UQU APS UQU ASSOCIATION OF POSTGRADUATE STUDENTS

PitchMyResearch.com

Competition:

UQUAPS 2017 "Pitching Research" Competition

Submission id:	Date submitted:
UQUAPS-2017-016	**27 Aug 2017 at 12:00 AWST**

Faculty or Institute:	School:
UQ Queensland Brain Institute (QBI)	**Queensland Brain Institute**

Programme:	Load:	Level:
PhD	**Full-time**	**7-9 months**

Name:

Kyna-Anne Conn

(A) Working Title:

Dissecting motivation from decision-making in schizophrenia using animal models

Word count: **925 words**

(A) Working Title	Dissecting motivation from decision-making in schizophrenia using animal models
(B) Basic Research Question	How does motivation influence cognition, in particular decision-making processes, in schizophrenia?
(C) Key paper(s)	Carandini, M. and A. K. Churchland (2013). "Probing perceptual decisions in rodents." Nature Neuroscience 16(7): 824-831.
(D) Motivation / Puzzle	"Choices are the hinges of destiny". Pythagoras c.500BCE Deficits in the ability to make suitable choices lies at the root of some of the most debilitating neuropsychiatric diseases, like schizophrenia, leading to dangerous and risky behaviours that can have serious consequences. Decision-making is a fundamental element of cognitive function, contributing to many aspects of daily lives, including school or work performance, or staying fit and healthy. Aberrant decision making can therefore negatively impact even the most simple of daily routines. Decisions are fuelled, in part, by motivation. Avolition, a decrease in motivation, can hinder the ability to initiate and perform self-directed purposeful activities. Altered decision making and avolition contribute to the cognitive and negative symptoms that form some of the greatest predictors of functional outcomes for people living with schizophrenia. We do not have a good understanding of how motivation influences decision making and the ability to make appropriate choices. It is plausible that improving motivation in schizophrenia patients could lead to enhanced decision-making capabilities. Can we oil the hinges for a brighter destiny?
THREE	**Three** core aspects of any empirical research project i.e. the "IDioTs" guide
(E) Idea	To investigate the underlying neural mechanisms behind motivation and cognition, we need to look to the striatum, a group of subcortical structures in the brain, as this area is responsible for the coordination of multiple aspects of cognition, including motor- and action-planning, decision-making, motivation, reinforcement and reward perception. One of the most robust pathophysiological findings in schizophrenia is aberrant striatal circuitry, leading to, for example, dopamine hyperfunction. If we are able to unpick specific pathways in this region and assess their contribution to motivational and cognitive dysfunction, we can better target interventions to improve daily functioning. There are three major dopaminergic striatal pathways in the brain that have been implicated, the meso-limbic, meso-cortic and nigro-striatal pathways. In the past, most studies conducted in human patients did not allow for the separate investigation of these pathways. However, with the application of new technology called Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in rodent models, we are able to dissect the roles of these pathways in detail. DREADDS allows us to activate or hinder striatal pathways and assess the effects through behavioural and cognitive testing.
	The rodent tasks selected in this project highly correspond to human versions of the task, therefore reducing the existing cross-species translational gap and the

(F) Data	number of animals used will give these experiments statistical power. After manipulating the different striatal pathways in mice, data will be collected on performance in a cognitive test battery designed to assess motivation, reward valuation, learning and decision-making through three operant tasks: 1) The Outcome-specific Devaluation Task which assesses reward valuation and the ability to integrate the updated value of rewards into action. Schizophrenia patients are capable of understanding the value of rewards, however they are unable to make the correct action selections based on this valuation. 2) The Progressive Ratio Breakpoint Task which examines incentive motivation. Schizophrenia patients with greater severity of avolition scores show a decrease in their incentive motivation. 3) The Probabilistic Reversal Learning Task which examines feedback driven reward learning and decision-making. Schizophrenia patients have a deficit in the ability to use feedback valence and prediction errors to update value representations and guide choice.
(G) Tools	DREADDs is an emerging chemogenetic tool increasingly used to deconstruct behaviour. Designer receptors are expressed in specific cell populations via the delivery of viral vectors containing the receptor DNA into regions of interests using microinjection mouse brain surgery. Post-surgery, systemic injection of a designer drug allows for the transient non-invasive manipulation of these cell populations by either activating or inhibiting neurons. During this manipulation, cognitive performance is assessed.
TWO	**Two** key questions
(H) What's New?	Novel approaches - The combination of these operant tasks to create a cognitive test battery examining reward valuation, motivation, learning and decision making in the mouse; and the application of DREADDs to investigate the role of specific striatal circuitry in these distinct cognitive domains.
(I) So What?	Avolition and altered decision making lead to inappropriate choices that further disadvantage people with schizophrenia through functional impairments and reduced quality of life. Currently, antipsychotic medication tends not to be effective in ameliorating these symptoms and there are no other approved treatments for them, highlighting a need for novel approaches. By understanding the role of specific striatal pathways through outcomes measured on rodent tasks, we can translate the findings back to the human brain allowing us to design and develop interventions that specifically address motivational and cognitive dysfunction in schizophrenia.
ONE	**One** bottom line
(J) Contribution?	Though the duration of a PhD is not enough time to find the cure for schizophrenia, elucidating the underlying circuitry involved in motivation and decision-making could lead to discovering new therapeutic targets that would result in a significant improvement in every single aspect of patient's lives.
(K) Other Considerations	Collaborations with researchers from University of New South Wales and University of California, San Diego, have been established to share expertise and protocols for the operant tasks, and within the Queensland Brain Institute to optimise the application of DREADDs. My background knowledge and training gained from experience as an honours student and research assistant piloting behavioural work in this laboratory over three years will be crucial for conducting these experiments. Target journals include Neuron, Neuropsychopharmacology and Biological

	Psychiatry as similar research has been published in these. There is a low risk of obsolescence but a higher risk of competition as many research groups are turning to DREADDs technology to investigate behaviour.