Improving The Translational Validity Of Rodent Models For Cognitive And Affective Neuroscience

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In neuroscience, animal models are the foundation of fundamental research used to investigate both normal and pathological behaviour and their relationship to psychiatric and neurological disorders. For most of these disorders, cognitive and/or emotional symptoms are the most widely used methods to define disease and are the target for therapeutic interventions. However, being able to translate findings from animal models to human symptom domains can be challenging due to differences in how these are measured. For psychiatric disorders, subjective self-reported symptoms are used for diagnosis and in clinical trials. Where more objective methods are used, such as computer-based tests of learning and memory or emotional processing, these often use language-based tasks or measuring behaviours which cannot be readily quantified in non-human animals. Even when tasks have been designed to recapitulate behaviours measured in computer-based cognitive task, studies in humans provide verbal or written instructions while, animal studies require prolonged graduated training protocols. This can often mean that the behaviours have become strongly driven by procedural learning limiting their translational relevance. Rather than trying to develop tasks for rodents that 'look like' a human task, we have sought to develop methods which build on the underlying neuropsychology and use species relevant behaviours e.g. foraging-based tasks and using cues in domains most relevant to rodents e.g. olfactory or tactile cues vs visual cues.

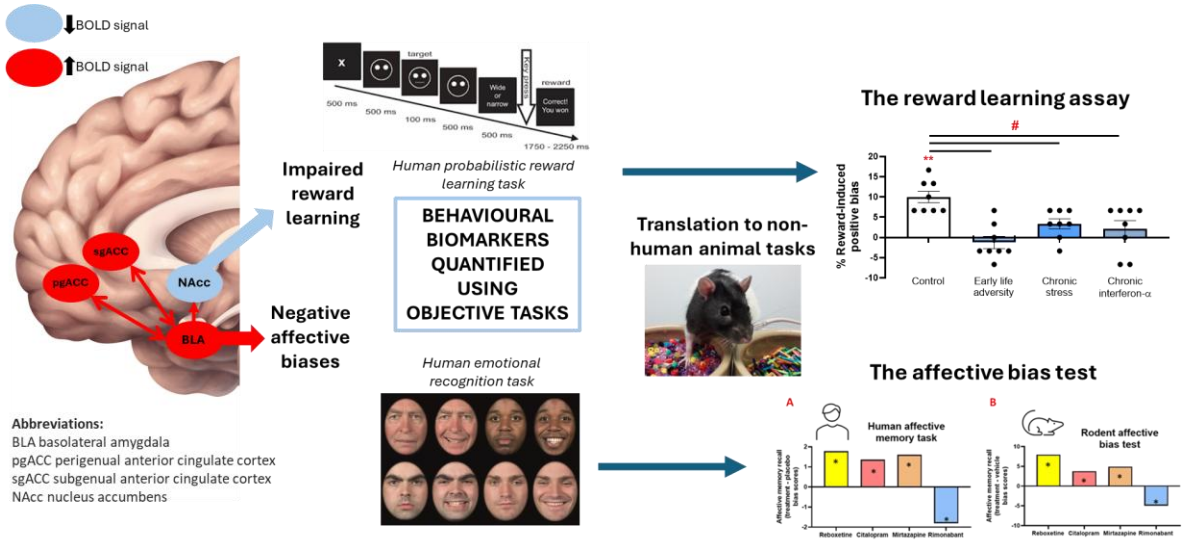

Figure 1: Translational tasks developed to quantify impairments in reward learning and affective bias modification in rodents. *MDD is associated with negative affective bias and impaired reward learning which can be objectively measured using emotional processing tasks or a probabilistic reward learning task respectively. Integrating these tasks with fMRI has identified activity changes in key brain regions in MDD patients which are remediated with effective antidepressant treatment*

(Pizzagalli and Roberts, 2022). The rat reward learning assay (RLA) can detect reward learning impairments in animal models of depression associated with different risk factors for MDD and acute pharmacological manipulations of affective state quantified using the affective bias test (ABT) show similar findings with antidepressant and pro-depressant drugs to those observed in a human affective memory task. Both tasks are based on associative learning and memory and the pairing of specific cues (digging substrates) with rewards (Hinchcliffe et al., 2024a). Biases in the reward-associated memory have been shown to be modified by affective state at the time of learning and can also be attenuated at retrieval by RAADs (Stuart et al., 2013, 2015; Hinchliffe et al., 2024b).

In this talk, I will discuss how we approached the development of a novel behavioural method to quantify emotional behaviour in rodents. Our affective bias test and reward learning assays use natural foraging behaviours where animals learn substrate-reward associations. By quantifying learning and memory for these associations when they are learnt under different affective states, we have been able to show their sensitivity and translational validity. We now have methods which provide an objective approach to quantifying both core (reward-induced biases) and short term (affective-state induced biases) changes in affective state. We have used these methods to study depression related phenotypes and their treatment with antidepressants as well as asking questions relevant to animal welfare. The final part of the talk will discuss how we are using a similar approach to develop new tasks to study different cognitive domains as well as testing the hypothesis that the current methods used to house and manage laboratory rodents may not provide the more appropriate control populations for cognitive and affective neuroscience.

References

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