstract Title:
Video-based tutorial on the clinical diagnosis of progressive supranuclear palsy based on the MDS-PSP criteria (Video-basiertes Tutorial über die klinische Diagnose der PSP nach den MDS-PSP-Kriterien)

Abstract Text:
Introduction: Progressive supranuclear palsy (PSP) is defined neuropathologically by the intracerebral aggregation of tau. A correct and

early clinical diagnosis of patients with PSP remains a challenge due to the various clinical presentations of the disease. Not only for assessment of prognosis, but also for correct placement of patients into therapeutic trials, an early and correct diagnosis is of major importance. Therefore, in 2017 the International Parkinson and Movement Disorder Society (MDS)-endorsed PSP Study Group proposed new clinical diagnostic criteria for PSP (MDS-PSP criteria) for use in clinical practice and research.
Target: We aim to develop a video-based tutorial in which clinical examination techniques and associated abnormal and normal findings are depicted and explained, to help clinicians to apply the MDS-PSP criteria.
Methods: To create the tutorial, a study group of international PSP experts was initiated. Guidelines for recording particular examination techniques and PSP-associated clinical signs were established by the steering committee to ensure good video quality. After written informed consent, patients were videotaped according to the guidelines by members of the study group. Videos were then uploaded on a password protected online space to allow the study group to select the most appropriate videos.
Results: Videos on the following diagnostic PSP-associated signs and appropriate clinical examination techniques according to the MDS-PSP criteria were created: Ocular motor dysfunction: vertical supranuclear gaze palsy, slow velocity of vertical saccades, frequent macro square wave jerks, eyelid opening apraxia; Postural instability: repeated unprovoked falls, tendency to fall on pull-test, more than two steps backward on pull-test; Akinesia: progressive gait freezing, akinetic-rigid parkinsonism (predominantly axial), parkinsonism with tremor and/or asymmetry; Cognitive dysfunction: nonfluent agrammatic primary progressive aphasia, progressive apraxia of speech, frontal cognitive behavioral presentation and corticobasal syndrome. Currently we are working on the production and publication of the video tutorial.
Conclusion: Here we present the current status on our video-based tutorial to help and encourage clinicians to correctly apply the MDS-PSP criteria in order to optimize early, sensitive and specific diagnosis of PSP.

Abstract No.:
359

Authors:
Büttner, Charlotte; Maack, Marike; Witt, Karsten

Abstract Title:
Long-term effects of deep brain stimulation on quality of life in Parkinson's disease: a meta-analysis

Abstract Text:
Introduction: An important consideration in the treatment of Parkinson's Disease (PD) with deep brain stimulation are the effects on quality of life (QoL). Several studies have shown a positive impact of subthalamic stimulation on QoL, as measured by the results of the Parkinson's Disease Questionnaire (PDQ-8 or PDQ-39). However, there is inconsistent evidence on whether this QoL improvement remains constant or whether the effect is only temporal.
Target: This meta-analysis aims to identify studies that provide information on change in QoL after subthalamic stimulation in patients with PD and to summarize and compare results from these studies, focusing on different time points of the follow-up assessment.
Methods: An electronical search for relevant articles was performed between July and September 2018 using the following databases: PubMed, Science Direct, and Scopus. In total, five meta-analyses were performed, considering different follow-up periods (6 months, 12 months, 24 months, 36 months, and 60 months). Data were analysed using the meta package in R. We calculated the standardised mean difference (SMD) between baseline and follow-up PDQ scores for each analysis, to ensure generalizability between studies using the PDQ-8 and the PDQ-39. Interpretation was based on a random-effects analysis.
Results: We found ten studies measuring the PDQ total score at 6 month follow up, twelve studies measuring a follow-up after 12 months, seven studies including a follow-up at 24 months and three studies each, evaluating the PDQ 36 and 60 months after surgery. After 6 months, the mean difference between the baseline PDQ score and the PDQ score at follow-up was SMD = 0.69 [0.58; 0.81], $z = 12.15$, $p < 0.0001$. The effects of subthalamic stimulation remained similar over 36 months, with all analyses showing a significant increase in QoL when compared to baseline. Compared to baseline, after 60 months, studies showed a non-significant SMD of -0.18 [-1.18; 0.81], $z = -0.36$, $p = 0.7187$.
Conclusion: This analysis revealed the improvement in QoL following subthalamic stimulation in PD to stay constant over approximately 36 months. However, assessments after 60 months indicated a trend back to baseline scores. The findings of this meta-analysis highlight the necessity of longer follow-up periods, since only three of the included studies followed the development of QoL after deep brain stimulation for as long as 5 years. Further, it is still not clear what factors influence the change in QoL following subthalamic stimulation. This also needs to be addressed by future studies.

Abstract No.:
360

Authors:
Stengl, Alea; Rauschenberger, Lisa; Knorr, Susanne; Grundmann-Hauser, Kathrin; Volkmann, Jens; Ip, Chi Wang

Abstract Title:
Striatal monoamine analysis hints at dopaminergic dysregulation in a phenotypic DYT1 mouse model (Die Analyse des striatalen Monoaminspiegels deutet auf dopaminerge Dysregulation im phänotypischen DYT1 Mausmodell)

Abstract Text:
Introduction: DYT1 dystonia is the most common hereditary dystonia caused by a GAG deletion on chromosome 9 and still unclear pathophysiology. 30% of mutation carriers develop generalized dystonia in childhood, often following an external trigger. hΔGAG3 mice express the human torsinA mutation while not showing a dystonic phenotype per se. We induced dystonia-like movements in genetically predisposed hΔGAG3 mice, determining metabolic changes in the striatum.
Target: We examined whether environmental factors have a lasting effect on the development of a dystonic phenotype and aimed to analyze metabolic alterations in the striatum of symptomatic hΔGAG3 mice.
Methods: We analyzed wildtype (wt) and hΔGAG3 mice, subdivided into naïve, sham and nerve injured groups. Before and after unilateral sciatic nerve crush injury dystonia-like movements of hindlimbs were scored during tail suspension test (TST) with a 0–5 points scoring scale. For each animal, electroneurography of sciatic nerves was performed before, directly after and 10 weeks after nerve trauma. After brain dissection at week 12 the striatum was analyzed by HPLC to quantify relative levels of catecholamines and its metabolites.
Results: Both wt and hΔGAG3 mice developed dystonia-like movements after sciatic nerve crush injury during TST. However, hΔGAG3 mice displayed a significantly higher long-lasting dystonia-like movements score compared to wt mice (week 12: 2.1 ± 0.3 vs. 0.4 ± 0.2, $p < 0.0001$). The comparison of nerve conduction velocity (NCV) and compound muscle action potentials (CMAP) did not show any significant differences between both genotypes, although reduced NCV and CMAP were observed 10 weeks after nerve trauma

compared to control mice in both genotypes (hΔGAG3: 23.97 m/s ± 1.8 m/s vs. wt: 25.30 m/s ± 2.8 m/s). When analyzing dopamine (DA) levels of the contralateral striatum, hΔGAG3 mice displayed a mild hyperdopaminergic state at baseline (1.15 ± 0.12). Crush injury led to a significant decrease of dopamine levels in wt mice (0.79 ± 0.06) compared to hΔGAG3 mice (1.03 ± 0.18, $p < 0.05$).
Conclusion: This study demonstrates that a peripheral nerve trauma is able to trigger a dystonic phenotype in genetically predisposed, asymptomatic hΔGAG3 mice. Electroneurography excluded an impairment of peripheral nerve regeneration after crush injury as cause of increased dystonia-like movements in hΔGAG3 mice compared to wt mice. Moreover, hΔGAG3 mice revealed a striatal dopaminergic dysregulation, supporting a two hit hypothesis.

Abstract No.:
361

Authors:
Schweyer, Kerstin; Piot, Ines; Respondek, Gesine; Grimm, Max-Joseph; Schenk, Thomas; Sckopke, Philipp; Stebbins, Glenn; Höglinger, Günter

Abstract Title:
The Progressive Supranuclear Palsy Functional Disability Scale (PSPFDS) (Die Functional Disability Scale für die progressive supranukleäre Blickparese (PSPFDS))

Abstract Text:
Introduction: Progressive Supranuclear Palsy (PSP) can present with diverse clinical predominance types, leading to progressive disabilities in different functional domains. Few scales are currently being used to evaluate the severity and progression of PSP, e.g. the PSPRS, MDS-UPDRS, PSP-QoL, SEADL. These scales are often used jointly to evaluate the functional disability in PSP, which is laborious, imprecise and not feasible for clinical routine.
Target: We aimed to generate one single scale to cover all major functional domains relevant for PSP patients. For routine clinical practice, the scale should be concise enough to be completed within few minutes. For clinical trials, the tool should provide clinically meaningful information on the patients' status.
Methods: The PSPFDS has been conceptualized by specialists in movement disorder and rating scales. Based on the MDS-PSP diagnostic criteria, the PSPFDS covers six functional domains (ocular motor dysfunction, postural instability, akinesia-rigidity, bradyphrenia, communication, dysphagia), to cover the entire spectrum of clinical PSP phenotypes. The information required for PSPFDS rating is collected through a semi-structured interview with the patient and/or a reliable caregiver and a short structured clinical examination. All domains are rated by operationalized distinctions with a score ranging from 0 to 3, corresponding to no, mild, moderate, or severe deficits. The sum of individual scores provides a total range from 0 (no deficit in any domain) to 18 (severe deficit in all domains) and can be transformed into four disease stages (I-IV). Based on systematic cognitive pre-testing, a PSPFDS user instruction has been developed to standardize its application. Cross-sectional and prospective clinical data with the PSPFDS were collected in the multicenter DZNE DESCRIBE-PSP study patients with Richardson's syndrome (n = 55) and variant PSP phenotypes (n = 33).
Results: Cognitive pretesting attested the PSPFDS to be easily applicable.

Principal component analysis and Crohnbach's alpha revealed a good internal consistency of the scale.

We found strong correlations of the PSPFDS total score and its subitems with established clinical scales, e.g. with PSPRS (R = 0.80), UPDRS III (R = 0.63), SEADL (R = − 0.64) and CGI-S (R = 0.59). The scale proved to be an adequate measurement for variant PSP phenotypes showing even stronger correlations than for PSP with Richardson's syndrome. With increasing disease severity, PSPFDS stages reflected well the number of clinical milestones reached, limiting the independence in activities of daily living.
Conclusion: The PSPFDS is a new and simple tool to monitor functional disability in PSP patients with Richardson's syndrome and variant phenotypes. Current investigations address the inter-rater reliability, test-retest reliability and sensitivity to change over time.

Abstract No.:
362

Authors:
Koirala, Nabin; Serrano, Lucas; Paschen, Steffen; Anwar, Abdul Rauf; Kuravi, Pradeep; Deuschl, Günther; Groppa, Sergiu; Muthuraman, Muthuraman

Abstract Title:
Mapping of subthalamic nucleus using microelectrode recordings during deep brain stimulation

Abstract Text:
Introduction: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been established to be an effective treatment option in advanced Parkinson's disease (PD) patients. Alongside stereotactic magnetic resonance imaging, microelectrode recording (MER) is used during the surgery for optimal target localisation.
Target: The aim of this study is to optimise STN mapping using MER analytical patterns which could directly improve the clinical testing by introducing objective variables from MER.
Methods: 16 patients (12 males, age 64.06 ± 7.68, Hoehn & Yahr (H&Y) 3.19 ± 0.66) underwent bilateral STN-DBS. Pre-operative MRI was used for stereotactic planning. MER was performed in awake patients and spike activity was rated from 0 (no activity) to 4 (high activity) by visual inspection. Recording was done simultaneously for 3–5 microelectrodes in a setting of Ben's-gun pattern. Thus obtained data was analysed using Spike2® and wave_clus® software for artefacts correction, segmentation and spike sorting. Finally, number of spikes (firing rate), root-mean square (RMS) of the background activity, Fourier transform of background activity and mean and maximum amplitude in beta and gamma frequency range were computed. For clinical testing, the improvement in motor scores (bradykinesia, rigor) and the threshold of side effects were compared for the mapped STN borders. The target point with the lowest threshold for clinical improvement and highest threshold for side effects was used for the permanent electrode placement.
Results: Using spike analysis (firing rate) the proper STN location for lead placement with the best clinical effect/side effect ratio was predicted successfully in 85% (27/32) of the implantation. Prediction based on mean amplitude of background activity in the beta frequency range showed an accuracy of 82% (26/32). Additionally, mean amplitude in gamma frequency band 78% (25/32) and maximum RMS 75% (24/32) were also able to predict the target with relatively good accuracy.
Conclusion: MER can be used for STN mapping and intraoperative decisions for the implantation of DBS electrode leads with a high accuracy. Spiking and background activity in the beta range are the most promising independent parameters for the delimitation of the proper anatomical site.

Abstract No.:
363

Authors:
Eickhoff, Claudia; Hoffstaedter, Felix; Caspers, Julian; Mathys, Christian; Südmeyer, Martin; Reetz, Kathrin; Heller, Julia; Amunts, Katrin; Schnitzler, Alfons; Eickhoff, Simon B.

Abstract Title:
Advanced brain age in Parkinson's disease is related to disease duration but not severity (Zusammenhang des geschätzten Hirnalters bei an Parkinson erkrankten Patienten mit Erkrankungsdauer, nicht jedoch mit Erkrankungsschwere)

Abstract Text:
Introduction: Machine-learning models have demonstrated their ability to reliably predict subjects' age from structural imaging data and revealed that subjects with Alzheimer's disease and to a lesser degree mild cognitive impairment show an advanced brain age relative to their chronological age (Varikuti et al., 2018). Whether a similar pattern may be seen in Parkinson's disease (PD) in spite of its more localized pathophysiology, however, has not yet been established.
Target: To evaluate whether PD patients show accelerated brain aging using multivariate machine-learning algorithms trained on a large, independent reference sample.
Methods: Structural, T1 weighted MRI scans were acquired at 3T from 68 patients with idiopathic PD and 90 age- and sex-matched healthy controls (HC), preprocessed using the CAT12 toolbox and represented by the volume of 1273 regions from published brain atlases (Schäfer et al., 2017; Fan et al., 2016). Multivariate age-estimation was performed by a support vector machine ensemble with feature selection trained using age- and gender stratified sub-sampling of an independent dataset of 3851 healthy subjects. We computed the "BrainAGE score" (estimated—true age) and compared it between PD and HC subjects. Moreover we tested for its relation with clinical features among the patients.
Results: Across the HC subjects the age as predicted using a model trained on the reference sample closely matched their chronological age ($r = 0.80$, mean absolute error 4.6 years). Based on the same model PD patients were estimated on average 5.9 years older than their true age. BrainAGE scores were significantly elevated in PD patients ($p < 0.001$). Given variability within each group, however, individual diagnostic potential of the scores by themselves was only moderate (AUC = 0.71). Across patients, increase was not related to current symptoms as assessed by the UPDRS (on medication) or H&Y stage, but showed a positive correlation with disease duration ($r = 0.40$, $p < 0.05$).
Conclusion: Multivariate machine-learning algorithms provided a precise prediction of chronological age from structural MRI scans in healthy subjects but revealed a substantially advanced brain age in PD patients, which is in line with previous reports in neurodegenerative disorders (Varikuti et al., 2018; Koutsouleris et al., 2014). Interestingly, higher brain age gap for patients was correlated with disease duration but not severity or symptom load, contrasting reports in e.g., schizophrenia (Koutsouleris et al., 2014). Our data therefore indicates that duration of neurodegenerative processes may be more relevant to the advancement of global effects in PD, hence contrasting (motor) symptomatology that should be more specifically related to striatonigral degeneration (Lees et al., 2009).

Abstract No.:
364

Authors:
Kunz, Martin; Gorges, Martin; Huppertz, Hans-Jürgen; Liepelt-Scarfone, Inga; Storch, Alexander; Dodel, Richard; Hilker-Roggendorf, Rüdiger; Berg, Daniela; Kalbe, Elke; Baudrexel, Simon; Kassubek, Jan

Abstract Title:
Longitudinal 3D MRI data analyses from the LANDSCAPE study in patients with Parkinson's disease and cognitive impairment

Abstract Text:
Introduction: In vivo correlates from longitudinal imaging data for progressive cognitive impairment in Parkinson's disease (PD) are still limited.
Target: Here, we analysed morphological patterns from anatomical MR imaging data from PD patients in order to investigate whether the observed patterns are consistent with the Braak hypothesis.
Methods: Atlas-based volumetric (ABV) analysis to assess cortical and subcortical volumes from T1-weighted 3D MRI data (MPRAGE) was performed. In addition, Freesurfer was used to determine cortical thickness. Volumetric and cortical thickness data were evaluated over about 4 years; to this end, up to 5 measurements in 140 PD patients and 71 controls from the LANDSCAPE study were subjected to the final statistical analysis.
Results: We could identify three groups of PD patients: group 1 subjects ($n = 35$) presented with volumetric loss of subcortical structures including the striatum. Group 2 subjects ($n = 89$) displayed volumetric loss of group 1 and additionally cortical thinning of parieto-temporal areas and the hippocampus. Group 3 subjects ($n = 16$) were characterized by additional cortical volumetric loss in several prefrontal areas and volumetric loss of limbic structures. The data-driven and investigator-independent classification approach was significantly correlated with the cognitive status.
Conclusion: Morphological macrostructural cerebral changes in the course of PD with progressive cognitive impairment appear to develop in a sequential manner consistent with the Braak stages 4–6.

