www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2025;14(2):e140213
doi: 10.7363/140213
Published online: 2025 Oct 22

Lectures

Selected Lectures of the International Laboratory Meeting

CAGLIARI (ITALY) · OCTOBER 22ND, 2025

The International Laboratory Meeting, titled "Neurodegenerative and neurodevelopmental diseases: the hidden line connecting infancy with aging", is a Satellite Meeting of the 21st International Workshop on Neonatology and Pediatrics, Cagliari (Italy), October 22nd-25th, 2025.

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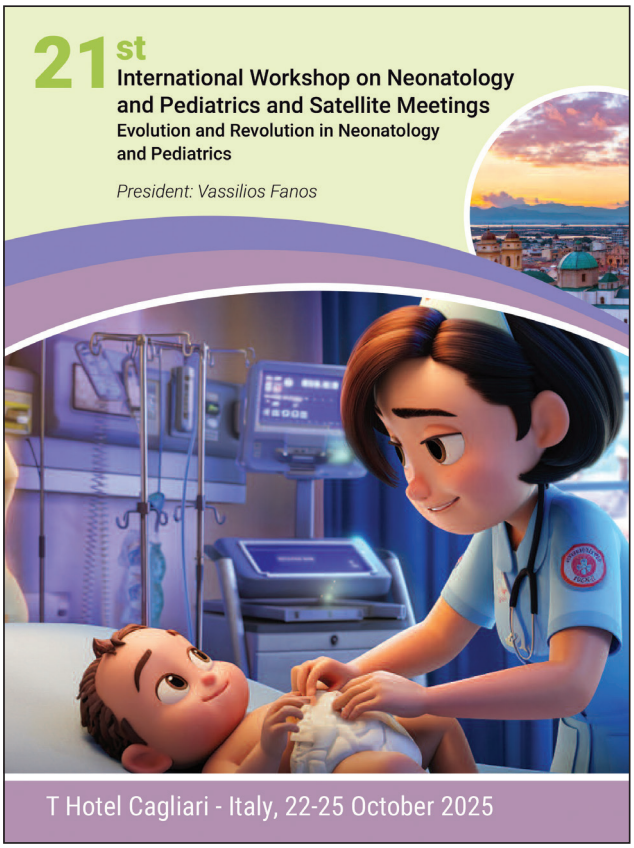

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How to cite

[Lecture's authors]. [Lecture's title]. In: Selected Lectures of the International Laboratory Meeting; Cagliari (Italy); October 22, 2025. J Pediatr Neonat Individual Med. 2025;14(2):e140213. doi: 10.7363/140213.

LECT 1

EPIGENETICS AND NEURODEVELOPMENT: FROM PRECONCEPTION TO ADOLESCENCE

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Epigenetic mechanisms have been recognized to play a crucial role in neurodevelopment during pregnancy, infancy and adolescence. The recent discovery of the remarkable ability of our genes to adapt their function in response to environmental inputs has opened up a fascinating new hypothesis for better understanding the etiopathogenesis of mental and degenerative diseases, including those that occur during the aging process. Accordingly, recent results suggest that the mother's lifestyle during preconception, pregnancy, and the neonatal period plays a crucial role in the neurodevelopment of their offspring, and has consequences for the aging brain.

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LECT 2

THE ROLE OF BLOOD BIOMARKERS FOR NEURODEGENERATIVE DISEASES

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As the global burden of neurodegenerative diseases is dramatically growing, the call for timely and accurate diagnosis has never been more urgent. As a result, dementia research is "on the cusp of a breakthrough." The molecular mechanism of neurodegenerative diseases consists of the combination of various factors closely interconnected to each other, including (a) genetic polymorphisms; (b) the progressive formation of insoluble misfolded proteins leading to aggregates; and (c) the concomitant development of neuroinflammation and neurotoxicity. The final result is the gradual loss and death of neurons and synaptic connections, promoting cognitive decline. Notably, molecular changes may begin decades before clinical symptoms appear; thus, the early and accurate diagnosis is critical for improving outcomes for people with neurodegenerative diseases. Amyloid and tau positron emission tomography (PET) imaging are considered the gold standards for the diagnosis of Alzheimer's disease (AD) and dementia, respectively. As the protein aggregation progresses, the cognitive impairment aggravates and the cost of care rises significantly, placing a considerable burden on caregivers and health systems. Timely diagnosis provides individuals and their loved ones with the opportunity to plan for care, make lifestyle changes, and access treatment options to help manage the disease. Misfolded proteins represent a set of biomarkers measurable in the cerebrospinal fluid and in blood to detect the presence of amyloid plaques and tau tangles, as well as to assess the risk of developing AD earlier [1]. Several proteins have been tested in tens of clinical studies on AD and Parkinson's disease, including the isoforms 40 and 42 of the amyloid-β protein, phosphorylated tau protein (p-tau) isoforms, such as p-tau217 and p-tau181, neurofilament light chains, glial fibrillary acidic protein, and α-synuclein. By using a machine learning algorithm and plasma biomarkers in AD, a very recent study demonstrated that plasma biomarker-based stratification strikes an ideal balance between diagnostic accuracy and cost-effectiveness when compared to amyloid PET [2]. According to updated diagnostic criteria for AD, adults positive for AD biomarkers without cognitive decline should not be diagnosed with AD but instead classified as "at risk" [3]. Interestingly, proteins implicated in neurodegenerative diseases of the elderly play a crucial role in the development of the nervous system during prenatal and early postnatal life. Specifically, p-tau217 plasma levels are significantly higher in newborns compared to healthy adults and those with cognitive impairment, suggesting a key role of this isoform for the

physiological neurodevelopment of the baby [4]. Over the first month of life, p-tau217 plasma levels decline in full-term neonates but not in premature babies, remaining elevated for several weeks longer.

