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Speaker Abstracts

Keynote Lecture 1

Knowing the past, looking to the future: The importance of international collaboration in advancing medical knowledge

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As with other areas of medicine, the discipline of neuropathology has benefited enormously from international collaboration over the past many decades, with activities ranging from international congresses and consensus meetings to scientific partnerships and visiting lectureships. Through a review of letters and a painting, Dr. Louis will discuss the contributions of Dr. Pierre Charles Alexandre Louis, the 19th-century Parisian physician, to medicine in general and specifically to the training of Boston-area doctors affiliated with the Massachusetts General Hospital – a story that illustrates the value of mentorship, education and collaboration in medicine. Similar recent examples in our field include WHO, cIMPACT-NOW and ADAPTR efforts – all highlighting the value of neuropathologists with different viewpoints and overlapping expertise from different countries coming together to facilitate medical progress.

Keywords: Pierre Charles Alexandre Louis – neuropathology – collaboration – mentorship

Keynote Lecture 2

AI-guided neuro-oncological pathology

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Artificial intelligence (AI) promises unprecedented transformation in many fields, including neuropathology. This development can be seen both as an opportunity and a threat. In fact, opportunities may themselves become threats if handled incorrectly – through over-reliance on unvalidated models, or by leveraging emerging technologies too late, too lightly, or inappropriately. This presentation will offer a selective overview of current AI developments relevant to neuropathology and, most importantly, serve as a basis for further discussion.

Keywords: artificial intelligence – digital neuropathology

Keynote Lecture 3

CCG expansion in ABCD3 causing oculopharyngodistal myopathy and other novel non-coding repeat expansions diseases

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Purpose/Focus: overview of recently identified non-coding repeat expansion diseases, including RFC1 repeat expansion and CGG repeat expansion associated with Oculopharyngodistal myopathy. Key Points: clinical, genetic and disease-mechanism of RFC1 repeat expansion causing CANVAS and disease spectrum. Identification of CCG expansion in ABCD3 causes oculopharyngodistal myopathy in individuals of European ancestry. Use of novel sequencing technologies for the diagnosis of non-coding repeat expansion diseases. Audience takeaways: non-coding repeat expansions are increasingly recognized as a common cause of missing heritability in neuromuscular diseases. Novel sequencing technologies will likely further boost their identification and assist clinicians with their diagnoses.

Keywords: repeat expansion diseases – oculopharyngodistal myopathy – CANVAS

Keynote Lecture 4

The pathogenesis of α-synucleinopathies

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The abnormal accumulation of α-synuclein (αSyn) plays a central role in the pathogenesis is synucleinopathies, such as Parkinson's disease (PD) and dementia with Lewy body (DLB). αSyn neuronal aggregates are rich in membranous structures, including vesicles, lysosomes and vesicles, suggesting that the build-up of disrupted organelles contribute cellular neurodegeneration in PD. αSyn undergoes various post-translational modifications (PTMs) that critically affect its structure and aggregation propensity in synucleinopathies. Understanding the subcellular αSyn localization and its interactors might hold important clues for developing disease-modifying therapeutic strategies in PD and DLB. To gain more insight in the abundance of αSyn PTMs in brain lysates and synaptosomes, we used inhouse developed AlphaLISAs. In addition, we studied the subcellular localisation of aSyn proteoforms, including different PTMs, using an extensive panel of well-characterized epitope- and PTMs-specific αSyn antibodies, cell-type specific and organelle markers. Here, we show that pSer129 and c-terminal truncated (CTT) αSyn is markedly upregulated under pathological conditions. aSyn epitope and PTM specific antibodies show different bindings profiles across brain regions and synucleinopathies. pSer129 synaptic enrichment was

present in early disease stages and increased in remaining swollen dopaminergic terminals during disease progression in iLBD, PD and DLB. CTT and N-terminal αSyn were enriched within lysosomes, mitochondria and synapses in nigral dopaminergic neurons and in glial cells. Our data suggest that CTT aSyn lysosomal accumulation and impairment precedes Lewy body formation. These findings highlight the potential role of promoting αSyn degradation by modulating lysosomal protease activity as a therapeutic strategy to prevent the progression of αSyn pathology.

Keywords: α-synuclein posttranslational modification – lysosomal clearance – cellular neurodegeneration – STED microscopy – Parkinson's disease – dementia with Lewy body

Keynote Lecture 5

Adaptive immune response in the brain in healthy and inflammatory conditions

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Purpose/Focus: The human brain is characterized by a tight control of inflammation. Recent developments improved our understanding on how recruitment of lymphocytes into the borders of the central nervous system (CNS) is regulated in a healthy state. This provides a useful framework to better understand perturbances in CNS lymphocytes in the context of multiple sclerosis (MS) as most prevalent chronic inflammatory CNS disease. Key Points: In this lecture, I will highlight recent findings of our group on the perivascular tissue-resident memory T cell as dominant lymphocyte encountered in the non-diseased human CNS. The routes of and phenotypic changes associated with CNS T cell-homing will be elaborated on by analyzing lymphocyte fractions isolated from post-mortem human blood, choroid plexus, leptomeninges, cerebrospinal fluid and white matter. With these findings as a reference, we will explore lymphocyte accumulation in association with MS white matter lesions. The presence of ongoing activity in white matter lesions at autopsy associates with accumulation of perivascular lymphocytes. The case for local interaction between resident CD4+ T cells and B cells as driver of white matter lesion initiation and activity will be made by integrating data from immunohistochemistry, spatial transcriptomics, and flow cytometry. Implications for putative therapeutic strategies to suppress progressive disability in MS will be discussed. Audience takeaways: By attending this talk, the audience will obtain more knowledge on the regulation of lymphocyte recruitment in the human CNS. This knowledge may provide attendees with some new perspectives on drivers of ongoing white matter lesion-activity in advanced MS.

Keywords: Central Nervous System – T lymphocytes – B lymphocytes – Multiple Sclerosis

Keynote Lecture 6

Neural stem cells origin, heterogeneity and regulation in the adult mammalian brain

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The mammalian Ventricular-Subventricular Zone (V-SVZ), in the walls of the lateral ventricles, retains the largest reservoir of Neural Stem Cells (NSCs) in the postnatal brain. These NSCs have been identified as a sub-population of astroglial cells with a small apical contact with the lateral ventricle (B1 cells). The long-term persistence of B1 after birth is considered key for the protracted generation of glial cells and neurons in the brain of juveniles and adults. In adult mice, B1 cells generate oligodendrocytes and large numbers of young neurons that migrate a long distance to reach the olfactory bulb. I will discuss how B1 cells are directly derived from radial glia and specified in the embryo. During these early developmental stages, B1 cells acquire regional identity that determines the types of neurons they will produce in postnatal life. However, recent work in mice suggests that B1 cells are largely depleted during juvenile and early adult life. In contrast, neurogenesis continues at a relatively higher rate into adulthood. I will present new data indicating that a second population of astroglial cells, which do not contact the lateral ventricle (B2 cells), have transcriptomic properties of both quiescent and activated NSCs and can generate new neurons and glial cells well into adulthood. We have developed methods for the identification of B1 and B2 cells, and confirmed that B1 cells are largely depleted in early adulthood, but B2 cell numbers increase postnatally and are maintained into adulthood. Similarly, we have found that B1-like cells in humans are depleted soon after birth, but a population of B2-like cells persists into adulthood. The work provides a new understanding of the cellular mechanism by which adult neurogenesis is maintained in the adult and aged rodent brain. This process could help understand the extent to which gliogenesis and neurogenesis continue in the postnatal human V-SVZ.

Keywords: adult neurogenesis – neural progenitors – ventricular zone – subventricular zone – primary cilia – neuronal replacement – subependymal zone

Symposium 01 cIMPACT-NOW updates

Chairs: Pieter Wesseling (the Netherlands) and Guido Reifenberger (Germany)

SY01-1

Introduction

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Soon after publication of the revised 4th edition of the WHO CNS tumor classification in 2016, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy – Not Official WHO (cIMPACT-NOW) was established. Important goals of this consortium are to provide guidelines for practicing diagnosticians and guideposts for future WHO classification. Between publication of the revised 4th and the 5th edition of the WHO CNS tumor classification (WHO CNS5; 2021), seven cIMPACT-NOW updates were published. Following publication of WHO CNS5, cIMPACT-NOW began to work on six practical updates again, three of which will be discussed in this symposium.

SY01-2

Meningiomas

Felix Sahm[1], Kenneth D. Aldape[2], Priscilla K. Brastianos[3], Daniel J. Brat[4], Sonika Dahiya[5], Andreas von Deimling[1], Caterina Giannini[6], Mark R. Gilbert[7], David N. Louis[8], David R. Raleigh[9], Guido Reifenberger[10], Sandro Santagata[11], Chitra Sarkar[12], Gelareh Zadeh[13], Pieter Wesseling[14], and Arie Perry[15]

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The 2021 WHO classification of CNS tumors introduced the first molecular markers for meningiomas, namely CDKN2A/B homozygous deletion and TERT promoter mutation. However, following the release of the CNS5+ classification, additional emerging markers and multi-marker approaches for meningioma grading have been identified. To provide guidance on the relevance and practical application of these evolving concepts, the cIMPACT Consortium has issued its first update specifically dedicated to meningiomas. cIMPACT 8 addresses both clarifications regarding the current WHO classification – including aspects such as brain invasion and the counting of mitotic figures – and offers specific recommendations for the use of molecular markers and complex assays such as methylation profiling and RNA signatures. This presentation will discuss these developments, with a particular focus on the novel molecular markers. A key recommendation from Z-Impact 8 is the proposal to classify meningiomas exhibiting a 1p deletion in combination with a 22q deletion as WHO grade 2, regardless of histological features that might otherwise suggest a lower grade. In summary, the cIMPACT 8 update is designed to provide pragmatic guidance for the integration of new molecular findings into the diagnostic work-up of meningiomas, supporting a more precise and biologically informed grading approach.

Keywords: meningioma – classification – molecular diagnostics

SY01-3

IDH- and H3-wildtype diffuse high-grade gliomas and posterior fossa ependymal tumors

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This talk will summarize the recent recommendations of the cIMPACT-NOW working group on the classification of IDH- and H3-wild-type diffuse high-grade gliomas and posterior fossa ependymal tumors. It will include several proposed changes that clarify issues from the current WHO classification and will also provide some practical examples.

Keywords: cIMPACT-NOW – IDH- and H3-wildtype diffuse high-grade gliomas – glioblastoma – posterior fossa ependymal tumors

SY01-4

How to define (new) tumor types

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Introduction: Molecular profiling studies have greatly advanced accuracy of central nervous system (CNS) tumor classification. In addition, groups of tumors featuring distinct molecular characteristics are increasingly identified that may represent novel CNS tumor types or subtypes. Objectives: The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) assembled a group of experienced neuropathologists and clinical neuro-oncologists with the aim to define consensus criteria required for recognition as a new CNS tumor type. Materials and methods: The cIMPACT-NOW working group discussed the roles of molecular, histological and clinical features, and what the burden of proof should be for recognition of a group of tumors as a new CNS tumor type. Results: The results of the discussions of the cIMPACT-NOW working group and the resulting final consensus recommendation will be presented. In brief, the proposed criteria consist of a combination of a (1) distinct clinical phenotype with at least two of the three following criteria: (2) a unique clustering pattern based on large-scale molecular profiling, e.g., DNA methylation analysis; (3) an associated molecular profile comprising either a single or a combination of two or more genetic driver alterations, and (4) associated microscopic (including immunohistochemical) features. As a formal requirement, characteristics of proposed new CNS tumor types should have been reported in at least two independent publications. Conclusion: This educational lecture will detail the cIMPACT-NOW consensus recommendation for recognition of new CNS tumor types. These criteria should provide a rationale framework for incorporation of proposed novel CNS tumor types into future CNS tumor classifications.

Keywords: CNS tumor classification – tumor type definition – cIMPACT-NOW

Symposium 02 Pathology, genetics and animal models in titinopathies

Chairs: Bjarne Udd (Finland) and Volker Straub (UK)

SY02-1

Muscle pathology of titinopathies

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Focus: The range of different types of titinopathies is extremely large with currently more than 12 different phenotypes delineated, and all are not yet identified. This makes the diagnostic process complicated and pathology may help to clarify unclear variants. Key points: – The choice of muscle for biopsy is key for understanding because of differences in involvement, – Muscle MRI is the best method to choose the optimal location, – Different genotypes and phenotypes have different pathology findings, – some common features are increase of internal/central nuclei and uneven oxydative stains, – Dominant titinopathies have rimmed vacuoles in target muscles and HMERF also cytoplasmic bodies. Rimmed vacoules may occur in recessive titinopathies with mutations in the C-ter gene. Takeaway for the audience: The diagnostics of titinopathies rely on genotyping and deep phenotyping where pathology can assist the process.

Keywords: muscle MRI – muscle selectivity large variation

SY02-2

Animal models in titinopathies

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Monoallelic truncating variants in titin (TTNtv) have been associated with cardiomyopathy with low penetrance, while biallelic TTNtv cause recessive muscle diseases, with or without cardiac involvement. An increasing number of missense variants – primarily in two hotspots, exon 344 and exon 364, but also outside these regions – appear to cause skeletal muscle disorders.Despite these findings, the mechanisms underlying titin-related diseases remain only partially understood. Likewise, the precise mechanical and functional roles of titin in muscle contraction have yet to be fully elucidated.Over the past few years, multiple animal models harboring TTN mutations have been generated, either to investigate the structural and biomechanical properties of specific titin domains or to replicate patient-relevant mutations. Here, we review the most extensively studied animal models, with a focus on recent findings from a medaka model of Hereditary Myopathy with Early Respiratory Failure (HMERF) and on transcriptomics and proteomics data from multiple mouse models. We highlight the insights gained from thorough analyses of these models, as well as the questions that remain unanswered.

Keywords: titin – animal models – titinopathies – mouse models – medaka

SY02-3

Digenic inheritance involving a muscle-specific protein kinase and the giant titin protein

Volker Straub and Ana Topf on behalf of the SRPK3 Study Group

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In true digenic inheritance (DI), pathogenic variants at two independent loci must be inherited together to result in disease manifestation. While thousands of monogenic diseases have been identified, only a very small number of DI diseases are known. We had originally proposed SRPK3, an X-linked serine/arginine protein kinase, as a candidate gene for centronuclear myopathy with cores. However, further interrogation of the SRPK3 pedigrees suggested that variants in this gene were not sufficient to cause disease. Through whole exome sequencing analysis, we identified heterozygous, predominantly truncating, variants in a second locus, the TTN gene, in all patients of the initial cohort. Thanks to an extensive international collaboration, we have now gathered a cohort of 36 families where pathogenic variants in both genes must be present for the myopathy to manifest. The double heterozygosity was not seen amongst 125,000 control individuals interrogated, nor is it due to an overall high frequency of TTN truncating variants, as these were significantly more common in the SRPK3 patients than in other genetically diagnosed recessive LGMD cohorts, strongly suggesting our findings are not due to chance. Furthermore, double mutant zebrafish reproduce our findings, where the srpk3–/–; ttn1+/– embryos show a severe muscle phenotype not observed in the srpk3–/– or ttn1+/– embryos alone. We therefore propose that this novel congenital myopathy is caused by digenic inheritance of pathogenic variants in SRPK3 and TTN.