Abstract No.:
365

Authors:
Gorges, Martin; Müller, Hans-Peter; Liepelt-Scarfone, Inga; Storch, Alexander; Dodel, Richard; Hilker-Roggendorf, Rüdiger; Berg, Daniela; Kalbe, Elke; Bautrexel, Simon; Kassubek, Jan

Abstract Title:
Microstructural alterations and their cognitive correlates in Parkinson's disease: DTI data from the LANDSCAPE Study

Abstract Text:
Introduction: The course of Parkinson disease (PD) is accompanied by cognitive decline in its advanced stages, a non-motor feature that can lead to the full picture of dementia.
Target: Here, we correlated the pattern of microstructural changes to the cognitive profile by using diffusion tensor imaging (DTI) and neuropsychological data from a total of 134 PD patients and 72 healthy controls participating in the multicenter LANDSCAPE study.
Methods: We used diffusion tensor imaging (DTI) and neuropsychological data from a total of 134 PD patients and 72 healthy controls participating in the multicenter LANDSCAPE study.
Results: Using three subgroups of patients, 56 cognitively normal patients, 67 patients with mild cognitive impairment (MCI), and 11 demented patients, we observed cognitive-status-dependent DTI alterations with microstructural damage in cognition-related brain

areas including fronto-occipital, uncinate, insular cortices, superior longitudinal fasciculi, corona radiata, and the corpus callosum.
Conclusion: These findings suggest that (1) cross-hemispherical connectivity is moderately impaired in cognitively normal PD, (2) the corpus callosum and the fronto-parieto-temporal network is disrupted in PD-MCI, and (3) mainly fronto-parieto-temporal fibre bundles are additionally involved in PD dementia.

Abstract No.:
366

Authors:
Buchwitz, Timo; Eggers, Carsten

Abstract Title:
Improving self-awareness of patients with Parkinson's Disease by using mindfulness—a qualitative and quantitative study (Verbesserung der Selbstwahrnehmung von Parkinsonpatienten durch Achtsamkeit)

Abstract Text:
Introduction: Anosognosia for motor impairment in non-demented patients with Parkinson's Disease (PD) was rarely considered in the past. More recent research has suggested that impaired self-awareness of motor symptoms (ISAm) exists in non-demented patients. An impaired self-awareness is associated with lower adherence, as well as higher patient mortality and caregiver burden and has therefore a high clinical relevance.
Target: This study investigates the improvement of ISAm using IPSUM, a newly developed, body-oriented mindfulness intervention. In order to evaluate the effectiveness of this 8-week long intervention, cognitive, emotional, behavioral and structural neurological changes are evaluated.
Methods: Non-demented, non-depressed patients with idiopathic PD, who show signs of ISAm, are randomized to an intervention or a waitlist-control group. Applying an adaptive Pre-Post-Design, patients are measured for their self-awareness of motor symptoms by using a recently validated scale for impaired motor-awareness (see Maier et al., 2015) at three points in time: before, directly after, and 8 weeks after participating in the intervention. The effectiveness of the intervention is determined by significant differences of ISAm between both groups, whereas the intervention group's awareness is expected to be higher (after their participation). Also, neuropsychological and self-report measures are applied to evaluate cognitive and affective changes. Performance monitoring for cognitive performance is used as an indicator for impaired self-awareness of cognitive symptoms. Some patients undergo a resting-state fMRI scan before and directly after the intervention. Additionally, qualitative data for changes of body and self-awareness is collected in a semi-structured interview during post-measurement. A maximum of 180 patients will be included. Because of an adaptive group sequential design, several interim analyses are carried out over time and the trial might be stopped beforehand (efficacy stop).
Results: The intervention manual has been created. Two implementations for feasibility testing are planned. If necessary, some changes to the manual will be applied. As the main outcome, we expect an improvement of quantitative measured ISAm over time in the intervention but not the control group.
Conclusion: We expect this new mindfulness intervention, designed for the specific needs of PD patients, to improve ISAm and thus enhancing their quality of life on many levels.

Abstract No.:
367

Authors:
Yin, Jing; Koprich, James; Brotchie, Jonathan; Volkmann, Jens; Ip, Chi Wang

Abstract Title:
Progressive alterations of pro- and antidegeneration markers in the nigrostriatal tract of the AAV1/2-A53T-a-synuclein rat model of Parkinson's disease

Abstract Text:
Introduction: Degeneration of the nigrostriatal tract plays an essential role in Parkinson's disease (PD). However, there is no therapy available to delay or halt neurodegeneration so far. Several crucial neuronal pro-and antidegeneration markers (e.g., SARM1, NMNAT2, HDAC1, Nrf2, Tau) were described to be altered in other disease models accompanied by neurodegeneration like models for ischemic stroke and multiple sclerosis.
Target: To investigate if SARM1, NMNAT2, HDAC1, Nrf2, Tau are altered during neurodegeneration in the nigrostriatal tract of the AAV1/2-A53T-α-synuclein (aSyn) rat model of PD that is based on an AAV1/2 mediated overexpression of mutated human A53T aSyn.
Methods: AAV1/2-A53T-aSyn or AAV1/2 empty control vector (EV) were unilaterally injected into the substantia nigra (SN) of male adult SD rats at a concentration of 2.55×1012 genomic particles/ml. At respectively 2 weeks, 4 weeks and 6 weeks post injection, motor deficits were assessed by the cylinder test and the single pellet reaching task. At the same time points, immunofluorescence double stainings for tyrosine hydroxylase (TH) to label dopaminergic neurons and either SARM1, NMNAT2, HDAC1, Nrf2 or Tau were performed on horizontally cut rat brains sections.
Results: We observed significant paw use asymmetry in the cylinder test of AAV1/2-A53T-aSyn groups compared to EV controls at 4 and 6 weeks post injection ($P < 0.001$; $P < 0.001$) and impaired motor performance in the single pellet reaching task at 4 and 6 weeks post injection ($P < 0.05$; $P < 0.05$). 6 weeks after injections, immunofluorescence stainings demonstrated downregulation of Nrf2 in dopaminergic neurons and axons ($P < 0.05$; $P < 0.05$). At 4 and 6 weeks post injection, upregulation of HDAC1 in the dopaminergic axons were detected ($P < 0.05$; $P < 0.05$). In addition, a non-significant decrease of Tau expression in SN and a slight increase in axons were shown. However, we did not find an evident alteration of SARM1 and NMNAT2 at all time points.
Conclusion: These data suggest that Nrf2, HDAC1 and Tau might be involved in the neurodegeneration process in PD and by this pointing towards putative novel therapeutic targets to prevent nigrostriatal dopaminergic degeneration.

Abstract No.:
368

Authors:
Warnecke, Tobias; Happe, Svenja; Krouß, Sabine; Lewe, Luisa; Overbeck, Jeanette; Palesch, Anja; Perick, Jürgen; Rose, Olaf; Schnieder, Laura; Siebecker, Frank

Abstract Title:
Parkinson's Network Muensterland + : objectives, development and perspectives (Parkinsonnetz Münsterland + : Ziele, Entwicklung und Perspektiven)

Abstract Text:
Introduction: Throughout the last years an increasing number of basic and clinical research studies have provided continuous knowledge for an improved treatment of Parkinson's disease (PD). Comprehensive multidisciplinary care network may enhance the

ability to translate these findings directly to the patients. The Parkinson Network Muensterland + (PNM +) is a recently initiated regional network of all professionals/institutions involved in Parkinson's care including patients and caretakers.

Target: The objective of the PNM + is to optimize treatment by means of:

1. Exchange between all professionals/stakeholders (trust building)
2. Knowledge training tailored to regional needs
3. Experience and expertise sharing
4. Regional care consensus (care standards)

These measures are intended to result in patient-centred health care offers accessible to the right patient at the right time, e.g. early and specific referral to non-pharmacological therapies or timely recognition of necessary changes of treatment strategy (including escalation therapies). Further objectives are improving communication between professionals, increasing appropriate individual treatment settings and using telemedicine in a purposeful manner.

Methods: PNM + starts in May 2017 and emerged based on a bottom-up approach with integration of more than 100 stakeholders as crucial component. The current regional care status was analyzed to identify the most important unmet needs. Based on this region-specific analysis the network set up topic-related working groups as the main driving module for a continuously development. The diversity of ideas and input of these groups pushes a constant needs-based progress through action learning.

Results: Participants show a high level of motivation, participation and satisfaction in the PNM + buildup process. Working together established a strong climate of trust as a basis for cooperation. Quick cards for optimizing interface communication and coordination of care options are a major part of the first developmental step. A quick card on specific dysphagia management in the PD population was already being piloted. Quick cards on physiotherapy and neuropsychology will follow shortly. Projects including wearables, apps and teleconsultations have been started. Specific training sessions for physiotherapists and speech language therapists have taken place. A systematic evaluation of the effect on daily practice is in preparation.

Conclusion: In a challenging situation characterized by an increasing prevalence and incidence of PD due to demographic change while facing a shortage of health care resources the presented buildup process of the PNM + offers the opportunity to identify general hurdles that need to be crossed before starting the implementation of such a multidisciplinary care network.

Abstract No.:
369

Authors:
Nickl, Robert; Reich, Martin; Pozzi, Nicolo; Fricke, Patrick; Lange, Florian; Roothans, Jonas; Volkmann, Jens; Matthies, Cordula

Abstract Title:
Rescuing suboptimal outcomes of subthalamic deep brain stimulation in Parkinson's Disease by surgical lead revision

Abstract Text:

Introduction: Clinical trials have established subthalamic deep-brain-stimulation (STN-DBS) as a highly effective treatment for motor symptoms of Parkinson's disease (PD), but in clinical practice outcomes are variable. Experienced centers are confronted with an increasing number of patients with partially "failed" STN-DBS, in whom motor benefit doesn't meet expectations. These patients require a complex multidisciplinary and standardized workup to identify the likely cause.

Target: To describe outcomes in a series of PD patients undergoing lead revision for suboptimal motor benefit after STN-DBS surgery and characterize selection criteria for surgical revision.

Methods: We investigated nine PD patients with STN-DBS, who had unsatisfactory outcomes despite intensive neurological management. Surgical revision was considered if the ratio of DBS versus levodopa induced improvement of UPDRS-III (DBS-rr) was below 75% and the electrodes were found outside the dorsolateral STN.

Results: Fifteen electrodes were replaced via stereotactic revision surgery into the dorsolateral STN without any adverse effects. Median displacement distance was 4.1 mm (range 1.6–8.42 mm). Motor symptoms significantly improved (38.2 ± 6.6 to 15.5 ± 7.9 points, $p < 0.001$); DBS-rr increased from 64 to 190%.

Conclusion: Patients with persistent OFF-motor symptoms after STN-DBS should be screened for levodopa-responsiveness, which can serve as a benchmark for best achievable motor benefit. Even small horizontal deviations of the lead from the optimal position within the dorsolateral STN can cause stimulation responses, which are markedly inferior to the levodopa response. Patients with an image confirmed lead displacement and preserved levodopa response are candidates for lead revision and can expect significant motor improvement from appropriate lead replacement.

Abstract No.:
370

Authors:
Otte, Karen; Röhling, Hanna; Rasche, Ludwig; Ellermeyer, Tobias; Mansow-Model, Sebastian; Paul, Friedemann; Brandt, Alexander U.; Lipp, Axel; Schmitz-Hübsch, Tanja

Abstract Title:
Quantitative analysis of MDS-UPDRS III finger tapping and hand grip test using visual perceptive computing (Quantitative Analyse von Handfunktionstest des MDS-UPDRS Teil III mittels Tiefenvideo-Aufnahmen)

Abstract Text:

Introduction: The MDS-UPDRS is the most commonly used clinical scales to assess disease severity in patients with Parkinson's Disease. Rater-based part III of the scale covers relevant motor symptoms. Critiques of these clinical scales are often their lack of sensitivity to smaller changes and expert-based rating. The automated calculation of quantitative motor parameters by means of visual-perceptive computing might be able to address these problems.

Target: To explore an automated quantitative parametrization of finger and hand tasks based on marker-less depth data and for the use in patients with Parkinson's disease.

Methods: From ongoing studies, 19 patients with Parkinson's Disease (age: 44–81, MDS-UPDRS III: 7–52) performed a set of 12 different motor tasks (PASS-PD), including two items from MDS-UPDRS (finger tapping (FTT), hand grip (HGT)). Performance was recorded in ON and OFF medication states by an infrared depth sensor (Microsoft Kinect™ V2). We used custom-written software (Motognosis Labs) to extract kinematic parameters for the description of tapping and gripping frequency, arrhythmicity and movement amplitudes. Parameters were calculated for each item and each body side respectively.

Results: Patients showed lower average finger tapping movement frequency in OFF state (2.33 Hz) than in ON state (2.70 Hz) (ES − 0.41, $p = 0.02$) with similar results in hand gripping (OFF: 2.15 Hz ON: 2.28 Hz; ES − 0.28), though not statistically significant, while no difference was seen in FTT finger amplitude. Movement frequencies showed moderate to strong correlations with MDS-UPDRS III (FTT Freq: − 0.560; $p < 0.001$ and HGT Freq: − 0.745; $p < 0.001$). Correlation with FTT amplitude was − 0.564 ($p < 0.001$), though no inter-correlation was seen between FTT finger amplitude and movement frequency. In few cases, visual inspection of signal time series revealed a decline in movement amplitude throughout the task, that can be described by arrhythmicity measures.

Conclusion: This pilot data demonstrated good applicability and acceptance for VPC recording. It extends previous findings concerning the potential of visual perceptive computing to objectively quantify motor symptoms of Parkinson's disease. Results suggest a specifically strong association between movement frequency and disease severity that is unrelated to the aspect of decreased movement amplitude.

Abstract No.:
371

Authors:
Brücher, Sarah; Jakob, Verena; Klucken, Jochen; Stallforth, Sabine; Winterholler, Martin

Abstract Title:
Inpatient Parkinson Complex Therapy and gait: a pilot study using three dimensional gait analysis (3D-GA) (Parkinsonkomplextherapie und Gang: eine Pilotstudie mit Hilfe der dreidimensionalen Ganganalyse (3D-GA))

Abstract Text:
Introduction: Inpatient Parkinson Complex Therapy (IPCT; G-DRG B49Z) is a structured therapy program widely used in German Neurological Parkinson Clinics. This concept combines pharmacotherapy with a multidimensional training program lasting 2–3 weeks. Until now there is only limited data about the short and long-term effects of IPCT for Parkinson's disease (PD). Three dimensional gait analysis (3D-GA) allows to gain objective, rather independent data about gait parameters and gait quality. Gait velocity, step length, as well as increasing gait phase variability are characteristic for the progress of PD.
Target: Evaluate the short and long-term effects of IPCT on gait in PD in a Bavarian Parkinson Clinic with three dimensional gait analysis.
Methods: We included a non-selected random group of 28 patients (14 women) with a mean age of 72 ($\pm$ 10) years, Hoehn & Yahr 3 ($\pm$ 1), UPDRS 43 ($\pm$ 17). All patients gave their written consent for this study. UPDRS and 3D-GA were performed at the beginning and the end of IPCT as well as 3 months after demission. For 3D-GA we used an 8-camera-system with 29 reflective markers (Simi Reality Motion Systems GmbH). Gait velocity, cadence, step width, cycle time, stride length and duration of swing phase were analyzed. To minimize the short-term effects of the medication, all examinations were performed during the "on" phase.

Statistics: The results were analyzed with a two sampled t-Test for paired groups within MS Excel. The significance level was set at $p < 0.05$ (*).
Results: We found an improvement in mean UPDRS "on" from 43 (admission) to 31 at demission. Results were stable for most patients after 6 months (in the patients examined, analysis ongoing). A significant improvement in 3D-GA was found in 4 of 6 gait parameters (gait velocity, cadence, cycle time left and right).
Conclusion: Our data mirror the effect of IPCT (G-DRG B49Z) as widely practiced in German Parkinson Clinics in a non-selected severely impaired group of PD patients. We found a significant effect on UPDRS as well as on gait parameters which are related to gait stability (step width) and independency (gait velocity). There is a need for more validated objectives to measure outcomes of different interventions in PD in the long term. We believe that gait analysis as well as wearable devices will help to identify effective and economic interventions in the future. (See also Maetzler W, Klucken J, Horne M.A. Mov Disord. 2016 Sep;31(9):1263–71.)

Abstract No.:
372

Authors:
Balck, Alexander; Borsche, Max; Kasten, Meike; Trinh, Joanne; Lohmann, Katja; Seibler, Phillip; Brüggemann, Norbert; Klein, Christine

Abstract Title:
Discordance in monozygotic twins with Parkinson's disease—continuum instead of dichotomy?

