Neural circuitry in the dorsal anterior cingulate cortex underlying goal directed behaviour

Treatment of mental illness such as schizophrenia and ADHD costs the government of Canada ~$50 billion per year, and will rise as the incidence of psychological diseases rises **[1]**. These diseases have disparate symptomologies and treatments, suggesting diverse disease sources. However, a recent meta-analysis of more than 15,000 patients found a systematic and reliable deformation in the dorsal anterior cingulate cortex (dACC) as a predictor of mental illness **[2]**. This implies that the dACC is a central common path that underlies dysfunctional mental states, perhaps due to its role in the flexible adjustment of behaviours **[3]**. Thus, to understand the role of the dACC in disease, an essential question is how neural activity is normally coordinated, and how processing in downstream areas is affected.

Addressing this question in humans poses significant obstacles. Non-invasive methods have poor temporal and spatial resolution, making it difficult to map out the mechanistic circuitry underlying cognition. To address this, precise temporal and spatial coordination of neural circuits are studied in non-human primates (NHPs). My project will thus use focal micro-electrode recordings and fine-grained, cutting-edge information theoretic analysis to examine neural circuits in the dACC in NHPs, with an explicit aim to translate such results to humans. In this way, I will study how activity in the human dACC is organized to affect areas responsible for controlling goal directed behaviour.

A fundamental problem of neural coordination is integrating information contained in local cell assemblies across long-distances and diverse brain areas. An emerging view gaining widespread support is that neurons aggregate into assemblies by band-limited oscillatory activity acting at different spatial and temporal scales. Nesting high frequency within low frequency activity can help organize and route information in neural assemblies across long-distances **[4]**. Importantly, oscillations are implicated in pathological disease, where they can be overactive (coordinating areas that shouldn't be coordinated), or underactive (severing the link between areas that must be coordinated) **[4]**.

During my Master's research, I have shown that nested-frequency coordination between the dACC and prefrontal cortex during attention shifts predicts correct decisions (*see* Previous Thesis) **[5]**. Now, I will build on these insights and identify the large-scale mechanisms of the dACC that support behavioural adjustment. This will entail a three-part approach; (1) describing how specific information is encoded in the dACC and downstream areas via oscillatory coordination; (2) studying how natural circuits react to focal micro-stimulation; and (3) conducting translational experiments in NHPs and humans to understand how oscillatory coordination is instantiated in humans. For goals (1) and (2), I will analyze electro-physiological recordings in macaques performing a selective attention and learning task using information theoretic techniques to map information flow, and high-fidelity classification methods to determine specific cell types and circuits that are the substrates of oscillatory coordination. For goal (3), I will obtain intracranial recording from epileptic patients who have had diagnostic electrodes implanted. I will perform a novel, naturalistic learning task that can be performed by both NHPs and humans. By performing an analogous experiment in NHPs and humans, I will be able to compare and evaluate oscillatory activity as a marker of cognitive control. This approach allows the inference of an explicit link between specific mechanistic circuits in the dACC and behavioural adjustment.

The development of the new, trans-species task will be done in collaboration with international fellows at the lab of Dr. Thilo Womelsdorf at York University. Human intracranial recordings will be through current, ongoing collaboration with neurosurgeons at the University Health Network in Toronto. To tease apart relationships hidden in a dense recordings, I will use the massive parallel-computing power of an inter-institutional consortium organized by Compute Canada. Importantly, I will seek to evaluate my results in terms of overt behaviour. This will help delineate what neural signatures are most informative of behavioural outcomes and cognitive states, and thus provide clues for how they may be manipulated in pathological conditions. With the generous contribution of the NSERC Scholarship, I am positive we can help unlock some of the secrets of the dACC, and its role in human cognition.

[1] Smetanin et al. 2011. *Ment Heal Comm Canada* **[2]** Goodkind et al. 2015. *JAMA Psychiatry* 72,4 **[3]** Shenhav. 2013. *Neuron* 79,2 **[4]** Voytek etal. 2015. *Biol Psyc* 77, 12 **[5]** Voloh et al. 2015. *PNAS* 112, 27