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Molecular Mechanisms of Cognitive Impairment and Intellectual Disability—Virtual ESN Mini-Conference in Conjunction with the FENS Forum, July 11–15, 2020

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Overview

Cognitive impairment and intellectual disability affect a large population of children suffering from neurodevelopmental diseases as well as the elderly population succumbing to age-associated cognitive impairments. Understanding the molecular mechanisms of these disorders will aid in better diagnosis and improved treatments. The European Society for Neurochemistry (ESN) Virtual Mini-Conference held in conjunction with the FENS Forum 2020 has featured several hot topics in the field including leading genes causing autism/intellectual disability syndromes, like ADNP and SLC9A6, as well as electrophysiological and molecular mechanisms underlying intellectual disability. The role of environmental factors as well as the basic mechanisms of synaptic transmission and neuro-glial interactions has also been elucidated in the conference talks. Finally, innovative drug development has been discussed towards better cognitive functioning both in children and the elderly as presented by the scientists from the UK-based Simons Initiative for the Developing Brain.

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Anthony J. Turner (UK) - Abstract Committee

Program

Saturday, 11 July 2020
09:00–12:30 (GMT + 1)

Pre-recorded Talks

Development and Intellectual Disabilities

9:00–9:20
Gozes Illana (Tel Aviv University, Israel) - ADNP autism and mild cognitive impairment
9:20–9:40
McKinney R Anne (McGill University, Montreal, Canada) - Insight from Christianson syndrome on how deficits of endosomal pH impair cognition
9:40–10:00
Nalivaeva Natalia N (Institute of Evolutionary Physiology and Biochemistry, St Petersburg, Russia) - Role of prenatal

stress in development of cognitive disorders and search for therapy

Key Mechanisms and Drug Development

10:00–10:20
Hirrlinger Johannes (Carl-Ludwig-Institute for Physiology, Leipzig; Max-Planck-Institute of Experimental Medicine, Göttingen, Germany) - Neuronal cell energy metabolism – the glial aspect
10:20–10:40
Michetti Fabrizio (Catholic University, Rome, Italy) - The S100B protein as a biomarker and effector in neural disorders: a potential novel therapeutic target
10:40–11:00
Mothet Jean-Pierre (CNRS, Marseille, France) - Emerging roles of D-amino acids in the healthy and diseased brain

Simons Initiative for the Developing Brain

Young investigator lectures (electrophysiology and molecular mechanisms of intellectual disability)
11:00–11:20
Booker Sam A (SIDB, Edinburgh, UK) - Overcompensation of cellular excitability in the Fmr1-/y mouse
11:20–11:40
Ribeiro dos Louros Susana (SIDB, Edinburgh, UK) - Perturbed proteostasis in ID/ASD

Open Live Virtual Discussion

11:40–12:30
Moderators: Gozes Illana, (ESN Secretary, Conference Chair), Nalivaeva Natalia N. (ESN President, Conference Committee Member), Hirrlinger Johannes (ESN Treasurer, Conference Committee Member), Blumrich Eva-Maria (ESN Council Member, Conference Co-Chair)

Posters of ESN Travel Award Winners

11:40–12:00
Hadar Adva (Rehovot and Tel Aviv, Israel) - Genomic biomarkers for Alzheimer disease
Li Catherine (Sydney, Australia) - Changes in cerebral glucose metabolism in chemotherapy-induced cognitive impairment
Pershina Ekaterina (Pushchino, Russia) - Metabotropic glutamate receptors in the hippocampus and the prefrontal cortex in rats during neurodegeneration caused by trimethyltin chloride
Shcherbitskaia Anastasiya (Saint Petersburg, Russia) - Gestational hyperhomocysteinemia affects development of the nervous system in rat fetuses and offspring