Abstract Text:
Introduction: Previous twin studies (Tanner et al., 1999; Wirdefeldt, Adami, Cole, Trichopoulos, & Mandel, 2011) showed higher concordance rates for Parkinson's disease (PD) in monozygotic (MZ) vs. dizygotic (DZ) twins with an age at onset (AAO) $\leq$ 50 years, compared to almost identical rates with an AAO $\geq$ 50 years. It was concluded that factors other than a genetic predisposition impact on the development of PD. However, clinical motor and non-motor markers of prodromal PD were not fully investigated raising the question as to whether the unaffected twin may exhibit features of prodromal PD.
Target: Detection of possible features of prodromal PD in the putatively unaffected twin in MZ twin pairs discordant for PD.
Methods: Five monozygotic twin pairs with one twin each meeting the MDS clinical diagnostic criteria for PD were clinically assessed for motor and non-motor symptoms using the MDS-UPDRS I-IV, Montreal Cognitive Assessment (MoCA), Hospital Anxiety and Depression Scale (HADS) and Parkinson's Disease Sleep Scale 2 (PDSS-2)), focusing on clinical motor signs of prodromal PD. Additionally, the Brief Smell Identification Test (BSIT) and transcranial sonography (TCS) were performed. Pathogenic mutations in PD-causing genes were excluded.
Results: We found motor signs in 4/5 putatively unaffected twins, which, however, did not allow to establish a diagnosis of PD. Four of the affected and four of the putatively unaffected twins showed mild cognitive impairment. Hyposmia was found in one affected and three putatively unaffected individuals. Two putatively unaffected twins showed an increased hyperechogenicity of the substantia nigra. Four out of five affected but none of the putatively unaffected twins reported sleep problems. Depression was found in two twins with PD; three affected and one putatively unaffected twin reported obstipation. In summary, clinical motor and/or non-motor features were present in all five putatively unaffected twins.
Conclusion: All putatively unaffected twins displayed PD-related motor and/or non-motor abnormalities, which may be indicative of prodromal PD. These findings challenge the concept of a simple dichotomy of 'affected' vs. 'unaffected' in PD twin studies. Therefore, deep phenotyping is warranted to detect twins at risk of developing PD or having mild PD. Also, there should be long-term follow-up of the putatively unaffected twins to detect any possible progression or phenoconversion. A susceptibility for nigral pathology might be present in both twins and may reflect shared environmental exposures or genetic factors other than pathogenic mutations in established PD-causing genes.

Abstract No.:
373

Authors:
Peterka, Manuel; Odorfer, Thorsten; Volkmann, Jens; Zeller, Daniel

Abstract Title:
Proprioception in Parkinson's disease—explorative assessment of proprioceptive impairment and potential recalibration by LSVT-BIG therapy (Propriozeptive Störungen bei Morbus Parkinson)

Abstract Text:
Introduction: There is growing evidence that proprioception is dysfunctional in Parkinson's disease (PD). Whether this is caused by impaired sensorimotor integration in the basal ganglia circuits or by pathological processing of proprioception at a different stage is still under debate. A special training program, called LSVT-BIG, which aims at increasing movement amplitudes in PD patients, has been shown to be effective in PD patients regarding motor skills and mobility, presumably by proprioceptive recalibration.
Target: To assess proprioceptive impairment in PD patients as compared to matched controls and to probe potential recalibration effects of the LSVT-BIG therapy on proprioception.
Methods: 27 PD patients and 15 healthy controls participated in this prospective case-control study. After initial assessment, 11 PD patients (BIG) followed a 4 weeks LSVT-BIG therapy protocol, while 16 PD patients (HOME) performed a 4 weeks standard physical therapy. Outcome measures included the Unified Parkinson's Disease Rating Scale (UPDRS), fine motor skill tasks, and proprioceptive tasks, including perception of limb position and pointing tasks. Post-intervention evaluations were conducted at weeks 4 and 8.
Results: Compared to healthy controls, PD patients showed significantly larger pointing errors, while perception of limb position was comparable. At follow-up, performance in the pointing tasks improved significantly in the BIG group, but not in the HOME group.
Conclusion: Our findings are in line with the notion that proprioception is impaired in PD patients. Though confirmation in a larger cohort of PD patients is required, our data indicate that LSVT-BIG therapy may indeed act by recalibrating altered proprioception.

Abstract No.:
374

Authors:
Waldmann, Amelie; Zeller, Daniel

Abstract Title:
The rubber hand illusion in patients with Parkinson's disease in medical ON and OFF (Die Puppenhandillusion bei Patienten mit Morbus Parkinson im medikamentösen ON und OFF)

Abstract Text:
Introduction: The feeling of body ownership as well as the perception of illusions related to this feeling are believed to be products of multisensory integration. The basal ganglia have been shown to play an important role in successful integration of multisensory inputs. An impairment of basal ganglia circuits is one of the pathophysiological core features of Parkinson's disease (PD).
Target: To assess the susceptibility to the rubber hand illusion (RHI) in a group of PD patients and matched controls. To probe the influence of the dopaminergic system in a subgroup of patients OFF medication.
Methods: We applied the RHI paradigm to 42 PD patients (median MDS-UPDRS III 25, IQR 17–31) and 48 healthy age-matched controls. In this experimental setup, stroking a visible rubber hand simultaneously with the participant's covered real hand elicits the feeling of ownership over the seen hand. Asynchronous stroking served as control condition. Proprioceptive bias and an illusion score based on questionnaire responses were used as measures of the illusion. A subgroup of 17 PD patients additionally underwent the experiments in an OFF-medication state.
Results: PD patients showed higher proprioceptive bias than controls independent of the stroking condition ($p = 0.015$). The illusion score indicated that PD patients experienced the RHI stronger in the asynchronous condition as compared to controls, while during synchronous stroking, scores were less affirmative in PD than in controls ($p < 0.05$). Comparison between ON- and OFF-medication state did not show significant differences, neither for the proprioceptive drift, nor for the illusion score.
Conclusion: PD patients may be more susceptible to the RHI due to a less stable body representation, probably resulting from internal noise during the process of multisensory integration. The lack of a difference of RHI measures between synchronous and asynchronous stroking within PD patients may point to an impairment of temporal discrimination in PD. The fact that RHI measures were similar in the ON- and OFF-medication states may indicate that RHI alterations in PD patients may be attributed to non-dopaminergic systems.

Abstract No.:
375

Authors:
Isaias, Ioannis Ugo; Brumberg, Joachim; Pozzi, Nicoló Gabriele; Marotta, Giorgio; Pezzoli, Gianni; Volkmann, Jens

Abstract Title:
Brain metabolic alterations herald falls in patients with Parkinson's disease

Abstract Text:
Introduction: Pathophysiological understanding of gait and balance disorders in Parkinson's disease is insufficient; late recognition of fall-risk patients limits efficacious follow-up to prevent/delay falls. Despite detailed testing of gait and balance, the specific factors that are critical to fall prediction and prevention in PD remain elusive and the best single variable to predict falls is two or more falls in the previous year.
Target: Brain metabolic imaging with [18F]-fluorodeoxyglucose (FDG) and positron emission tomography (PET) can reliably identify symptom-specific brain network changes and functional imaging biomarkers for tracking the progression of neurodegenerative processes and their response to treatment. Finding a falls signature prior to the occurrence of the first fall is fundamental to prevent its devastating consequences.
Methods: We retrospectively evaluated the clinical records and molecular imaging findings of over 200 patients with a diagnosis of idiopathic PD who underwent FDG PET at our center between 2012 and 2016. We identified one group of 11 patients (8 M; age 64 ± 8 years; disease duration: 7 ± 4 years; age at onset: 57 ± 11 years; UPDRS-III: 37 ± 14; LEDD: 829 ± 405 [baseline]) who experienced their very first fall episode between 6 and 12 months after the execution of the FDG PET. We then collected the clinical and imaging data of a second group of 32 patients (16 M; age 61 ± 9 years; disease duration: 8 ± 4 years; age at onset: 54 ± 8 years; UPDRS-III: 28 ± 14; LEDD: 753 ± 373) and a group of 12 healthy controls (HC) matched for demographic and clinical data. Brain metabolic differences between fallers, non-fallers and HC were tested by Statistical Parametric Mapping (SPM) with age and disease duration as covariates, and a post hoc volume-of-interest (VOI) analysis.
Results: Clinical and demographic data did not differ significantly between groups. PD fallers showed distinctive hypometabolism in the left parietal cortex (inferior and superior parietal lobules) and increased bilateral cerebellar glucose consumption.

Conclusion: Falls in Parkinson's disease might arise from altered cortical processing of spatial orientation between discrete body parts, possibly predicted by abnormal cortical metabolism. The increased cerebellar activity in PD fallers could be a compensatory attempt for poor adaptability to motor patterns due to an impaired parietal cortex signaling.

Abstract No.:
376

Authors:
Isaias, Ioannis Ugo; Pozzi, NIcoló Gabriele; Canessa, Andrea; Palmisano, Chiara; Brumberg, Joachim; Reich, Martin; Steigelwald, Frank; Pacchetti, Claudio; Pezzoli, Gianni; Volkmann, Jens

Abstract Title:
The neural mechanism of freezing of gait in patients with Parkinson's disease

Abstract Text:
Introduction: Freezing of gait (FOG) is a common symptom of Parkinson's disease (PD) that causes paroxysmal inability of effective stepping. FOG severely worsens patients' quality of life, triggering falls and hospitalization. The treatment of FOG is challenging and limited by its unclear pathophysiology.
Target: Recent molecular brain imaging studies showed a supraspinal locomotor circuit impairment in PD patients with FOG, but did not describe the functional alterations causing it. We envisioned a derangement of the locomotor network oscillation dynamics, a mechanism of brain coordination, during gait freezing in patients with PD.
Methods: We investigated the coupling between the cortex and the subthalamic nucleus (STN), two main nodes of the locomotor network, during (effective) walking and gait freezing in five freely-moving PD patients with deep brain stimulation (DBS). Five additional PD patients implanted for bilateral STN DBS and not suffering from FOG were recruited as controls. Recording were performed with a portable 64-channels EEG system (MOVE, BrainAmp) and novel DBS devices that allow on-demand measurements months after surgery (Activa PC + S®, Medtronic PLC or AlphaDBS, Newronika Srl). Neurophysiological recordings were combined with kinematic and molecular brain imaging studies.
Results: Cortices and STN coupled in low-frequency band (θ-α range 4–13 Hz) during (effective) walking. Gait freezing was selectively characterized by the suppression of this low-frequency coupling in favour of inter-hemispheric subthalamic β-coupling (13–35 Hz). This switch anticipated the occurrence of FOG and it was restored with the recovery of an effective walking pattern. This cortical-subthalamic derangement was sustained by a loss of striatal dopaminergic innervation.
Conclusion: These findings show for the first time the neural mechanism underpinning FOG in PD. The cortical-subcortical communication derangement during FOG can prevent the update of the ongoing gait pattern to environmental needs. These results foster the management of FOG with neuromodulation techniques, possibly adaptive DBS.

Abstract No.:
377

Authors:
Hobert, Markus; Helmers, Ann-Kristin; Hensler, Johannes; Schlürmann, Timo; Synowitz, Michael; Deuschl, Günther; Paschen, Steffen

Abstract Title:
Deep brain stimulation with directional electrodes for the optimization of the treatment in patients with essential tremor (Tiefe Hirnstimulation mit direktionalen Elektroden zur Therapieoptimierung bei Patienten mit essentiellem Tremor)

Abstract Text:
Introduction: Deep brain stimulation (DBS) in the ventral intermediate nucleus (VIM) of the thalamus is a widely accepted treatment in essential tremor (ET). Typical side effects of this treatment are dysarthria, ataxia, contractions and dysesthesia. With progression of the symptoms it is more difficult to adjust the stimulation to reduce tremor without increasing side effects. Directional electrodes help to achieve this goal, as the electric field can be modified to avoid stimulation of structures which cause side effects, such as the internal capsule. Programming of DBS with directional electrodes can be time-consuming due to the many opportunities. Especially rotation of the implanted directional electrode varies.
Target: Objective: To investigate whether determination of the rotation of the directional DBS electrodes with 3D-X-ray is helpful for programming and to avoid side effects in patients with VIM DBS in ET.
Methods: We included the first four of 20 planned patients in this preliminary analysis. All patients underwent DBS surgery with implantation of directional electrodes (Vercise Cartesia™, Boston Scientific) in the VIM of the thalamus for the treatment of ET at the University Hospital Kiel, Germany. We performed a standardized assessment of the effects of VIM DBS on tremor and sides effects of each contact of both electrodes separately. The rotation of the electrode was determined by 3D-X-ray. In this first analysis, we evaluated the angle of the contact with (1) the earliest effect and (2) the earliest occurrence of dysarthria.
Results: In a preliminary analysis of the results of the first 4 patients we found the earliest effect in a mean angle of 266° ± 48° to the anterior–posterior axis for the right electrode and in a mean angle of 144° ± 45° for the left electrode. The angle for the earliest occurrence of dysarthria was 172° ± 128° for the right and 145° ± 34° for the left electrode.
Conclusion: The angle of the earliest effect points to latero-posterior. The angle of the earliest dysarthria (side effect) points to posterior. Due to small sample size variation is quite large and inclusion of further patients is necessary for confirmation.

Abstract No.:
378

Authors:
Reich, Martin M.; Hsu, Joey; Roothans, Jonas; Pistorius, Regina; Isaias, Ioannis U.; Paschen, Steffen; Deuschl, Günther; Volkmann, Jens; Fox, Michael

Abstract Title:
Predicting delayed neuromodulation side effects using the connectome

Abstract Text:
Introduction: Deep brain stimulation (DBS) is an effective treatment for Parkinson's disease and essential tremor but can be complicated by side-effects such as cognitive decline and gait ataxia. There is often a delay before these side-effects are apparent and their

mechanism is unknown, making it difficult to identify patients at risk or select appropriate DBS settings.
Target: To identify the functional connectivity profile of deep brain stimulation (DBS) sites causing delayed-onset adverse effects and try to identify patients at risk based on connectivity.
Methods: Here, we test whether connectivity between the stimulation site and other brain regions can predict these side-effects. We studied two unique DBS cohorts where side-effects were relieved with re-programming without change in motor benefit: cognitive decline following subthalamic DBS for Parkinson's disease (n = 10) and gait ataxia following thalamic DBS for essential tremor (n = 7). Connectivity between the stimulated tissue and other brain regions was computed using publically available human connectome data (resting-state functional connectivity MRI from 1000 healthy subjects). Using a novel within-subject design, we contrasted the connectivity of stimulation sites causing side-effects with those that did not, identifying connections specific to each side effect.
Results: Stimulation sites causing cognitive decline were connected to the anterior cingulate, caudate nucleus, parahippocampal gyrus, and cognitive regions of the cerebellum. Stimulation sites causing delayed-onset gait ataxia were connected to the pallidum, vermis, and motor areas of the cerebellum. These DBS connectivity profiles were side-effect specific and correlated with clinical response. We then validated our connectivity profiles by showing that they could predict cognitive decline in an independent cohort of DBS patients with Parkinson's disease (n = 33) and predict ataxia in an independent cohort of patients with essential tremor (n = 38).
Conclusion: These results lend insight into the mechanism of delayed-onset DBS side-effects and suggest that connectivity maps based on surprisingly small cohorts can identify patients at risk for these side effects at independent clinical centers.

Abstract No.:
379

Authors:
Reich, Martin M.; Ewert, Siobhan; Lange, Florian; Roothans, Jonas; Krauss, Joachim; Kühn, Andrea; Deuschl, Günther; Volkmann, Jens; Study Group, GPi Sweetspot

Abstract Title:
Probabilistic mapping of the antidystonic effect of pallidal neurostimulation: multicentre imaging study

Abstract Text:
Introduction: Deep brain stimulation of the internal globus pallidus is a highly effective and established therapy for primary generalized and cervical dystonia, but therapeutic success is compromised by a non-responder rate of up to 25%, even in carefully-selected groups. Variability in electrode placement and inappropriate stimulation settings may account for a large proportion of this outcome variability.
Target: Here, we present probabilistic mapping data on a large cohort of patients collected from several European centres to resolve the optimal stimulation volume within the pallidal region.
Methods: A total of 105 dystonia patients with pallidal deep brain stimulation were enrolled and 87 datasets (43 with cervical dystonia and 44 with generalized dystonia) were included into the subsequent "normative brain" analysis. The average improvement of dystonia motor score was $50.5 \pm 30.9\%$ in cervical and $58.2 \pm 48.8\%$ in generalized dystonia, while 19.5% of patients did not respond to treatment ($< 25\%$ benefit). We defined a significant probabilistic volume of anti-dystonic effects by aggregating the individual volumes of tissue activated in normative atlas space and ranking voxel-wise for outcome distribution.
Results: The most beneficial stimulation volume was located within the posterior-ventral part of the GPi adjacent to subpallidal white matter and strongly predicted, also at a single subject level, the clinical efficacy of deep brain stimulation. Stimulation of this region was achieved by a variety of different electrode positions and stimulation settings.
Conclusion: Probabilistic outcome brain mapping is a reliable tool to estimate the expected benefit, and it advances computer-assisted planning and programming of deep brain stimulation.

