南方科技大学生命科学学院
SUSTech · SCHOOL OF
LIFE SCIENCES

KING'S College LONDON

SUSTech-KCL Student Exchange Program

Research Project Application Form 2021/22

Project Nr. 1

PROJECT INFORMATION	
Research Area(s)	Neuroscience / Brain Research
Project Title	Associations between resting state functional connectivity and behavioural outcomes in very preterm and full-term born children
Supervisor (s) Name	Chiara Nosarti
Co-supervisor	Laila Hadaya
Abstract	**Background**: Very preterm (VPT) birth (i.e., <32 weeks of gestation) has been associated with alterations in resting state functional connectivity from foetal to adult life. However, most studies in VPT cohorts have investigated region specific connectivity patterns rather than whole-brain connectivity. Furthermore, little is currently known about associations of such patterns with behavioural outcomes, i.e., cognitive abilities, socio-emotional development, mental health. **Objectives**: to compare whole-brain functional connectivity in children born VPT and term-born controls at different levels of spatial resolution: global, regional and edgewise. Identify associations between functional connectivity patterns and behavioural outcomes. **Methods**: VPT children previously enrolled in the Evaluation of Preterm Imaging study (EudraCT 2009-011602-42) and full-term born controls, recruited from the community, are currently undergoing resting-state functional Magnetic Resonance Imaging and neuropsychological assessments at age 7-10 years. Functional connectivity (FC) matrices will be calculated as Pearson correlations between pairs of all regional timeseries. This will be achieved at different levels of spatial resolution: global, regional and edgewise. To test for differences in global, regional and edgewise FC between the very preterm and full-term groups, linear models and Network Based Statistics will be performed.
References	• Edwards, A David et al. "Effect of MRI on preterm infants and their families: a randomised trial with nested diagnostic and economic evaluation." *Archives of disease in childhood. Fetal and neonatal edition* vol. 103,1 (2018): F15-F21. doi:10.1136/archdischild-2017-313102

	• Kanel, Dana et al. "Advances in functional and diffusion neuroimaging research into the long-term consequences of very preterm birth." *Journal of perinatology : official journal of the California Perinatal Association* vol. 41,4 (2021): 689-706. doi:10.1038/s41372-020-00865-y • Hadaya, Laila, and Chiara Nosarti. "The neurobiological correlates of cognitive outcomes in adolescence and adulthood following very preterm birth." *Seminars in fetal & neonatal medicine* vol. 25,3 (2020): 101117. doi:10.1016/j.siny.2020.101117 • Zalesky, Andrew et al. "Network-based statistic: identifying differences in brain networks." *NeuroImage* vol. 53,4 (2010): 1197-207. doi:10.1016/j.neuroimage.2010.06.041
Benefits/skills for student	• Good/moderate proficiency in R • Good/moderate understanding of statistical analyses approaches, such as linear models • Interest in exploring brain-behaviour relationships • Interest in child neurodevelopment
Maximum No. of students	1

Project Nr. 2

PROJECT INFORMATION	
Research Area(s)	Neuroscience / Brain Research
Project Title	Role of MECP2 in glia-to-neuron conversion
Supervisor (s) Name	Prof. Dr Benedikt Berninger
Co-supervisor	Dr Nicolas Marichal
Abstract	Direct lineage reprogramming of glia into induced neurons emerges as an innovative strategy for brain repair. However, while glial cells can be converted into neurons with functional properties in the mouse brain in vivo, there is increasing evidence for their functional immaturity. Methyl CpG binding protein 2 (MECP2) is a nuclear protein that becomes very highly expressed as normal neurons mature, and its deficiency results in Rett Syndrome which is associated with a loss of mature traits in neurons. Here we will examine the hypothesis that induction of MECP2 is a bottleneck step successful of glia-to-neuron conversion. MECP2 expression will be compared between glia-derived induced neurons and their endogenous counterparts by immunofluorescence and single-molecule fluorescence in-situ hybridisation. Furthermore, we will study whether MECP2 gain-of-function by retrovirus-mediated expression in induced neurons can promote their maturation. This project will provide crucial insights into molecular mechanisms underpinning and/or limiting maturation of induced neurons.
References	Heinrich C, Bergami M, Gascón S, Lepier A, Viganò F, Dimou L, Sutor B, Berninger B*, Götz M*. (2014) Sox2-mediated conversion of NG2 glia into induced neurons in the injured adult cerebral cortex. Stem Cell Reports. 3(6):1000-14. Karow M, Camp JG, Falk S, Gerber T, Pataskar A, Gac-Santel M, Kageyama J, Brazovskaja A, Garding A, Fan W, Riedemann T, Casamassa A, Smiyakin A, Schichor C, Götz M, Tiwari VK, Treutlein B*, Berninger B*. (2018) Direct pericyte-to-neuron reprogramming via unfolding of a neural stem cell-like program. Nat Neurosci 21(7):932-940. Lentini C, d'Orange M, Marichal N, Trottmann MM, Vignoles R, Foucault L, Verrier C, Massera C, Raineteau O, Conzelmann KK, Rival-Gervier S, Depaulis A, Berninger B, Heinrich C. (2021) Reprogramming reactive glia into interneurons reduces chronic seizure activity in a mouse model of mesial temporal lobe epilepsy. Cell Stem Cell 28(12):2104-2121.e10.
Benefits/skills for student	Inisghts into the conceptual framework of neuronal fate specification, lineage plasticity and reprogramming Development of skills in confocal microscopy, quantitative image analysis, immunofluorescence. RNA Scope, retrovirus production, mouse brain stereotaxis Scientific and cultural exchange in a highly dynamic research environment
Maximum No. of students	1