Open Discussion Highlighting E-Posters

12:00–12:30
Ahmad Muddasir Khan Saara (Karachi, Pakistan) - The efficacy of herbal interventions in the pathogenesis of diabetes and neuropsychological deficits on Streptozotocin-induced diabetic rats.
Árabe Laila Blanc (Belo Horizonte, Brazil) - Effects of maternal separation on microglia profile and anxiety-like behavior of male and female mice
Baker Kate (Cambridge, UK) - Gene functional networks influence autism spectrum characteristics in young people with intellectual disability
Gigliucci Valentina (Milan, Italy) - Region-specific effects of IGF-1 and oxytocin on KCC2 in MeCP2 KO mice
Kozlova Daria (Saint Petersburg, Russia) - Effect of prenatal hypoxia on cholinesterase activity in blood serum of rats
Nikitina Veronika (Saint Petersburg, Russia) - Neonatal bacterial endotoxin exposure exacerbates stress-induced changes of NMDA and AMPA receptor expression in the rat brain
Parodi Chiara (Milan, Italy) - Paving the way for future therapeutic strategies in Cornelia de Lange Syndrome modulating defective Wnt pathway
Reiche Laura (Düsseldorf, Germany) - C21orf91 as a new regulator of gliogenesis and Down syndrome neuropathology
Schultzberg Marianne (Solna, Sweden) - Studies on the resolution of inflammation in Alzheimer's disease
Trofimov Alexander (Saint Petersburg, Russia) - Prolonged treatment with medium chain triglycerides (C8, C10) induces positive effect on cognitive abilities of intact rats
Vasilev Dmitrii (Saint Petersburg, Russia) - The caspase-3 inhibitor Ac-DEVD-CHO normalizes neprilysin expression in brain tissue of rats subjected to prenatal hypoxia
Zakharova Elena (Moscow, Russia) - Spatial contextual memory consolidation: key dopaminergic and cholinergic functional connections and their vanishing under brain hypo-perfusion
Zhuravin Igor (Saint Petersburg, Russia) - Histone deacetylase inhibitor sodium valproate restores cognitive and olfaction impairments in rats subjected to prenatal hypoxia

Abstracts Without Posters

Basson M Albert (London, UK) - CHD8 autism and intellectual disability
Benbenishty Amit (Rehovot, Israel) - Longitudinal in vivo imaging of perineuronal nets in fragile-X syndrome

Gabrielli Martina (Milan, Italy) - Microglia-derived extracellular vesicles propagate early synaptic dysfunction in Alzheimer's Disease

Rimpi Arora (Punjab, India) - Embelin negated the development of intracerebroventricular streptozotocin and β-amyloid induced Alzheimer's Dementia (AD) model in Rats

Extended Virtual Mini-Conference Report

Originally planned as a live European Society for Neurochemistry (ESN) Mini-Conference in conjunction with the FENS Forum 2020, this scientific event has been held on a web-based platform after the COVID19 pandemic–driven FENS decision to go virtual. The focus of the Mini-Conference was set on deciphering the molecular mechanisms of cognitive impairment and intellectual disability, a highly important and diverse neurochemical topic. Its coverage has displayed the diversity of research performed by ESN members and collaborating international scientists and Institutions, including the Edinburgh-based Simons Initiative for the Developing Brain (SIDB). A significant part of this Mini-Conference was dedicated to the poster session, with posters available for viewing online before and after the conference and abstracts displayed in the abstract (https://neurochemsoc.eu/). Moreover, four very talented young scientists who have been awarded ESN travel grants to attend the FENS Forum (Adva Hadar, Tel Aviv & Rehovot, Israel; Catherine Li, Sydney, Australia; Ekaterina Pershina, Pushchino, Russia; Anastasiya Shcherbitskaia, Saint Petersburg, Russia) have been given an opportunity to present their posters as short talks at the Mini-Conference.

The topic covered at the Mini-Conference has featured three main areas as follows below. Our summary presents our own point of view including abstracts that were submitted but not presented due to the COVID19 pandemic. Only a handful of references are cited, providing an overview of a timely topic, rather than a comprehensive literature survey.

Development and Intellectual Disabilities

In the opening talk "ADNP autism and mild cognitive impairment" *Prof I. Gozes* (Tel Aviv University, Israel) elucidated the role of the de novo mutations in the activity-dependent neuroprotective protein (ADNP) gene in the autism/intellectual disability (named ADNP syndrome) (e.g., Hacohen-Kleiman et al. 2018; Levine et al. 2019). By using RNA sequencing, somatic mutations were discovered in hundreds of genes, including the *ADNP* gene, in post-mortem Alzheimer's disease (AD) patients' brains. Many of these mutated genes/proteins are linked to the cytoskeleton and were identified in the databases encompassing genes/proteins linked with autism and intellectual disabilities. *ADNP* mutation frequency paralleled increases in AD tauopathy. Treatment with the ADNP smallest active fragment, a drug candidate NAP (CP201), protected against ADNP-mutation microtubule disruption effects. Specifically, NAP protected microtubule dynamics and enhanced Tau-microtubule interactions (Ivashko-Pachima et al. 2019). With tauopathy being a major hallmark paralleling cognitive decline in AD, the most recent discovery by the Gozes laboratory of tau pathology also in the post-mortem ADNP syndrome patient's brain (7-year-old) suggests tauopathy as a converging mechanism of intellectual disabilities in the young and cognitive decline in the elderly (Grigg et al. 2020). It was also shown that ADNP/NAP modulate the microtubule-dependent immune response, linked with microbiota composition, and ADNP deficiency is associated with the changes in commensal gut microbiota composition, which can be treated with NAP (CP201) (Kapitansky et al. 2020).