Abstract No.:
380

Authors:
Großmann, Anne; Roothans, Jonas; Lange, Florian; Nickl, Robert; Volkmann, Jens; Reich, Martin

Abstract Title:
Gait alterations in Parkinson's Disease after subthalamic neurostimulation (Gangveränderungen bei Patienten mit idiopathischem Morbus Parkinson nach Simulation des Nucleus subthalamicus)

Abstract Text:
Introduction: Bilateral deep brain stimulation of the subthalamic nucleus (STN-DBS) is an established therapy for advanced idiopathic Parkinson's Disease. A reduction of the motor symptoms (40–60%) and a significant positive impact on the Quality of Life are observed in big clinical trials. Nevertheless, individual outcomes varied and often residual (or de novo) gait disturbances after the implantation prevent ameliorated mobility. The exact lead localisation and stimulation parameters may be responsible for this aspect. So far, no study has been able to identify an "optimal efficacy volume" in respect of Mobility and Gait for DBS within the STN.
Target: We investigated Volumes of Tissue activated (VTA) in subjects with Parkinson's Disease undergoing STN-DBS. We aimed to distinguish anatomic areas that, affected by DBS, have a positive effect on gait and those, where DBS may provoke gait disturbances.
Methods: 82 subjects with idiopathic Parkinson's Disease (Hoehn & Yahr 2.9 ± 0.7, UPDRS III 48.7 ± 12.3, disease duration 16.0 ± 4.8 years) undergoing bilateral STN-DBS (implanted within the years 2010–2016 in Wuerzburg) were stratified for motor improvement. To take a closer look at gait disturbances, we divided our subjects into groups according to their change in gait items of UPDRS III. To correlate the clinical outcome with the exact anatomical location of stimulation, we simulated VTAs in subject's related MRI space and associated them with gait alterations. All patient images were registered to a common MNI-space. Only voxels that were overlapped by ≥ 6 VTAs were visualized to define a volume, where DBS has a positive effect on gait disturbances (= "sweet spot"), and "bad areas", where stimulation may provoke gait problems.
Results: Our STN-DBS Parkinson-cohort shows an average motor improvement of 51.13% by stimulation alone (reduction of 24.9 ± 13.2 points in UPDRS III). 24 subjects experienced a complete remission of gait problems by STN-DBS, meanwhile 9 subjects show de-novo gait disturbances 1 year after the implantation. We observed no differences in stimulation parameters and global parkinsonism control between these two groups. Interestingly, the anatomic area of stimulation allows a clear separation of the groups. For individuals with an improvement of gait by DBS, the most commonly stimulated area was located more dorsal and antero-medial than the spot stimulated in individuals with a worsening of gait problems. Stereotactic coordinates for the centre of mass in improvement on gait were L = 13.1, A = 2.5, I = 3.0 and coordinates for aggravation of gait problems were L = 14.2, A = 1.2, I = 3.2 (based on AC-PC in mm).
Conclusion: In this study, we were able to show that the exact anatomical localisation of stimulation is correlated with gait alterations by STN-DBS in patients with Parkinson's disease. The most beneficial spot to stimulate is located more dorsal and antero-medial,

within the transition zone of the sensory-motor part of the STN and bordering white matter. In the future, these results could improve re-programming attempts in patients suffering from gait difficulties after STN implantation.

Abstract No.:
381

Authors:
Rijntjes, Michel; Meyer, Philipp T.

Abstract Title:
Parkinsonism due to ayurvedic medicines (Parkinsonsyndrom durch ayurvedische Medikamente)

Abstract Text:
Introduction: Herbal supplements, the most popular form of alternative medicine, have a prevalence of about 20% in western countries. In a competitive society, patients might want to demonstrate their independence in managing their health problems, using a "natural" treatment that they believe to be without side effects because of its availability without prescription. Therefore, the majority of patients in western countries take herbal medicines as self-medication, often additionally to prescriptions from physicians, without mentioning this spontaneously or even when asked directly.
Target: To raise awareness that Parkinson syndrome can be caused herbal supplements
Methods: A 56-year old man presented himself with bilateral, left-dominant rest and postural hand tremor since approximately 2.5 years that had increased progressively. Physical examination showed general bradykinesia, rigor of the left arm and diminished amplitude on tapping tasks. He felt a general loss of interest in social contacts and had become less motivated in his work. UPDRS-MDS III was 18, BDI was 15. Since 3 years, he only took herbal tablets for hypertension, recommended by an ayurvedic physician. Because non-motor symptoms other than his depressed mood were absent and ultrasound showed normal echogenicity of the substantia nigra, an FP-CIT-SPECT was performed that showed pathologically reduced uptake in the striatum bilaterally, but without the usual anterior–posterior gradient typical for Parkinson's disease.

On further questioning, he told that the ayurvedic tablets for hypertension were called Normalin and Serpina. Both contain root extract of Rauwolfia serpentina (English: "snakeroot"; German: "Schlangenwurzel") which contains reserpine, an irreversible inhibitor of vesicular monoamine transporter (VMAT), preventing uptake of the neurotransmitters dopamine, serotonine and norepinephrine. He was advised to stop this medication immediately and regular follow-up showed gradual improvement. After 3 months, the FP-CIT-Scan had normalized completely, all Parkinson symptoms had disappeared and his working motivation and social contacts had returned to previous normal levels.
Results: Reserpine, isolated from Rauwolfia serpentina in 1952, was the first successful drug for hypertension and widely used for psychosis in the 1950s because of its sedative effects, but discontinued after reports of parkinsonism and depression as side-effects. The observation that mice dramatically recovered from a reserpine-induced sedative state when given L-Dopa was the foundation of modern therapy for Parkinson's disease. In the present case, neither the patient, nor his general practitioner, nor the neurologist at first thought the herbal supplements to be relevant.
Conclusion: In patients presenting with Parkinson syndrome, medication history should include all supplements.

Abstract No.:
382

Authors:
Hermann, Wiebke; Ecke, Lydia; Wittig, Dierk; Hausbrand, Denise; Brandt, Moritz; Reichmann, Heinz; Storch, Alexander; Ziemssen, Tjalf

Abstract Title:
Autonomic symptoms as biomarker in REM sleep behavior disorder compared to Parkinson's disease (Autonome Störungen als Biomarker bei Patienten mit REM Schlafverhaltensstörung und der Parkinsonkrankheit)

Abstract Text:
Introduction: Autonomic symptoms are well-known non-motor symptoms in alpha-synucleinopathies, especially in Multi System Atrophy (MSA) and moderate to late stages of Parkinson's Disease (PD). Nevertheless, autonomic disturbances may occur in early and even prodromal stages of the disease progress as in clinically isolated REM Sleep Behavior disorder (iRBD) and may therefore serve as a biomarker and/or progression marker to predict conversion of prodromal disease stages to alpha synucleinopathies.
Target: This study was designed to measure autonomic and eye (dys) function in iRBD compared to PD and disease controls (with other sleep disturbances) including longitudinal follow-up assessments to evaluate their potential to serve as novel biomarkers.
Methods: We included 20 iRBD patients with polysomnographically proven RBD (age 71 $\pm$ 7, range 57–83; f 7: 13 m) and 20 sex- and age-matched PD patients (age 71 $\pm$ 8, range 53–82; f 7: 13 m, UPDRS total 19 $\pm$ 9, H&Y 2.1 $\pm$ 0.4) as well as 19 disease controls (age 70 $\pm$ 7, range 53–78; f 7: m 12). Exclusion criteria comprised any ophthalmological or other conditions interfering with measurements (e.g. glaucoma, heart rate abnormalities, severe hypertension/diabetes and peripheral pathology as well as dementia. Detailed evaluations were performed including clinical examinations (Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr staging), questionnaires on autonomic and sleep symptoms (e.g., Non-Motor-Symptoms Questionnaire (PD-NMSQ), Pittsburg Sleep Quality Index (PSQI) etc.) and objective measurements including Ocular coherence tomography (SD-OCT), Pupillary light reflex testing, galvanic skin response (SudoScan), tilt testing and gait analysis (GAITRITE).
Results: Subjective autonomic burden as assessed by the NMSQ was significantly elevated in patients with iRBD ($p < 0.001$) and PD ($p < 0.001$) compared to disease controls. In OCT central macula thickness (fovea) was significantly reduced in PD patients compared to disease controls without differences comparing iRBD with PD and controls. Mean retinal nerve fiber layers were not significantly different in PD and iRBD compared to controls. Pupillary light reflex findings showed significant differences between PD patients and controls as well as iRBD patients and controls (e.g., amplitude, relative amplitude). Also impairment of galvanic skin response in the hands was detectable in PD patients compared to controls ($p < 0.014$, $p < 0.022$). Additionally, significant differences in gait analysis were detected comparing iRBD patients, PD patients and controls.
Conclusion: First preliminary data of our detailed evaluations of subjective and objective measures of autonomic dysfunction showed differences between iRBD, PD and disease controls. These differences will be further evaluated by longitudinal measurements of iRBD patients to assess their value as prospective markers of conversion or progression.

Abstract No.:
383

Authors:
Lange, Florian; Musacchio, Thomas; Volkmann, Jens; Reich, Martin; Roothans, Jonas

Abstract Title:
Trouble shooting stimulation induced dysarthria in STN DBS using 30 μs short pulsed width (Pulsweiten als Lösungsansatz für stimulationsinduzierte Dysarthie bei der STN-THS)

Abstract Text:
Introduction: Dysarthria in Parkinson's Disease is a common symptom, reported by approx. 70% of patients within the disease course (Törnqvist, 2005). Due to reduction of intelligibility and speech capacity, as well as stigmatization, dysarthria leads to a significant loss in quality of life (Schröter-Morasch, 2005). While STN-DBS is a very effective treatment option for rigidity, akinesia and tremor, the effect on dysarthria (measured by the use of the UPDRS) is less pronounced. Furthermore, dysarthria is not only less improved by STN DBS but sometimes also aggravated or appearing as a new symptom by the stimulation (Beric, 2001; Klostermann, 2008; Thobois, 2002). High amplitudes as well as high frequencies have been identified as risk factors (Törnqvist, 2005).
Target: To identify troubleshooting pathways for stimulation induced dysarthria in chronic STN DBS.
Methods: Due to technical advances it is now feasible to use pulse widths as low as 30 μs. In these patients we decided to try a bilateral 30 μs program. While reducing pulse width, amplitudes were increased to gain the full therapeutic potential. This led to a remarkable improvement of stimulation-induced dysarthria without reduction of the overall beneficial stimulation effect. Interestingly even though the amplitude was increased by 20%, the current injection (pulse duration × amplitude) was lower but yielding the equivalent therapeutic effect.
Results: As the diameter of the STN is only a couple of millimeters and the current spread with standard stimulator settings from the DBS electrode is estimated to be around 2–5 mm (Volkmann, 2006), it seems reasonable to assume an inadequate modulation of formations surrounding the STN for this stimulation-induced-dysarthrogenic effect (Dromey, 2000; Gentil, 1999; Pinto, 2005; Rousseaux, 2004).

Physiological concepts suggest that shorter pulses could improve the selectivity of DBS for particular neural elements and might lead to a better distinction between desirable and adverse stimulation effects.

As technology advances, 30 μs pulse-width stimulation is increasingly useful to 'sharpen' the volume of tissue activated (VTA) and hereby widening the therapeutic window as well as dealing with stimulation-induced side effects.
Conclusion: To conclude, we suggest using a 30 μs pulse programming approach could be useful and effective for troubleshooting stimulation-induced dysarthria in STN DBS.

Abstract No.:
384

Authors:
Zajki-Zechmeister, Tibor; Kögl, Mariella; Kalsberger, Kerstin; Zajki-Zechmeister, László; Schmidt, Reinhold; Schwingenschuh, Petra

Abstract Title:
Quantification of tremor severity with a mobile tremor pen (Quantifizierung des Tremorschweregrades mittels mobilem Tremor Stift)

Abstract Text:
Introduction: Quantifying tremor severity is a challenging procedure. Standardized questionnaires for assessing tremor are subjective, available objective devices have a high complexity or are immobile. The evaluation of tremor intensity is however necessary to document the general course of disease and to adjust individual therapy.
Target: The aim of the study was to analyze the following questions: (1) What differences of clinical significance emerge if tremor is quantified in a wearable constellation (M2) and a hand-held constellation (M1) (2) Which clinical significance does the Total Power of a tremor measurement provide in contrast to the Power of Main Peak (3) Is an accelerometer-based or gyroscope-based tremor measurement more reliable?
Methods: Tremor measurements were made with the Tremitas system in 14 patients with Parkinson's disease tremor (PD) (assessment of rest tremor) and 16 patients with essential tremor (ET) (assessment of postural tremor). The Tremitas system is a pen-shaped sensor that can capture tremor and calculate relevant tremor parameters: The Power of Main Peak (PMP), the Peak Frequency (PF) and the Total Power (TP).
Results: The study showed that tremor severity assessed by the Tremitas System significantly correlated with tremor severity in the relevant subitems of the MDS-UPDRS (Part III Subscores 3.17 + 3.18 (sum)) and TETRAS (Performance Part –Point 4a right and left (sum)) ($r = 0.644$–0.797). Ad (1): There was no significant difference between M1 and M2 constellations in PD and ET ($p > 0.05$). (2) TP is slightly less robust as a tremor indicator (Difference of $R = 0.07$ on average) than PMP, but is still above the $r = 0.6$ threshold. (3) The gyroscope sensor was superior within a wearable constellation, while the accelerometer was superior in a handheld constellation.
Conclusion: We showed that a handheld tremor quantification tool with an accelerometer is a robust method to quantify rest tremor in PD and postural tremor in ET. PMP and TP were found useful as surrogate markers for tremor amplitude. Further investigations in a home-monitoring environment are being prepared.

Abstract No.:
388

Authors:
Zapf, Alexandra; Florin, Esther; Kahler, Larissa; Reker, Paul; Barbe, Michael; Kalbe, Elke

Abstract Title:
The impact of a social context on risk-seeking behavior and self-estimation in Parkinson's disease (Der Einfluss des sozialen Kontexts auf Risikoverhalten und Selbsteinschätzung bei Morbus Parkinson)

Abstract Text:
Introduction: Previous research has demonstrated that patients with Parkinson's disease (PD) frequently show risky decisions. However, the commonly used paradigms typically neglect the social context. Furthermore, to what extent individuals with PD can correctly estimate themselves in such a social setting is largely under-investigated.
Target: We aimed at investigating risky decision making and self-estimation in a social competitive experimental task. We

hypothesized that PD patients show greater maladaptive social behavior by overestimating their own performance and by engaging in more risky decision-making as compared to healthy controls (HC).
Methods: In this study, a computerized experimental setting (Florin et al., 2013) was used in which 50 PD patients according to UK Brain Bank Criteria (mean age = 67.8 ± 8.9 years; median Hoehn & Yahr = 2, range 2–3) and 34 HC (mean age = 64.0 ± 8.3 years) in groups of four performed a mathematical addition task where they were asked to calculate as many sums as possible in 5 min. Participants further had to make a choice for their preferred compensation scheme (i.e. decision making). They could choose between a piecerate compensation where each correct answer was rewarded with 50 cents, independent from the performance of the others, and a tournament compensation where only the best of the four players received 2€ per correct answer. Participants further had to evaluate their performance in relation to the rest of the group (i.e. self-estimation).
Results: An ex-post optimal decision strategy (i.e. which compensation scheme should have been chosen based on the probability of winning the tournament) was computed and compared with the participants' actual decisions. Both groups showed a significantly higher proportion of overestimation as compared to underestimation of performance. However, while the HC group showed significantly more often risky decisions, the PD group displayed significantly more often risk averse decisions: In the HC group, 59.4% chose the tournament option whereas only 38.2% should have chosen the tournament option. In the PD group, 40.8% chose the tournament compensation whereas 52% should have chosen the tournament compensation.
Conclusion: This data suggests that patients with PD might be more risk averse within a group (i.e. social) situation as compared to settings without a social component. Such risk-averse behavior might have relevant implications for the social and work life of PD patients. Future research is needed to determine the impact of the social setting on risk-seeking behavior.

Abstract No.:
389

Authors:
Lingor, Paul; Roser, Anna-Elisa; Jain, Gaurav; Maass, Fabian; Caldi Gomes, Lucas; Bähr, Mathias; Fischer, André

Abstract Title:
Massive parallel small RNA sequencing identifies a specific miRNA signature in CSF of PD patients (Massive parallel small RNA sequencing identifiziert eine spezifische miRNA-Signatur im Liquor von Parkinson-Patienten)

Abstract Text:
Introduction: The diagnosis of idiopathic PD is still based on clinical criteria with no biomarker available that allows an accurate diagnosis or the monitoring of disease progression and response to therapeutic approaches. Circulating microRNAs (miRNAs) in cerebrospinal fluid (CSF) are promising biomarker candidates as they are accessible by a minimally-invasive approach and changes in their expression are associated with disease-relevant pathophysiological processes.
Target: We analyzed the CSF-miRNAome of PD patients and age-matched controls (AMC) to identify disease specific miRNA signatures that can be used as a diagnostic biomarker for PD.
Methods: Microvesicles and exosomes were purified from lumbar CSF of 54 AMC and 53 PD patients. Total RNA was isolated from the vesicular fraction by TRIzol extraction and RNA quantity and quality were assessed by Bioanalyzer. miRNA expression was analyzed by massive parallel small RNA sequencing (Illumina HiSeq 4000) and differential expression analysis as well as machine learning algorithms were used to identify a putative PD specific signature.
Results: It was possible to isolate enough RNA with sufficient quality from 4 ml human CSF to prepare small RNA sequencing libraries of good quality. miRNAs were by far the most abundant small non-coding RNA species present in the sequenced samples, accounting for 97.41% in AMC and 95.82% in PD patients. With sufficient read numbers (≥ 5) we detected 205 out of 2654 known human miRNAs in CSF. Differential expression analysis revealed 66 significantly regulated miRNAs in the CSF of PD patients compared to AMC. Interestingly, among the significantly regulated miRNAs with a meaningful log2 fold change (≥ 1 or ≤ -1), the majority is up-regulated in PD patients. Several of the differentially expressed miRNAs have been already reported to be relevant in a neurodegenerative disease or neuronal context, underlining the possibility to gain insight in disease mechanisms by using an accessible bioliquid like CSF.

