PhD project title: Investigating the neural underpinnings of individual variation in conditioned and motivated behaviour associated with substance use disorders.
Project funder: The Open University, Milton Keynes.
Key words: addiction, substance abuse, substance use disorder, SUD, dopamine, nucleus accumbens, Pavlovian conditioning, dendritic spine, psychostimulant, cocaine, amphetamine, opioid, morphine, oxycodone, heroin
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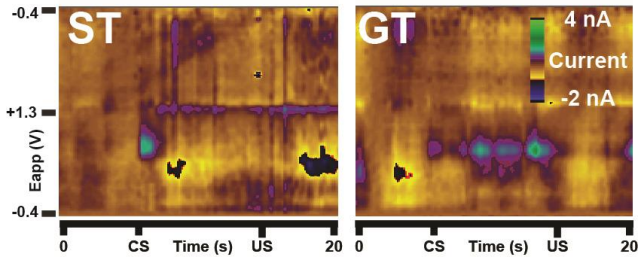
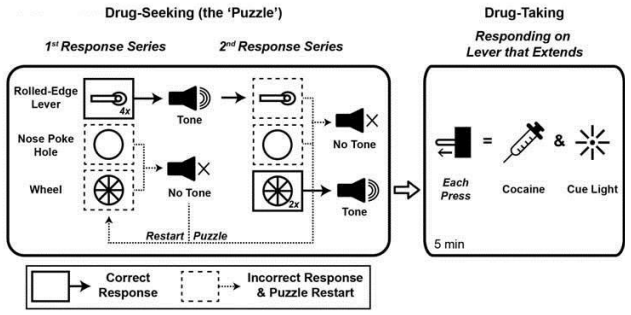
The neural underpinnings of individual variation in conditioned and motivated behaviour associated with substance use disorders.



Project 1, 'Real Time' Dopamine Measurements: Fast-scan cyclic voltammetry (FSCV) is used to recording dopamine levels in awake-behaving rats in a specific brain region. Individual rats show different patterns of behaviour and corresponding dopamine neurotransmission. Dopamine was recorded from 2 different rats (ST and GT) during presentation of a Pavlovian conditioned stimulus (CS), and shortly thereafter when sugar pellet reward is given (the unconditioned stimulus, US).



Project 2, Addiction Model: The drug-seeking phase requires the completion of 2 distinct response sequences. If either the 1st or 2nd response sequence during the drug-seeking period is performed incorrectly (indicated by dashed lines), no tone is presented, and the animal would have to restart the puzzle from the beginning.

Laboratory Objective

Effective treatment options and long-lasting recovery from substance dependence have been elusive because of the propensity of drug abusers to relapse into drug-seeking and -taking. The reinstatement of these behaviours is often precipitated by re-exposure to conditioned stimuli (CS), or cues, associated with drug use (1–4). Importantly, there is considerable individual variation in the degree to which cues exert motivational control over behaviour (1,5,6). Therefore, we need to develop pharmacological and behavioural treatments for addiction that are tailored to each specific individual's needs, with the goal of reducing cue-evoked drug craving and potential relapse into substance misuse. Students will work on elements of one of the two projects described below.

Project 1

We have found that individual variation in dopamine (DA) neurotransmission contributes to the variability in the extent to which reward cues acquire motivational value (5,6). It is unknown why this occurs, and whether altering DA transmission (and activity in related neural pathways) can reduce the ability of cues to drive aberrant reward-seeking. Through the study of conditioned and motivated behaviour in both animals and humans, we are interested in pursuing several research questions, including:

1) Using similar behavioural procedures in both animals and humans, how can we accurately identify variability in cue-elicited motivation?
2) Are some individuals more motivated by reward-paired cues than others because of differences in the pre-synaptic regulation of dopamine release and uptake?

3) Are some individuals more motivated by reward-paired cues than others because of differences in the post-synaptic excitability of dendritic spines?
4) Can we alter certain aspects of dopamine neurotransmission to reduce the motivational power these cues have over behaviour?

