| Project Details | |
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| Project Code | MRC23NMHEx Shaw |
| Title | Developing computational models of psychosis to explore the impact of schizophrenia-associated CNVs on cortical microcircuitry. |
| Research Theme | Neuroscience and Mental Health |
| Summary | Breakthroughs in genetics have identified specific CNVs that substantially increase risk for schizophrenia. These CNVs impact NMDA & GABAA receptors, but how this disrupts cortical function is unknown. You will develop computational models that capture changes in NMDA and GABA receptor dynamics in CNV carriers. These models will be applied to existing neuroimaging (MEG) and cognitive data to make novel insights connecting genetics to brain function and cognition. |
| Description | Recent progress in understanding the genetics of schizophrenia has identified that specific rare but highly penetrant copy number variants (CNVs, deletions or duplications of segments of DNA) are associated with substantially increased risk for the condition. Pathway analyses have shown that these schizophrenia-associated CNVs have convergent impacts on synaptic genes, particularly those involved in the NMDA receptor complex, associated post-synaptic density and selected GABAA receptor complexes. Brain imaging using magnetoencephalography (MEG) provides a means to explore the neural basis of convergent phenotypic effects in carriers of CNVs. Importantly, MEG signals are generated and modulated by synaptic coupling and dynamics in cortical columns, which when modelled, allow inference on changes at the synapse from non-invasive data. You will work largely with existing MEG data to build and refine cortical models that will link the downstream effects of schizophrenia-associated CNVs to changes in the MEG signals from CNV carrying individuals. This work will involve training in brain imaging analyses and mathematical dynamical systems modelling as well gaining a broad background understanding of clinical neuroscience, neuroimaging, pharmacology, genetics and computational modelling. Work Packages (WP). WP1: You will review the state-of-the-art computational neuroscience literature, model architectures and Dynamic Causal Modelling. Based upon this, you will design and implement (in MATLAB or python) a suite of possible cortical column architectures that maximise biological veracity and sensitivity to key receptor dynamics. WP2: Using MEG data from experiments employing pharmacological manipulations of key neurotransmitter systems, you will test the ability of the models identified in WP1 to explain pharmacologically induced differences in receptor dynamics. You will quantitively compare the models. WP3: Using data from carriers of SZ-CNVs you will use the identified and validated models from WP1 and 2 to perform an "in silico assay" of NMDA and GABAA function. You will use the parameters of fitted models to explain individual differences in behaviour and cognitive scores. This combination of studies will lead to the development of a set of core cortical models that are suitable, and validated, for use in clinical neuroscience research. WP3 will significantly further our understanding of the consequences of SZ-CNVs on cortical function. Support: You will be encouraged to present work regularly at conferences (e.g. MEG UK) and in lab meetings, as well as in high-impact peer reviewed papers. You can expected weekly meetings with primary |

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| | supervisor and monthly with the co-supervisors. You will be embedded in a supportive, friendly and diverse research group at Exeter. Location: You will be primarily based in Exeter. Knowledge exchange and project supervision with co-supervisors will take place primarily online. Shaw, Hall and Singh already work closely as part of the ongoing 'Converge' project and we will leverage this relationship to provide an inclusive and supportive network for the student, including monthly meetings. |
| Supervisory Team | |
| Lead Supervisor | |
| Name | Dr Alexander Shaw |
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| Co-Supervisor 1 | |
| Name | Professor Jeremy Hall |
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