Keywords: digenic inheritance – titin – SRPK3 – congenital myopathy

Symposium 03 Epilepsy and neurodevelopmental disorders: Novel tools to study the molecular and functional network complexity

Chairs: Sara Baldassari (France) and Homa Adle-Biassette (France)

SY03-1

Epileptic networks in mTORopathies: Single-cell genotyping and transcriptomic profiling in focal cortical dysplasia

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Focal cortical dysplasia type II (FCDII) is a neurodevelopmental malformation and a leading cause of drug-resistant epilepsy in children. FCDII is caused by somatic mutations activating the mTOR signaling pathway. Using single-nucleus RNA sequencing and genotyping on surgical cortical samples from FCDII patients, we found that these somatic mutations are more broadly distributed across cell types than previously anticipated. Notably, only a minority of mutated cells exhibited cytomegalic features. We also observed cell-type-specific transcriptional dysregulations, particularly in synaptic and neurodevelopmental pathways in FCDII glutamatergic neurons, which may contribute to epileptogenic activity via non-cell-autonomous mechanisms. Additionally, we identified cell-autonomous alterations in mitochondrial metabolism pathway, along with evidence of mitochondrial damage in dysmorphic neurons, hallmark cells of FCDII. These findings provide new insights into the complex interplay between genetic mutations and cellular networks in epilepsy, and highlight the potential for precision therapies targeting specific cell populations and molecular pathways involved in mosaic mTORopathies.

Keywords: FCD2 – mTOR – somatic mutations – epilepsy – omics

SY03-2

DNA methylation-based classification of malformations of cortical development

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Accurate classification of epilepsy-associated brain lesions, particularly malformations of cortical development (MCD), remains a significant diagnostic challenge in neuropathology. DNA methylation profiling has emerged as a promising tool to complement histopathology, offering increased diagnostic precision through objective, reproducible molecular signatures. In a multi-center retrospective study, genome-wide DNA methylation data from 308 resected brain specimens – including a broad spectrum of MCD subtypes, non-MCD epilepsies, and non-epileptic controls – were used to train a deep learning classifier. This model reliably identified disease-specific methylation patterns across entities and age groups. Its diagnostic performance was validated in an independent test cohort from the ILAE FCD consensus study, which included particularly challenging cases. The classifier correctly assigned all samples to their corresponding diagnostic categories. Further studies in glioneuronal tumors and polymicrogyria demonstrated a strong correlation between DNA methylation signatures and somatic brain variants, highlighting the potential of epigenomic data to predict genotype from epigenotype. This work supports the development of an integrated molecular classification framework for structural epilepsies, akin to advances already implemented in brain tumor diagnostics. Attendees will learn how epigenomic profiling can improve diagnostic accuracy, aid in classifying ambiguous cases, and lay the groundwork for prognostic assessment and the development of minimally invasive biomarkers.

Keywords: epigenetics – epilepsy – brain malformations – biomarker

SY03-3

Somatostatin Interneuron Immaturity in Tuberous Sclerosis Complex and the Contribution of SSTR3 to Cortical Network Dysregulation

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Introduction: Tuberous Sclerosis Complex (TSC) is a genetic neurodevelopmental disorder marked by cortical malformations, mTOR hyperactivation, and early-onset epilepsy. hile GABAergic dysfunction has been implicated in TSC, the maturation and function of specific interneuron subtypes remain unclear. Here, we focus on somatostatin-positive (SST^+) interneurons and their role in cortical network disruption. Methods: We performed single-cell RNA sequencing (scRNA-seq) on resected cortical tissue from individuals with TSC and age-matched controls to assess transcriptional maturation of GABAergic subtypes. Differential expression of developmental and maturation markers was used to evaluate interneuron trajectories. To explore the functional consequences of SST pathway dysregulation, we conducted downstream gene expression analyses and Xenopus oocyte experiments to characterize SST receptor signaling. Results: SST^+ interneurons in TSC cortex emerged as the most transcriptionally immature GABAergic subtype, retaining developmental gene expression and lacking key maturation markers. We observed dysregulation of SST and its receptor SSTR3, with increased variability in SSTR3 expression among SST^+ cells. Functional assays demonstrated that SST modulation of GABAA receptor function was altered in TSC, along with an impaired response to a SSTR3 antagonist. Discussion: Our findings reveal that SST+ interneurons in TSC cortex are both developmentally delayed and functionally compromised. Moreover, disrupted SSTR3 signaling likely contributed to impaired inhibitory control and increased network excitability in TSC, identifying this pathway as potential novel therapeutic target in mTOR-related epilepsies.

Keywords: tuberous sclerosis complex – GABA – somatostatin, immaturity – single-cell sequencing

SY03-4

mTOR hyperactivation drives mutation-specific hyperactivity in hIPSC-derived neuronal networks through altered GABAergic signaling

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The mTOR pathway is a pivotal cellular signaling pathway that im-

pacts neuronal differentiation and function. However, disrupted mTOR signaling in neurodevelopmental disorders remains poorly understood. Genetic mutations leading to hyperactivation of the mTOR pathway, collectively termed as mTORopathies, cause rare genetic and systemic disorders with profound effects on brain development and a strong clinical association with epilepsy. Immature GABAergic signaling resulting in altered excitatory/inhibitory balance in developing neuronal networks is thought to be a key mechanism underlying the etiology of mTORopathies. Using human induced pluripotent stem cells (hiPSCs) and CRISPR/Cas9 genome editing, we generated a panel of isogenic hiPSC lines carrying mutations in key mTOR regulator genes, including gain of function mutations in RHEB, MTOR, PIK3CA, as well as a loss of function mutation in TSC2. In hiPSC-derived neuronal networks composed of glutamatergic and GABAergic neurons on microelectrode arrays, we observed that all induced varying degrees of neuronal network hyperactivity, each with a distinct functional fingerprint. Pharmacological interrogation of the networks during development suggests that these mutation-specific fingerprints may arise from delayed or incomplete maturation of GABAergic signaling. This hypothesis is further supported by our findings on chloride cotransporter expression regulation over time. Furthermore, we observed alterations in glutamatergic and GABAergic synapse density, along with changes in neuronal morphology, indicating distinct structural consequences for neuronal network organization. Our findings reveal mutation-specific hyperactive network phenotypes, undercoring the complex interplay between genetic factors and mTOR pathway signaling that may underlie the clinical complexity of mTORopathies.

Keywords: mTOR hyperactivation – iNeurons – MEA – epilepsy

Symposium 04 Movement disorders

Chairs: Wilma van de Berg (the Netherlands) and Romana Höftberger (Austria)

SY04-1

Alphasynucleinopathies: Pathological entities en comorbidities

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Parkinson's disease (PD), Dementia with Lewy bodies (DLB) and Multiple system atrophy (MSA), so called synucleinopathies, are complex and heterogeneous neurodegenerative disorders characterized by variable clinical progression and the presence of neuronal or glial α-synuclein (αSyn) aggregates in predicted brain regions at autopsy. AD pathology, microvascular lesions and inflammation may vary among individuals and contribute to disease entities. We studied the prevalence, regional patterns and clinical relevance of co-pathologies in 500 PD, DLB and MSA brain donors, collected by the Netherlands Brainbank in the period 1997 until 2023. Clinical records from all donors were systematically reviewed. Neuropathological assessment consisted of Braak α-synuclein staging, MSA α-syn stage, Braak tau stage, Thal Aβ phase, TDP-LATE stage, cerebral amyloid angiopathy (CAA), neuritic plaques assessed by Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score, the presence of aging-related tau astrogliopathy (ARTAG) and argyrophilic grain disease (AGD). Lewy pathology was present in 85% of clinically-defined PD donors. A wide variety of other types of pathology, such as AD co-pathology, glial cellular inclusions (GCIs), ARTAG and vascular lesions were present. Mixed synucleinopathies showed a shorter disease duration, higher frequency of APOE-ε4 alleles, higher α-synuclein load and more microglial activation in limbic regions. More α-synuclein-positive Lewy bodies and astrocytes were present in parahippocampal and temporal regions of mixed cases. The amygdala was most severely affected in mixed PD/DLB+AD, but less pronounced in MSA. A higher burden of α-synuclein, AD co-pathology and inflammation in limbic regions may contribute to a more rapid cognitive decline in synucleinopathies.

Keywords: amyloid-β plaques – neurofibrillary tangles – microglia activation – misdiagnosis – APOE-ε4 genotype

SY04-2

A pathology update on 51 spinocerebellar ataxias (SCAs)

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Spino-cerebellar ataxias (SCAs) are rare and both clinically and genetically a very heterogeneous group of autosomal dominantly inherited diseases, currently comprising 51 subtypes. SCAs are primarily characterized by progressive cerebellar ataxia, but many subtypes also present with extracerebellar symptoms due to widespread neurodegeneration. The neuropathological correlate of ataxia is damage or dysfunction of the cerebellum and/or its afferent and efferent fiber connections. An overview of all these aspects will be given during the presentation.

Keywords: ataxia – autosomal dominant – multisystem disorder

SY04-3

Prion disease: mechanism of protein misfolding, neuropathology, and epidemiology of transmission

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Purpose and focus: Explaining the principles of protein misfolding in the context of prion disease, including the history of discovery milestones for historical context. Providing a correlation between histological findings, protein phenotypes and genotypes. The lecture will comprise animal models and how these contributed to understand human disease. Finally, we will explain the transmission of prions within humans and into humans. Key points: transmissibility of mis-folded proteins, neurotoxicity of mis-folded proteins, protein only hypothesis. Audience takeaway: you will understand how mis-folded proteins represent key to prion pathogenesis. Three mechanisms are currently known: de novo generation (e.g. sporadic CJD), transmission (BSE, scrapie, Kuru, iatrogenic CJD), and genetic forms (familial prion diseases). Mouse models will be explained, and how they contributed to understanding prion pathogenesis human disease. Transmission of prion disease will be explained with examples from human-human transmission (Kuru), and BSE and subsequent variant CJD will be explained as example of prion zoonosis, and how this can be identified by strain typing, and substantiated in large epidemiological studies. There will be a short introduction of transmission of other mis-folded proteins (specifically, amyloid beta), underpinning the principle of transmission of mis-folded proteins.

Keywords: protein misfolding – prion disease – transmissible spongiform encephalopathy – CJD – BSE

SY04-4

The pathology of IgLON5 and PSP

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Anti-IgLON5 disease is a rare neurological, probably autoimmune disorder that was originally identified in patients with a prominent REM and non-REM sleep dysfunction. First autopsy studies in two patients revealed a peculiar tauopathy that was characterized by a prominent neuronal accumulation of phospho-Tau (pTau), comprising of 3R-tau and 4R-tau isoforms, mainly in the hypothalamus, tegmentum of the brainstem and anterior and posterior horns of the spinal cord. Since the first neuropathological classification of the disease based on 6 cases in 2016, more than 20 subsequent autopsy cases of patients with different disease courses and durations have been investigated. These show a spectrum of neuropathological changes ranging from inflammation with IgG4 deposition in tissue to protein-associated neurodegeneration including one case with overlapping features of PSP. In this talk, the audience will learn about patterns of tau deposition and underlying pathomechanisms in different stages of anti-IgLON5 disease and compare these to findings in PSP.

Keywords: anti-IgLON5 disease – tauopathy – IgG4 – PSP

Symposium 05 Infectious encephalitis

Chairs: Christian Thomas (Germany) and Marianna Bugiani (the Netherlands)

SY05-1

Metagenomic sequencing of viral encephalitis

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Purpose/Focus: Viral encephalitis often remains unexplained when cerebrospinal fluid tests are negative and only archival formalin-fixed paraffin-embedded (FFPE) brain tissue is available. Hybrid-capture viral enrichment coupled to metagenomic next-generation sequencing (mNGS) offers a single-workflow solution for recovering viral genomes from such challenging material. Key Points: A probe set covering > 3,000 RNA and DNA viruses routinely boosts viral reads 200- to 1,100-fold over conventional “shot-gun” mNGS, lowers host background from ~ 99 to ~ 50%, and achieves near-complete genome coverage – even in blocks stored for > 20 years or harbouring only a few infected cells. Depths exceeding 8,000× enable strain typing, resistance-mutation screening and mapping of viral-host integration sites, while non-targeted agents (e.g., bornaviruses) still emerge at diagnostic coverage. The bench workflow mirrors familiar hybrid-capture oncology panels, requiring no additional equipment and fitting within routine turnaround times. Audience Takeaways: Participants will understand (1) why enrichment-mNGS outperforms PCR, immunohistochemistry and traditional “shot-gun” sequencing for low-quality neuropathology specimens; (2) the practical steps – from nucleic-acid extraction and library preparation to open-source bioinformatics and quality control – needed to implement the method in clinical and research settings; and (3) how the approach transforms FFPE archives into dynamic viromic resources that sharpen diagnostics, enable retrospective cohort studies and support outbreak-level phylogenetics. The workshop will provide a roadmap for integrating capture-based mNGS into neuropathology practice.

Keywords: viral enrichment – metagenomic sequencing – FFPE tissue – viral encephalitis

SY05-2

Viral encephalitis: the hidden aspect. Lessons to be learned from long COVID as a lasting post-infectious syndrome

Mireille Laforge

3I Brain- "Immune system and Brain interactions in physiology, infections and inflammation" at the UMR 1141 NeuroDiderot- INSERM and Paris Cité University research unit, Paris, France/ASTREMIHA Therapeutics

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According to the World Health Organization (WHO), infectious diseases remain one of the top three causes of death worldwide and are the leading cause in developing countries. Viruses can trigger a toxic effect in two ways: directly through viral replication or indirectly through bystander effects like cell death, inflammation, and dysmetabolism. These effects can disrupt immune homeostasis, lead to comorbidities, and have a lasting impact on brain functions and mental health. Our view of viral infection changed after the emergence of the long-term post-infectious syndrome known as long-COVID, which has been identified as having multiple causes, including viral persistence in reservoirs such as the brain and intestines. Viral encephalitis, caused by various latent viruses that are reactivated during our lifetime, or by emerging viruses that can persist in the brain with low noise replication and cause chronic neuroinflammation, progressive cognitive and intellectual complications. There is mounting evidence today of the effects of latent viruses such as EBV, HSV on the brain, as well as emerging viruses such as arboviruses, which are a grave threat and cannot be overlooked in terms of their long-term impact on the brain. We need good diagnostic tools for viral encephalitis so that we can better monitor and control these harmful effects on the brain. Achieving this will be possible once we can track the replication and reactivation of neurotropic viruses from the periphery more effectively. This will be done using immune-metabolic fingerprinting, which will allow for appropriate, targeted treatment, such as vaccination or antiviral treatment.