Furthermore, machine learning algorithms identified a putative PD-specific miRNA signature in the CSF of patients. Relevant miRNAs will be validated by qRT-PCR in a different patient cohort (25 AMC/25 PD) to further exploit their potential as diagnostic markers for PD.
Conclusion: Our findings show that miRNAs can be readily detected and found differentially expressed in CSF and thus represent promising diagnostic biomarkers for PD.

Abstract No.:
390

Authors:
Heinzel, Sebastian; Hobert, Markus A.; Nussbaum, Susanne; Heger, Tanja; Berg, Daniela; Maetzler, Walter

Abstract Title:
Wearable-sensor assessments of progressive gait deficits in early- and mid-stage Parkinson's disease (Sensor-gestützte Messung progressiver Gangdefizite im Verlauf der Parkinson-Erkrankung)

Abstract Text:
Introduction: Changes in gait occur during all stages of Parkinson's disease (PD) and progressively impact mobility in PD patients. Commonly, clinical rating scales, such as the UPDRS-III, are used to assess PD motor symptoms related to gait. The potential of gait parameters measured using wearable-sensor technologies to quantify gait deficits as well as their progression over the disease course has largely not been investigated. Key aspects that may qualify these quantitative gait parameters as progression markers in PD remain elusive, e.g. short interval progression characteristics over longer observation spans, progression depending on PD stage and normal aging, and differences of progressive gait deficits under convenient or challenging walking conditions.
Target: To investigate longitudinal changes in normal- and fast-pace gait parameters from a lower-back wearable-sensor in PD patients in early and mid-stages of the disease (E-PD, M-PD) compared to controls.
Methods: Straight walking (20 m) with normal (convenient) pace and fast pace (individual maximum) was performed every 6 months for up to 5 years in 22 E-PD (< 4 years baseline disease duration), 18 M-PD (> 5 years) and 24 controls. For each visit, normal- and fast-pace gait parameters (step number, step time, step velocity, step variability) were quantified using a wearable-sensor at the lower back (Dynaport Hybrid, McRoberts B.V.) Longitudinal changes in gait parameters, group differences in these changes, and associations of gait parameters MDS-UPDRS-III were tested using generalized estimating equations.
Results: Step number (annual change in E-PD: 2.1%, Group*Time effect: $p = 0.001$) and step time variability (8.5%, Group*Time effect: $p < 0.05$) under normal pace conditions longitudinally increased in E-PD compared to controls (0.7%, − 12%). For fast

pace, no significant group differences in longitudinal changes of gait parameters were observed. Also, longitudinal changes in M-PD did not differ significantly from controls. Fast pace parameters and gait parameters in M-PD showed large inter- and intra-individual variability. MDS-UPDRS-III was largely associated with normal-pace parameters in M-PD.
Conclusion: Wearable-sensors can be used to quantify progressive gait deficits in early-stage PD. In particular, step number and step variability measures constitute robust progression markers of gait deficits in early-stage PD. However, gait parameters during fast pace gait and in mid-stage PD patients exhibit heterogeneous PD progression characteristics and thus possess limited potential as PD progression markers.

Abstract No.:
391

Authors:
Moldovan, Alexia-Sabine; Hartmann, Christian Johannes; Trenado, Carlos; Meumertzheim, Nicola; Slotty, Philipp Jörg; Vesper, Jan; Schnitzler, Alfons; Groiss, Stefan Jun

Abstract Title:
Less is more—Pulse width dependent therapeutic window in deep brain stimulation for essential tremor (Einfluss der Impulsbreite auf das Therapeutische Fenster bei der Therapie des Essentiellen Tremors mit Tiefer Hirnstimulation)

Abstract Text:
Introduction: Deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) is an effective therapy for essential tremor (ET). Shorter pulse widths than conventional pulse width settings may lead to a reduction of side effects such as ataxia and dysarthria and therefore be a valuable therapeutic option for DBS in ET patients.
Target: The aim of this study was to compare the DBS effect of shorter pulse width at 40 μs to conventional pulse width at 60 μs on the therapeutic window in ET patients.
Methods: 9 ET patients treated with VIM/posterior subthalamic area (PSA)-DBS for at least 3 months participated in this prospective, randomized, double-blind study. DBS with a pulse width of 40 μs was compared to 60 μs by using the best therapeutic contact. The therapeutic window was calculated by determining thresholds for efficacy and side effects in both conditions. The Fahn-Tolosa-Marin Tremor Rating Scale (TRS) and Kinesia tremor analysis were used to compare clinical efficacy between 40 and 60 μs DBS just below the side effect thresholds. Volume of neural activation (VNA) was calculated for efficacy and side effect thresholds at both pulse widths. Total electrical enery delievered (TEED) and total charge per pulse (TCPP) were also measured in both conditions.
Results: Stimulation at 40 μs resulted in a significantly larger therapeutic window compared to 60 μs mainly due to higher side effect thresholds. Both conditions significantly improved tremor compared to the DBS-OFF condition, while the efficacy of 40 μs (TRS and Kinesia analysis) was comparable to 60 μs. Comparison of the VNA window did not reveal a significant difference between the two pulse widths. Mean values of TCPP and TEED at the efficacy threshold were significantly lower at 40 μs compared to 60 μs pulse width.
Conclusion: DBS at pulse width of 40 μs is equally effective on tremor as 60 μs, whereas it has a higher threshold for side effects. Reduction of pulse width may therefore be a reasonable programming option for chronic DBS in ET to avoid side effects and still maintain satisfying tremor suppression.

Abstract No.:
392

Authors:
Fliegen, Sabine; Nikolov, Petyo; Hartmann, Christian; Slotty, Philipp; Vesper, Jan; Schnitzler, Alfons; Groiß, Stefan

Abstract Title:
Is directional stimulation of the VIM superior to omnidirectional stimulation in patients with essential tremor? (Ist die direktionale Stimulation des VIM bei Patienten mit ET effektiver als die omnidirektionale Stimulation?)

Abstract Text:
Introduction: Deep brain stimulation of the VIM is a well-established therapy in the management of essential tremor but is frequently associated with side effects like gait ataxia. Directional current steering may be a way to activate fiber tracts more selectively, thereby widening the therapeutic window.
Target: To determine whether directional stimulation of the VIM is superior to the conventional omnidirectional stimulation regarding the therapeutic window.
Methods: For this prospective, randomized, double-blind study 10 patients with ET (5 men, 5 women) treated with chronic deep brain stimulation (DBS) of the ventral intermediate thalamic nucleus (VIM) were recruited. To compare efficacy of current steering in VIM-DBS, therapeutic window was calculated under directional (3 directions) and omnidirectional stimulation by determining effect and adverse effect thresholds. Clinical efficacy was assessed by comparing impact of directional and omnidirectional stimulation settings on tremor rating scales (TRS, TETRAS), ataxia rating scales (mICARS, SARA) and accelerometry (Kinesia©). Total electrical energy delivered (TEED) was measured under both conditions.
Results: Therapeutic window under best directional stimulation tended to be wider than under omnidirectional stimulation. This resulted from a significantly lower effect threshold under best directional stimulation compared to omnidirectional stimulation, while there was no difference in terms of adverse effects. Best and second-best directional stimulation had a significantly wider therapeutic window than the third-best directional stimulation. In terms of clinical efficacy, we did not find significant differences. TEED at the adverse effect threshold was significantly higher under directional than under omnidirectional stimulation.
Conclusion: Directional stimulation is at least equally effective, compared to omnidirectional stimulation. Regarding effect threshold, our data even suggest a superiority of directional stimulation settings. Moreover, superiority of certain directions of stimulation may indicate a directional stimulation to be advantageous in case a DBS lead is not optimally placed. Under directional stimulation higher energy levels are needed to evoke adverse effects than under omnidirectional stimulation.

Abstract No.:
393

Authors:
Lawson Mclean, Aaron; Kalff, Rolf; Walter, Jan

Abstract Title:
Automated dissemination of DBS research findings using a Twitter bot (Automatisierte Verbreitung von DBS-Forschungsergebnissen mithilfe eines Twitter-Bots)

Abstract Text:
Introduction: Social media platforms such as Twitter, which has 335 million monthly active users, have immense potential to directly disseminate research findings to scientists, clinicians and patients interested in the field of deep brain stimulation (DBS), thereby

helping to overcome the challenges of keeping abreast of the scientific literature. Bots are automated agents that exist across online social networks, created for a range of purposes, including marketing, political infiltration and spreading malicious content. However, bots may also be used for more community-minded, positive purposes and this study illustrates the use of a Twitter bot to disseminate DBS research findings to Twitter users interested in this field.
Target: To demonstrate how a Twitter bot may be used for the automated, wide-scale dissemination of DBS research findings across the Twitter social media platform.
Methods: A Twitter bot named NeuroModBot was created using PubMed's Really Simple Syndication (RSS) service and the dlvr.it automated social media manager. This bot contemporaneously posts details of newly indexed DBS articles to account followers, so that they may be presented with DBS research findings with relatively minimal effort and can investigate such research further should they desire.
Results: During the period 01.04.18 to 13.10.18, NeuroModBot posted 142 Tweets on the subject of DBS, each stating the title of a new DBS research article and linking to the respective PubMed record of the article. These 142 Tweets generated a total of 21,660 impression (an instance of a Tweet being seen on a user's monitor), with a mean impression rate of 153 impressions/Tweet (standard deviation 67). Over the most recent 28-day period (to 14.10.18), NeuroModBot posted 24 Tweets, which generated a total of 3083 impressions, an increase of 30.4% in comparison with the previous 28-day period. Over the first 199 days of its existence, NeuroModBot accrued 307 followers (72% male and 28% female). 54% of the audience is US- or UK-based (each 27%) and 11% is based in India. Based on analysis of the publicised biographical details of followers, the most common professional positions of followers were neurosurgery resident, research fellow and assistant professor. The most common disease entities posted about were Parkinson's disease, obsessive compulsive disorder and essential tremor.
Conclusion: NeuroModBot and the Twitter platform may be used to disseminate DBS research outputs in an effortless, automated and targeted fashion to clinicians, academics and other networks interested in the field.

Abstract No.:
394

Authors:
Weber, Franziska; Brunner, Janine; May, Caroline; Marcus, Katrin

Abstract Title:
Evaluation of alpha-synuclein aggregation in a Parkinson mouse model (Evaluation der Alpha-Synuclein-Aggregation im Parkinson-Mausmodel)

Abstract Text:
Introduction: A pathological trait of Parkinson's disease (PD) is the appearance of so-called Lewy-bodies in some of the still intact dopaminergic neurons. Lewy-bodies are eosinophilic cytoplasmic inclusions consisting mostly of alpha-synuclein. Whether the effect of alpha-synuclein aggregation on the tissue is positive or negative is still discussed controversially (McGowan 2006; Schulz-Schaeffer 2010; Kalia and Kalia 2015).

Braak and colleagues postulated that these aggregates appear in the caudal parts of the brainstem first before migrating via the SNpc to the amygdala and the neocortex (Braak, Del Tredici et al. 2002).

Recent publications clearly prove an aggregation of alpha-synuclein in the spinal cord, the peripheral and enteric nervous system during early stages of the disease (Del Tredici and Braak 2012; Klingelhoefer and Reichmann 2015). Non-motorial clinical symptoms of PD such as constipation or urinary retention or a change in the sensation of pain support these results (Braak, Sastre et al. 2007; VanderHorst, Samardzic et al. 2015).

Target: The aim of this study is to evaluate the transmission of alpha-synuclein from the enteric nervous system via the spinal cord towards the brain. We hope to gain further knowledge of the pathology of PD. Additionally new approaches for an early diagnosis might open up.
Methods: For this, we use an established PD Rotenon-mouse model. Rotenon is an insecticide that causes pathological changes similar to those found in PD. We are going to establish a fluorescent staining for alpha-synuclein in the spinal cord. Then we will compare the alpha-synuclein aggregation in the spinal cord and the intestine.
Results: Due to anatomical connections (Bender, R*emi et al. 2015), we expect to find correlations in alpha-synuclein aggregation between the thoracic and lumbar spinal cord and the small intestine and proximal parts of the colon. The remaining parts of the big intestine are expected to show a correlation to sacral neurons.
Conclusion: Alpha-synuclein aggregates possibly start to develop in the enteric nervous system and migrate via the spinal cord into the brain.

Abstract No.:
395

Authors:
Lindlar, Sebastian; Hartmann, Christian; Dinkelbach, Lars; Jockwitz, Christiane; Ferrea, Stefano; Moldovan, Alexia; Südmeyer, Martin; Caspers, Svenja; Schnitzler, Alfons

Abstract Title:
Correlation of non-motor symptoms in Parkinson's disease with volume changes in cortical and subcortical brain areas: a longitudinal morphometry study (Korrelation nicht-motorischer Symptome bei M. Parkinson mit Volumenveränderungen…)

Abstract Text:
Introduction: Quality of life in patients with Parkinson's disease (PD) is significantly decreased by non-motor symptoms (NMS). Morphometric cross-sectional studies suggest an association between NMS and volumes of responsible brain structures. In particular, an association between thalamic volume and fatigue was shown.
Target: To evaluate an association between change of thalamic volume and changes in cortical brain areas with the extent of NMS, especially fatigue, over time.
Methods: 21 patients with PD (5 women, mean age 56 ± 11.66 years, mean disease duration 37 ± 20 months) were annually examined for 2 years (three visits). At each visit, the Fatigue Scale for Motor and Cognitive Functions (FSMC), PD-Nonmotor Scale (PD-NMS), PD-Questionnaire 39 (PDQ-39), the motor scale of the Unified PD Rating Scale (UPDRS III) and structural MRI were obtained. Longitudinal morphometric analyses of the thalamus und pre-defined cortical regions were performed using Freesurfer. SPSS and the application Qdec from Freesurfer were used to detect and evaluate longitudinal correlations of thalamic and cortical structural alterations with changes in FSMC- and PD-NMS-Scores.
Results: There was no significant longitudinal correlation between changes in thalamic volume and changes in NMS or fatigue. However, exploratory longitudinal analysis showed that alterations in several cortical brain areas correlated significantly ($p < 0.05$) both with NMS and fatigue. Both the NMS in general and the extent of fatigue correlated with the changes of cortical thickness of the superior frontal gyrus, the lateral orbitofrontal gyrus and the temporal pole on the left hemisphere and the parahippocampal gyrus on the right hemisphere. The degree of Fatigue additionally correlated with the changes of cortical thickness of the left transverse temporal gyrus.
Conclusion: As the extent of NMS and fatigue correlates with regional brain changes over time, it suggests that quantification of distinct morphometric changes may help predicting the development of NMS in PD patients.

Abstract No.:
396

Authors:
Pritzkow, Sandra; Shahnawaz, Mohammad; Mueller, Joerg; Soto, Claudio

Abstract Title:
A highly sensitive and specific biochemical diagnostic test of Parkinson's disease based on detection of alpha-synuclein oligomers in cerebrospinal fluid

Abstract Text:
Introduction: Parkinson's disease (PD) is the second-most common neurodegenerative disorder, which has no cure or disease modifying therapy. One of the greatest obstacles for therapeutic development for PD is the lack of early diagnosis. To date, there is no definite, sensitive and predictive laboratory test available that can identify individuals well before they show clinical manifestations. The central event in PD is the misfolding, aggregation and accumulation of alpha-synuclein (αSyn). Compelling evidence suggests that misfolding and oligomerization of αSyn begins years or decades before the appearance of clinical symptoms. Most importantly, these oligomers have been found circulating in biological fluids, such as cerebrospinal fluid (CSF) and blood. Thus, detection of these circulating oligomers in biological fluids holds promise for early and specific diagnosis.
Target: To develop a highly sensitive and specific biochemical diagnostic test of Parkinson's disease based on detection of α-synuclein oligomers in cerebrospinal fluid.
Methods: We have developed a sensitive method to detect tiny amounts of αSyn oligomers present in CSF adapting our protein misfolding cyclic amplification (PMCA) technology. PMCA has been widely used for the detection of misfolded prion protein (PrPSc) implicated in prion diseases that share similar molecular mechanisms of protein misfolding with PD. PMCA exploits the functional properties of these oligomers to seed soluble monomers used as substrates thus facilitating their detection.
Results: Using CSF, PMCA amplification of αSyn oligomers allowed us to distinguish PD patients with 88.5% sensitivity and 96.9% specificity from control individuals. Importantly, PMCA results for different PD patients correlated with the clinical severity. Recently, we validated our αSyn-PMCA assay using a large number of well characterized CSF samples from the Michael J. Fox's BioFIND collection (109 PD patients and 82 healthy controls). The results of this blind study showed 95.41% sensitivity and 90.24% specificity. In ongoing experiments we have been optimizing the αSyn-PMCA assay for detection of α-Syn oligomers in blood plasma, with promising results from small cohort. We have also shown that the assay permits to discriminate between PD and multiple system atrophy (MSA), a clinically similar synucleinopathy, by analysis of the biochemical and structural characteristics of the product of the αSyn-PMCA assay.
Conclusion: These findings laid the foundation towards the development of a highly sensitive and specific biochemical test for the diagnosis of PD, which could be useful to monitor disease progression and to help drug development.