Project Nr. 3

PROJECT INFORMATION	
Research Area(s)	Brain Research
Project Title	Probing brain function in children with complex neuropsychiatric problems
Supervisor (s) Name	Professor Paramala Santosh
Co-supervisor	Dr Federico Fiori Dr Jatinder Singh
Abstract	This research project addresses an important area of improving behavioural and physiological outcomes in children with neurobiological difficulties. Children with complex neurodisability present with severe emotional and behavioural problems. Clinically, this situation is often found in children who do not respond to treatment and have poor communication. Managing this issue is of importance as patients and parents rarely fully understand what activities produce physiological stress and what activities / interventions can help to normalize the physiological state and make the child feel better. One hurdle to the successful management of symptoms is the identification and validation of reliable outcome measures and biomarkers. A more directed approach to outcome measures and biomarkers is proposed. Although there are established diagnostic criteria and genetic testing in children with complex neuropsychiatric problems, there remains an unmet clinical need for biomarkers to noninvasively and quantitatively monitor brain function in response to treatment and physiological stressors (Gualniera *et al*., 2021). In this patient population, conventional neuroimaging approaches (fMRI) are not readily suited because sedation is required. Functional near-infrared spectroscopy (fNIRS) offers a non-invasive imaging technique for studying functional activations by measuring changes in the brain's hemodynamic properties (Liu *et al*., 2017). The aim of this project is to use fNIRS in children aged 5-18 with complex neurodisability, to monitor neurological activity of the frontal and temporal areas of the brain in response to ongoing treatment and cognition-based tasks. In combination, real-time monitoring of physiological data (cardio-respiratory monitoring) using wearable sensors will be used to provide a measure of autonomic dysregulation in these individuals. We hypothesise that patients with complex neurodisability would show lower brain activity and increased Emotional, Behavioural and Autonomic Dysregulation (EBAD) in comparison to healthy subjects. It is hoped that the combination of this rich neurological data, combined with longitudinal data from the wearable sensor monitoring of patient's physiology will revolutionise our ability to personalise treatment for children with EBAD. The project will allow us to probe the neurobiological mechanism underlying functional impairment in EBAD and to longitudinally monitor progression of complex neurodisability and response to treatment.
References	1. Liu T, Liu X, Yi L, Zhu C, Markey PS, Pelowski M. Assessing autism at its social and developmental roots: A review of Autism Spectrum Disorder studies using functional near-infrared spectroscopy. Neuroimage. 2017; S1053-8119. 2. Gualniera L, Singh J, Fiori F, Santosh P. Emotional Behavioural and Autonomic Dysregulation (EBAD) in Rett Syndrome - EDA and HRV monitoring using wearable sensor technology. J. Psychiatr. Res. 2021;138:186-193.
Benefits/skills for student	This is an exciting opportunity for a research student(s) with a strong interest in brain research and neuropsychiatry. The research will be based in the Centre for Interventional

	Paediatric Psychopharmacology and Rare Diseases (CIPPRD) headed by Professor Santosh at the Maudsley Hospital, South London and Maudsley Hospital Trust (SLaM). The student(s) will also be part of a multi-disciplinary team of medical and scientific professionals, and be actively involved in different aspects of data collection and analyses.
Maximum No. of students	*2*

Project Nr. 4

PROJECT INFORMATION	
Research Area(s)	Disease Research / Systems Biology / Neuroscience / Brain Research (Delete as applicable)
Project Title	Modelling Malan syndrome associated with macrocephaly
Supervisor (s) Name	Setsuko Sahara
Co-supervisor	Prof. Eugene Makeyev, Prof Benedikt Berninger
Abstract	Malan syndrome (Sotos syndrome 2) is an overgrowth syndrome characterised by an unusual facial phenotype, tall stature, macrocephaly associated with an intellectual disability. Mutations in Nfix transcription factors have been identified as a causal gene of the syndrome, however, the mechanistic explanations leading to the neurological pathogenic phenotypes have been little explored. We have recently identified alternative Nfix isoforms in mouse nervous system development, including the previously undocumented one that begins directly at exon2 (TSS3). Excitingly, our preliminary data by employing ES cell-based cortical differentiation and in vivo mouse cortex argue for the importance of the TSS3-Nfix isoform and the control of alternative promoter choice in general in regulating the transition of a key stage determining the progenitor neurogenic competency being expansive to neurogenic. These suggest the mechanistic explanation underlying macrocephaly of Malan syndrome. In this proposal, the student expects to analyse several mutant ES cell lines recapitulating human Malan syndrome by latest prime-editing and CRISPR gene editing technology to investigate isoform-specific roles of Nfix in pathogenic brain size controls. The student will learn various latest molecular, cellular and anatomical techniques including ES cell-based neuronal differentiation and gene editing.
References	1. Chen, P. J. *et al.* Enhanced prime editing systems by manipulating cellular determinants of editing outcomes. *Cell* **184**, 5635-5652.e29 (2021). 2. Piper, M., Gronostajski, R. & Messina, G. Nuclear Factor One X in Development and Disease. *Trends in Cell Biology* **29**, 20–30 (2019).
Benefits/skills for student	Gene editing, ES cell-based disease modelling
Maximum No. of students	1