SY05-3

The neuropathogenesis of bird flu (H5Nx) viruses in mammals

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Highly pathogenic avian influenza A (HPAI) H5Nx viruses of the A/Goose/Guangdong/1/96 lineage continue to circulate in bird populations and frequently cross species barriers, infecting various mammals, including humans. While most transmission events result in isolated cases, outbreaks have been reported in marine mammals, minks, and, more recently, dairy cows. These events highlight the concerning pandemic potential of these viruses. Infection with H5Nx viruses in mammals is associated with severe respiratory and neurological disease. Notably, the neurological manifestations – such as ataxia, tremors, convulsions, paralysis, and seizures – are a distinguishing feature of HPAI H5Nx viruses compared to other influenza A viruses. However, the mechanisms underlying this neurovirulence remain poorly understood. To address this, we investigated the neuroinvasion, neurotropism, and neurovirulence of H5Nx viruses using ferret models and stem cell-derived neural systems. In ferrets, we demonstrated that H5Nx viruses can efficiently access the central nervous system (CNS) via cranial nerves, especially the olfactory nerve. Both in vivo and in vitro studies show that these viruses infect and replicate in a wide range of neural cell types, enabling rapid viral spread. This leads to extensive brain lesions in vivo, characterized by inflammatory cell infiltration, glial cell activation, edema, malacia, and occasionally hemorrhage. Ongoing research aims to identify the viral and host factors that drive the neurovirulence of H5Nx viruses.

Keywords: influenza A viruses – pathogenesis – neurological disease – bird flu – central nervous system – neuroinvasion – neurotropism – neurovirulence

SY05-4

COVID-19 and neurodegeneration

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Increasing clinical evidence suggests that Sars-CoV-2 infection can trigger neurological symptoms and potentially accelerate neurodegeneration. This study aims at defining the cellular neurodegeneration, including protein aggregation, axonal damage, and cellular stress and neuroinflammation in lethal COVID-19 donors, aged 31 to 86 years. Neuropathological characterization was performed using formalin-fixed paraffin-embedded post-mortem brainstem, limbic and cortical brain regions of 27 lethal COVID-19 donors. Cellular stress was evaluated using the autophagic marker p62, and axonal damage using Bielschowsky silver staining. The astrocytic and inflammatory response near axons and blood vessels was investigated using multiplex immunofluorescence and confocal imaging. Extensive inflammatory response was present in the ollfactory bulb and medulla oblongata of COVID-19 donors. α-synuclein pathology was observed in the locus coeruleus, substantia nigra in 11% of the COVID19 cases, whereas 33% showed neurofibrillary tangles and threads in limbic regions. pSer129-asyn immunopositivity was also observed in the meninges and blood vessels. Only two individuals showed pTDP43 in the limbic regions. Interestingly, P62 was observed in 88% cases, mainly in the CA1, CA4 and subiculum region in the hippocampus. We observed reduced numbers of neuromelanin- and tyrosine-hydroxylase (TH)-positive dopaminergic neurons and fibers in most COVID-19 patients compared to age-matched controls. Axonal frag-

ments and swellings were observed in substantia nigra and medial frontal cortex. Axonal and vascular damage was accompanied by reactive gliosis and microglial activation. Our findings highlight the importance of meningeal and vascular protein aggregation, severe inflammation and axonal damage in lethal cases of COVID-19.

Keywords: α-synuclein pathology – vascular lesions – axonal degeneration – inflammation – astrogliosis – Sars-CoV-2 infection

Symposium 06 CNS Vasculitis/Stroke

Chairs: Colin Smith (UK) and Melek Ahmed (Belgium)

SY06-1

Identifying diagnostic and prognostic factors in CAA-related inflammation

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Purpose: Cerebral amyloid angiopathy (CAA)-related inflammation (CAA-RI) is a potentially reversible CAA manifestation, histopathologically characterized by transmural and/or perivascular inflammatory infiltrates. We aimed to identify clinical, radiological, and laboratory variables capable of improving the diagnosis or predicting/influencing the prognosis of CAA-RI, and retrospectively evaluated therapeutic approaches. Key point: Clinical and neuroradiological observations of 7 new CAA-RI cases, including neuropathological findings of 2, were included in a systematic analysis of probable/definite CAA-RI cases published in literature until 2021. Descriptive/associative analyses were performed, including clinical, radiological, and laboratory variables to predict short-term, 6-month and 1-year outcomes and mortality, first in definite and second in probable/definite CAA-RI. Data on 205 definite and 100 probable cases were analyzed. CAA-RI had younger symptomatic onset than non-inflammatory CAA, without sex preference. Transmural/vasculitic pathology was more likely to be associated with the co-localization of microbleeds with confluent white matter hyperintensities on MRI. Incorporating leptomeningeal enhancement and/or sulcal non-nulling on FLAIR enhanced the sensitivity of the criteria. Cerebrospinal fluid pleocytosis was associated with decreased probability of clinical improvement and longer-term positive outcomes. Future lobar hemorrhage was associated with adverse outcomes, including mortality. Immunosuppression was associated with short-term improvement, with less clear effects on long-term outcomes. The superiority of high-dose corticosteroids was not established. Audience takeaways: This is the largest retrospective associative analysis of published CAA-RI cases and the first to include an expanded probable/definite cohort to identify diagnostic/prognostic markers. We propose points for further crystallization of the criteria and directions for future prospective studies. Neuropathol Appl Neurobiol. 2024; *50:* e12946.

Keywords: amyloid-β-related angiitis – cerebral amyloid angiopathy – cerebral amyloid angiopathy-related inflammation – criteria – diagnosis – outcome

SY06-2

Pitfalls in the diagnosis of vasculitis in the brain – frequent and uncommon causes and mimics

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Cerebral vasculitis, no matter whether as primary angiitis of CNS (PACNS) or as cerebral manifestation of systemic vasculitides plays a major role in the differential diagnosis of stroke, encephalopathy and headache. Very often, a mononuclear inflammatory infiltrate within the vessel wall without other definite criteria such as destructive mural changes (fibrinoid necrosis) or thrombosis remains the only pathologic alteration captured in the biopsy. This is a non-specific finding which in combination with the rarity of the disease in itself, makes the exclusion of a plethora of other diagnoses essential. Therefore, the diagnostic work-up for neuropathologists includes not only biopsy findings, but also information about patient's symptoms and signs, laboratory and cerebral spinal fluid (CSF) analyses, magnetic resonance imaging (MRI), and angiography, in addition to a thorough knowledge about the catalogue of differential diagnoses. This presentation summarizes some essential steps that lead to the diagnosis of cerebral vasculitis, describes some of its frequent and uncommon causes and mimics and discusses the red flags and pitfalls.

SY06-3

Differential diagnosis of primary angiitis and other vasculitides of the central nervous system: Histopathological challenges

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Differentiating primary angiitis of the central nervous system (PACNS) from other vasculitides involving the CNS is critical due to distinct therapeutic and prognostic implications. Histopathological evaluation remains the gold standard but requires careful interpretation to avoid misdiagnosis. PACNS typically exhibits granulomatous, lymphocytic, or necrotizing vascular inflammation, yet these patterns can overlap with those seen in systemic vasculitides secondarily affecting the CNS, infectious vasculitis (such as viral or fungal etiologies), and inflammatory cerebral amyloid angiopathy. Common pitfalls include sampling errors, nonspecific perivascular inflammation, and secondary changes mimicking primary vasculitis. Key distinguishing features, including vessel wall infiltration patterns, presence of infectious agents, and association with amyloid deposits, are crucial for an accurate diagnosis. Clinical correlation and ancillary studies are often necessary to support histological findings. Participants will learn to recognize the histopathological nuances that differentiate PACNS from other CNS vasculitides, understand the main diagnostic traps, and apply a structured approach to enhance diagnostic precision in challenging cases.

Keywords: CNS vasculitides – CNS primary angiitis – histopathology – differential diagnosis

Symposium 07 Neuropathies/skin and nerve biopsy pathology

Chairs: Maria Nolano (Italy) and Martin Lammens (Belgium)

SY07-1

Pathology of axonal degeneration in the PNS

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Lesions disrupting axon continuity cause Wallerian degeneration. Axonal breakdown followed by myelin removal is also seen in many polyneuropathies. A less severe axonal lesion, axonal atrophy, refers to abnormally small axons for their myelin sheaths and is found in various neuropathies, including metabolic, toxic, and hereditary types. Small accumulations of membranous or granular material in axons are common in biopsies but must be interpreted in context; larger accumulations indicate degeneration. More specifically, focal axonal swellings from neurofilament accumulation are seen in neuropathies due to industrial chemicals like acrylamide and methyl-n-butyl-ketone, and in hereditary conditions such as giant axonal neuropathy (GAN) and CMT2E (NF-L). Microtubular alterations are observed in taxol- and vincristine-induced neuropathy. Axonal spheroids, containing granular, vesicular, or membranous material and mitochondria, are found in neuroaxonal dystrophy, other axonopathies, and due to axonal transport blockages like in CMT2E. Spheroids resemble growth cones but lack accompanying regenerating fibers. Congregations of dysmorphic mitochondria are a hallmark of CMT2A (MFN2). Defects in proteins involved in endoplasmic reticulum shaping and autophagy are linked to hereditary spastic paraplegia and sensory-autonomic neuropathy. Affected axons show characteristic, yet not entirely specific axoplasmic reticulum widening and laddering. Abnormal adaxonal Schwann cell cytoplasm invaginations into the axon to sequester abnormal axoplasmic organelles predominantly develop at paranodal regions and appear in early degeneration. Axonal lesion may also involve secondary demyelination. In conclusion, studying axonopathic patterns enhances understanding of neurological diseases in both the PNS and CNS. Nerve biopsies actually present a unique opportunity to study such mechanisms in human tissue.

Keywords: cytoskeletal alterations – abnormal autophagy – spheroids – dysmorphic mitochondria – axoplasmic reticulum laddering – axon-Schwann cell networks

SY07-2

Skin nerve fiber pathology in neurodegenerative diseases: From Parkinsonism to ALS

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Purpose/Focus: Skin biopsy provides a unique and minimally invasive tool to investigate neurodegenerative diseases by detecting peripheral nerve changes that mirror central nervous system pathology. Understanding these alterations can enhance early diagnosis, differential diagnosis, and disease monitoring. Key Points: In Parkinson's disease (PD), intraepidermal nerve fiber (IENF) loss, particularly on the more affected side, is an intrinsic feature of the disease that is independent of L-dopa treatment. This denervation, which also affects Meissner's corpuscles and autonomic nerves, progresses alongside disease severity and duration, reflecting peripheral nerve plasticity. Sensory and autonomic denervation occurs early also in multiple system atrophy-parkinsonian type (MSA-P) and, in the distal leg, nerve loss appears even more severe than in PD. Additionally, the distribution of the "in vivo biomarker" phosphorylated α-synuclein (p-αSyn) deposits in autonomic nerves appears to differentiate PD from MSA-P. Contrasting findings have been reported on the correlation between p-αSyn deposits and cutaneous innervation and disease severity and progression. In amyotrophic lateral sclerosis (ALS), a small fiber pathology has also been described. A study on a large ALS cohort stratified according the King's stages showed progressive Meissner's corpuscle loss and increased IENF density, both findings were associated with reduced survival. Audience Takeaways: Attendees will gain

insights into the role of skin biopsy as a powerful tool for early differential diagnosis, disease monitoring, and prognosis in neurodegenerative disorders. This approach may refine clinical strategies and improve patient management.

Keywords: cutaneous biomarkers – autonomic denervation – sensory denervation

SY07-3

Nerve biopsy pathology update

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Nerve biopsy is an examination whose indications are more restricted than in the past due, among other things, to the advent of molecular biology. Nevertheless, certain indications remain essential to know and appear essential in patient management. This is particularly the case for vasculitis, neurolymphomatyosis or neuropathies associated with monoclonal gammopathy to understand the mechanism involved. In addition, the nerve requires specific techniques for optimal analysis, and certain techniques are to be favored according to the indications. While most of the techniques used have remained unchanged for several years, others have evolved. However, it seems essential to manage the nerve in such a way as to be able to perform all possible techniques if the observed lesions are not those expected, in order to get the most out of the sample. For example, the search for autoantibodies and the analysis of longitudinal sections by electron microscopy in cases of suspected nodo-para-nodopathies, the search for clonality in cases of neurolymphomatosis, the systematic use of immuno-electron microscopy in cases of gammopathy or the performance of complementary techniques in cases of suspected vasculitis now make it possible to increase the diagnostic performance of nerve biopsy. Despite the reduction in indications, nerve biopsy remains an essential examination in the management of certain patients and the technique must be demanding to maximize the biopsy and achieve the diagnosis.

Keywords: nerve biopsy – technique – electronic microscopy – vasculitis – gammopathy – nodo-paranodopathy

Symposium 08 Alzheimer's disease and modern omics

Chairs: Annemieke Rozemuller (the Netherlands) and Mark Fiers (Belgium)

SY08-1

The interactome of soluble amyloid-β across the Alzheimer's disease continuum

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Purpose: In Alzheimer's disease (AD), knowledge about interacting partners of amyloid-β (Aβ) can provide potential insight into the microenvironment present during pathological Aβ aggregation. Key points: Using affinity purification mass spectrometry with Aβ-antibodies on human brain tissue, we detected 129 proteins, including APOE and GFAP. Co-expression analysis revealed two protein modules involved in synaptic vesicle cycles, neurofilament cytoskeletal organization, septins, clathrin-mediated endocytosis, and viral-mediated pathways that interacted with soluble Aβ and were associated with AD progression. Further validation showed that Aβ interacting regions were in silico predicted in 70 of the 129 interacting proteins. In vitro binding confirmed that 64% of these proteins bound to Aβ, mainly at the C-terminal interacting region of Aβ. Take-away for the audience: This work will provide insight into the soluble Aβ interactome, which covers (1) Aβ interactors potentially modifying the amyloidogenic process of Aβ aggregation by interacting with Aβ interacting regions, and (2) non-amyloidogenic Aβ interactors possibly involved in physiological Aβ interactions. Presence of Aβ interacting regions in interacting proteins primarily to the C-terminus of Aβ might explain the well-known neuropathological "N-terminally truncated Aβ species", representing Aβ plaque initiation. In this context, the combined profile of changing levels with AD progression and confirmed Aβ-binding suggest a pathobiological rationale for e.g., PCSK1 as a candidate biomarker.