Abstract No.:
397

Authors:
Köglsperger, Thomas; Kurz, Anna; Schirra, Joerg; Hoeglinger, Guenter; Boetzel, Kai

Abstract Title:
MiRNA sequencing in routine colonic biopsies from PD patients: the ENTERIC-PD study protocol

Abstract Text:
Introduction: Parkinson's disease (PD) is the most common neurodegenerative movement disorder characterized by a selective loss of dopaminergic neurons in the substantia nigra (SN) and the gradual appearance of neuronal protein aggregates termed Lewy bodies (LBs). More recent research suggested the additional affection of the enteric nervous system (ENS) since biopsy and autopsy studies consistently demonstrated LBs in the submucous (SMP) and myenteric (MP) plexus of the ENS of the majority of PD patients. In accord to these pathological findings, gastrointestinal (GI) symptoms such as e.g. constipation are common in PD, complicate the pharmacological treatment of PD and sometimes even appear years prior to the motor signs of the disease. These results prompted the hypothesis that PD is caused by an environmental pathogen that breaches the mucosal barrier of the GI tract to initiate a pathological process in enteric neurons and that this process progresses towards the CNS via the autonomic nerves of the gut. Characterizing disease-specific molecular alterations in the gut of PD patients will thus support the understanding of GI symptoms in PD and contribute to establish the gut as a potential initiation site of PD pathology.
Target: MicroRNAs (miRNAs) are a class of small, endogenous RNAs of 21–25 nucleotides (nts) in length. They play an important regulatory role in animals and plants by targeting specific mRNAs for degradation or translation repression. The role of miRNA-regulated gene expression in PD is currently unknown.
Methods: In the present work, we conducted a prospective diagnostic study termed ENTERIC-PD to examine the expression of miRNAs in routine colonic biopsies from PD patients (n = 13) and control subjects (n = 16) by miRNA sequencing. All study participants were evaluated prior to colonoscopy for disease severity (UPDRS) and associated non-motor symptoms were quantified (REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ); Sniffin Sticks®; Montreal Cognitive Assessment (MOCA). GI symptoms were assessed separately by the Rome-III Questionnaire.
Results: Subsequent to testing, all participants underwent a routine colonoscopy and biopsies were obtained from the ascending colon using standard techniques. Total RNA was extracted and subjected to miRNA sequencing.
Conclusion: In the present poster, we summarize the ENTERIC-PD study protocol, characterize the study cohort and present first results from the sequencing and bioinformatic analysis that is currently in progress.

Abstract No.:
398

Authors:
Pauly, Martje; Ripke, Annekatrin; Bäumer, Tobias; Münchau, Alexander

Abstract Title:
Translate-NAMSE and DASNE—novel expertise based networks for patients with rare neurological diseases (Translate-NAMSE und die DASNE—neue expertenbasierte Netzwerke für Patienten mit seltenen neurologischen Erkrankungen)

Abstract Text:
Introduction: In Germany, approximately 4 million people suffer from a rare disease (RD). In these patients, a correct diagnosis is often delayed considerably. Centers of rare diseases (CRD) and several multi-site and interdisciplinary health care projects including, for instance, Translate-NAMSE aim at facilitating diagnostic processes and improving the care of patients with RDs. Core features of Translate-NAMSE are multi-disciplinary case discussions and case conferences (MCDs) on the basis of medical data provided by patients and treating physicians, and the establishment of expertise based rational decision processes for innovative diagnostics such as whole exome sequencing.
Target: To delineate how newly implemented CRD structures and processes related to the project Translate-NAMSE contribute to the diagnostic process in the CRD at the University of Lübeck.
Methods: All enquires to the CRD Lübeck in 2018 were analyzed with respect to the number of MCDs, participants of the MCDs, whether patients were also assessed personally in a specialty clinic of the CRD Lübeck, as well as whether innovative diagnostics was implemented.
Results: All enquires were handled by a physician, and presented and discussed in an MCD leading to the following scenarios: (1) If it was either most reasonable for a previously involved clinic to complete diagnostics and/or to reevaluate the case or if another clinic appeared better qualified for a suspected diagnosis or a given field of expertise, the patient was referred to this clinic. (2) If a diagnosis was previously made and available documents left no doubt as to the validity of such a diagnosis the patient was informed accordingly in a written letter. (3) If the patient was suspected to suffer from a movement disorder, the patient was invited to one of our specialty clinics and personally assessed by movement disorder specialists. If no clear diagnosis could be made one (or several) of the following steps were taken: Reevaluation in another MCD on site; case discussion with national and international experts, and/or presentation to a broader group of experts during the annual meeting of the German Academy for Rare Neurological Disorders (DASNE); initiation of further diagnostics.
Conclusion: The field of neurology is in the process of further subspecialization. Also, new diagnostic methods have become available and novel diseases are being continuously identified. In light of this development, it is crucial to establish and maintain novel networks based on expertise. Projects such as Translate-NAMSE and the DASNE can contribute substantially in improving the care of patients with RDs.

Abstract No.:
399

Authors:
Prasuhn, Jannik; Strautz, Robert; Lemmer, Felicitas; Dreischmeier, Shalida; Berg, Daniela; Klein, Christine; Kasten, Meike; Heldmann, Marcus; Brüggemann, Norbert

Abstract Title:
Imaging of iron and transcranial sonography in Parkinson's disease: complementary imaging modalities to map nigral neurodegeneration?

Abstract Text:
Introduction: Transcranial sonography (TCS) is a non-invasive method to support the diagnosis of Parkinson's disease (PD). So far, it is widely unknown which microstructural alterations are the underlying cause for the observed hyperechogenicity (HE) in PD. Substantia nigra-specific MR sequences might facilitate the further understanding of underlying disease mechanisms and additionally yield the potential of discovering novel neuroimaging biomarkers for PD.
Target: To investigate the potential use of susceptibility-weighted imaging (SWI) (i) to discriminate PD patients from healthy controls and (ii) to find associations to the HE in TCS.
Methods: Thirty-six PD patients (mean age: 68 $\pm$ 7.6 years) and 37 age- and gender-matched healthy controls (mean age: 70.0 $\pm$ 6.5 years) were investigated using a 3T MRI scanner (Siemens Skyra, 64 channel head coil) and an ultrasound device (Esaote MyLab Alpha). MR images were acquired with a magnetization transfer prepared dual echo gradient echo sequence. SN segmentation was performed using a thresholding method (mean intensity of non-SN midbrain tissue $\pm$ 3 SD, $\pm$ 4 SD, and $\pm$ 5 SD). The largest segmentable SN area (per slice) was analyzed for each hemisphere separately. Additionally, the HE was determined using unblinded planimetric measurement of the SN during TCS.
Results: ANCOVAs (as implemented in SPSS 25), taking age and gender as covariates into consideration, were employed for further analysis. Only the liberal threshold of $\pm$ 3 SD resulted in a significant group difference [$F(3,1) = 2.892$; $p = 0.042$] for the largest segmentable SN area. However, the thresholds of $\pm$ 4 SD [$F(3,1) = 2.465$; $p = 0.070$] and $\pm$ 5 SD [$F(3,1) = 2.642$; $p = 0.056$] were also showing trends towards significance. The HE significantly differed between PD patients and healthy controls [$F(3,1) = 6.199$; $p = 0.001$]. None of the ipsilateral SWI measures correlated significantly with the corresponding HE.
Conclusion: SWI is a promising new tool to segment the SN in PD patients and healthy controls. It can therefore be of future use in improving the understanding of the pathophysiology of PD and for the development of new neuroimaging markers to improve diagnostic accuracy or to map disease progression. However, different methodological limitations (e.g. defining suitable thresholds) should be taken into consideration before applying this method. The lack of statistically significant correlations between the HE and the SWI findings might be caused by complementary aspects of nigral neurodegeneration. Potentially, the combination of different MRI modalities (e.g. with free-water corrected diffusion metrics) might be a more fruitful approach for upcoming studies.

Abstract No.:
400

Authors:
Henn, Philipp; Böhler, Christoph; Weise, Christopher; Baum, Petra; Weise, David

Abstract Title:
Long term treatment with botulinum neurotoxin for focal dystonia—effect of dose and dilution (Langzeittherapie mit Botulinumneurotoxin bei fokalen Dystonien—Einfluss von Dosis und Verdünnung)

Abstract Text:
Introduction: Botulinum neurotoxin (BoNT) is used for the symptomatic treatment of neurological diseases including focal dystonia. It is known that dilution and volume of BoNT preparations have an effect of potency and adverse drug reactions (Ramirez-Castaneda et al. 2013). Compared to the majority of BoNT centres, the outpatient department at the clinic of neurology at Leipzig University Hospital uses a higher dilutation rate for all common BoNT preparations (Abobotulinumtoxin 500 mouse units (MU)/10 ml, Ona-/Incobotulinumtoxin 100 MU/5 ml, most centers: 500 MU/1–5 ml and 100 MU/1–2.5 ml, respectively). Especially when injected into facial muscles, higher injection volumes may lead to more diffusion and hence more adverse reactions of treatment.
Target: The aim of this study was to evaluate efficacy and safety of high BoNT dilutions in patients with focal dystonia treated at our specialized outpatient clinic.
Methods: We retrospectively extracted data from reports of patients with cervical dystonia (CD) and blepharospasm/Meige syndrome (B/M) over a 10-year treatment period (08/2008–07/2018). Analyses included dose, treatment period, subjective patients' satisfaction and adverse events. Patients' satisfaction was measured with a three-step score (no effect/light or moderate effect/satisfying effect). Dose of Abobotulinumtoxin was normalised by using a conversion ratio of 2.5 to Ona-/Incobotulinumtoxin doses.
Results: We included a total of 240 patients (161 with CD and 73 with B/M) with a total of 5001 treatment sessions.

Mean normalised BoNT dose was 159.2 ± 85.0 MU in patients with CD and 40.2 ± 26.8 MU in patients with B/M ($p < 0.001$). Treatment periods were 13.2 ± 4.3 weeks in CD vs. 12.9 ± 4.4 weeks in B/M ($p = 0.66$). Patient's satisfaction did not differ between groups, too (2.6 ± 0.6 in CD vs. 2.5 ± 0.6 in B/M; $p = 0.09$). Appearance of adverse events were similar between both groups (rate of complications 8.5% in CD vs. 9.5% in B/M; $p = 0.66$).
Conclusion: In conclusion, we could show that the high BoNT dilution rates used in our centre are efficient and safe. However, compared to other BoNT utilising centres (e.g. Kollewe et al. 2014; Hsiung et al. 2002) we used lower BoNT doses, especially in CD. Lower single doses may decrease the risk of developing BoNT antibodies and/or give the opportunity of lower treatment intervals. Further studies in a prospective design will be needed to compare different dilution rates in focal dystonia.

Abstract No.:
401

Authors:
Weber, Juliane; Frings, Lars; Rijntjes, Michel; Urbach, Horst; Fischer, Judith; Weiller, Cornelius; Meyer, Philipp Tobias; Klebe, Stephan

Abstract Title:
Chorea-acanthocytosis presenting as epilepsy-sensitive molecular imaging and a novel VPS13A mutation (Chorea-Akanthozytose mit dem Phänotyp einer Epilepsie-sensitive molekulare Bildgebung und eine neue VPS13A Mutation)

Abstract Text:
Introduction: Chorea-acanthocytosis (ChAc) is a rare adult-onset neurodegenerative disease that belongs to the neuroacanthocytosis syndromes. The disease course is typically characterized by a progressive movement disorder, cognitive and psychiatric changes accompanied by acanthocytes in the blood. ChAc is caused by mutations of the VPS13A gene with an autosomal recessive transmission. It is still a challenge in diagnostics and therapy.
Target: We report a consanguineous Turkish family with an extraordinary clinical phenotype of ChAc presenting as autosomal recessive epilepsy. The diagnostic course of the male index patient who suffered from bilateral temporal lobe epilepsy provides new insight in diagnostic tools to establish a correct diagnosis in this rare disease.
Methods: Molecular imaging gave the first and crucial hints towards a neurodegenerative disease. These findings lead to an extensive neurological examination, the family was then referred for a genetic testing.
Results: A key finding in the index patient was a prominent decline in striatal glucose metabolism on [18F]FDG-PET at 31 years of age, without a significant clinical correlate at that time. [123I]FP-CIT-SPECT revealed a moderate loss of striatal dopamine transporter availability. The brain MRI now showed bilateral atrophy of the nucleus caudatus. Exome sequencing detected a homozygous novel truncating mutation c.4326 T>A (p.Tyr1442*) in VPS13A in all three affected siblings.
Conclusion: With the present case we demonstrate that ChAc can clinically manifest with temporal lobe epilepsy lacking any significant motor symptoms due to a new corresponding mutation in the VPS13A gene. [18F]FDG-PET and [123I]FP-CIT-SPECT are sensitive in detecting striatal involvement. We therefore encourage structural and molecular imaging as a sensitive diagnostic tool in this orphan disease. Exome sequencing is important to establish a correct diagnosis in familial cases of neurological disorders with various symptoms.

Abstract No.:
402

Authors:
Musacchio, Thomas; Eva, Grauer; Pluta, Natalie; Müller, Petra; Zeller, Daniel; Ip, Chi Wang; Volkmann, Jens; Kunstmann, Erdmute

Abstract Title:
A novel homozygous splice site mutation in the KIF1C gene causing SPAX2/SPG58 found in a consanguineous family (Eine neue homozygote Spleißmuation in einer konsanguinen Familie ursächlich für SPAX2/SPG58)

Abstract Text:
Introduction: Mutations in the KIF1C gene cause autosomal recessive spastic ataxia type 2 (SPAX2) also termed hereditary spastic paraplegia type 58 (SPG58). Both are very rare diseases with until now only five published affected families caused by four known different mutations. Severe cerebellar ataxia with dysarthria and

pyramidal tract dysfunction are the main symptoms. Additional peripheral neuropathy was suggested in one family but electrophysiological data are not available.
Target: We present clinical, electrophysiological and genomic data of a consanguineous family with two affected siblings suffering from spasticity and severe ataxia.
Methods: We performed extensive clinical and electrophysiological investigations in one affected sibling. Genomic DNA of the index patient was used for analysis of spastic ataxia associated genes by exome enrichment using the Nextera Rapide Capture Exome Kit followed by next generation sequencing (NGS) on a NextSeq desktop sequencer (Illumina). Data analysis was done by the software GensearchNGS (PhenoSystems), pathogenicity and splice predictions were carried out using the algorithms embedded in Alamut (Interactive Biosoftware).
Results: The parents of the female proposita are consanguineous and originate from Turkey. Their daughter reported first symptoms of progressive gait disturbance and coordination problems at the age of 8 years. Physical examination at age 21 exhibited cerebellar dysarthria, complex oculomotor dysfunction, spasticity and proximal paresis of the lower limbs as well as severe cerebellar ataxia resulting in wheelchair-dependency. The family reported that the 5 years older brother suffers from similar symptoms. Electrophysiological investigations of the index patient showed severe sensorimotor neuropathy and highly pathologic evoked potentials. NGS analysis revealed a homozygous new sequence variant c.864 + 1G>A at the donor splice site of exon 10 in the KIF1C gene. This variant was consistently predicted by multiple algorithms to disrupt the splice site resulting in skipping of exon 10 and (probable) subsequent protein dysfunction. Autosomal recessive inheritance was proven by segregation analysis.
Conclusion: We present a new splice site mutation in KIF1C causing a disease phenotype consistent with spastic ataxia type 2 and we extend the clinical spectrum to additional sensorimotor neuropathy.