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LECT 3

THINKING FORWARD: THE ROLE OF METABOLOMICS FOR BRAIN HEALTH AND DISEASE

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Metabolomics, the comprehensive analysis of small-molecule metabolites in biological systems, is emerging as a translational approach for advancing our understanding of brain health and disease. The brain is an organ with high metabolic demand, susceptible to alterations in energy, lipid, and amino acid metabolism. Recent studies demonstrate that metabolomic profiling can reveal early biochemical changes preceding clinical symptoms, offering unique opportunities for risk prediction and early diagnosis of neurodegenerative and psychiatric disorders. Perturbations in pathways such as branched-chain amino acids and the tryptophan-kynurenine axis have been linked to cognitive decline, depression, and neuroinflammation. Looking forward, metabolomics holds significant promise for identifying novel biomarkers, guiding precision medicine, and informing nutritional or pharmacological interventions aimed at preserving brain health across the lifespan. Despite current challenges of standardization and reproducibility, the field is rapidly evolving, positioning metabolomics as a critical component in the future landscape of brain research and clinical neuroscience.

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LECT 4

BUILDING RESILIENCE THROUGH EXPERIENCE. THE CONCEPT OF COGNITIVE RESERVE

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The concept of cognitive reserve has been a cornerstone in explaining why individuals with similar levels of brain pathology can show strikingly different clinical outcomes. Since Stern's seminal works in the early 2000s [1], cognitive reserve has become central to research on aging, dementia, and resilience, shaping both theoretical frameworks and intervention strategies. Education, occupational complexity, and intellectually stimulating activities have long been considered primary contributors to reserve, supporting the idea that life experiences can protect against decline.

However, recent evidence – such as the cross-national longitudinal analysis of cohorts across 33 Western countries [2] – has begun to challenge this view. In particular, these findings suggest that education (typically defined as years of formal schooling or highest attained degree) may not provide the protective effects against late-life cognitive decline once thought, raising important questions about how cognitive reserve is conceptualized, measured, and operationalized.

This talk will provide a historical overview of the development of the cognitive reserve concept, from its origins in Stern's work to contemporary debates fueled by new evidence. While the construct remains valuable, it requires a more rigorous methodological foundation to disentangle causal mechanisms from correlational patterns. Methodological improvements, including the use of harmonized longitudinal data and of robust analytic approaches, can help refine our understanding.

Ultimately, it is essential to emphasize that studies that commence in early life and follow individuals throughout their life course can provide crucial insights. By considering the developmental origins

of reserve and examining how early-life experiences interact with later exposures and structural brain changes, we can move toward a more nuanced and dynamic account of resilience. This shift has implications not only for research design but also for interventions and public health strategies aimed at promoting healthy cognitive aging.

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LECT 5

NEUROFILAMENTS IN THE DIAGNOSIS OF BRAIN INFLAMMATION AND NEURONAL DAMAGE

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Neurofilaments are neuron-specific cytoskeletal proteins, primarily found in long myelinated axons of both the central and peripheral nervous systems, that provide structural support, regulate axonal diameter, and facilitate rapid nerve conduction. Neurofilaments consist of three subunits, light (NfL), medium (NfM) and heavy (NfH), which, along with alpha-internexin and peripherin, form the backbone of the axonal cytoskeleton. Upon axonal damage of some sort, neurodegenerative processes and ongoing neuronal turnover release NfL into the interstitial fluid, which subsequently enters the cerebrospinal fluid (CSF) and, to a lesser extent, the blood. Hence, in physiological conditions, NfLs are present in low concentrations in both CSF and serum, but levels rise proportionally to the extent of axonal injury [1]. Reference intervals for NfL are essential for distinguishing pathological elevations from normal physiological variability, as several factors influence NfL concentrations. Age is a significant determinant, with the highest serum NfL levels observed in neonates, followed by a decline throughout childhood and adolescence, and a gradual linear increase in adulthood. Sex does not appear to significantly affect NfL levels, while other factors (body mass index, renal function, and comorbidities) can contribute to variability, especially in adults [2]. Age-adjusted Z-scores and percentile curves facilitate the accurate interpretation of individual NfL values relative to a normative population, thereby supporting their utility [3]. The clinical utility of NfL as a biomarker has been extensively demonstrated in various neurological diseases affecting adults. In multiple sclerosis (MS), NfL is used to detect subclinical axonal injury, monitor disease progression, and inform therapeutic decisions. Elevated NfL levels correlate with the frequency of relapses, brain atrophy, and disability progression, while decreasing levels reflect treatment efficacy. NfL has also been studied in neurodegenerative disorders such as amyotrophic lateral sclerosis, Alzheimer's disease and in patients with traumatic brain injury, where it serves as a prognostic and monitoring biomarker. In pediatrics, NfL has emerged as a valuable tool for assessing axonal injury in both chronic and acute neurological conditions. Elevated NfL levels have been observed in pediatric-onset MS, spinal muscular atrophy, myelin oligodendrocyte glycoprotein antibody-associated disease, and encephalitis. In conclusion, NfL is a robust biomarker of axonal injury with wide-ranging applications in both adult and pediatric neurology [4]. Advances in ultrasensitive immunoassays and the establishment of age- and assay-specific reference intervals have enabled its use for diagnosis, monitoring disease progression, and evaluating treatment response. Ongoing efforts to standardize assays, expand reference datasets, and integrate NfL measurement into clinical workflows will further enhance its utility as a universal biomarker of neuronal integrity.

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