Keywords: Alzheimer's disease – affinity purification mass spectrometry – Aβ interactome – PCSK1 – soluble amyloid-β – APR homology – aggregation-prone regions

SY08-2

Epigenome-wide profiling in the dorsal raphe nucleus highlights cell-type-specific changes in TNXB in Alzheimer's disease

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Background: Emerging evidence suggests that the dorsal raphe nucleus (DRN) is among the first brain regions affected during the early stages of Alzheimer's disease (AD) pathogenesis. Recent epigenome-wide association studies (EWAS) have further implicated epigenetic alterations as central contributors to AD development. However, disease-specific epigenetic signatures in the DRN have not yet been systematically explored. Materiald and methods: As part of the EPI-AD project (http://www.epi-ad.eu/), we performed an EWAS to assess both DNA methylation and hydroxymethylation profiles in bulk DRN tissue. Follow-up analyses were conducted on laser capture microdissected serotonergic and non-serotonergic DRN cells using adapted limiting dilution bisulfite pyrosequencing to examine cell-type-specific DNA modification signatures. Results: We identified Braak stage-associated epigenetic alterations at a TNXB locus previously implicated in association with cortical AD neuropathology, alongside other dysregulated loci. Notably, when comparing TNXB modification levels between isolated serotonergic neurons and non-serotonergic cells from the DRN, we observed a significant interaction between cell type and disease condition. AD-associated modification changes were opposite in direction between serotonergic neurons and non-serotonergic cells, with the latter mirroring the bulk tissue EWAS results. Conclusion: Our findings highlight both previously known and novel epigenetic signatures in the DRN that may play pivotal roles in early AD development. Moreover, we demonstrate that TNXB epigenetic dysregulation in the DRN is dependent on both disease status and cell type, underscoring the importance of cell-type-specific neuroepigenetic analyses in AD research.

Keywords: Alzheimer's disease – dorsal raphe nucleus – epigenome-wide association study (EWAS) – single cell – limiting dilution bisulfite pyrosequencing (LDBSP)

SY08-3

Spatial transcriptomics uncovers microglia driven inflammation as a driver in Octogenarian and Centenarian Alzheimer's patients

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Alzheimer's disease (AD) progression is shaped by cellular context, yet the spatial and transcriptional determinants of resilience remain unclear. We integrated spatial transcriptomics and single-nucleus RNA-seq in brains from healthy individuals, demented and non-demented octogenarians AD patients, and cognitively diverse centenarians (CEN). This multimodal approach resolved six discrete cellular microenvironments, capturing transitions from Aβ deposition to pTau accumulation. We map a dynamic microglial trajectory from early innate responses to late antigen presentation, coinciding with neurodegenerative onset. Centenarians showed preserved cognition despite high Aβ, with reduced pTau and a distinct inflammatory signature. Our data illustrate how spatial and single-cell technologies help in dissecting neuroinflammatory states linked to pathology and resilience in Alzheimer's disease.

Keywords: Alzheimer's Disease – spatial transcriptomics – neuroinflammation

Symposium 09 Abusive head trauma in children and infants

Chairs: Jan Beckervordersandforth (the Netherlands) and Bela Kubat (the Netherlands)

SY09-1

Introduction to abusive head trauma in infants

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Abusive head trauma (AHT) in infants, historically referred to as "shaken baby syndrome" (SBS), is a clinical condition characterized by subdural hemorrhages, retinal hemorrhages, and diffuse brain injury, typically without external signs of trauma. Neuropathological findings include hypoxic-ischemic encephalopathy, traumatic axonal injury, and cerebral edema. Traditionally, these findings have been attributed to violent shaking; however, in recent years, alternative theories – such as hypoxic events, accidental short falls, or underlying medical conditions – have been proposed to explain similar neuropathological patterns. These alternative interpretations have sparked controversy, particularly in legal and forensic contexts, challenging the diagnostic certainty of AHT. Coping with this complexity requires a multidisciplinary approach involving neuropathologists, pediatricians, forensic experts, and legal professionals. Emphasis should be placed on evidence-based standards, transparency about diagnostic limitations, and continued research to refine our understanding of AHT and its differential diagnoses.

Keywords: abusive head trauma – forensic neuropathology – controversy

SY09-2

Infant head injury by shaking trauma – Part I: A biomechanical engineering perspective and field update

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Head injuries in abusive situations are a major cause of infant morbidity and mortality. Their causes are topic of much debate and include various forms of violence such as blunt force impact, shaking and compression. Victims may show subdural hemorrhages, retinal hemorrhages and various degrees of encephalopathy, often with absent or inconsistent history, commonly with co-injuries indicative of abuse, like fractures and bruises. Signs of direct impact to the head are lacking in many victims. It is unclear whether violent shaking without impact to the head may cause intracranial injuries, not least because literature seems conflicting at first sight. This updated overview of the current state of art is based on our series of literature reviews and volunteers studies with instrumented dolls and will shed light on how biomechanical studies on infant head injury by shaking trauma (IHI-ST) can be so seemingly contradictive. Results were put in a "7-Step model of IHI-ST", describing kinematical chain of events with motion, velocities and accelerations being transferred from the torso of an infant being shaken, via the neck to the skull and the internal anatomy, eventually resulting in injury. Our findings suggest that various oftencited (in scientific literature and court) studies on shaking and the relations between kinematics and injury made some understandable, but unfortunate simplifications. Hence, potentially harmful aspects of shaking kinematics were overlooked or ignored until now. Furthermore, accelerations and velocities have often been compared to injury thresholds that are only valid in very different scenarios and hence shouldn't be used.

Keywords: child abuse – biomechanical model – inflicted head injury by shaking trauma – head kinematics – abusive head trauma

SY09-3

Infant head injury by shaking trauma – Part II: Comparing the kinematics of shaking a 1-year-old vs. 6-week-old surrogate

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Due to violent shaking, annually 14 – 41 per 100.000 infants get mildly to lethally injured or severely disabled. The incidence is highest in the first few months and diminishes with age. Especially mortality is highest in months 1 to 4. However, some of the injuries are also seen in non-abusive cases. Discerning accidents from violence is crucial: misjudgement may leave vulnerable infants with abusive caretakers or falsely convict innocent loving ones. Various animal, computational and physical models have been used to study the mechanisms of inflicted head injury by shaking trauma (IHI-ST). However, to the best of our knowledge, these all focused on very young and hence lightweight and small infants. The goal of the current study was to quantify and compare the kinematics of violently shaking smaller versus larger infants. This was investigated by having two instrumented test-dummies representing a 6-week-old and 1-year old child shaken by 33 and 40 participants, respectively, while recording the kinematics of the dummies' heads and torsos. Participants were instructed to shake the dummies as hard as possible (primary goal), and to keep that up for as long as possible (secondary goal). Participants could shake the 6-week-old surrogate more fiercely, with particularly

peak rotational accelerations of the head being much higher than in the 1-year-old surrogate. Since it has been hypothesized that rotational motion of the head may result in some of the main injury mechanisms in shaking, these results suggest that shaking a smaller child more easily produces loads that cause IHI-ST.

Keywords: child abuse – biomechanical model – inflicted head injury by shaking trauma – head kinematics – abusive head trauma

Symposium 10 Cancer neuroscience and (other) new therapeutic avenues

Chairs: Michel Mittelbronn (Luxembourg) and Patrick Harter (Germany)

SY10-1

A H3K27M-targeted vaccine in adults with diffuse midline glioma

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Substitution of lysine 27 to methionine in histone H3 (H3K27M) defines an aggressive subtype of diffuse glioma and represents a promising target for therapy. The talk will present results from treatment of eight adult patients with progressive H3K27M+ diffuse midline glioma with a long H3K27M-specific peptide vaccine on a compassionate use basis. Five patients received H3K27M-vac combined with anti-PD-1 treatment based on physician's discretion. Repeat vaccinations with H3K27M-vac were safe and induced CD4+ T cell-dominated, mutation-specific immune responses in five of eight patients across multiple human leukocyte antigen types. Median progression-free survival after vaccination was 6.2 months and median overall survival was 12.8 months. One patient with a strong mutation-specific T cell response after H3K27M-vac showed pseudoprogression followed by sustained complete remission for > 31 months. Following TCR clonotypes over time in this patient we saw a marked increase of the top 10 TCR clonotypes in peripheral blood and also found 3 of these expanded clonotypes in CSF at the time of pseudoprogression. Functional testing revealed that 7 of the top 10 clonotypes expanded after vaccination were indeed H3K27M-reactive. Our data demonstrate safety and immunogenicity of H3K27M-vac in patients with progressive H3K27M+ diffuse midline glioma.

Keywords: H3 K27M – diffuse midline glioma – immunotherapy – peptide vaccination – immunooncology – INTERCEPT H3

SY10-2

Early steps in brain metastasis and novel prevention strategies

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Brain metastases represent a major clinical challenge in neuro-oncology, often arising as late complications of systemic cancer. Understanding the early steps of metastatic colonization in the brain is critical for developing effective prevention strategies. This talk will highlight recent advances in preclinical models that mimic the complex biology of brain metastasis, including blood-brain barrier remodeling, niche adaptation, and microenvironmental interactions. We will explore how these models are used to dissect early metastatic events and test novel interventions aimed at interrupting seeding and outgrowth.

Keywords: brain metastasis – prevention – preclinical modelling

SY10-3

Immune dynamics: What lies behind a picture?

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Immune cells are a major component of the tumor microenvironment, where they are often co-opted to support tumor growth. Although these cells originate in the blood with anti-tumor potential, they undergo a dynamic reprogramming process within the tumor that shifts them toward a pro-tumor phenotype over time. Reversing this reprogramming is a key therapeutic goal in cancer immunology. However, studying the time-dependent nature of immune cell reprogramming has been limited by static, end-point methods that require biopsies or sacrificing the animal, precluding insights into longitudinal changes. To overcome this limitation, we developed Zman-seq, a novel single-cell technology that enables high-resolution, time-resolved tracking of immune cell states in vivo. This approach opens new avenues for understanding immune dynamics and guiding the development of more effective immunotherapies.

Keywords: glioblastoma – tumor microenvironment – single-cell technology – temporal analysis

SY10-4

Skull bone T cells in patients with glioblastoma

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This presentation reflects on the recent discovery of potential local activity of the adaptive immune system in the bone marrow proximal to malignant brain cancers. The study was supported by data from clinical CXCR4 PET imaging, histology, flow cytometry-based immune-phenotyping and single cell RNA + VDJ sequencing. Patients with glioblastoma, in contrast to non-malignant disease, showed CD8+ T cell activation in the skull bone next to the tumor tissue. Skull bone T cells had specific antimoral function and their clonotypes distributed into the tumor tissue. Consequently, the authors observed a correlation of the CXCR4 PET signal with survival in a pilot cohort of patients. The findings will be discussed in light of the prevailing view of immunologically "cold" tumor tissue, arising new data on the topographical organization of the brain's immune system, and the consequences for fighting the continued high medical need in the care of patients with glioblastoma.

Keywords: brain cancer – glioblastoma – brain immunology – T cells – human skull bone

Symposium 11 Auto-immunity and MS

Chairs: Nina Fransen (the Netherlands) and Romana Höftberger (Austria)

SY11-1

Autoimmune encephalitis: A clinical and diagnostic overview

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Autoimmune encephalitis (AE) is a group of severe inflammatory brain diseases associated with a variety of neuropsychiatric symptoms. Early recognition of AE is highly important, as immunotherapy has a beneficial effect in most patients. In the past decade, various new autoantibodies against extracellular antigens have been identified, in addition to earlier described autoantibodies against intracellular ("onconeuronal") antigens. Neuropathological studies are crucial for understanding unknown pathogenic mechanisms of AE. In this case-oriented lecture, an overview of the most important clinical presentations of AE is provided. In addition, the most important steps in the diagnostic evaluation of suspected AE will be discussed.

Keywords: autoimmune encephalitis – autoantibodies – neuroimmunology

SY11-2

Neuropathology of autoimmune encephalitis

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Antibody-associated autoimmune encephalitis is a group of disorders that involves various immune effector mechanisms with significant differences in disease course and prognosis. Autoimmune encephalitis associated with antibodies against intracellular antigens are mostly characterized by a T cell dominated inflammation with neuronal loss, astrogliosis, and microglial nodules. Lesions typically present a prominent neuronal pSTAT1 expression, accompanied by abundant resident memory CD8+ T cells and CD8+/granzymeB+ T cells in close apposition to neurons. Early and late disease stages may show significant morphological differences, such as in anti-glial fibrillary acidic protein meningoencephalomyelitis with loss of astrocytes only in the very early lesions, whereas in subacute and chronic stages astrocytes are mostly replenished. In contrast, surface autoimmunity is mostly characterized by a dysfunction of neurons in the absence of immune mediated neuronal damage. The interaction of surface antibodies with their target antigen and the resulting downstream mechanisms are variable and can range from an internalization of the receptor in well-preserved neurons in anti-N-methyl-D-aspartate receptor encephalitis to an irreversible internalization and blocking of the receptor that may be associated with an accumulation of phosphorylated tau in specific brain regions in anti-IgLON5 disease. In this talk, the audience will learn about pathomecha-

nisms and patterns of tissue damage in different disease stages of antibody-associated autoimmune diseases, which is important for accurate diagnosis and interpretation of the disease.

Keywords: autoimmune encephalitis – anti-NMDAR-encephalitis – anti-GFAP meningoencephalomyelitis – antibodies

SY11-3

Pathological correlates of disease progression in MS

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Multiple sclerosis (MS) is the most frequent inflammatory and demyelinating disease of the CNS. The histopathological hallmarks of MS are multifocal demyelinated lesions. Current treatments reduce relapse activity and the formation of new lesions but have limited impact on disease progression. Clinical trials targeting progression often fail due to insufficient understanding of its underlying mechanisms. In my presentation, I will discuss currents concepts of MS disease progression as well as the results from a study, in which we compared the histopathological characteristics of brain donors with opposite disease trajectories of slow versus rapid progression selected from a well-characterized MS autopsy cohort from the Netherlands Brain Bank. Our results demonstrate that rapid disease progression is associated with pronounced activation of myeloid cells in broad perilesional rims in a subgroup of patients and indicate that such patients could benefit from pharmacological treatments targeting the innate immune response in MS.

