Computational Psychiatry Meets Genetics: Reinforcement Learning in Early Psychosis and In Relation to Clinical and Molecular Genetic Risk for Schizophrenia

Graham Murray[1], Marcella Montagnese[1], Franziska Knolle[1], Juliet Griffin[1], Joost Haarsma[1], Alexander Richards[2], Petra Vertes[1], Bea Kiddle[1], Michael Owen[2], Peter Jones[1], Peter Fonagy[3], Michael Moutoussis[3], Ed Bullmore[1], Ray Dolan[3], and Ian Goodyer[1]

Author affiliations

[1] University of Cambridge

[2] Cardiff University

[3] University College London

Background

Computational psychiatry offers opportunities for increased mechanistic understanding of mental disorder and to aid in the integration between psychiatry and neuroscience. By developing and testing mathematical models of behaviour, the computational psychiatry approach aims to provide increased understanding in how disordered neurobiology manifests in particular clinical phenotypes. A computational approach may further aid in measuring intermediate (latent) phenotypes that may be more readily linked to causes (whether genetic or environmental) than observed phenotypes. However, as yet, computational psychiatry researchers have, in the main, focused on pathophysiology rather than attempting to integrate aetiological factors with computational models of behaviour. Here, we take a computational

psychiatry approach to investigate learning in psychotic illness, and test whether modelled (latent) learning variables relate to molecular polygenic risk for schizophrenia. Reinforcement learning (learning from feedback) has been proposed to be of potential mechanisitc importance in underpinning positive symptoms and/or negative symptoms including anhedonia and avolition.

Methods

We first gathered case control data on behavior during a Go/NoGo reinforcement learning task (GNG) in three groups of young adults (total n=91): controls, help-seeking patients at clinical risk (CR) for psychosis and FEP (First-episode psychosis). The task contains separate conditions when a "Go" action is required to win a reward, or to avoid a punishment, or withholding action ("No-Go") is required to win or avoid punishment. We additionally gathered behavioural data on the same learning task in 700 healthy adolescents and young adults from NSPN "U-change" who also provided DNA samples. We tested several computational models of task behaviour, and settled on the best fitting model, which provides 6 latent modelled measures thought to underpin performance on the task: Learning rate, Go bias (tendency to act), Pavlovian Bias (tendency to act for reward and withhold action to avoid punishment), Sensitivity to reward, Sensitivity to punishment, and Randomness. We examined case control differences on these. We generated schizophrenia polygenic risk scores (based on Petronas et al) in U-Change and related these to modelled task measures. We also plan to examine depression polygenic risk scores in relation to task measures as altered reinforcement learning may also play a role in the pathogenesis of depression.

Results

Compared to controls, FEP patients show significantly lower learning rate, higher Pavlovian bias (a tendency to act to gain rewards and withhold actions to avoid punishment) and lower sensitivity to punishment. After exclusions (poor task engagement or performance, genotype failures, ethnicities in which polygenic risk scores do not predict schizophrenia) DNA and adequate behaviour were available on 390 members of the general population. Schizophrenia polygenic risk score (PRS) did not predict task latent modelled measures.

Discussion

There are cognitive deficits in reinforcement learning in those presenting with early psychosis, but performance in CR is broadly intact, and molecular genetic risk for schizophrenia does not predict task-derived measures in a sample of 390 individuals from the general population. Results will be discussed both in terms of this particular task and the strengths and weaknesses of the general approach.

Disclosure

Nothing to disclose.