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Review

Measuring behaviour in rodents: Towards translational neuropsychiatric research

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HIGHLIGHTS

- Rodent behavioural models are indispensable to advance the understanding of neuropsychiatric disorders.
- However, many behavioural models for rodents have a poor pathophysiological basis.
- Behavioural tests should fractionate behaviour into perception, motivation, activation and switching.
- And more precisely implement human task parameters determining which neural circuits are activated.

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ABSTRACT

Rodent behavioural tasks are indispensable to advance the understanding of gene × environment interactions in neuropsychiatric disorders and the discovery of new therapeutic strategies. Yet, the actual translation of rodent data to humans, and thereby the understanding of the pathophysiology of neuropsychiatric disorders is limited. The main reason for the translational flaw is that many behavioural tasks for rodents are based on face or predictive validity, whereas these types of validity often lack a pathophysiological basis. Furthermore, many behavioural tasks for rodents do not implement human task parameters or use task parameters in a controlled manner, whereas they are parameters that provide the environmental challenges to test gene function. The aim of this perspective is to address the status quo of behavioural tasks for rodents, their limitations and their strengths, and the reasons why they could lead to suboptimal translational research. I also suggest an approach to come closer to neuropsychiatric behavioural tasks for rodents, namely a more careful implementation of human task parameters and subdivision of behaviour into perceptional, motivational, activational and switching domains. Finally, I will touch upon behavioural tasks for rodents that are currently lacking and needed to catch up neuropsychiatric research.

Contents

Abbreviations: 5-HTTLPR, serotonin transporter linked polymorphic region; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorders; BDNF, brain derived neurotrophic factor; BOLD, blood oxygen level dependent; CS, conditioned stimulus; DA, dopamine; ED, extradimensional; GWAS, Genome-Wide Association Studies; ID, intradimensional; MRI, magnetic resonance imaging; OCD, obsessive–compulsive disorder; PET, positron electron tomography; PPI, prepulse inhibition; PTSD, post-traumatic stress disorder; SSRT, stop signal reaction time task; TCI, temperament and character inventory; US, unconditioned stimulus; WCST, Wisconsin card sorting test.

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1. Preface

The terms 'nature' and 'nurture' are used as popular terms for the roles of respectively heredity and environment in the emergence of neuropsychiatric disorders. It is widely accepted that nature and nurture interact, but research is focusing more on nature than nurture. This is what hampers progress in the understanding of the pathophysiology of neuropsychiatric disorders and their treatment. As stated by van Os and colleagues [1]: "It is likely that mass genome-wide molecular genetic approaches, "enriched" with a few measures of "environmental" exposures will create invalid and confusing findings, largely because of the extent of multiple testing and the opportunities for post hoc analyses afforded by such studies. It is of paramount importance to consider the study of G(ene) × E(nvironment) as a separate discipline, requiring a highly specialized and multidisciplinary approach taking both environment and genes seriously". The limited focus on nurture may account, at least in part, for the so-called 'missing heritability' phenomenon as encountered in Genome-Wide Association Studies (GWAS). These studies aim to link behaviour to genes, as twin studies have revealed that there is a substantial genetic component contributing to neuropsychiatric disorders. However, these twin studies also demonstrate that the genetic contribution is not 100% and differs across diagnostic methods [2]. Since genetic and environmental factors interact, reciprocally [3], it is not as simple that 'missing heritability' can be filled in by purely environmental factors. Because neuropsychiatric disorders are per definition disorders characterized by improper responses to environmental stimuli, this 'missing heritability' cannot be unravelled without investigation of how genes interact with the (external and internal) environment. To give an example, whereas the serotonin transporter (5-HTT) promoter polymorphism (5-HTTLPR) was introduced as risk factor for depression by increasing stress sensitivity [4,5], there is now accumulating evidence that the 5-HTTLPR is associated with reduced risk for depression under favourable environmental conditions [6]. Hence, the 5-HTTLPR does not mediate stress sensitivity per se, but rather increases sensitivity to environmental stimuli, both aversive and beneficial ones [7,8]. Yet, this explanation derived from human studies is still not precise enough to understand 5-HTT gene function. Because human studies are hampered by substantial ethical and practical constraints, such as the inability to control environmental factors and long duration of longitudinal studies, we need experimental animal models to investigate how genetic factors interact with the environment, to understand gene function, and thereby to come closer to the understanding of the pathophysiology of neuropsychiatric disorders.

Rodents – whose brains and behaviour share striking functional similarities with those of humans – are essential to fill in this void, as their genome and environment can be routinely and relatively easily controlled. Regarding genetic control, the genome of both the mouse and rat has been sequenced and many types of genetic rodent models, including conditional knock-out and knock-down rodents are already available and continuously being developed. Furthermore, revolutionary tools like viral-mediated gene manipulations and optogenetics have already proven to allow spatially targeted temporally controlled modulation of neural activity and behaviour. However, the environmental control of neural activity and behaviour in rodent tasks is still suboptimal as most of the behavioural paradigms in use have been developed decades ago and are based on anthropomorphic interpreted similarity in symptoms and pharmacological efficacy in rodents and humans, rather than similarity in pathophysiology. For instance, the Porsolt swim test for depression has been developed in 1978 [9] and is based on the ability of antidepressant drugs to reduce 'depressive' immobility ('giving up') behaviour in this inescapable stress test, whereas the neural correlates are unclear, the test is widely debated (immobility may actually be an 'adaptive' coping strategy under the inescapable stress conditions), and drug screening in this test has been disappointing. Yet, because of the lack of better alternatives the test is still widely used. Behavioural studies using 5-HTT knockout mice and rats to model the 5-HTTLPR have revealed increased immobility in the forced swim test, which at first sight appears to fit the idea that the 5-HTTLPR is a risk factor for depression [10]. However, the same animals also show decreased learned helplessness (Van der Doelen, Kozicz, Homberg, unpublished data) and improved reversal learning [11,12], whereas depressed patients show increased helplessness [13] and impaired reversal learning [14]. To understand 5-HTT function we tested 5-HTT knockout rats in a series of associative learning tests in which we implemented human task parameters and/or manipulated specific parameters in a controlled manner. Thereby we revealed that the 5-HTT gene mediates sensitivity to discrete conditioned stimuli [11,15–17] which drive behaviour towards most adaptive response under the given circumstances. When exposed to conditioned stimuli predicting adversity they show the highest conditioned avoidance/withdrawal behaviour, but when exposed to conditioned stimuli predicting reward they show the highest conditioned approach behaviour. And when the first conditioned response (read associative memory trace) has to compete with the latter, the conditioned avoidance response can be decreased [17]. Hence, without insight in the environmental component that is 'targeted' by genetic factor, we will be unable to understand gene function and to detangle the pathophysiology of neuropsychiatric disorders. As such, the 5-HTTLPR polymorphism may predispose to depression by increasing associative learning for adverse events, leading to stimulus-bound habitual responses that are also expressed when the actual adversity is not present anymore. What we need to understand gene function in greater detail and increase the translational value of rodent data are behavioural tasks for rodents that model human task parameters or (if unavailable) allow the manipulation of specific environmental components (read: task parameters) to unravel gene function, as we also do genetically in animal models. These task parameters