Keywords: multiple sclerosis – myeloid cells – disease progression

SY11-4

α and β interferonopathies

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Type I interferonopathies are a group of severe and potentially lethal inborn errors of immunity that affect the central nervous system, often together with other organs such as the skin and lungs. They are due to a disruption of a complex signaling pathway regulating the relationship between nucleic acid metabolism and innate immune receptors leading to excessive and persistent production of IFN-I, a potent cytokine class regulating expression of hundreds of genes with the aim to promote an antiviral response and activate the adaptive immune system. Brain pathology manifestations include basal nuclei calcifications, leukodystrophy, vascular events, progressive atrophy and chronic meningitis. Understanding of the mechanisms underlying these manifestations proved fundamental in conceptualizing treatment strategies.

Symposium 13 Predictive markers/ therapeutic targets in CNS tumors in adults

Chairs: Leonille Schweizer (Germany) and Dieta Brandsma (the Netherlands)

SY13-1

Predictive markers and therapeutic targets in CNS metastases

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Central nervous system (CNS) metastases, including brain metastases and leptomeningeal disease, represent a significant cause of morbidity and mortality in adults with systemic cancer. Advances in molecular profiling have identified predictive biomarkers that not only forecast CNS involvement but also guide targeted therapeutic strategies. Key alterations, such as HER2 amplification in breast cancer, EGFR mutations and ALK rearrangements in lung adenocarcinoma, and BRAF-V600E mutations in melanoma, have emerged as critical determinants of treatment response. Liquid biopsy technologies, including cerebrospinal fluid (CSF) circulating tumor DNA (ctDNA) analysis, offer promising avenues for real-time monitoring of CNS disease and early detection of resistance mechanisms. Parallel to biomarker discovery, therapeutic innovations such as next-generation tyrosine kinase inhibitors, immune checkpoint inhibitors, and novel antibody-drug conjugates demonstrate enhanced CNS penetrance and efficacy, reshaping treatment paradigms. However, challenges persist, including tumor heterogeneity, the blood-brain barrier, and limited predictive power of existing markers across diverse tumor types. Ongoing translational research and clinical trials aim to refine molecular stratification and expand the therapeutic arsenal, with a focus on combinatorial regimens that overcome resistance and improve CNS control. Current knowledge on predictive markers and therapeutic targets in adult CNS metastases will be summarized, highlighting emerging strategies poised to transform outcomes in this high-risk population.

Keywords: brain metastases – predictive markers – therapeutic targets

SY13-2

Predictive markers/therapeutic targets in CNS tumors in adults – Primary CNS tumors, “non-immuno”

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Recent advances in the molecular characterization of adult central nervous system (CNS) tumors have identified several predictive biomarkers and actionable therapeutic targets that are reshaping clinical management. Particularly for gliomas and meningiomas, evidence-based frameworks such as the European Association of Neuro-Oncology (EANO) guidelines have reviewed and summarized recommendations for testing of molecular alterations in different tumor types. The talk will discuss the clinical utility and limitations of biomarkers and targets, along with the challenges of translating molecular findings into effective, individualized therapies for adult CNS tumor patients. A particular focus will be given to molecular testing strategies, comparing the implications of focused versus broader sequencing approaches in the diagnostic and therapeutic workup of adult CNS tumors.

Keywords: molecular testing – predictive biomarkers – therapeutic targets – CNS tumors in adults

SY13-3

Primary CNS tumors, "immune"

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This talk will focus on predictive markers and therapeutic targets in the field of immunotherapy for CNS tumors. Topics will include tumor mutational burden, mismatch repair deficiency, and responses to immunotherapies. Additionally, the role of PD-L1 immunohistochemistry and tumor immune microenvironment will be discussed. The presentation will conclude with novel insights obtained through spatial profiling of the microenvironment post-immunotherapy and highlighting of spatial immune checkpoint marker heterogeneity.

Keywords: TMB – MMRD – PD-L1 – microenvironment – spatial

SY13-5

Clinical perspective on predictive markers/therapeutic targets in CNS tumors in adults – the wrapping up

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In this presentation, I will discuss the current clinical value of the assessment of predictive markers for individual patients with CNS tumors. Can the current, potential promising markers already be implemented in clinical practice? If not, what is needed to do this in future? Which improvements of the techniques should be performed? And should these markers be measured in selected patients only or used in a broader patient population?

Keywords: predictive markers – CNS tumors – implementation – patient selection

Symposium 14 Inflammation in neurodegeneration

Chairs: Henne Holstege (the Netherlands/Belgium) and Jeroen Hoozemans (the Netherlands)

SY14-1

Neuroinflammatory profiles in Alzheimer's disease variants

Jeroen J. M. Hoozemans

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Alzheimer's disease (AD) presents with clinical heterogeneity, including typical amnestic and atypical non-amnestic variants such as behavioural/dysexecutive AD and posterior cortical atrophy (PCA AD). While the distribution of amyloid-beta (Aβ) and phosphorylated tau (pTau) in these variants is studied, the neuroanatomical distribution of neuroinflammation remains less explored. Furthermore, various amyloid deposit morphologies exist with varying clinical relevance. This work investigates the distribution of activated myeloid cells, astrocytes, and complement alongside Aβ and pTau in clinical AD variants and the association of these neuroinflammatory markers with clinical relevant Aβ deposits. Our data suggest that different involvement of neuroinflammation may contribute to clinical heterogeneity in AD. The neuroinflammatory response is distinctly distributed across AD clinical variants. Furthermore, different plaque types can be characterized by distinct morphological, biochemical, and clinical features. Some plaques are notably associated with specific pathological contexts, such as early-onset Alzheimer's disease. Variations in composition – such as differing ratios of Aβ40 and Aβ42 – and their associations with neuroinflammation or vascular involvement help distinguish these plaques from one another. Disentangling specific Aβ deposits and neuroinflammatory profiles between AD subgroups may be important for developing disease-mechanistic-based therapies and biomarkers.

Keywords: neuroinflammation – amyloid beta – Alzheimer's disease

SY14-2

Cognitively healthy Centenarians, what can we learn from them?

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Short description: A Dutch woman who died at age 115 without any symptoms of cognitive decline proved that cognitive decline is not inevitable. To learn about the molecular mechanisms underlying this extraordinary phenomenon, we set up the 100-plus Study, a longitudinal cohort study of cognitively healthy centenarians with the primary aim to identify protective genetic and biomolecular factors that associate with the escape of cognitive decline. Currently the cohort includes more than more than 500 centenarians from whom we collect blood samples, DNA samples, and faeces samples, and ~ 30% of the centenarians agree to post mortem brain donation. We perform yearly visits to the centenarians where we subject them to a comprehensive cognitive testing battery such that we can follow who maintains cognitive health and who declines. We have previously shown that centenarians are enriched with genetic variants that protect against Alzheimer's Disease and depleted with risk-increasing genetic variants, which may have a profound effect on maintaining cognitive health. In my talk I will outline what we have learned thus far from our intense investigations in the centenarian brains. I will touch upon where neurofibrillary tangles (NFTs) and Amyloid-β (Aβ) plaques have accumulated in the brains of these healthy but very old brains. I will touch upon the effects of primary age-related tauopathy (PART), and how centenarians with the highest levels of cognitive health resist the build-up of cortical p-tau and Amyloid-β (Aβ). Furthermore, I will show preliminary data how microglia are activated in healthy aged individuals in relation to AD-like pathology.

Keywords: centenarians – neuropathology – PART – amyloid – tau – genetic – proteomics

SY14-3

Hippocampal microglial subtypes define neurodegenerative hotspots in Alzheimer's disease

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Introduction: Microglia exhibit diverse responses in Alzheimer's disease (AD), influencing both neuroprotection and pathology. Two key subtypes have been identified: plaque-associated microglia (PaM), clustering around amyloid-β (Aβ) plaques, and coffin-like microglia (CoM), a newly described population in the CA2/CA1 hippocampal layer, often engulfing neurons and associating with tau tangles and phosphorylated α-synuclein. Objectives: This study aims to (1) characterize the molecular and morphological features of PaM and CoM, (2) examine their interactions with astrocytes and immune cells, and (3) assess their role in hippocampal deterioration. Materials and methods: We analyzed post-mortem AD and control samples using Deep Spatial Profiling (DSP), multiplex chromogenic immunohistochemistry, and confocal microscopy to map microglial subtypes and their cellular environments. Results: PaM and their associated astrocytes displayed complement activation, ErbB signaling, and metabolic dysfunction. CoM showed markers of protein degradation and immune signaling, including STING, TGF-β, and NF-κB. While CD8+ T cells were not linked to either subtype, CD163+ perivascular macrophages were often incorporated into PaM. Conclusion: Our findings highlight microglial heterogeneity and distinct neuroimmune interactions in AD. By defining the molecular landscapes of PaM and CoM, this study provides insight into hippocampal vulnerability and potential microglia-targeted therapies.

Keywords: Alzheimer's disease – hippocampus – microglia – astrocytes – macrophages – spatial profiling

Symposium 15 The role of glia in neurodevelopmental disorders

Chairs: Angelika Mühlebner (the Netherlands) and Homa Adle-Biassette (France)

SY15-1

DeepCellMap as a novel tool to study microglial cartography in human tissues

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Mapping microglial organization in human tissues during development and disease presents significant challenges because of the changing anatomical topography. We developed here DeepCellMap, a deep learning and spatial statistics tool available as open-source software and mapped microglial morphotypes in developing human brain tissues in normal conditions and when the mothers contracted SARS-CoV-2 and the fetal brains developed hemorrhages. We uncover here microglial morphological diversity during development, identify the territories occupied during colonization and demonstrate a robust association between microglia and blood vessels due to SARS-CoV-2. These findings offer insight into how microglial cells are organized using an integrated pipeline. DeepCellMap can be adapted to any cell type and is a powerful tool to study cellular organization in the context of normal processes but also neurodevelopmental disorders.

Reference to the published paper is here: https://www.nature.com/articles/s41467-025-56560-z

Background papers to DeepCellMap: https://www.cell.com/developmental-cell/fulltext/S1534-5807(22)00546-9?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1534580722005469%3Fshowall%3Dtrue and https://link.springer.com/article/10.1007/s00401-023-02629-2

Keywords: DeepCellMap – microglial cartography

SY15-2

Microglia-mediated synaptic pruning as a key deficit in neurodevelopmental disorders: Hype or hope?

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There is a consensus in the field that microglia play a prominent role in neurodevelopmental processes like synaptic pruning and neuronal network maturation. Thus, a current momentum emerged of associating microglia deficits with neurodevelopmental disorders (NDDs), such as autism, intellectual disability and schizophrenia. This concept is challenged by rodent studies and clinical data. Intriguingly, reduced numbers of microglia or altered microglial functions do not necessarily lead to overt NDD phenotypes, and neuropsychiatric symptoms seem to develop primarily in adulthood. Hence, it remains open for discussion whether microglia are truly indispensable for healthy neurodevelopment. We will cdiscuss the role of microglia in synaptic pruning and highlight area- and age dependency. An updated model of microglia-mediated synaptic pruning in the context of NDDs will be proposed and we discuss the potential of targeting microglia for treatment of these disorders.

Keywords: immune system – microglia – neurodevelopmental disorders – synaptic pruning

SY15-3

Astroglial mitochondrial dysfunction and calcium signaling in tuberous sclerosis complex

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Tuberous Sclerosis Complex (TSC) is a multisystem genetic disorder characterized by the development of benign tumors in various organs, including the brain, and is often accompanied by epilepsy, neurodevelopmental comorbidities including intellectual disability and autism. A key hallmark of TSC is the hyperactivation of the mechanistic target of rapamycin (mTOR) signaling pathway, which induces alterations in cortical development and metabolic processes in astrocytes, among other cellular functions. These changes could modulate seizure susceptibility, contributing to the progression of epilepsy and its associated comorbidities. Epilepsy is characterized by dysregulation of calcium (Ca2+) channels and intracellular Ca2+ dynamics. These factors contribute to hyperexcitability, disrupted synaptogenesis, and altered synchronization of neuronal networks, all of which contribute to seizure activity. This study investigates the intricate interplay between altered Ca2+ dynamics, mTOR pathway dysregulation, and cellular metabolism in astrocytes. The transcriptional profile of TSC patients revealed significant alterations in pathways associated with cellular respiration, ER and mitochondria, and Ca2+ regulation. TSC astrocytes exhibited lack of responsiveness to various stimuli, compromised oxygen consumption rate and reserve respiratory capacity underscoring their reduced capacity to react to environmental changes or cellular stress. Furthermore, our study revealed significant reduction of store operated calcium entry (SOCE) along with strong decrease of basal mitochondrial Ca2+ concentration and Ca2+ influx in TSC astrocytes. In addition, we observed alteration in mitochondrial membrane potential, characterized by increased depolarization in TSC astrocytes. Lastly, we provide initial evidence of structural abnormalities in mitochondria within TSC patient-derived astrocytes, suggesting a potential link between disrupted Ca2+ signaling and mitochondrial dysfunction. Our findings underscore the complexity of the relationship between Ca2+ signaling, mitochondria dynamics, apoptosis, and mTOR hyperactivation. Further exploration is required to shed light on the pathophysiology of TSC and on TSC associated neuropsychiatric disorders offering further potential avenues for therapeutic development.

Keywords: astrocytes – calcium signaling – epilepsy – mitochondria – tuberous sclerosis complex – mTOR

SY15-4

The niche matters: Origin, function and fate of CNS-associated macrophages during health and disease

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The two key immune cells present in a normally developing brain are the microglia and the barrier-associated macrophages (BAMs that comprise perivascular, choroid plexus, and meningeal macrophages). We will describe the origin of these innate immune myeloid cells and how they progressively invade the brain parenchyma and barriers during normal brain development, in animal models, and when data are available, in human samples. In normal conditions, very neutrophils and T cells can be detected by FACS or MACS in the rodent brain parenchyma. As an example of pathological brain development, we will focus on the encephalopathy of prematurity (EoP). We will briefly review the incidence, the known pathophysiological/hypothetical mechanisms, and the main clinical consequences. We will highlight the key neuropathological hallmarks of the EoP. We will also address the more recent concept of primary, secondary, and tertiary phases of the EoP. The human post-mortem data focus on the primary and secondary phases. Furthermore, the few existing studies for the EoP are more than 10 years old and did not benefit from the recent techniques allowing to characterize in depth the reactivity and infiltration of immune cells over the different phases of EoP, highlighting the need for further studies. However, some animal models of EoP have been produced and characterized. We will review the behavior of innate immune cells (microglia, BMAs, monocytes-macrophages, and neutrophils) and of T cells of the course of modelled EoP.

