

is central to tumor progression in preclinical models. NLGN3 is necessary for the growth of gliomas in a range of preclinical models, and therapeutic targeting of NLGN3 is presently under clinical investigation. Thus, neuronal-glial interactions not only modulate neural circuit structure and function in the healthy brain, but paracrine and synaptic neuron-glioma interactions also play important roles in the pathogenesis of glial cancers. The mechanistic parallels between normal and malignant neuron-glial interactions underscores the extent to which mechanisms of neurodevelopment and plasticity are subverted by malignant gliomas, and the importance of understanding the neuroscience of cancer.

INSP-04. CONFIRMATORY ADAPTIVE DESIGNS FOR SURVIVAL TRIALS WITH SEVERAL TIME-TO-EVENT ENDPOINTS

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Confirmatory adaptive designs comprise a range of statistical methods that allow to modify the sample size of an ongoing trial in a data-dependent way without compromising control of the type I error rate. For short-term endpoints (e.g., 3-month response rate), comprehensive methodology of adaptive designs exists. However, clinical trials in oncology often have a special focus on long-term outcome and therefore often choose a time-to-event endpoint as the primary endpoint. Typical examples are progression-free survival (PFS) or overall survival (OS). But subtle statistical problems arise when adaptively analysing survival trials. Classical designs for survival trials are therefore commonly limited to a single primary endpoint, which combines the occurrence of progression, toxicities, deaths, and other events of potential interest into a single statistical measure (composite endpoint). However, the complexity of oncological diseases can be mapped more accurately using multi-stage models, where the occurrence of progressions, toxicities and deaths is modelled jointly instead of combining them into a single composite endpoint. We present and discuss adaptive design methodology for single-arm phase II survival trials for testing hypotheses on the joint distribution of several time-to-event endpoints in the context of multi-state models. We illustrate the methodology using the example of adaptive hypothesis tests for the joint distribution of progression-free survival (PFS) and overall survival (OS) in the context of an illness-death model. The methodology is motivated from application in pediatric oncology.

INSP-05. DEVELOPMENT OF FAST CORTICAL RHYTHMS IN HEALTH AND MENTAL DISEASE

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Synchronization of neuronal activity in fast oscillatory rhythms is a commonly observed feature in the adult cerebral cortex. While its exact functions are still a matter of debate, oscillatory activity in gamma frequency range (20-100 Hz) has been proposed to organize neuronal ensembles and to shape information processing in cortical networks. Gamma activity emerges from reciprocal interactions between excitatory and inhibitory neurons. A fine-tuned balance between excitatory drive and inhibitory feedback is mandatory for circuit function underlying cognitive performance, whereas imbalance between excitation and inhibition and resulting gamma disruption have been proposed to cause cognitive disabilities in psychiatric disorders. Despite extensive investigation of gamma activity in adult brain, its development and function early in life are still poorly understood. The talk will highlight recent experimental findings that uncover the mechanisms and role of fast oscillatory activity throughout development. We will uncover how different neuronal populations interact to generate gamma oscillations. Moreover, we will show that these early oscillations are necessary for the adult cognitive abilities. On the flip side, poorer mnemonic and social abilities that have been characterized in several psychiatric disorders, such as schizophrenia and autism, might result from developmental miswiring of the brain. Our data support this hypothesis by demonstrating that weaker fast oscillatory rhythms, sparser connectivity and lower communication are present in the core circuit of cognitive processing, including the prefrontal cortex, hippocampus and entorhinal cortex, in mouse models of these disorders. Together, these findings highlight the relevance of fast cortical rhythms early in life for the adult brain function.

INSP-06. RECENT ADVANCES IN IMPROVING NEUROPSYCHOLOGICAL OUTCOMES FOR PAEDIATRIC BRAIN TUMOUR PATIENTS - ARE WE ENTERING A NEW ERA?

