Whole-brain modelling of how psychedelics work in health and disease

After a long hiatus, psychedelic (mind-manifesting) drugs have made a strong comeback (Nichols, 2016; Pollan, 2018), promising to deliver effective and safe treatments for neuropsychiatric diseases including treatment-resistant depression (Carhart-Harris *et al.*, 2021; Carhart-Harris *et al.*, 2016) and addiction (Bogenschutz *et al.*, 2015; Johnson *et al.*, 2017). While not without risks, the evidence shows that the potential benefits of psychedelics far outweigh the harm (Johnson *et al.*, 2018; Johnson *et al.*, 2019). In order to fulfil the great therapeutic expectations and mitigate any harmful effects, a better understanding is urgently needed of how psychedelics work in the human brain.

We have made important progress using the paradigm of whole-brain modelling to shed new light on how psychedelics work through serotoninergic 5-HT2A receptor modulation of brain activity (Deco *et al.*, 2018). More recently, we have created a biophysically realistic neuromodulator whole-brain model to demonstrate the importance of dynamic mutual coupling between neuronal and neuromodulation systems (Kringelbach *et al.*, 2020).

The D.Phil. project will use state-of-the-art whole-brain modelling to test the hypothesis that psychedelics work by modifying the brain's hierarchical processing in a dose-dependent manner, as proposed by a recent, influential theory by Carhart-Harris and Friston (Carhart-Harris and Friston, 2019). Specifically the research will extend our recent measures of hierarchy such as normalised directed transfer entropy (Deco *et al.*, 2021d), functional harmonics (Atasoy *et al.*, 2018a; Atasoy *et al.*, 2017; Atasoy *et al.*, 2018b; Glomb *et al.*, 2021), turbulence (Deco *et al.*, 2021a; Deco and Kringelbach, 2020; Deco *et al.*, 2021c) and non-equilibrium dynamics (Deco *et al.*, 2021b; Sanz Perl *et al.*, 2021)

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