Keywords: microgliabarrier-associated macrophagesencephalopathy of prematuritytertiary phase

Workshop 01 Neuromuscular cases

Chairs: Anne Schänzer (Germany) and Werner Stenzel (Germany)

Workshop with interactive presentations with difficult, unusual, or unsolved muscle cases.

Workshop 02 Novel methods in neuropathological neurodegenerative research

Chairs: Zane Jaunmuktane (UK) and Anke Dijkstra (the Netherlands)

WS02-1

Digital and quantitative neuropathology

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Histological evaluation to detect hallmark features, such as Lewy bodies, amyloid plaques, and neurofibrillary tangles, remains central to the neuropathological diagnosis and staging of neurodegenerative diseases. Traditional staging schemes, based on the regional distribution of misfolded proteins, have been instrumental in advancing our understanding of conditions like Alzheimer's and Parkinson's disease. However, these manual approaches are time-intensive and subject to inter-observer variability. The emergence of digital pathology and artificial intelligence (AI) is transforming this landscape. Machine learning-based quantification and vision-driven algorithms enable systematic interrogation of histological slides, revealing patterns and features that may yield deeper mechanistic insights beyond the capabilities of traditional assessment. These tools provide high-throughput, reproducible identification of pathological features, such as regional burden of misfolded protein pathology, that are critical for accurate staging and diagnosis. Moreover, AI-powered analyses are beginning to uncover subtle and previously unrecognized histological changes, offering opportunities for novel biomarker discovery. Integrating AI with complementary data modalities, including genomics, transcriptomics and longitudinal clinical information, holds promise for a more comprehensive understanding of mechanisms and progression of neurodegenerative diseases.

Keywords: digital pathology – machine-learning – automated pathology quantification – neurodegenerative diseases

WS02-2

Neuropathology of novel repeat expansion diseases (FXTAS, polyG diseases and CANVAS)

Anke A. Dijkstra[1,2], Sanne M.M. Vermorgen[2], Nina L. Fransen[2], and Annemieke J.M. Rozemuller[2]

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Purpose/Focus: Repeat expansion (RE) diseases are a group of neurodegenerative disorders caused by the abnormal expansion of short nucleotide sequences within specific genes. These expansions often result in toxic gain-of-function, loss-of-function, or RNA-mediated mechanisms that subsequently cause neuronal dysfunction and cell death. Through repeat-associated non-AUG (RAN) translation, peptides with repetitive sequences can aggregate leading to the neuropathological hallmark of intranuclear and cytoplasmic inclusions. These peptides can be detected though p62/ubiquitin immunostaining, and im-

munostaining against the repetitive peptide to identify the specific type of RE. However, not all RE disorders show aggregation, and some RE disorders remain undiagnosed in the absence of genetic data or clear pathological markers. Key points: – Novel antibodies targeting polyG RAN-translated peptides in brain FMR1-premutation carriers, including Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) and Fragile X-associated Neuropsychiatric Disorders (FXAND) can aid in pathological diagnosis when no genetic data is available. – In cases with biallelic REs in RFC1 overt inclusion pathology is lacking. We will discuss the pathological hallmarks and clinical presentation of this disease termed CANVAS. – Finally, we will show cases with RE pathology where the gene bearing the RE is not known. These cases often have a psychiatric presentation and represent a novel group of RE diseases. Audience takeaways: Our findings show the value novel markers that can support the identification of RE disorders across a broad clinical and pathological spectrum, and when genetic information is unavailable or incomplete. In addition, our findings will help to recognize and classify novel RE-related neurodegenerative diseases.

Keywords: repeat expansion – nuclear inclusions – immunohistochemistry – RFC1 – FXTAS

Workshop 03 Leukodystrophy case discussions

Chairs: Marianna Bugiani (the Netherlands) and Wilfred den Dunnen (the Netherlands)

During this workshop we will demonstrate several rare leukodystrophy cases based on pathological changes and pathogenetic mechanisms. We will do so using live demo of digital microscopy. In the meantime we would like to have discussion/interaction with our audience, like we do during the Euro-CNS courses.

The link to the cases that will be discussed: https://edubox.nl/Instructie2016Html5.aspx#section=leereenheid&itemnr=1&itemid=&leereenheidid=4410.

Workshop 04 Profiling-based diagnosis of CNS tumors

Chairs: Patrick Harter (Germany) and Sybren Maas (the Netherlands)

WS04-1

Update: Next-generation sequencing in neuro-oncology

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Molecular diagnostics have become a cornerstone in the classification and management of neuro-oncological diseases. The integration of next-generation sequencing (NGS) into routine diagnostics has significantly enhanced the precision of tumor profiling, enabling refined subclassification and therapeutic stratification. This presentation provides an update on the application of NGS – and, where appropriate, whole-genome sequencing (WGS) – in the diagnostic work-up of central nervous system (CNS) tumors. Specific scenarios where NGS has demonstrated clear clinical utility, including the differentiation of histologically ambiguous gliomas will be discussed. The talk will address the practical considerations in implementing these technologies but also scenarios where different techniques such as whole-genome methylation profiling add more relevant information.

Keywords: sequencing – neuro-oncology – NGS – diagnostics

WS04-2

Update: New EPIC classifiers

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The presentation will provide an overview of recent developments in DNA methylation classifiers. It will focus on the updates to the Heidelberg brain tumor and sarcoma classifiers, as well as new advances in other cancer fields. Cross-platform classifiers will also be briefly discussed.

Keywords: DNA methylation Classification

WS04-3

When methylation classifiers fail – Challenges in LEAT diagnostics

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Short description: DNA methylation-based classification has significantly advanced the molecular diagnosis of brain tumors, offering objective and reproducible insights, especially for diagnostically challenging entities. However, in the case of low-grade epilepsy-associated tumors (LEAT), the approach is not without limitations. Our work highlights critical points of failure in methylation-based diagnostics for LEAT, including inconclusive classifier results, low calibrated scores, or misclassification into biologically implausible entities. These issues often stem from low tumor purity, complex glioneuronal histology, and also from the underrepresentation of LEAT variants in reference datasets. In particular, mixed lesions with developmental features or overlapping methylation profiles with focal corti-

cal dysplasias present recurrent challenges. In this talk, we will present a series of representative LEAT cases from our cohort where methylation-based diagnostics failed or misled interpretation. We will discuss how integrative approaches – including transcriptomics, histopathology, and clinical context – can help rescue classification and guide clinical decisions. The talk aims to provide practical insight into the limitations of current classifiers and outline directions for improving molecular diagnostics in the epilepsy neuro-oncology interface.

Keywords: methylation profiling – rare brain tumors – tumor classification – neuro-oncology

WS04-4

Molecular diagnostics from cell free DNA

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Cell-free DNA (cfDNA) analyses tries to redefine molecular diagnostics in neuro-oncology by enabling minimally invasive detection and monitoring of central nervous system (CNS) tumors. This talk will focus on the unique challenges and opportunities of using cfDNA – particularly from cerebrospinal fluid (CSF) – to profile the molecular landscape of brain tumors. We will examine current techniques for cfDNA analysis, discuss their clinical utility in diagnosis and potential utility for prognosis and treatment response.

Keywords: cfDNA – CSF – liquid biopsy

WS04-5

Update: RNA sequencing based classifiers

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The accurate classification of brain tumors remains a diagnostic challenge, driven by overlapping histological features and growing molecular complexity. We have developed an RNA sequencing-based classification algorithm for routine use in neuro-oncology diagnostics. By leveraging transcriptomic profiles in combination with machine learning-based classifiers, this approach enables robust identification of tumor types and subtypes across a wide range of brain neoplasms. In addition, the role of RNA sequencing will be discussed in the context of existing molecular techniques, including methylation array-based classification, highlighting complementarities and potential advantages in specific diagnostic settings.

Workshop 05 Small vessel disease

Chairs: Anne Sieben (Belgium) and Catherine Humphreys (United Kingdom)

WS05-1

Current thoughts around SVD neuropathology

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Cerebral small vessel disease (SVD) is a common pathology causing significant morbidity and mortality, but as highlighted by Humphreys et al. in 2021 neuropathologists still use mixed terminologies when describing these pathological changes. This is a reflection of a continued lack of insight into the pathobiology of the pathological changes. In this talk I will cover some of the historical aspects of SVD including the more widely accepted definitions. We are now in a new era of vascular biology research, with a molecular atlas of cerebral vascular cell types providing previously unknown insights. Recent studies have highlighted the potential role of endothelial dysfunction in SVD, impacting on the blood brain barrier and the neuro-glio-vascular unit. Monogenic forms of SVD have provided useful insights into potential mechanisms of vascular alterations and have highlighted alterations in the smooth muscle layer as a potential driver of intracerebral hemorrhage. Moving forwards it is important that neuropathologists use standardized approaches to SVD quantification in human brain samples as these samples will increasingly be used to further interrogate the basic pathophysiological dysfunction at play in this common pathology.

Keywords: SVD – pathology – arteriolosclerosis – lipohyalinosis

WS05-2

Standardized reporting of vascular pathology: Challenges in scoring

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In close to 15 years the neuropathologist have assessed protein alterations such as hyperphosphorylated τ, amyloid β-protein, α-synuclein and transactive DNA binding protein 43, in the postmortem brains of aged. It has been shown that these assessable protein alterations are relatively common and the extent of these alterations increase with age. The protein alterations listed above are considered being causative regarding cognitive impairment and ultimately dementia. These alterations can be assessed in a standardized way following published international consensus criteria. In 1980s, the cognitive impairment was attributed to vascular pathology in a substantial number of aged. Since then, a successful treatment of hypertension, cardiovascular diseases and diabetes has influenced the incidence of cerebrovascular pathology. As there are very few aged subjects lacking altered proteins in their brain the cerebrovascular pathology is today considered by many to contribute rather

than to be the cause of the symptomatology of cognitive impairment. In 1980s, the interest was primarily on the size of the infarcts or their location. During the last years several assessment strategies of cerebrovascular pathology have been suggested in publications discussing the significance of arteriosclerosis, cerebral amyloid angiopathy, myelin loss and infarcts. In some of the studies cerebrovascular alterations have been assessed in parallel with protein alterations. Based on some of the studies cerebral amyloid angiopathy and infarcts seem to have a significant contributing impact. In this presentation the background and the current state of this topic is discussed.

WS05-3

The impact of capillary cerebral amyloid angiopathy

Dietmar Rudolf Thal[1,2], Jolien Schaeverbeke[1,3], Bas Lahaije[1,4,5], Rik Vandenberghe[3,6], Christine von Arnim[7], Markus Otto[8], Pedro Magalhães[5], and Anne Wiedmer[1,4,5]

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Cerebral amyloid angiopathy (CAA) is characterized by the deposition of the amyloid β-peptide in the wall of cerebral blood vessels. All types of blood vessels, including cortical capillaries, can become involved. Interestingly, the involvement of cortical capillaries is restricted to a distinct type of CAA: CAA type 1 which is strongly associated with the apolipoprotein ε4 allele. Both types of CAA, i.e., CAA type 1 with capillary involvement and CAA type 2 without capillary CAA, are associated with Alzheimer's disease (AD) and seen in 80 – 100% of AD cases. Capillary CAA has an impact on blood flow as shown in an amyloid precursor protein transgenic mouse model (APP23). In these mice, capillary CAA develops in the thalamus, which is associated with bloodflow disturbances as visualized by magnetic resonance imaging (MRI) angiography. In the human brain the presence of CAA type 1 is associated with allocortical microinfarcts, especially in the CA1/subiculum region and with an increased level of dementia as represented by the clinical dementia rating (CDR) score. Here, we will discuss the impact of capillary CAA on the human proteome, its solubility as represented by the protein distribution over four different physicochemical tissue fractions and biological pathways involved. Funding: FWO - G065721N, G024925N; Alzheimer's Association - 22-AAIIA-963171.

Keywords: cerebral amyloid angiopathy – proteomics – Alzheimer's disease

Workshop 06 Developmental neuropathology: malformations

Chair: Homa Adle-Biassette (France)

This Workshop will start with a lecture and continue with case presentations and discussions.

WS06-1

Recent findings in microcephalies

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Microcephaly-associated neurodevelopmental disorders are characterized by a reduced neocortical size, primarily due to insufficient expansion of neural progenitor cells (NPCs) during development. While acquired insults (e.g., alcohol exposure, CMV, or Zika virus infection) affect multiple developmental processes – including neuronal migration – most genetic causes predominantly impair NPC proliferation. To date, 30 loci associated with primary microcephaly (MCPH) are listed in the OMIM database. Notably, the majority of the corresponding genes are involved in centrosome function and mitotic spindle orientation. However, pathogenic variants have been identified in fewer than 50% of patients with microcephaly. Recent research underscores the critical role of metabolism in regulating NPC proliferative capacity during neocortical development. In the early stages of mouse neurogenesis, NPCs exist in a hypoxic environment due to limited brain vascularization, promoting glycolytic metabolism. Elevated glycolysis maintains NPCs in a proliferative state and delays neuronal differentiation. As vascularization progresses, increased oxygen availability relieves hypoxia, allowing NPCs to transition toward neuronal differentiation. In parallel, glutaminolysis – a metabolic pathway converting glutamine into alpha-ketoglutarate – is essential for sustaining high NPC proliferation. In mice, glutaminolysis is supported by the MCPH1 protein, which operates in mitochondria. In humans, the mitochondrial protein ARHGAP11B, which is human-specific, further enhances glutaminolysis in basal progenitors. Despite these insights, the mechanisms regulating metabolism across diverse NPC subtypes – and their impact on proliferative capacity – remain incompletely understood.

Workshop 07 Age estimation in traumatic changes in the CNS

Chairs: Jan Beckervordersandforth (the Netherlands) and Bela Kubat (the Netherlands)

Description of Workshop: this workshop will have case presentations and discussions.

Workshop 08 Rapid (intraoperative) molecular diagnostics of CNS tumors

Chairs: Lukas Marcelis (Belgium) and Matthew Loose (UK)

WS08-1

Chairs: Lukas Marcelis (Belgium) and Matthew Loose (UK)

The session starts with a live demonstration and finishes with the analysis and discussion.