On the ADNP-related topic, the short talk by *A. Hadar* (Tel Aviv University, Israel) presented in depth data on RNA sequencing of post-mortem human olfactory bulbs revealing a significant number (over 600) of mutations in hundreds of genes, 104 of which presented disease-causing mutations. Further data mining of publicly available RNA sequencing libraries identified thousands of putative somatic mutations. The number and average frequency of AD-related mutations per subject were higher in AD patients compared with those in controls. Overlapping all tested brain areas identified unique and shared mutations, with ADNP standing out as a gene associated with autism/intellectual disability/AD (Ivashko-Pachima et al. 2019).

The poster by *Dr K. Baker* (University of Cambridge, UK) focused on functional gene networks, which influence autism spectrum characteristics in young people with intellectual disability. The data presented suggest that genes associated with intellectual disability converge on cellular functional networks, e.g., chromatin regulation and neuronal communication, and that the disorders in these functional networks can predict some autism spectrum characteristics. A more detailed report on the research of this group has been recently published (Baker et al. 2020).

Another neurodevelopmental disorder that results from altered early brain development is Christianson Syndrome (CS) that presents with intellectual disability, epilepsy, ataxia, autistic behavior, and progressive neurodegeneration. As presented in the talk by *Prof R.A. McKinney* (McGill University, Montréal, Canada), CS arises from mutations in the *SLC9A6* gene encoding the sodium/proton exchanger isoform 6 (NHE6), which is localized in the synapse, and modulates its activity. The lack of properly functioning NHE6 can result in learning and cognition deficits (Ilie et al. 2019). Patient-derived NHE6 mutations, resulting in non-functioning NHE6 neurons, impair AMPA-type glutamate receptor (AMPAR) trafficking and structural plasticity at the cellular and circuit levels, which

might underlie learning and memory impairments in CS patients. A CS animal model based on these observations is now used for testing novel therapeutic interventions to improve cognition in CS patients (Ilie et al. 2020).

Molecular mechanisms underlying Rett syndrome, which is a rare genetic disorder affecting brain development and resulting in severe mental and physical disability, have been reported in the poster by *V. Gigliucci* and colleagues (CNR Institute of Neuroscience, Milan, Italy). Methyl-CpG binding protein 2 (Mecp2) knockout mice (*MeCP2*-KO mice) show a dysregulation of K^+/Cl^- cotransporter 2 (KCC2), impaired polarity of GABAergic response, and recapitulate many symptoms of the Rett syndrome. In these mice, the researchers found region-specific alterations in IGF-1/oxytocin (OXT) signaling cross-talk that modulates KCC2. This suggests a possibility for region-selective innovative therapeutic strategies aimed at normalizing the E/I balance in the key brain regions related to the Rett syndrome symptomatology.

The directions for future therapeutic strategies in Cornelia de Lange Syndrome (CdLS), a rare developmental disorder affecting almost any organ including the CNS, were presented in the poster by *C. Parodi* and colleagues (Università degli Studi di Milano, Milan, Italy). This disease is caused by mutations in a number of genes encoding proteins of the cohesin complex, which plays a pivotal role in chromatin organization and gene expression. This study confirmed that the canonical Wnt pathway is impaired in CdLS models and that rescue strategies using chemical activation of the Wnt pathway with lithium chloride (LiCl) or other activators might represent a future therapeutic strategy to ameliorate this disorder.

Interestingly, Wnt signaling as well as altered ion channel expression may also interact with the ADNP syndrome (Grigg et al. 2020), and similarities were found between the ADNP syndrome and the Rett syndrome (https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=404448).