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Children and youth treated for brain tumours can sustain a brain injury as a consequence of the tumour and curative therapy leaving them with significant cognitive challenges. Advances in treatment for paediatric brain tumours – particularly the delivery of radiotherapy – have been associated

with improved neuropsychological outcome in survivors, however. This presentation will first focus on work documenting the impact of changes in cranial radiotherapy delivery and modality on neuropsychological late effects in children treated for medulloblastoma. Outcomes in patients treated on modern protocols are substantially improved relative to prior therapy, however challenges remain. Second, novel approaches for cognitive recovery and brain repair in survivors of paediatric brain tumours will be discussed, with a focus on novel approaches for fostering endogenous neuroplasticity for cognitive recovery and brain repair in children and youth treated for paediatric brain tumours.

INSP-07. IMPROVING COGNITIVE OUTCOMES FOR CHILDREN TREATED FOR CANCER: MOVING BEYOND THE CURE

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With improved survival rates, increasing numbers of childhood cancer survivors are living with long-term cognitive deficits that negatively impact their ability to attain important life milestones. Our collaborative research program has focused on characterizing cognitive outcomes associated with specific treatment modalities to inform modifications in front-line therapy. This line of investigation has demonstrated the negative cognitive impact of high radiation dose/large treatment volume, posterior fossa syndrome, treatment-related ototoxicity, and lower socioeconomic status (SES). Research-informed, treatment approaches under investigation include proton radiotherapy and hippocampal sparing irradiation, molecularly based risk-adapted therapy, surgical approaches with reduced risk of injury, and on-therapy otoprotectants, as well as identification of modifiable factors that are driving the protective effects of higher SES. Our research also strives to improve specification of cognitive deficits following treatment, at the behavioral and neural systems level, to identify targets for intervention. Study findings have revealed disease- and treatment-related alterations in neural systems supporting attention, working memory, and executive functions, as well as genetic factors that increase risk for cognitive late effects. We are now using sophisticated connectivity brain mapping with enhanced sensitivity to behaviorally-relevant changes in brain organization and sensitivity to intervention-based neuroplasticity to guide cognitive intervention development. A primary research focus moving forward is development of empirically validated interventions that prevent or mitigate cognitive late effects among childhood cancer survivors. Our studies have demonstrated the efficacy of stimulant medications, computerized cognitive training, and aerobic exercise for children treated for cancer, as well as the limitations to these approaches. Current investigations include use of neuroprotectant agents during radiotherapy, combining multiple interventions, interventions tailored to children undergoing treatment in infancy, and the use of virtual reality to increase intervention engagement. Our ultimate benchmark of success is ensuring children are not only cured of cancer but also experience a high quality of life.

INSP-08. CEREBELLAR MUTISM SYNDROME: INCIDENCE, SYMPTOMS, RISK FACTORS, PROGNOSIS. RESULTS AND FUTURE PERSPECTIVES FROM THE NORDIC-EUROPEAN STUDY OF THE CEREBELLAR MUTISM SYNDROME

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Cerebellar mutism syndrome (CMS) can be a devastating consequence of paediatric fossa posterior tumour surgery. This prospective observational multi-centre study was designed to investigate incidence, symptoms, risk factors and prognosis of CMS. It has been running since 2014 and is currently involving 28 centres in 10 countries. So far 600 patients have been included as of 1.2.22, and with the aim of including a total of 1000 the study is still ongoing. Analysis of the first 500 patients has described the incidence, course and associated risk factors of postoperative speech impairment (POSI). Midline location, histological diagnosis of medulloblastoma and ATRT and younger age are associated with increased risk of POSI in our cohort. Route of surgical access specifically comparing telovelar to transvermian approach does not seem to influence the risk of POSI. Second surgery is associated with a lower risk of POSI than primary surgery, whereas we found no difference in risk of cranial nerve dysfunction. Left-handedness is not associated with an increased risk of POSI. Further and ongoing analysis include language analyses of recorded patient speech samples, detailed imaging analysis and description of associations between POSI and other neurological symptoms. The results aim to facilitate pre-operative risk assessment and postoperative robust scoring methods for use in clinical trials. Presented on behalf of the CMS study group, clinicaltrials.gov: Nordic study of the cerebellar mutism syndrome.