WS08-2

Rapid molecular diagnostics of CNS tumors: General principles and a Belgian perspective

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The development of novel CNS tumor classifiers based on sparse methylation profiles, combined with continuing advancements in sequencing technologies, has made rapid – even intraoperative – molecular diagnosis of CNS tumors possible. The purpose of this first introductory talk in the session is to review basic concepts and address the fundamental questions: What?, How?, Why?, and When? Key points include: What are these novel "third/fourth-generation" sequencing technologies? A comparison of Illumina (San Diego, CA, USA), PacBio Sequencing (Menlo Park, CA, USA), and Oxford Nanopore Technologies (ONT, Oxford, UK). How does it work? An explanation of the underlying concept of patient-agnostic, transfer-learned neural networks enabling rapid tumor classification from sparse methylation profiles, using STURGEON as an example. Why implement these technologies? Benefits include reduced turnaround time, low-cost setup, in-house analysis, and the potential for peroperative guidance for surgeons. When? Implementation in practice: A discussion of the challenges and opportunities based on the ongoing Belgian (UZ Leuven) experience. Attending this talk will enhance your understanding of the principles underlying rapid (intraoperative) molecular diagnostics of CNS tumors, and the potential benefits for both patients and the medical professionals involved in their care.

Keywords: molecular diagnostics – CNS tumors – rapid diagnostics – third generation sequencing

WS08-3

The Swiss Experience

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In this presentation, the Swiss experience with rapid molecular diagnostics of tumors of the CNS (and beyond) will be covered. More specifically, based on our experience gained from ultrafast methylome profiling of more than 1,800 tumors, the advantages, challenges, and limitations of our nanopore sequencing approach will be discussed.

Keywords: methylome profiling – nanopore sequencing – molecular

WS08-4

The German experience

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Nanopore sequencing of cell-free DNA (cfDNA) from cerebrospinal fluid (CSF) represents a promising minimally invasive approach for the diagnosis of central nervous system (CNS) tumors by detecting tumor-specific copy number alterations and methylation profiles to inform classification. In this monocentric retrospective study, we analyze CSF cfDNA samples subjected to nanopore low-pass WGS which we introduced into clinical routine at Charité in 2024 for non-invasive diagnosis of high-grade glioma, CNS lymphoma and solid brain metastases. Methylation and copy number profiles were correlated with final clinical diagnosis. Diagnostic performance, especially sensitivity and specificity to detect and correctly classify CNS tumors, and clinical impact on the diagnostic workup (e.g., the decision to perform stereotactic biopsy) were assessed. We report high specificity of cfDNA-based nanopore sequencing for classification of malignant primary and secondary CNS tumors, albeit with entity-specific limited sensitivity. With real-world evidence, we demonstrate the potential of CSF liquid biopsies using nanopore sequencing as a low-risk diagnostic modality in neuro-oncology.

Keywords: nanopore – liquid biopsy – cell-free DNA (cfDNA) – cerebrospinal fluid (CSF) – central nervous system (CNS) tumors

WS08-5

ROBIN – Rapid nanopOre Brain intraoperatIve classificatioN in the UK

Simon Deacon[1,2], Inswasti Cahyani[3], Nadine Holmes[3], Graeme Fox[3], Rory Munro[3], Satrio Wibowo[3], Thomas Murray[3], Hannah Mason[2], Mark Housley[2], Daniel Martin[2], Abdi Sharif[2], Areeba Patel[4], Robert Goldspring[2], Sebastian Brandner[5], Felix Sahm[4,6], Stuart Smith[1,2], Simon Paine[1,2], and Matthew Loose[3]

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ROBIN (Rapid nanpOre Brain intraoperatIve classificatioN) is a clinical tool designed to support real-time molecular classification of central nervous system (CNS) tumors using PromethION nanopore sequencing technology. We are currently piloting its integration into diagnostic workflows within the UK National Health Service (NHS), aiming to provide earlier classification data to complement existing standards of care. Epigenetic profiling has become central to CNS tumor classification, but conventional approaches, such as microarray-based methods, can result in long turnaround times. ROBIN leverages real-time nanopore sequencing to generate intraoperative methylation-based classifications within minutes, potentially supporting surgical decision-making. Full integrated classification may still require follow-up testing for somatic mutations or complex structural variants. ROBIN uses dynamic adaptive sampling to enrich for genomic regions of diagnostic relevance and to support the detection of deletions and insertions during sequencing. It combines three methylation classifiers – Sturgeon, CrossNN, and RapidCNS2 – to improve reliability in intraoperative settings. To date, we have applied ROBIN to over 100 prospectively collected CNS tumor samples, including 50 intraoperative cases. In these, initial classifications were typically available within 2 hours of sequencing, with 90% concordance observed against final integrated classifications. The same assay also supported the detection of single nucleotide variants (SNVs), copy number variants (CNVs), and structural variants (SVs) within 24 hours. Our early experience indicates that nanopore-based classification is feasible within NHS workflows and may offer timely molecular information to support clinical decision-making.

Keywords: CNS – methylation – intraoperative – realtime

WS08-6

Rapid (intraoperative) molecular diagnostics of CNS tumors: The Dutch experience

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Focus: CNS tumors are the most frequent solid tumors in children, representing the leading cause of pediatric cancer-related deaths. First line treatment mostly includes neurosurgical tumor resection in which tumor type is important to determine the correct balance between maximizing extent of resection (EoR) and minimizing risk of neurological morbidity. In our national pediatric oncology center in the Netherlands, we analyze the impact of rapid intraoperative nanopore sequencing of CNS tumor tissue on neurosurgical decision making. Key points: Sturgeon is a deep learning approach trained on simulated nanopore sequencing data generated from readily available methylation array data which can accurately classify tumor types based on intraoperatively generated sequence data [Vermeulen et al, Nature 2023]. Sturgeon delivers correct diagnoses < 40 minutes after starting sequencing in 45 of 50 retrospectively sequenced samples (no diagnosis in the remaining 5). Implementation in real time surgery results in a turnaround time between taking out sample material to diagnosis in < 90 minutes. The impact on neurosurgical decision making is analyzed in the Princess Máxima Center with an average of 115 pediatric CNS tumor resections a year. Neurosurgical decision making is defined by aimed surgical EoR (SR0-3) before surgery and during surgery (before/after frozen section and nanopore results). After surgery, achieved EoR is evaluated by integrating surgical grading with radiological assessment on MRI (MR0-3). Takeaway message: Rapid intraoperative molecular diagnostics of (pediatric) CNS tumors using nanopore sequencing is not only feasible and reliable, but also can provide guidance to neurosurgeons towards the most optimal surgical strategy.

Keywords: nanopore sequencing – pediatric CNS tumors – neurosurgery – intraoperative

Workshop 09
What makes a good paper?

Views from editors of neuropathology journals.

Chairs: Werner Paulus (Germany) and Johannes Attems (UK)

Invited speakers: Johannes Attems, Markus Glatzel, Tom Jacques, Christian Mawrin, Werner Paulus

Description of the Workshop: While interaction with journals represents an important and often emotional part of scientific life, affecting output, standing and careers, little is known about the mechanisms behind the editorial curtains. This workshop addresses the nature of a "good paper". The editors of six neuropathology journals that originate from Europe (Acta Neuropathol, Acta Neuropathol Commun, Brain Pathol, Clin Neuropathol, Free Neuropathol, Neuropathol Appl Neurobiol) present their personal views on the ingredients of papers they would like to see as submissions to their journals. We expect considerable variability in the editors' criteria of selecting papers. The workshop is intended as being informational rather than promotional. The audience is invited to share their thoughts and suggestions.

Workshop 10 Bridging Alzheimer's disease (AD) and frontotemporal dementia (FTD)

Chairs: Johannes Attems (UK) and Sandra Tomé (Belgium)

WS10-1

Fluid pathological biomarkers for frontotemporal lobar degeneration spectrum

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Purpose/Focus: Frontotemporal lobar degeneration (FTLD) spectrum encompasses distinct entities with great clinical and pathological heterogeneity. CSF, blood and other biomarkers have been explored to reflect FTLD-related pathological processes. Key Points. No fluid biomarkers specific for FTLD are available to date, but a pletora of markers can help distinguishing FTLD entities from other disease. CSF and blood biomarkers of Alzheimer's disease (AD) pathology, such as amyloid peptides and phosphorylated tau proteins, can be used for differential diagnosis of dementia disorders, but unspecific increase also in FTLD can be observed due to copathology or other mechanisms. Neurofilament light chain (NfL) and heavy chain (NfH) proteins are used to assess neuroaxonal damage. Increased CSF/blood NfL and NfH level was associated with frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) and have been proposed for routine clinical use. Also, NfL can help distinguishing typical vs. atypical parkinsonian disorders (e.g., progressive supranuclear palsy, PSP, and corticobasal degeneration, CBD), being higher in the latter group. Novel biomarkers, such as astroglial markers (es., glial fibrillary acidic protein, GFAP) and synaptic proteins (e.g., neurogranin and beta-synuclein), may increase diagnostic and prognostic confidence but preliminary results need extensive clinico-pathological validation. Finally, seed amplification assays (SAAs) represent promising novel techniques to identify protein aggregates (e.g., tau, TDP43) in different biological matrices, raising hopes for routine uses. Audience takeaways: CSF- and blood-based biomarkers can be used to investigate the neuropathological heterogeneity of FTLD in vivo.

Keywords: biomarkers – CSF – FTLD – neurofilament light chain – glial fibrillary acidic protein – phosphorylated tau protein

WS10-2

TDP-43 pathology in "pure" LATE differs from when coexisting with Alzheimer's Disease

Sandra O. Tome[1,2,3,10], Klara Gawor[1], Simona Ospitalieri[1], Markus Otto[4], Christine Von Arnim[5], Estifanos Ghebremedhin[6], Celeste Laureyssen[7,8], Kristel Sleegers[7,8], Rik Vandenberghe[9,10], Joost Schymkowitz[2,3], Frederic Rousseau[2,3], Peter T. Nelson[11], and Dietmar R. Thal[1,12]

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Focus: Limbic-predominant age-related TDP-43 encephalopathy (LATE) has been recently recognized as a cause of dementia in the elderly. LATE and Alzheimer's disease (AD) share similar clinical pictures, and their neuropathological changes – LATE-NC and ADNC – commonly co-occur. Still, the morphological and molecular features of TDP-43 lesions in dementia remain underresearched. Here, we investigated TDP-43 lesion morphology and immunoreactive species in pure LATE (degree of ADNC: low or not), and AD with LATE-NC (AD+LATE-NC). Audience takeaways: Pure LATE cases were older at death, had a lower prevalence of APOEε4 and lower Lewy body pathology. LATE cases displayed a mesh-like pattern of dystrophic processes in the hippocampus, generally extending from CA1/2 to subiculum. This like pattern was present in 81% of LATE cases and only in 18% of AD+LATE-NC. LATE cases showed higher predominance of dystrophic neurites, while AD+LATE-NC cases showed higher predominance of neuronal cytoplasmic inclusions in the amygdala. TDP-43 pS409/pS410 burdens were associated with both AD+LATE-NC and LATE, but the burdens of the remaining TDP-43 species (S403/pS404, non-phosphorylated C- and N-terminal TDP-43) were mostly associated with pure LATE, especially in the hippocampus.

Keywords: limbic-predominant age-related TDP-43 encephalopathy – Alzheimer's Disease – TDP-43 – neuronal inclusions

WS10-3

Mixed pathologies in AD with focus on LBD & LATE-NC

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The defining neuropathological features of Alzheimer's disease (AD) are amyloid-β (Aβ) plaques, neurofibrillary tangles and neuropil threads, containing hyperphosphorylated tau (tau), and neuritic plaques. However, as in all age associated neurodegenerative diseases, additional neurodegenerative pathologies are frequently present in AD; Lewy body pathology (α-synuclein) and TDP-43 pathology, as described for limbic-predominant age-related TDP-43 encephalopathy (LATE), are seen in AD in up to 30% and 70%, respectively. It does indeed become increasingly clear that the clinical picture of dementia in most aged patients results from mixed pathologies rather than from one single disease. We now refer to this phenomenon as mixed pathology, which includes various combinations of all known neurodegenerative proteinopathies as well as combinations of the latter and other cerebral diseases such as cerebrovascular disease (CVD), irrespective of their severity. We propose three distinct subgroups of mixed pathology: 1. Low level concomitant pathologies not causing any symptoms, 2. One main severe pathology causing symptoms with additional low level concomitant pathologies, and 3. Two (or more) severe pathologies, each of which could cause clinical symptoms (i.e., mixed dementia). Regardless of the clinical diagnosis a post-mortem neuropathological examination should include immunohistochemistry for the major protein aggregates (tau, Aβ, α-synuclein, and TDP-43) to allow for the detection of all possible major pathologies. A thorough neuropathological assessment of mixed pathology is indeed necessary to accurately stratify of clinico-pathological cohorts. The latter is crucial for a meaningful interpretation of clinical data on symptoms, biomarkers, and therapeutic effects.

Keywords: AD – LBD – LATE – mixed pathologies

Workshop 11 Neuropathological diagnosis of pediatric CNS tumors; how to serve the patients the best we can?

Chairs: Katja von Hoff (Denmark) and Christine Haberler (Austria)

WS11-1

Molecular classification of pediatric brain tumors – the splitters versus the lumpers

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Integration of DNA methylation profiling and DNA/RNA sequencing of tumors of the central nervous system (CNS) has considerably improved diagnostic accuracy. As a result, many new molecularly defined tumor types and subtypes have been included in the 5th edition of the WHO classification of CNS tumors and more new. Identification of more distinct molecular subtypes provides a better insight in the molecular heterogeneity of CNS tumors but on the other hand becomes more challenging for the clinic what to do with all this information and how to treat patients.

WS11-2

Clinical neuropathologists perspective

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Recent advances in molecular pathology have revolutionized CNS tumor classification. Tumors in the pediatric population comprise a large number of different types and subtypes, which require precise and reliable diagnosis due to their different biological behavior and treatment. Altogether it demands the integration of histological and molecular data, taking as well into account the patient's age and tumor location. This poses several challenges for neuropathologists. In addition to morphological experience, a wide range of complementary laboratory methods are required, including simple immunohistochemical stains and sophisticated molecular analyses (DNA methylation profiling, NGS, whole genome sequencing). In resource-limited settings, these analyses may not be available, leading to a NOS diagnosis with negative implications for patient management and outcome. In this situation, tumor tissue should be referred to a specialist center for further analysis if possible. Considerable experience is required for the interpretation of molecular data, which demands appropriate training and continuous education. Moreover, at least 7 – 15% of pediatric tumors arise in the context of a genetic tumor syndrome. Genetic variants found in tumor tissue that suggest a syndrome should be reported. They lead to the offer of genetic counselling of the patients and their families and may also influence the treatment. Last but not least, the time to diagnosis is critical. Techniques such as nanopore sequencing have the potential to overcome this hurdle. Together with other new developments, such as liquid biopsy, which is important for monitoring response to treatment and early detection of tumor recurrence, this will continue to challenge neuropathologists.