Delayed development of brain functions and higher risk of neurodegeneration and intellectual disability in later life are tightly linked to various types of prenatal stress including prenatal hypoxia (Nalivaeva et al. 2018). As highlighted in the talk by *Dr N.N. Nalivaeva* (Institute of Evolutionary Physiology and Biochemistry, RAS, Saint Petersburg, Russia), individuals subjected to prenatal stress are predisposed in later life to develop neurodegenerative disorders including AD, which is underpinned by the changes in expression of several neuronal genes related to amyloid-β (Aβ) peptide metabolism and clearance, including the neuropeptidase neprilysin (NEP) (Zhuravin et al. 2019). This topic has been further elucidated in the poster by *Dr D.S. Vasilev* and colleagues from the same laboratory reporting that injections of the caspase-3 inhibitor Ac-DEVD-CHO normalized NEP expression in brain tissue of rats subjected to prenatal hypoxia. Furthermore, the poster by *Dr I.A. Zhuravin* and colleagues demonstrated that administration of the histone deacetylase inhibitor sodium valproate restored cognitive and olfaction impairments in these animals. Another poster from the same group (*Dr D.S. Kozlova* and colleagues) shows that prenatal hypoxia also affects the activities of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) in the blood of rat offspring which underlie changes in the peripheral reactions of animals to different types of stressors.

Another prenatal factor impairing cognitive functions and causing intellectual disability in the offspring is maternal hyperhomocysteinemia, which causes a disruption of neuroblast generation and migration in the cortex of rat pups and is accompanied by an increased number of apoptotic cells as well as increased glial reaction and IL-1β content in the cortex (poster and a short talk by *Dr A.D. Shcherbitskaia*, Saint Petersburg, Russia). A more detailed report on this study has recently been published (Shcherbitskaia et al. 2020).

The role of maternal separation in the development of anxiety-like behavior in male and female mice was covered by the poster presented by *L.B. Árabe* (Universidade Federal de Minas Gerais, Belo Horizonte, Brazil). This work demonstrated that early-life stress also affected microglia morphophysiology in pre-pubertal male and female mice and that females were more resilient to a maternal separation protocol, even before hormonal influence.

The data presented in this section underline the crucial importance of understanding the genetic foundation of intellectual disability, no matter at which stage of life and in which exact form it occurs, for development of effective treatments.

Key Mechanisms and Drug Development

Changes in neuronal cell energy metabolism caused by various factors are among the key mechanisms affecting normal brain development potentially leading to cognitive disorders. Understanding their cellular targets will lead to designing valid therapeutic strategies. As highlighted in the talk given by *Prof J. Hirrlinger* (University of Leipzig/Max-Planck-Institute of Experimental Medicine, Göttingen, Germany), axonal pathologies in neurological disorders may be caused by impaired oligodendrocyte-to-axon supply of energy substrates. They showed a disruption in energy metabolism through complex alterations of metabolic oligodendrocyte-axon coupling in mice deficient of the proteolipid protein, a mouse model of X-linked spastic paraplegia type-2 (SPG2).

Reduced numbers of neurons and oligodendrocytes, hypomyelination, and astrogliosis are characteristic for Down syndrome (DS), or trisomy 21, which is the most common genetic cause for cognitive impairments and intellectual disability (for review see Reiche et al. 2019). It also involves C21orf91, a protein considered a key modulator of aberrant CNS development in DS. Studies of the role of C21orf91 in oligodendrogenesis and myelination of

primary oligodendroglial progenitor and primary neural stem cell culture, as shown in the poster by *L. Reiche* and colleagues (Heinrich-Heine-University, Düsseldorf, Germany), revealed that this protein is important for accurate oligodendroglial differentiation and suppression of its gene restricts morphological maturation. On the other hand, C21orf91 overexpression induces a gliogenic shift towards the astrocytic lineage reflecting observations in DS brains. Further transplantation experiments will confirm whether C21orf91 gene manipulation could be beneficial for targeted regulation of cell fate.

The role of microglia in propagation of synaptic dysfunction has been evaluated in the abstract by *M. Gabrielli* and colleagues (CNR Institute of Neuroscience, Milan, Italy) who demonstrated that microglia-derived extracellular vesicles (EV) carrying amyloid Aβ peptide can induce synaptic alteration and spread the peptide among connected brain regions, e.g., between the entorhinal cortex and the dentate gyrus leading to impaired LTP. Importantly, coating EV with annexin-V could limit Aβ-EV motion resulting in unaltered propagation of LTP. This opens new therapeutic avenues in the treatment of Aβ-related pathologies, including AD.