Abstract No.:
403

Authors:
Musacchio, Thomas; Krause, Katharina; Boelmans, Kai; Maltese, Virginia; Zeller, Daniel; Isaias, Ioannis; Volkmann, Jens; Klebe, Stephan

Abstract Title:
Biological course and natural history of hereditary spastic paraplegia type 11 (Biologischer Verlauf der Hereditären Spastischen Spinalparalyse Typ 11)

Abstract Text:
Introduction: SPG11 is a complicated form of HSP with autosomal-recessive transmission caused by loss of function mutations in the SPG11 gene encoding spatacsin. Additional features apart from spasticity and weakness of the lower limbs are severe mental impairment, thinning of the corpus callosum, and peripheral neuropathy. Until now there are only few biomarkers of the natural course of the disease and little is known about disease progression.
Target: We aim to establish biological markers for the natural history and course of hereditary spastic paraplegia (HSP) type 11 (SPG11) using multiple readout parameters as a basis for upcoming therapeutic trials.
Methods: All patients underwent standardized clinical examination cross-sectionally and longitudinally for a period of 2 years. For neuropsychologic testing items of seven standardized tests were used. We additionally performed extensive electrophysiological measurements as well as video-supported posturography. Furthermore all subjects underwent optical coherence tomography (OCT) as potential biomarker of disease progression.
Results: 13 patients (6 females, 7 males) of 12 families all with compound heterozygous mutations were included in the study. Average age at onset was 15 ± 7 years, identified anamnestically by the relatives as gait abnormalities and spasticity. Average disease duration at baseline was about 17 ± 9 years. On the Spastic Paraplegia Rating Scale, which ranges from 0 to 52 points, patients scored 30.8 ± 7.8 at baseline and 34.1 ± 6.3 after 12 months, reflecting disease progression. Electrophysiologically patients showed severe axonal neuropathy and increased central motor conduction time. Posturography revealed a statistically significant difference in the number of extreme antero-posterior excursions of the Centre of Pressure. Cognitive testing showed a significant reduction of mental flexibility over time as measured by the ratio of the two Trail Making Test subitems. OCT revealed atrophy of retinal and optical nerve structures in most patients.
Conclusion: Our results provide multidimensional biomarkers for the biological course of SPG11 which can be used as reference in further therapeutic trials and close a gap in our knowledge of this disease.

Abstract No.:
404

Author:
Lee, Bolam

Abstract Title:
JN403 reduces alpha-synuclein induced inflammatory parameters in in vitro microglia, but fails to attenuate the reduction of TH immunoreactive nigral neurons in a focal alpha-synuclein overexpression mouse model of Parkinson's disease

Abstract Text:
Introduction: α7-nAChR agonists modulate the cholinergic anti-inflammatory pathway to attenuate proinflammatory signals and reduce dopaminergic neuronal cell loss in toxin-induced experimental murine models of PD, as well as in respective parkinsonian non-human primate models. However, no research has been performed to evaluate the effect of α7-nAChR agonists in αSyn mediated models.
Target: To investigate whether JN403, a novel selective agonist of α-7-nicotine-acetylcholine-receptors (α7-nAChRs) can suppress inflammation and toxicity in human alpha-synuclein (αSyn) induced in vitro and in vivo Parkinson's disease (PD) models.
Methods: We tested the effect of JN403 in primary mouse microglia cells exposed to human αSyn fragment 61–140, followed by inflammatory parameters measurement. In addition, we performed unilateral stereotactic operation targeting the substantia nigra pars compacta (SNc), to deliver a recombinant adeno-associated viral vector (rAAV) containing wild-type-human αSyn (WT-αSyn) or luciferase (luc). JN403 30 mg/kg or vehicle was administered daily for 10 weeks beginning on postoperative day 8. Further stereology and histology were performed accordingly. The viral-mediated vectors were provided by the Michael J. Fox Foundation.
Results: Human αSyn fragment 61–140 treatment increased the release of Nitric Oxide (NO), TNF-α and IL-6, and decreased cell viability. In contrast, 100 nM of JN403 pre- and co-incubation significantly reduced the level of NO and TNF-α release in the microglial cells. However, cell viability and IL-6 cytokine release were not changed. The rAAV-mediated WT-αSyn overexpression reduced 20% of the number of tyrosine hydroxylase (TH) immunoreactive (ir) nigral neurons after 10 weeks. Subcutaneous daily treatment JN403 over 10 weeks did not revert to the number of TH ir nigral neurons (nor Iba1 ir density) in WT-αSyn or luc overexpression mouse model. The reduced density of TH-ir striatal terminals in the WT-αSyn groups was also not recovered from the JN403 treatment.
Conclusion: In summary, JN403, an α7-nAChR specific agonist showed a beneficial effect on ameliorating proinflammatory signals in

αSyn exposed microglia cells, however, no significant treatment effect was found in intranigral WT-αSyn overexpression in vivo mouse model. Therapeutic responses vary per experimental models employed, and long-lasting nAChRalpha7 activation may be required for clinical efficacy in future translational in vivo research of PD.

Abstract No.:
405

Authors:
Pistorius, Regina; Paschen, Steffen; Roothans, Jonas; Pozzi, Nicolo; Großmann, Anne; Lange, Florian; Deuschl, Günther; Volkmann, Jens; Reich, Martin

Abstract Title:
Gait disturbances after thalamic deep brain stimulation in essential tremor: a predictable risk? (Gangstörungen bei Patienten mit Essentiellem Tremor nach Tiefer Hirnstimulation: Analyse möglicher Risikofaktoren)

Abstract Text:
Introduction: Thalamic deep brain stimulation (DBS) is an established therapy for patients with essential tremor (ET). Average improvement of tremor amounts to 60–80%, but outcomes are often variable. Studies report DBS-induced side-effects in up to 25% of patients. A highly relevant side-effect in thalamic neuromodulation is the evolution of gait disturbances which deteriorate daily activities. So far, the exact proportion of this delayed DBS failure has been unknown, and no study has analysed risk factors.
Target: We investigated the long-term effect of bilateral thalamic DBS on the gait performances of ET patients. Along with the tremor improvement, we focused on demographic parameters to disentangle potential risk factors for this side-effect. We are also interested in differences in anatomic location of the volumes of individual stimulation therapy.
Methods: We collected ET subjects from 2 German DBS centres (implanted within 2003–2015 in Kiel and within 2009–2017 in Würzburg) with stable and effective bilateral thalamic stimulation. Based on video analysis of every subject, the Scale-for-the-Assessment-and-Rating-of-Ataxia (SARA) items 1–3 and the Tremor-Rating-Scale (TRS) were performed. Subjects were stratified in two groups for the presence of gait changes in long-term follow-up (SARA1–3 $\geq$ 4). For the correlation between the presence of gait disturbances and the anatomical location of stimulation, we simulated the volume of tissue activated (VTA) in subjects' related MRI space based on their stimulation parameters. After transformation to common (MNI-) space only voxels overlapped by $\geq$ 6 VTAs were visualized to define a volume, where stimulation may provoke gait problems.
Results: 76 ET subjects were collected: 31 subjects (13 males) in ET gait disturbances, 45 subjects (27 males) in ET control. A subset of 8 subjects showed gait difficulties (SARA1–3 $\geq$ 7), which require external support (e.g. cane, wheelchair). Compared to ET control, the subjects with gait disturbances (2.6 years after chronic DBS) were older at the disease onset [41 $\pm$ 18 years vs. 27 $\pm$ 18 years ($p < 0.001$)], and at the surgery [70 $\pm$ 6 years vs. 62 $\pm$ 12 years ($p = 0.002$)] and had more gait difficulties preOP [SARA1–3 preOP: 1.9 $\pm$ 1.6 vs. 0.7 $\pm$ 1.0 ($p < 0.001$)]. The relative worsening of gait was greater in this group [$-$ 140.5 ($\pm$ 177.0) % vs. $-$ 35.0 ($\pm$ 87.1) % ($p < 0.001$)] and the amount of tremor control smaller [24.1 ($\pm$ 42.3) % vs. 60.9 ($\pm$ 20.1) % ($p < 0.001$)]. Furthermore, the anatomic areas of stimulation allow a clear separation of the groups. For individuals with gait changes, the spot most commonly stimulated was located more posterior and inferior compared to non-effected subjects [ET gait disturbances: lateral = 11.90, posterior = 3.42, inferior = 3.4 vs. ET control: l = 11.62, p = 2.60, i = 2.89(based on AC-PC in mm)].
Conclusion: Changes in gait pattern were detected in 31 subjects (40.8%) of the cohort. Those changes do not necessarily affect patients' daily routine, but 10.5% of patients show a relevant gait ataxia and require support for walking. Potential risk factors are gait difficulties before the surgery, a higher age at disease onset or at surgery combined with anatomical suboptimal placed stimulation therapy. Further investigations are needed to define strategies to prevent and overcome this adverse effect in thalamic DBS.

Abstract No.:
406

Authors:
Barkovits, Katalin; Katrin, Marcus; Kathy, Pfeiffer; Mollenhauer, Britt; Tönges, Lars; Kruse, Niels

Abstract Title:
Detection of artificial blood contamination in CSF and its impact on the quantitative analysis of alpha-synuclein (Nachweis artifizieller Blutkontamination im Liquor und deren Auswirkungen auf die quantitative Analyse von alpha-Synuclein)

Abstract Text:
Introduction: Analysis of cerebrospinal fluid is important for diagnosis of neurological diseases. Here specific proteins, which are released from the CNS are monitored quantitatively. Especially, in the field of neurodegenerative diseases abnormal protein abundance is a potential marker. However, the quality of the CSF sample is a key factor for the outcome and e.g. blood contamination can have tremendous impact on the analysis.
Target: In this study we compared Combur test strips, hemoglobin ELISA and bottom up mass spectrometry (MS) based proteomics for the determination of blood contamination in CSF samples. Futhermore, we evaluated the impact of blood contamination for the quantification of alpha-Synuclein.
Methods: For the identification of CSF blood contaminations, three different methods were used including hemoglobin ELISA, Combur10-Test Strip, and mass spectrometry (MS)-based analysis. Furthermore, we examined the contamination impact on the quantitative analysis of alpha synuclein (aSyn) using ELISA and quantitative label free MS.
Results: Comparable results were achieved with all three approaches enabling detection of artificial blood contamination in CSF of 0.001%. With Combur test strips and MS artificial contaminated as well as native CSF samples were categorized to the same contamination grade out of 5 grades (including no blood, very little blood, little blood, much blood and very much blood). Furthermore, quantitative label free MS revealed an incipient impact on the CSF proteome with blood contamination of 0.1% suppressing the abundance of CSF proteins. In contrast to this, the concentration of aSyn increased with enhanced blood contamination taking up the problematic of authentic quantification of this protein in CSF.
Conclusion: Our results show a useful utilisation of Combur test strips for a fast and cost effective detection of blood contamination.

Abstract No.:
407

Authors:
Löhle, Matthias; Mangone, Graziella; Hermann, Wiebke; Hausbrand, Denise; Wolz, Martin; Mende, Julia; Reichmann, Heinz; Hermann, Andreas; Corvol, Jean-Christophe; Storch, Alexander

Abstract Title:
Predictive value of a functional polymorphism in intron 13 of the MAO-B gene for dyskinesias in Parkinson's disease (Prädiktiver Wert des funktionellen Polymorphismus in Intron 13 des MAO-B-Gens für Dyskinesien beim Mb. Parkinson)

Abstract Text:
Introduction: Parkinson's disease (PD) is associated with motor complications, such as wearing-off and levodopa-induced dyskinesia (LID), in about 50% of patients after 5 years of treatment, which can significantly impair quality of life in affected patients. It has been hypothesized that functional gene polymorphisms encoding enzyme activity in the catabolic enzymes dopa-carboxylase (DDC), monoamine oxidase B (MAOB) and catechol-O-methyltransferase (COMT) and dopamine transporter (DAT) activity might modulate the individual risk for levodopa-induced motor complications.
Target: To investigate the predictive value of common functional gene polymorphisms in dopamine metabolism for the onset of motor complications in PD.
Methods: We performed an observer-blinded follow-up study of 28 PD patients who underwent genotyping of DDC (rs921451), MAOB (rs1799836), COMT (rs4680) and DAT (VNTR) polymorphisms and were meticulously followed up from 2005 through 2018. Onset of wearing-off and LID was determined by blinded clinical assessments. Predictive values of genotypes for motor complications were evaluated using Cox proportional hazard models.
Results: During a median follow-up time of 11 years, 23 (77%) patients developed wearing-off, 16 (53%) dyskinesias, and 23 (77 %) any motor complication. Univariate and multivariate Cox regression analysis adjusting for relevant covariates revealed that the MAOB (rs1799836) polymorphism predicted development of LID with the $MAOB^{CC/(C)/CT}$ genotype (resulting in low/intermediate brain enzyme activity) being associated with smaller risk for LID development than the $MAOB^{TT/(T)}$ genotype. In contrast, functional polymorphisms in DDC (rs921451), COMT (rs4680) and DAT (VNTR) polymorphisms were not predictive of motor complications.
Conclusion: The MAOB intron 13 (rs1799836) polymorphism predicts LID in PD potentially by modifying compensatory changes in dopamine metabolism. Genotyping of this polymorphism might therefore be helpful to stratify patients with respect to their individual risk for LID and could comprise a first step toward patient-tailored therapeutic strategies to prevent or delay motor complications in the course of PD.

Abstract No.:
408

Authors:
Schmitz-Hübsch, Tanja; Chorschew, Anna; Schlapakow, Elena; Rönnefarth, Maria; Grosch, Anne-Sophie; Timmann, Dagmar; Synofzik, Matthis; Schöls, Ludger; Amunts, Katrin; Doss, Sarah; Minnerop, Martina

Abstract Title:
Use and utility of patient-reported outcomes in ataxia (Nutzen von Patientenfragbögen bei Ataxie-Erkrankungen)

Abstract Text:
Introduction: Patient-reported outcomes (PROM) are conceived as measures to assess the impact of disease and symptom severity on patients' lives as an important adjunct to clinical assessment. They also open the perspective to collect data on disease progression on a larger scale, e.g. through web-based registries.
Target: There are only few reports on the use and utility of PROM in ataxia disorders. The presentation aims to categorize the currently used PROM according to their construct, sum-up available evidence on their use in ataxia disorders and open discussion on best practice for selection of PROM in ataxia.
Methods: We performed a systematic literature search on PROM in ataxia, including search on specific generic instruments (SF-36, EQ-5D, WHO-5, FES-I, walk-12, Barthel, ABC) AND ataxia as search terms. We further analysed PROM data from an own cross-sectional observation in 26 subjects with genetically defined pure cerebellar ataxia.
Results: PROM on quality of life (SF-36, EQ-5D) in ataxia showed only moderate correlation with symptom severity or symptom progression. In contrast, PROM that address self-report of ADL (Barthel, UHDRS-IV) and balance functions (ABC) reached strong correlations with clinical measures of ataxia severity in several studies in different ataxia disorders as well as self-report on walking function (walk-12) that was used only in our study. In our ataxia cohort, ABC (rho 0.758) and walk-12 (rho − 0.893) were tightly correlated to ataxia severity as measured by SARA (scale for the assessment and rating of ataxia) (both $p < 0.001$). Both seemed sensitive even in cases of incipient manifestation, while ADL scales had a ceiling effect in less impaired subjects. Interestingly, our search did not yield any publication on the use of NeuroQOL or PROMIS in ataxia. Only very few studies report changes in PROM over time along with progression in clinical ratings.
Conclusion: Strong correlations of PROM that assess patients' perspective on ADL or specific motor functions suggest that they might be applied in studies as valid estimates of disease severity in ataxia. Effects of non-ataxia symptoms, e.g. cognitive/psychiatric comorbidity, on these relations needs further exploration as well as the ability of PROM to validly capture symptom changes.

Abstract No.:
409

Authors:
Dinkelbach, Lars; Hartmann, Christian; Roeber, Sigrun; Arzberger, Thomas; Felsberg, Jörg; Ferrea, Stefano; Moldovan, Alexia; Südmeyer, Martin; Schnitzler, Alfons; Caspers, Svenja

Abstract Title:
Patterns of atrophy in corticobasal syndrome: lessons learned from in vivo morphometry and post-mortem pathohistology (Hirnatrophiemuster bei Patienten mit CBS: neue Erkenntnisse aus in vivo Morphometrie und post-mortem Pathohistologie)

Abstract Text:
Introduction: Corticobasal syndrome (CBS) with its key features of asymmetric hypokinesia, ideomotoric apraxia, dystonia and cortical sensory loss is a relevant albeit rare differential diagnosis of idiopathic Parkinson's disease. Despite its marked clinical presentation, diagnoses upon neuropathologic examination vary, leading to the conclusion that not the histopathology per se but its cortical and subcortical distribution determines this specific clinical phenotype.
Target: Here, we aim to (a) describe the specific pattern of gray matter degeneration in CBS, (b) to evaluate its significance for CBS-specific symptoms and to (c) validate the in vivo findings with a post-mortem analysis of patterns of histopathological changes.
Methods: In 36 patients with clinical CBS and 24 healthy age and gender matched controls structural MR-images were obtained (3T, voxel-size 1 mm). The images were processed using the automatic pipeline of Freesurfer 6.0.0. Average cortical thickness and volumes

of selected subcortical structures were compared between patients and controls.

One seventy-year old patient with clinical CBS and neuropathologically defined PSP (PSP-CBS) underwent longitudinal high-resolution structural MRI-scans (voxel-size 0.75 mm, follow-up 26 months) and consented to donate his brain tissue under the auspices of the "Brain-Net" project of the Center for Neuropathology and Prion Research, University of Munich. The patient's right hemisphere was fixed in formalin, cut into 20 µm thick slices and stained using a modified silver stain (Merker, 1983). The cortical density of tufted astrocytes, the pathological hallmark of PSP, was quantified using a newly-established automatic machine-based learning approach.

Results: In comparison to controls, patients showed a broad pattern of reduced cortical thickness of bilateral pre- and postcentral gyri covering premotor (area 6), primary motor (area 4) and primary somatosensory (area 1 and 2) regions ($p < 0.002$). Subcortically, putaminal volumes were significantly reduced. Cortical thickness of premotor area 6 was associated with the occurrence of ideomotor apraxia ($p = 0.04$) while dystonia was related to putaminal volume loss ($p = 0.01$).