Keywords: pediatric CNS tumor – integrated diagnosis – molecular pathology

WS11-4

Improved assessment of predictive markers

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Precision oncology has transformed pediatric neuro-oncology, yet translating histo-molecular findings into individualized, effective therapies remains a major challenge. Biomarkers – diagnostic, prognostic, and predictive – are key to this transition. Predictive biomarkers are particularly critical for selecting patients for emerging treatments such as immunotherapy and theranostics, but their real-world application requires more rigorous validation. Recent data highlight these challenges. B7-H3, a promising CAR T-cell therapy target, shows heterogeneous expression across pediatric high-grade CNS tumors – challenging assumptions of uniform applicability. Similarly, theranostic targets (SSTR2A, CXCR4, FAP, PSMA) show variable expression, emphasizing the need to assess eligibility on a case-by-case basis. Our findings argue for individualized predictive biomarker testing, not class-level generalizations. Prognostic biomarkers are equally vulnerable to overinterpretation. In our cohort of pediatric low-grade gliomas, molecular drivers did not independently predict progression-free survival in multivariate analysis – despite their significance in prior univariate studies. This underscores the necessity of multivariate modeling and cohort-specific interpretation. Multi-omic diagnostics at the Princess Máxima Center now integrate methylation profiling, whole-RNA, and whole-exome sequencing in all CNS tumors. This approach enabled WHO-conform diagnoses in 95% of cases and identified targetable alterations in 94% of LGGs and 70% of HGGs. However, translation into treatment is still limited by tumor heterogeneity, rarity, and the blood-brain barrier. We advocate for shifting from tumor-type assumptions to patient-specific predictive biomarker validation. As emphasized in recent guidelines, biomarker testing must be clinically actionable, locally controlled, and pathologist-guided. Ultimately, biomarker utility must be assessed at the individual patient level – not based on preclinical models or group-level expectations.

Keywords: pediatric CNS tumors – biomarker – precision medicine

WS11-5

Clinical reality check

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Advances in neuropathological classification and comprehensive molecular profiling have significantly improved our understanding of tumour biology and heterogeneity, but the clinical implications are often less clear. As agreed in the European Society for Paediatric Oncology (SIOP-E), treatment of patients should optimally be applied within the context of a clinical trial or registry to facilitate the continuous improvement of treatments. In Europe, prospective clinical trials for primary treatment are currently available for patients with the most common tumour types, low-grade glioma, medulloblastoma, ependymoma and ATRT. Inclusion in these trials typically requires specific pathological and molecular analyses, and biomaterial collection for correlative analyses. For patients with rare tumour types, or patients with recurrent or refractory tumours, no standards for diagnostic workup have been defined. Likewise, in the absence of evidence-based standards of care, treatment often follows individual decisions, or patients are enrolled in paediatric precision oncology trials, but with generally poor outcomes. There is a medical need for accurate and rapid neuropathological diagnostics facilitating timely start of appropriate treatment. Moreover, advancing knowledge on the tumour biology, microenvironment, tumour predisposition, and prognostic and predictive biomarkers is required to improve stratification and selection of patients for evaluation of new treatment approaches such as immunotherapy. Liquid biopsy is of particular relevance for the future ability to introduce biomarker-based treatment modifications. Finally, correlative molecular-clinical data are needed to inform future trial designs. To facilitate availability of these data, harmonisation of diagnostic methods and data interpretation, as well as collaboration within international study consortia are considered essential.

Keywords: pediatric CNS tumors – treatment – molecular diagnostics

Workshop 12 Low-grade developmental and epilepsy associated brain tumors

Chairs: Angelika Mühlebner (the Netherlands) and Lucas Hoffman (Germany)

Description of the session: this session will have 1 talk, and for the rest it will be used for case presentations and discussions.

WS12-1

Low-grade epilepsy-associated tumors (LEAT) – An ongoing debate

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LEATs represent a diverse and evolving group of low-grade brain tumors that typically manifest with drug-resistant epilepsy in children and young adults. Despite increasing recognition, their classification remains an ongoing debate at the intersection of neuropathology, neuro-oncology, and epileptology. Histopathological variability, inconsistent nomenclature across centers, and overlapping molecular profiles with developmental lesions such as focal cortical dysplasias contribute to diagnostic uncertainty. Furthermore, the clinical behavior of LEATs does not always align with histological grading, and new molecular insights – ranging from MAPK pathway alterations to methylation and transcriptomic signatures – have raised further questions about their nosological status. This talk will examine

the current controversies surrounding LEAT, including entity boundaries, biological underpinnings, and implications for treatment. Drawing on data from our ongoing multi-center LEAT project, we will explore how emerging molecular classifications are reshaping our understanding, and how multidisciplinary collaboration is essential for advancing diagnostics and patient care. The debate over what constitutes a LEAT is far from settled – and this ambiguity has real consequences for clinical management and research stratification.

Keywords: rare brain tumors – epilepsy – molecular neuropathology

Workshop 13 Differential diagnosis of vacuolar myopathies and neuromyopathies

Chairs: Teresinha Evangelista (France) and Vincent Timmerman (Belgium)

WS13-1

Autophagy induction in HSPB8 pathology?

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Missense mutations in the small heat shock protein HSPB8 cause axonal Charcot-Marie-Tooth disease (CMT2F) or distal Hereditary Motor Neuropathy (dHMN). Frameshift mutations in HSPB8 were found in patients with distal myopathy and rimmed vacuolar myopathy. HSPB8 interacts with its co-chaperone BAG3 and both proteins function in the chaperone assisted selective autophagy complex (CASA). BAG3 mutations cause neuromuscular disease resembling CMT2 and cardiomyopathy. These rare diseases share a common deficit in chaperone mediated autophagy and have a major impact in protein and organelle quality control in neurons and muscles. Mutations in HSPB1 cause defects in the autophagy flux; mutant HSPB1 forces the autophagy receptor sequestosome-1 (p62/SQSTM1) to from large and rigid oligomers reducing p62 dynamics. We used embryonal fibroblasts from a K141N_Hspb8 knock-in mouse model to perform a compound screen with the aim to rescue autophagy deficits. We identified piplartine and pararosaniline as potent compounds able to increase autophagosome formation under canonical mTOR autophagy induction, promoting the degradation of LC3 and p62 soluble species as well as insoluble ubiquitinated proteins. Both autophagy inducers ameliorated phenotypes in HSPB1 and HSPB8 patient induced pluripotent stem cell-derived motor neurons. Next to these repurposed drugs, we currently study the effect of other small molecules that can induce autophagy. With the use of human induced pluripotent stem cells, we aim to understand the molecular aetiology of neuropathies and myopathies caused by failures in the autophagy flux.

Keywords: Charcot-Marie-Tooth neuropathy – distal hereditary motor neuropathy – myopathy – small heat shock protein – autophagy

WS13-2

The SIL1 disease gene in Marinesco-Sjögren syndrome, a multisystem disorder affecting neurons and skeletal muscle fibers

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Background: Marinesco-Sjögren syndrome (MSS) is a rare, autosomal recessive multisystem disorder characterized by cerebellar ataxia, cataracts, intellectual disability, and progressive myopathy. Moreover, axonal degeneration has been described. Pathogenic variants in the *SIL1* gene, encoding a nucleotide exchange factor critical for protein folding in the endoplasmic reticulum (ER), have been identified as a major genetic cause. Both a mouse model (woozy mice) and a zebrafish model have been established as suitable phenocopies that closely replicate the clinical features observed in humans. Objective: This presentation aims to elucidate the contribution of SIL1 dysfunction to skeletal muscle pathology and neuronal vulnerability in MSS, emphasizing molecular, structural, and histopathological changes. Methods: We analyzed muscle biopsies from genetically confirmed MSS patients with biallelic *SIL1* variants as well as from woozy animals using histological staining, immunohistochemistry, electron microscopy, and proteomic profiling. Moreover, neuronal cell populations were studied in these mice in addition to *Sil1* morpholino zebrafish. Molecular studies on cell culture models were preformed to further unravel molecular mechanisms and to identify modifiers. Results: Combined histological and electron microscopic analyses revealed marked mitochondrial abnormalities, vacuolar alterations, and distinct nuclear envelope pathologies. Protein-based investigations, including proteomics, demonstrated upregulation of ER-stress markers and enhanced autophagic activity across human muscle biopsies, woozy mouse tissues, and cell culture models. These findings further suggest involvement of pathophysiological cascades extending beyond the protein-folding machinery. Additionally, Ataxin-10 was identified as a potential modifier of neuronal vulnerability. Furthermore, microscopic and molecular studies demonstrated

that SIL1 deficiency leads to degenerative changes in peripheral nerves and neuromuscular junctions across fish, mice, and humans. Conclusion: These findings highlight that SIL1 deficiency contributes to multisystem degeneration in MSS by disrupting protein homeostasis, mitochondrial integrity, and nuclear architecture. The identification of Ataxin-10 as a potential modifier underscores the complexity of neuronal vulnerability and offers a possible target for future therapeutic strategies.

Keywords: *SIL1* – vacuolar myopathy – protein aggregation – nuclear envelope – ER-stress

WS13-3

Vacuolar myopathy and neurodegeneration caused by VCP mutation

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Mutations in the valosin-containing protein (VCP) gene are linked to a spectrum of disorders, including vacuolar myopathy, frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and Paget's disease of bone. VCP is a ubiquitously expressed ATPase that plays a crucial role in protein homeostasis, autophagy, and endoplasmic reticulum-associated degradation (ERAD). Mutations in this gene disrupt cellular protein clearance, leading to toxic protein accumulation and cellular dysfunction. During this presentation we aim to introduce the molecular and cellular mechanisms underpinning VCP-associated vacuolar myopathy and neurodegeneration. VCP mutations led to aberrant protein aggregation, mitochondrial fragmentation, and defective autophagic clearance. Muscle biopsy specimens revealed characteristic rimmed vacuoles and TDP-43 pathology. VCP dysfunction has a pivotal role in vacuolar myopathy and neurodegeneration.

Keywords: VCP mutations – vacuolar myopathy – neurodegeneration – autophagy – protein homeostasis

Workshop 14 Professional issues

Chairs: Tibor Hortobágyi (Switzerland/Hungary) and Colin Smith (UK)

Workshop description: Like many other areas of medicine the way we approach a diagnostic specimen is changing, and the way we practice neuropathology will change accordingly. This session will be an interactive session which will focus on areas of opportunity and areas of threat to the discipline of Diagnostic Neuropathology. In addition, we will discuss how Euro-CNS course and the European exam are changing to support new ways of working. Topics covered will include the role of molecular pathology in diagnostics, the implementation of digital pathology an dated application of AI/machine learning to diagnostic workflows.

Workshop 15 ALS – Understanding the spectrum of ALS and its genetically different forms

Chairs: Thomas Brännström (Sweden) and Robin Highley (UK)

WS15-1

Multi-omics approaches to identify the disease mechanisms of C9orf72-associated ALS

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ALS is a devastating neurodegenerative disorder, characterized by loss of motor neurons in the motor cortex, brain stem and spinal cord giving rise to progressive muscle weakness, spasticity and muscle wasting. The median survival after the occurrence of first symptoms is only 3 years, mostly due to respiratory failure. Few biomarkers exist for ALS and consequently, the molecular mechanisms involved in ALS onset and progression are poorly understood. The reasons for this can be attributed to several factors: inaccessibility of patient tissue, complexity of disease itself that cannot be traced to any one single gene, and limitations in molecular biology techniques that, until recently, did not allow for high dimensional omics data. To this end, we performed single cell transcriptomics, bulk proteomics and single cell spatial transcriptomics on post-mortem patient derived spinal cords to gain a comprehensive view of ALS, with a specific focus on C9orf72-associated ALS. We demonstrate the challenges involved in acquiring and integrating high dimensional RNA, protein and spatial information to generate a cohesive understanding of ALS, and highlight some disease mechanisms identified from the combined data.

Keywords: ALS – multi-omics – spatial transcriptomics

WS15-2

SOD1 mutations and amyotrophic lateral sclerosis

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Mutations in the SOD1 gene was the first discovered cause of ALS. Since then more than 200 different mutations in SOD1 has been linked to ALS. SOD1 mutations is one of the two most common causes of ALS. Inclusions of misfolded SOD1 has been shown to occur in neurons

and glia at autopsy in several of the SOD1 mutations. Mice transgenic for human SOD1 mutations show that aggregation of misfolded proteins starts early. In such mice at least three different aggregate types (A,B,C). One of these has also been shown to occur in patients with the same mutation. Inoculation of high molecular weight aggregates containing such misfolded SOD1 into transgenic mice confer the disease in a strain-specific manner and induce premature disease. SOD1 aggregate structure seems to be specific to intact CNS even though aggregates produced in cell lines has the ability to elicit ALS when inoculated inte transgenic mice the resulting aggregate structure differs widely.

Keywords: ALS – SOD1 – prion

WS15-3

The neuropathology of motor neuron disease and its diversity

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Purpose/Focus: Motor neuron disease is a progressive, ultimately fatal, neurodegenerative disease (or group of diseases). The incidence is ~ 1 – 4/100,000 persons/year with a median survival between 24 and 50 months. However, given delays in diagnosis, some cases with rapid disease processes may never receive a formal diagnosis in life. While the majority of cases are apparently sporadic, mutations in ~ 30 genes have been found to cause disease and there is a family history of disease in 5 – 16% of cases. Key points: The consistent pathological features of sporadic MND will be considered. In addition, the inter individual variability in pathology, seen in sporadic disease will be discussed. Some examples of monogenic disease with classical pathology will be discussed, while examples of monogenic MND with unique pathological features will be considered. Indeed some genetic cases have such unique pathology, they are arguably different diseases, raising questions about whether these mutations may be suboptimal for use in models of disease. Audience takeaways: The consistent and variable features of MND pathology for diagnosis and clinicopathological correlation; unique pathologies relating to monogenetic disease. Some tips for diagnostic practice will be given.

Keywords: motor neuron disease – amyotrophic lateral sclerosis – TDP-43 – Cystatin C – SOD1 – C9orf72

Session numbers and speaker abstracts:

All abstracts included above are invited speaker abstracts. Several workshops and symposia also have short oral presentations from selected abstracts. These regular abstracts are not included above, but can be found in the regular abstract book. Please consult the detailed scientific program for a complete overview of the content of the keynote lectures, the symposia and the workshops. The speaker abstract book does not reflect the full content of the scientific program.

Program

The full scientific program can be viewed on the ECNP2025 website: www.ecnp2025.nl.