Changes in cerebral glucose metabolism as presented in the poster and short talk by *C. Li* (UNSW Sydney, Australia) underlie chemotherapy-induced cognitive impairment that persists after cessation of chemotherapy and for which currently no treatment is available. Chemotherapy drugs such as doxorubicin (DOX) were shown to reduce the incorporation of labeled glucose into lactate in the cortex and increase the total pool size of aspartate in the hippocampus. Testing the ability of the NAD^+ precursor nicotinamide mononucleotide to prevent these changes, they found that this compound may increase cerebral blood flow and attenuate the energy deficits caused by DOX.

The poster by *Dr A. Trofimov* and colleagues (Institute of Experimental Medicine, St. Petersburg, Russia) presented the data that prolonged treatment with medium chain triglycerides (C8, C10) induced a positive effect on the cognitive abilities of rats and might be considered a strategy to improve brain functioning in the case of impaired brain energy metabolism.

Another mechanism for triggering tissue reaction to damage is overexpression and release of certain proteins (so-called Damage-Associated Molecular Pattern molecules) among which is S100B protein. In his talk, *Prof F. Michetti* (Università Cattolica S. Cuore, Rome, Italy) presented data on the role of S100B in experimental models of amyotrophic lateral sclerosis as well as in pathogenic processes occurring in multiple sclerosis which make S100B a viable biomarker and effector in neurodegenerative disorders sharing some common pathogenic features attributable to neuroinflammation (for review see Michetti et al. 2019).

Recent research outlined in the talk by *Prof J.-P. Mothet* (Université Paris-Saclay, Gif-sur-Yvette, France) has demonstrated emerging roles of D-amino acids as a novel and important class of signaling molecules in many organs including brain and endocrine systems. It is now apparent that D-serine, D-aspartate, and D-cysteine are essential for the healthy development and function of the central nervous system offering new therapeutic avenues in clinics for several brain diseases and for drug discovery (for review, see Mothet et al. 2019).

A specific role of receptor distribution in development of neurodegeneration has been suggested in the poster and short talk by *E.V. Pershina* (Institute of Theoretical and Experimental Biophysics, RAS, Pushchino, Russia) who presented a neurotoxic model of neurodegeneration based on rat treatment with trimethyltin chloride (TMT). This treatment was found to have different effects on expression of various subtypes of mGluRs (mGluR4, mGluR5, and mGluR7) in the hippocampus and prefrontal cortex of rats, which resulted in enhanced cell death in the hippocampus implying a different contribution of individual mGluR subtypes to neurodegeneration and/or neuroprotection (Kamaltdinova et al. 2020; Pershina et al. 2019).

Dysregulated glutamatergic transmission may also be implicated in post-traumatic stress disorder (PTSD), and neonatal pro-inflammatory activation affects brain maturation making it more vulnerable to stressful events later in life. As outlined in the poster by *V. Nikitina* and colleagues (Sechenov Institute of Evolutionary Physiology and Biochemistry and Institute of Experimental Medicine, Saint Petersburg, Russia), neonatal bacterial endotoxin exposure resulted in pronounced alterations in NMDA-type glutamate receptors (NMDAR) and AMPAR in rat brain structures, and these changes were more pronounced in animals injected with lipopolysaccharides. This testifies to the role of neonatal inflammation in development of stress-induced mental illnesses.

The importance of key dopaminergic and cholinergic functional connections for spatial contextual memory (SCM) consolidation has been revealed in the poster presented by *Dr E.I. Zakharova* and colleagues (Institute of General Pathology and Pathophysiology, Moscow, Russia) who demonstrated that under chronic cerebral hypo-perfusion (a 2VO model), the loss of dopaminergic connections results in impaired ability of animals to maintain higher level SCM consolidation.

With regard to the neurodegenerative diseases leading to cognitive impairment, several presentations at the Mini-Conference have addressed the importance of neuroinflammation as a leading factor in development of such neuropathology as AD. In the poster by *Prof M. Schultzberg* and colleagues (Karolinska Institutet, Solna, Sweden), they analyzed the role of the resolution of inflammation, especially of the specialized pro-resolving mediators (SPMs), in AD. Studying the effects of the SPMs on microglia and neurons as well as the levels of the receptors and synthetic enzymes in human and mouse brain, they found a decrease in SPMs in the human AD brain

and an increase of the receptors to ChemR23 and BLT1. They also suggested that SPMs can modulate the response of microglia towards Aβ by decreasing pro-inflammatory markers and increasing uptake of Aβ, which might be a possible treatment target. These studies were further extended also by *C. Emre* collaborating with *Prof M. Schultzberg* who presented a poster at the FENS Forum "Alterations in free fatty acids and phospholipids in single APP knock-in mouse model of Alzheimer's disease" and is a continuation of their work on molecular pathogenesis in AD (Emre et al. 2020).

