Modelling neural circuit mechanisms of nicotine action in the brain

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Nicotine, a highly addictive substance in tobacco smoke, acts through nicotinic acetylcholine receptors (nAChRs) that are widely expressed throughout the nervous system. I will discuss how we can understand the influence of nicotine on neuronal circuit dynamics acting through the various subtypes of nAChRs that are differentially expressed in the dopaminergic ventral tegmental area and also in the superficial layers of the prefrontal cortex. My talk will be divided into two parts: control over the dopamine circuit dynamics linked to nicotine addiction and control over pre-frontal cortex circuit dynamics linked to schizophrenia.

Dopaminergic (DA) neurons located in the ventral tegmental area (VTA) signal motivational properties of natural reinforcers and addictive drugs. Electrophysiological recordings have demonstrated that transient inputs to the VTA, e.g., glutamatergic (Glu) and cholinergic (ACh), convey salient information about the environment. I will first show how computational modelling can account for in vivo and in vitro data obtained during nicotine exposures and manipulations of VTA input structures. We then show that our model can account for nicotine responses to repeated injections in both wild-type and animals where the a4b2 nAChRs are and how nicotine may change reward signalling in the VTA.

In the second part, I will discuss our on-going work on modelling nicotinic control over resting state activity in the pre-frontal cortex (PFC) and its implications for disorders such as schizophrenia. Notably I will show how computational model of nAChR action can account for the observed changes in the ultra-slow oscillation structure of the resting state in the PFC under pathological mutations linked to schizophrenia and how nicotine appears to remedy this pathology.

In summary, modelling suggests that by its wide ranging action subverting normal cholinergic neuromodulation, nicotine may alter brain computations necessary for higher cognitive functions.