Project Details	
Project Code	MRC22NMHBr Jones
Title	Sleep as a lens through which to predict psychiatric risk and translate mechanisms of neural network dysfunction in schizophrenia
Research Theme	Neuroscience & Mental Health
Summary	Integrating genetics, psychiatry, neural network physiology and data science, this project will combine patient EEG and mouse high-density electrophysiology to determine whether sleep disruption is a “canary in the coalmine”, predicting psychosis and/or memory impairments in young people at high risk of schizophrenia.
Description	22q11.2 Deletion Syndrome (22q11.2DS) is a genetic disorder caused by hemizygous deletion of ~50 genes on chromosome 22 and is one of the strongest known biological risk factors for development of schizophrenia (Schneider…van den Bree et al. 2014 Am J Psychiatry 71: 627-39). 22q11.2DS patients and genetically altered animal models therefore present unique opportunities to map genomic information to a mechanistic understanding of disease. >50% of young people with 22q11.2DS have one or more psychiatric disorders, including autism, ADHD and anxiety disorder (Niarchou…van den Bree 2014 Br J Psychiatry 204:46-54) and the rate of psychotic experiences increases steeply between childhood and early adolescence (Chawner…van den Bree 2019 J Psychiatr Res 109:10-17). We have recently reported that 60% of young people with 22q11.2DS have sleep disturbances, which are associated with risk of cognitive impairment and psychiatric disorder (Moulding…Jones, van den Bree 2020 Psychol Med 50:1191-1202) However, the biological link between sleep disturbances and risk of psychosis remains theoretical. This PhD project will integrate patient and mouse electrophysiology to test the hypothesis that abnormal brain activity during sleep predicts the onset of psychosis and/or cognitive impairment in 22q11.2DS. Sleep neurophysiology is strongly heritable in healthy populations and correlates with brain health and cognitive function. Non-REM sleep EEG features two hallmark oscillations: deep non-REM (stage N3) is dominated by low-frequency slow oscillations (SO, 0.5-4Hz) whereas lighter non-REM (stage N2) is associated with 11-15Hz spindle oscillations. Sleep and the circuit mechanisms of spindle/SO generation are highly conserved in mammals, meaning sleep electrophysiology in rodents affords translational measures of circuit function directly comparable to clinical EEG in patients. For example, schizophrenia is consistently associated with reductions in EEG spindle measures and we have shown that impaired SO coordination correlates with memory impairments in adult schizophrenia patients (Bartsch…Jones 2019 NPJ Schizophrenia 4:18). Both these non-REM phenotypes can be recapitulated in rodent models (Phillips…Jones 2012 Neuron 76:526-33), but have not been quantified in 22q11.2 mouse models, which are known to show memory impairments and abnormal neural oscillations during wake. We propose to test whether sleep EEG abnormalities are evident in 22q11.2DS, and associate with psychiatric symptoms (in patients) or translatable phenotypes (in mice). This proposal is based around 3 main aims, though students will be encouraged to contribute to project design according to their own interests and preliminary results as the project unfolds: 1. Analyse

	a sleep EEG dataset recently acquired from ~20 22q11.2DS carriers and their unaffected (control) siblings, aged 10-18 years. [6 months] 2. Record and analyse sleep EEG from a well-established mouse model of 22q11.2DS. [18 months] 3. Analyse longitudinal sleep questionnaire and psychiatric interview and cognitive assessments data from a study of young people with 22q11.2DS [6 months] Overall, this PhD will embed the student in a vibrant collaborative network spanning Bristol and Cardiff and encompassing world-leading expertise in psychiatric genetics and systems neuroscience. The project will provide training in an integrated set of genetic, behavioural, neurophysiological and data science analyses.
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