Project 2

Despite the widespread adoption of animal models for the study of substance use disorder in the field of behavioural neuroscience, it remains a significant challenge to translate their results into treatments for addiction in people. One reason this might be is that current animal models paint an incomplete picture of the complexities of drug misuse and abuse. Therefore, we are interested in developing new animal models of substance use disorder that accurately reflect the human condition. For example, primarily based on older established animal models, substance use disorders are often characterized as "habitual" behaviours aimed at obtaining and administering drugs. Although the actions involved in consuming drugs may require a rigid repertoire of habitual behaviours, evidence suggests that addicts must be very creative and flexible when trying to procure drugs, and thus drug-seeking cannot be governed by habit alone. Therefore, we recently modelled flexible drug-seeking behaviour in rats by requiring animals to solve daily puzzles to gain access to cocaine (1). We found that habitual drug-seeking wasn't necessary for the development of addiction-like behaviour. Indeed, there was an escalation of intake, sensitization of motivation for drug, continued drug use in the face of adverse consequences and very robust cue-induced reinstatement of drug-seeking, especially in a subset of 'addiction-prone' rats. Furthermore, drug-seeking continued to require dopamine neurotransmission in the core of the nucleus accumbens, a signalling pattern which is thought to encoded motivated (but not habitual) behaviour. We wish to build upon this puzzle self-administration procedure. We believe that the promise of face validity observed in this animal model may prove useful for studying changes in neuropsychological function that promote the transition to addiction. Accordingly, using our model on non-habitual drug-seeking as a starting point, we wish to address the following research questions:

1) Are there differences in non-habitual drug-seeking between drug classes (e.g., psychostimulant vs opioid) and, if so, how does neurobiology reflect these differences?
2) Do different environmental conditions promote or discourage drug-seeking and -taking? If so, are these effects only observed in certain individuals or for specific drug classes?
3) In contrast to the puzzle self-administration procedure which models non-habitual *drug-seeking*, how do we model whether the act of *drug-taking* becomes habitual with extended drug use?

Techniques:
A range of expertise and equipment will be available at The Open University (http://www-acct.open.ac.uk/science/life-health-chemical-sciences/research) Labs. The student will be required to work in the Milton Keynes campus labs, but may be also asked to collaborate on portions of projects at nearby universities.

All experiments will involve behavioural testing, either in humans or animals. Research in people will utilize new technologies to identify individual variation in Pavlovian conditioning. Research involving rodents will utilize techniques such as drug self-administration, fast-scan cyclic voltammetry, optogenetics, fibre photometry, pharmacology, and biochemistry.

Funding information:
This three-year research studentship is funded by the Faculty of Science, Technology, Engineering and Mathematics (STEM) at The Open University and provides a stipend of £14,553 per year (2016 rate) and all academic fees (at UK/EU level) are covered. The project is supervised by Drs Bryan Singer, Christopher Heath, Claire Rostron, and Kerry Murphy. You would be required to live in the UK and within commuting distance of The Open University in Milton Keynes.

Requirements:
Applicants will be expected to have a degree (classification 2:1, or higher) in neurobiology, psychology, physiology or cell biology, biochemistry, or a relevant subject. Candidates with backgrounds in behavioural neuroscience or biological psychology are particularly invited to apply. Good numeracy, ICT, communication and organisation skills are highly desirable.

Contacts:
Informal enquiries relating to the project should be directed to bryan.singer@open.ac.uk.

How to Apply:
Please send an email with your CV, a completed application form and a personal statement (outlining your suitability for the studentship, what you hope to achieve from the PhD and your research experience to date) to STEM-LHCS-admin@open.ac.uk

Vacancy ID: 10896
Closing date: 23 February 2018

Interviews will be arrange promptly after the closing date, and can be conducted via Skype if appropriate.

LHCS holds Athena Swan Bronze status

Equal Opportunity is University Policy

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