Project Details	
Project Code	MRCNMH25Br Jones
Title	Computing and translating mechanisms of neural network dysfunction associated with psychiatric risk
Research Theme	Neuroscience & Mental Health
Summary	Psychotic disorders are common, chronic and poorly-treated; his cannot change until we understand their biological basis. This PhD project will integrate mouse electrophysiology and computational generative modelling, set in the context of patient-public involvement and engagement (PPIE) with children and young people, to define the neural network mechanisms contributing to psychiatric risk in people living with psychosis-associated genetic mutations. The project will be embedded in a vibrant, innovative, supportive and collaborative team spanning Bristol, Exeter and Cardiff universities and encompassing genomic, cellular, circuit, cognitive and clinical analyses in patients and mice.
Description	Recent progress in understanding the genetics of psychotic disorders has identified relatively rare (in the range of 1 in 2000 live births) but highly penetrant copy number variants (CNVs, deletions or duplications of DNA segments) that are associated with substantially increased risk for mental illness. These psychosis-associated CNVs have convergent impacts on synaptic genes, including those involved in the NMDA receptor complex, post-synaptic density and selected GABAA receptor complexes (PMID: 34974922). Can these synaptic effects be measured in living patients, modelled experimentally and used to inform diagnosis, prognosis and treatment? Recording of brain activity using magneto- or electro-encephalography (MEG or EEG) provides a non-invasive means to explore the neural basis of convergent phenotypic effects in carriers of CNVs (PMID: 36039635). Importantly, MEG/EEG signals are generated and modulated by synaptic coupling and dynamics in cortical and thalamo-cortical circuits which, when modelled using computational simulations of neural connectivity and activity, allow inference on changes at the synapse from data recorded accessibly and longitudinally during behaviour (PMID: 31219602). EEG recordings can also be back-translated to genetically altered rodents harbouring chromosomal deletions orthologous to human CNVs. Rodent electrophysiology allows us to test and refine model-based predictions derived from patient data, to pinpoint the neurodevelopmental timecourse of effects and to test potential therapies. This PhD project will integrate mouse electrophysiology and computational modelling, set in the context of patient-public involvement and engagement (PPIE), to define the neural network mechanisms contributing to psychiatric risk in people living with 16p11.2 duplications and related CNVs (PMID: 31056457). The project will be embedded in a vibrant, innovative, supportive and collaborative team spanning Bristol, Exeter and Cardiff universities and encompassing genomic, cellular, circuit, cognitive and clinical analyses in patients and animals. We will support the student in becoming progressively more involved in driving research priorities and approaches according to their interests, but the initial framework is as follows:

	Workstream 1 (WS1, Matt Jones lead supervisor): Recording of distributed limbic-thalamic-cortical network activity in a mouse model of 16p11.2 duplication. This will centre of chronic implantation of high-density EEG and/or deep-brain microelectrode arrays, allowing longitudinal quantification of neural network dynamics over the critical neurodevelopmental time window of pre- to post-adolescence. WS2 (Alex Shaw lead supervisor): This work will involve training in mathematical dynamical systems modelling. Models will be used to simulate experimental data derived from WS1, predicting the biophysical mechanisms underpinning genotype-dependent changes. Model parameters derived from mouse data will be compared across CNVs (for example, using our existing mouse EEG data related to 22q11.2 deletion syndrome) and species (using MEG data from patients, which are currently being collected) to test the hypothesis that different CNVs converge on shared synaptic phenotypes. WS3 (Marianne van den Bree and Jeremy Hall lead supervisors): Lived experience and pathways to translation. WS3 will focus on training the student in co-working and producing engagement and involvement materials optimised to appeal to target audiences including children and young people with complex neurodevelopmental syndromes. Our collaborative network enjoys the extensive insight and impact that comes from working closely with people with lived experience. In particular, we work with families and charities supporting people living with CNVs, convening advisory groups that help to set priorities, co-design protocols, advocate and disseminate outcomes.
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