The protective effect of embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone), a natural alkyl substituted hydroxy benzoquinone found in *Embelia ribes*, in a streptozotocin- and Aβ-induced AD rat model has been reported in the abstract by *R. Arora and R. Deshmukh* (ISF College of Pharmacy, Moga, and Maharaja Ranjit Singh Punjab Technical University, Bathinda, Punjab, India). This compound was shown to attenuate cognitive deficits and hippocampal neurochemical characteristics due to its antioxidant and anti-inflammatory properties (also see Arora and Deshmukh 2017).

Other natural compounds tested for their efficacy against neuropsychological deficits caused by streptozotocin-induced diabetes in rats were saffron, chamomile, and their co-administration as presented in the poster by *S.A.M. Khan and colleagues* (Aga Khan University, Karachi, Pakistan). They demonstrated that these compounds produced anxiolytic as well as antidepressant effects and improved memory, impaired by STZ-induced diabetes, when rats were tested in the Morris water maze.

Taken together, this section presents state of the art models and molecular tools to elucidate the function of natural and synthetic compounds in living organisms promising a more specific drug development in the future, while already allowing us to reduce the side-effects of existing drugs to date.

Young Investigator Lectures - Simons Initiative for the Developing Brain

The talks of two young scientists in this session have outlined the research undertaken by the Simons Initiative for the Developing Brain (SIDB, Edinburgh, UK; https://www.sidb.org.uk) which is a collaborative center with its main mission to decipher biological mechanisms underlying autism and deliver rational therapeutic interventions. *Dr S. Brook* presented the results of studies in an *Fmr1*$^{-/y}$ mouse model of the Fragile X Syndrome (FXS) which is another common inherited cause of intellectual disability and leading identified genetic cause of autism. This study revealed that an increased brain excitability characteristic for this disorder might be related to the changes in the axonal properties of the pyramidal cells in the hippocampus which affect cell excitability and lead to homeostatic alteration of cell functions. Another aspect of the research using the Fmr1 KO animals has also been presented in the talk by *Dr S. Ribeiro dos Louros*. In a recently published work (Asiminas et al. 2019), this group showed that *Fmr1* KO rats have a developmental delay and cognitive impairment in object-place-context recognition paradigms at any age tested although treatment with lovastatin in the first 3 months of development prevented these deficits. These findings suggest that impaired cognitive functions in neurodevelopmental disorders can be prevented by early pharmacological treatment.

ESN has been dedicated to supporting young scientists for over 40 years. Collaboration with the Edinburgh-based SIDB provided a great opportunity to showcase high-class emerging young researchers and local neurochemistry at the same time, as the Mini-Conference was originally meant to take place in Scotland and will hopefully enhance future connections.

Afterwards

This virtual Mini-Conference was a new experience for ESN and its members, and we are very grateful to all participants, presenters, and especially to FENS for providing us with such a unique opportunity as well as for their constant support and guidance. While we are looking back with very positive impressions, we also feel that a purely virtual event cannot compete with a face-to-face meeting. The captivating atmosphere of a scientific meeting starting from greeting your colleagues at the registration desk, talking to them over the poster sessions and symposia, and interacting with them at the social events is, despite all the attractiveness of the virtual conferences, irreplaceable. We feel that particularly for young scientists, face-to-face interaction with both junior and senior colleagues is a crucial career-shaping experience. Therefore, we are planning to continue the discussions started at this virtual Mini-Conference at further ESN meetings, starting with the 24th ESN Biennial meeting in St. Petersburg scheduled for May 2022. We are inviting you all to join us in Saint Petersburg, so please check the ESN website (https://neurochemsoc.eu/) for updates.

Just when this review paper was being finalized, we have learned about the death of one of the scientists participating in the ESN Mini-Conference, Dr Igor A Zhuravin (Saint Petersburg, Russia), who for many years was studying the role of prenatal stress in brain development and cognitive impairment. We dedicate this paper to Dr Zhuravin to commemorate him and his research in Neurochemistry. The full obituary for Dr Igor Zhuravin can be found at the ESN website at https://neurochemsoc.eu/.

Dr Igor Zhuravin (1944–2020)

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Compliance with Ethical Standards

Conflict of Interest Professor Illana Gozes serves as the Chief Scientific Officer of Coronis Neurosciences developing NAP (CP201) for the ADNP syndrome.

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