In the patient with PSP-CBS, a similar pattern of pericentral atrophy was found. The longitudinal change of cortical thickness within microstructurally defined cortical areas significantly correlated with the histological distribution of tufted astrocytes (Spearman's rho, $p = 0.01$).

Conclusion: This study provides evidence that MRI-based measures of atrophy are directly linked to underlying pathologic processes, can be associated to CBS-specific symptoms and thus bridge the gap between clinic and neuropathology in patients with CBS.

Abstract No.:
410

Authors:
Kirsten, Maja; Junak, Constantin; Gulberti, Alessandro; Gerloff, Christian; Hamel, Wolfgang; Moll, Christian; Pötter-Nerger, Monika

Abstract Title:
Deep brain stimulation via segmented leads in the subthalamic nucleus in Parkinson's disease—impact on axial symptoms (THS durch segmentale Elektroden im STN bei Personen mit Morbus Parkinson—Auswirkungen auf axiale Symptome)

Abstract Text:
Introduction: Axial symptoms such as gait deficits, freezing of gait and postural instability have a major impact on activities of daily living and quality of life in people with Parkinson's disease (PD). Conventional omnidirectional deep brain stimulation of the subthalamic nucleus (STN-DBS) has been shown to improve levodopa-responsive aspects of the Parkinsonian gait disorder such as gait hypokinesia although with considerable residual temporal gait deficits and freezing of gait. New technological opportunities with segmented lead stimulation has been demonstrated to increase the therapeutic window in terms of general motor symptoms, however the effect of directed stimulation on particular axial symptoms and gait is unknown.

Target: To compare omnidirectional and directed STN-DBS (anterior, postero-medial or postero-lateral) in PD patients.

Methods: The primary outcomes of the prospective, randomised, double-blind, clinical trial were acute changes of spatial-temporal gait parameters at different walking conditions, i.e. preferred speed, maximal speed and during adapted gait. These parameters were captured by the GAITRITE® system with different stimulation modes, i.e. ring-mode stimulation, stimulation of single segments (anterior, postero-medial, postero-lateral) and with the stimulator turned off on a single day in the medication off-state. Secondary outcomes were changes of freezing of gait (Ziegler Course), motor-symptoms (MDS-UPDRS motor part III, with focus on axial PIGD subitems), static and dynamic balance abilities (Berg Balance score—short-version).

Results: Preliminary results determine the effect of DBS in the STN on spatial gait parameters, freezing of gait, balance abilities and motor symptoms. The difference of conventional ring-mode DBS compared to each single segment (anterior, postero-medial, postero-lateral) seems to vary between outcome measurements with preferable findings for stimulation in the antero-medial direction.

Conclusion: Preliminary results support the positive impact of STN-DBS on axial symptoms in PD patients. It is proposed that unisegmental stimulation might take advantage of the somatotopic organisation of STN sub territories for further improvement of gait and postural stability.

Abstract No.:
411

Authors:
Harapan, Biyan Nathanael; Frydrychowicz, Clara; Müller, Wolf; Claßen, Joseph; Rumpf, Jost-Julian

Abstract Title:
α-synuclein and p-α-synuclein in gastrointestinal tissue: relevant for patients with Parkinson's disease? (α-synuclein und p-α-synuclein in gastrointestinalem Gewebe: von Bedeutung fuer Patienten mit Parkinson-Erkrankung?)

Abstract Text:
Introduction: Various studies indicate that α-synuclein (αSyn) aggregation, the pathological signature of Parkinson's disease (PD), may contribute to the pathogenesis and progression of PD. The αSyn pathology has been detected in peripheral tissues including the gastrointestinal tract, even years before PD diagnosis and appearance of neurological signs. Early clinical manifestations of PD such as constipation and other gastrointestinal dysfunctions often precede the occurrence of motor symptoms, which gives rise to the presumption that PD pathogenesis might have primary connections with the gut.

Target: We sought evidence of αSyn and serine 129-phosphorylated α-synuclein (Ser129p-αSyn) deposition in post-mortem tissues of the small intestine and colonic tissues of 46 study subjects, consisting of 26 patients with PD and 20 age-matched control subjects.

Methods: We used paraffin-embedded tissue blocks that were archived at the Universitätsklinikum Leipzig between 2008 and 2017. Immunohistochemical techniques were employed to visualize αSyn and Ser129p-αSyn. Different morphological structures were considered in the evaluation of a positive immunoreactivity (i.e. in neural structures, plexus and ganglion cells).

Results: The frequency of overall positive αSyn immunoreactivity was higher in the intestinal tissues of the control group ($n = 20$) than that of the PD group ($n = 26$) ($P < 0.05$). In both subject groups, there was no significant difference in the frequency of positive staining between small and large intestine. The number of different morphological structures (i.e. ganglion cells etc.) positive by immunohistochemistry also was significantly lower in the PD group compared to the control group for both αSyn and Ser129p-αSyn. This pattern of immunostaining was observed independent of patient age and sex.

Conclusion: In our study, the presence of aggregated αSyn and Ser129p-αSyn in the enteric nervous system of individuals with and without PD suggests that αSyn and Ser129p-αSyn in the small and large intestine seem to be a regular finding in adults and may not be considered as a pathological correlate. Positive staining was observed in all subjects with no known neurological disorders and αSyn was even abundantly expressed at a significantly higher rate than in PD patients. In our patient cohort, PD patients appear to have

significantly reduced neural structures in the gastrointestinal tract as compared to normal age-matched controls, which might be the underlying cause of constipation. Thus, we may have a morphological correlate of relevant clinical phenomena in PD characterized by disturbances of gastrointestinal motility due to loss of functional neuronal network. Further studies are necessary to determine the pathophysiological role of αSyn aggregation and its association with gastrointestinal symptoms.

Abstract No.:
412

Authors:
van Riesen, Christoph; Haumesser, Jens; Altschüler, Jennifer; Kühn, Andrea; Guettler, Christopher

Abstract Title:
The priming of Levodopa induced dyskinesias is mediated by increased cortical gamma oscillations

Abstract Text:
Introduction: Levodopa is the most efficacious drug in the symptomatic therapy of motor symptoms in Parkinson's disease (PD). The long-term treatment with levodopa is often complicated by the occurrence of troublesome involuntary hyperkinesia, so-called levodopa-induced dyskinesia (LID), which severely affects the quality of life of patients. Recent evidence suggests that LID might be mediated by increased gamma oscillations in the cortico-basal ganglia loop. However, it has not yet been investigated how gamma oscillations develop in the course of repeated levodopa treatment and how these changes in oscillatory network activity relate to the evolution of symptoms.
Target: The aim of our study was to characterize the temporal evolution of cortical gamma activity and the development of dyskinesia in 6-OHDA model of PD under chronic levodopa treatment.
Methods: Rats were implanted with chronic electrophysiological recording electrodes epidurally above the primary motor cortex, in the striatum and in the substantia nigra reticulata. After a baseline characterization of motor behavior and local field potential (LFP) activity, animals were treated with 6-OHDA to induce a degeneration of the nigrostriatal dopamine system. After the completion of the 6-OHDA lesion, animals were treated daily with levodopa for 21 days. Motor behavior was assessed and LFPs were recorded after 1, 4, 10, 16 and 21 levodopa injections.
Results: The motor assessment at baseline before the start of the levodopa treatment phase proofed severe hemi-akinesia as a sign for a successful completion of the 6-OHDA lesion. The repeated levodopa injections caused a stepwise increase of dyskinesia. In the analysis of the LFPs of the baseline recordings before the injections we found significantly enhanced beta oscillations that did not change along the course of the repeated injections. Levodopa treatment almost completely suppressed this beta activity. Furthermore, the injections triggered a large increase in cortical narrow-band gamma oscillations that were centered in the high gamma frequency range. In the course of the repeated levodopa injections there was an additional pronounced enhancement in cortical gamma activity from the first to the fourth day of treatment. Similarly, the peak frequency of the gamma oscillations rose from the first to the forth injection.
Conclusion: Our results provide new evidence for the hypothesis that chronic levodopa-induced dyskinesias are mediated by enhanced cortical gamma oscillations. We provide first evidence that the development of dyskinesia in the course of a chronic treatment with levodopa is reflected by change in the amplitude and peak frequency of cortical gamma activity.

Abstract No.:
413

Authors:
Karapantzou, Chrisanthi; Vale, Joao Pedro; Jakob, Mark; Canis, Martin

Abstract Title:
Botulinum toxin type A injections for functional and aesthetic restoration after facial paralysis (Botulinumtoxin Typ A Injektionen für die funktionelle und ästhetische Gesichtskorrektur nach Fazialisparese)

Abstract Text:
Introduction: There are multiple causes for Peripheral facial palsy. In most cases it is a mono-neuropathy with unilateral affection of the facial nerve and, thus, of the ipsilateral facial expression muscles. The consequences include aesthetic deformity, psychosocial stigmatization and functional morbidity with severe negative influence in quality of life. The majority of patients recover within 6 weeks, regardless of the initial treatment approach, but there are a significant number of the affected individuals who develop permanent sequelae like oral incompetence, dysarthria, involuntary metaparalytic hyperlacrimation, fasciculation, synkinesis and lagopthalmos, the last one being associated with events of keratopathy, cornea ulceration or even blindness.
Target: Therapeutic treatments including Botulinum Toxin type A injections, are designed to improve facial function, aesthetic appearance and support recovery.
Methods: Botulinum Toxin A can be injected every 3 to 6 months into the non paralytic side in order to restore facial symmetry and decrease functional disorders (fluid intake, food consumption, articulation, visus). The toxin application can be performed, in order to compensate the imbalance to the paralytic side, in mimic muscles of the healthy side to control hyperdynamic movements and rhytides of the forehead area, to extend the Musculus orbicularis on the periorbital area and on the perioral area to depress the angle of the mouth. Moreover, ipsilateral injections can be performed to treat specific metaparalytic features of the muscular system, but also into the Pars palpebralis of the lacrimal gland, to control hyperlacrimation. The effectiveness of the treatment can be assessed 2–3 weeks after injection.
Results: As described from other authors in literature, Botulinum Toxin Type A is an effective and well tolerated method in the management of facial palsy. It improves facial symmetry, especially during mimic muscles activation, and affects positively the postparalytic functional consequences that the patients experience.
Conclusion: Although in most cases the injections have to be repeated frequently, the main benefits of this treatment option are its minimal invasivity and safety. In cases with long-term facial paralysis (more than 2 years) with severe symptomatology, the situation should be re-assessed and more invasive techniques such as tarsorraphy, gold-eyelid weight implantation, hypoglossal facial nerve transfer, gracilis free flap transplants, browlift, and others, should be considered as a more permanent solution and additionally offered to patients.

Abstract No.:
414

Authors:
Steigerwald, Frank; Capetian, Philipp; Volkmann, Jens

Abstract Title:
How to implement available DBS innovations in clinical routine of STN-DBS in Parkinson's disease

Abstract Text:
Introduction: Over the last years, the field of DBS has seen many technical innovations like current steering, short pulse width, directional DBS, anodal stimulation or multiple frequencies.
Target: To guide the DBS beginner thorough the jungle of increasing possibility to optimize STN-DBS in real-life
Methods: Summary of available evidence and eminence (!) of the mentioned new programming possibilities and their application.
Results: Novel programming options offer possibilities to individually fine-tune DBS and can yield better clinical outcomes.
Conclusion: While the complexity of programming is increased at first glance, a systematic approach is a key strategy to optimize DBS and to balance time-burden for programming with the chance to improve patient outcomes.

Abstract No.:
415

Authors:
Steigerwald, Frank; Volkmann, Jens; DBS study group for dystonia

Abstract Title:
Programming DBS in dystonia: new aspects from a multi center study

Abstract Text:
Introduction: Current recommendations for programming DBS in dystonia are pragmatic recommendations based on expert opinion, rather than clinical evidence.
Target: We tried to identify acute clinical features, which could serve as predictors of the long-term response to stimulation settings determined by an algorithm applied in a multi center DBS study for dystonia
Methods: The original trial was a double-blind, sham-controlled study for 3 months, followed by an open-label extension for up to 5 years, including 40 patients with pharmacologically-intractable, primary generalized or segmental dystonia. The algorithm to determine the active stimulating electrode was defined in the study protocol.
Results: Dystonia motor score decreased by 73 ± 24 % at 3 years and 63 ± 38 % at 5 years for contacts that exhibited acute improvement of dystonia (n = 17) during the monopolar review. Contacts without acute benefit improved by 58 ± 30 % at 3 years (n = 63) and 53 ± 31 % at 5 years (n = 59). Interestingly, acute worsening or induction of dystonia/dyskinesia (n = 9) correlated significantly with improvement after 3 years, but not 5 years.
Conclusion: Acute improvement, as well as worsening of dystonia, predicted a good long-term outcome, while induction of phosphenes did not correlate with outcome.

Abstract No.:
416

Authors:
Hartmann, Christian J.; Pieperhoff, Peter; Krause, Holger; Ferrea, Stefano; Moldovan, Alexia S.; Wojtecki, Lars; Zilles, Karl; Amunts, Katrin; Schnitzler, Alfons; Südmeyer, Martin

Abstract Title:
Longitudinal deformation-based morphometry in parkinsonian variant of multiple system atrophy (Longitudinale deformationsbasierte Morphometrie bei der Multisystematrophie vom Parkinsontyp)

Abstract Text:
Introduction: The parkinsonian variant of multiple system atrophy (MSA-P) is a rare alpha-synucleinopathy characterized by autonomic failure and rapidly progressive parkinsonian syndrome which typically hardly responds to dopaminergic treatment. While cerebral magnetic resonance imaging (MRI) may reveal typical abnormalities in cross-sectional analyses, the courses of local brain structural changes in MSA-P in the long-term follow-up and their clinical relevance are poorly understood.
Target: Aim of this study was to characterize the dynamics of neurodegenerative processes in MSA-P and to identify alterations of distinct brain regions associated with the course of the disease.
Methods: A total of 13 patients with probable MSA-P and 15 matched healthy probands were prospectively recruited for longitudinal neurological, neuropsychological, and MRI assessments (MSA-P: 14.6 ± 5.4 months, range 7–24 months, 3–7 serial MRIs; Controls: 19.7 ± 5.7 months, range 11–28 months, 2–4 serial MRIs). Utilizing repeated registrations of MRI, deformation-based morphometry (DBM) was used to compute the local volume ratio (LVR) of predefined brain regions, hence allowing for quantification of temporal changes within each region.
Results: During the follow-up period, 8 patients died, and 2 of these patients donated their brains for autopsy, which confirmed clinical diagnosis. Compared to healthy control subjects, MSA-P patients revealed a progressive atrophy in the basal ganglia, the primary sensorimotor and premotor cortex as well as the pons and the cerebellum. Worsening of motor deficits was associated with increased rates of ponto-cerebellar, basal-ganglia and motor-cortical atrophy in MSA-P.
Conclusion: Longitudinal DBM analysis provides new insights to the individual dynamics of neurodegenerative disease progression in MSA-P and reveals a common atrophy pattern within the ponto-cerebello-thalamo-cortical circuit in association with worsening of motor symptoms.

Abstract No.:
441

Authors:
Schöllmann, Anna; Scholten, Marlieke; Govindan, Rathinaswamy B.; Gharabaghi, Alireza; Siegel, Markus; Plewnia, Christian; Weiss, Daniel

Abstract Title:
Removal of tDCS-related artefacts in a simultaneous tDCS-EEG study in Parkinson's disease

Abstract Text:
Introduction: Transcranial direct current stimulation (tDCS) may alleviate motor symptoms in Parkinson's disease (PD). However, the neurophysiological effects of tDCS on cortical activation, synchronization, and the relation to clinical motor symptoms in PD need characterization.
Target: We aimed to explore the real-time effect of tDCS over the left sensorimotor area on cortical activity and synchronization in

relation to clinical motor outcome. Therefore, we developed an approach for artefact-cleaning in a simultaneous EEG-tDCS setting.
Methods: In this double-blind randomized sham-controlled clinico-neurophysiological study we investigated ten idiopathic PD patients and 6 matched healthy controls on 2 days at rest during combined, simultaneous EEG and during 'verum' and 'sham' anodal tDCS (20 min; 1 mA; anode [C3], cathode [Fp2]). We also recorded EEG and EMG before ('pre') and directly after stimulation (post) at rest. We merged the stimulation data with the 'pre' and 'post' data. We identified tDCS-induced artifacts using independent component analysis (ICA) by exploring the time-series with respect to lower frequency activation (1–3 Hz), the variance of spectral components over time, as well as the topography of the components.
Results: tDCS artifacts and physiologic artifacts exaggerated by tDCS can be identified using ICA. tDCS artifacts localize around the stimulation electrodes and show specific low-frequency characteristics. As main reason for this low-frequency activation, impedance and conductivity changes of cerebral blood volume in association to the cardiac rhythm seem to be the main mechanistic cause.
Conclusion: In this analysis we show feasibility to clean tDCS-related artifacts in combined tDCS—EEG experiments. With this method at hand, the pathophysiological cortical activation and synchronization changes and their correlation to clinical outcome will be studied.