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Assessment of intradimensional/extradimensional attentional set-shifting in rats

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ABSTRACT

The rat intradimensional/extradimensional (ID/ED) task, first described by Birrell and Brown 18 years ago, has become the predominant means by which attentional set-shifting is investigated in rodents: the use of rats in the task has been described in over 135 publications by researchers from nearly 90 universities and pharmaceutical companies. There is variation in the protocols used by different groups, including differences in apparatus, stimuli (both stimulus dimensions and exemplars within), and also the methodology. Nevertheless, most of these variations seem to be of little consequence: there is remarkable similarity in the profile of published data, with consistency of learning rates and in the size and reliability of the set-shifting and reversal 'costs'. However, we suspect that there may be inconsistent data that is unpublished or perhaps 'failed experiments' that may have been caused by unintended deviations from effective protocols. The purpose of this review is to describe our approach and the rationale behind certain aspects of the protocol, including common pitfalls that are encountered when establishing an effective local protocol.

1. Introduction

Rats and mice account for more than 70% of animals used in the UK under the Animals (Scientific Procedures) Act 1986, with a third of these being in the translational research category of 'Applied – human medicine' (UK Home Office, 2017). Although there has been a recent retreat from translational neuroscience in psychiatry, in part due to a lack of understanding the neurobiology of psychiatric disorders (Insel et al., 2012), research with non-human animals is providing important insight into the nature of cognitive impairments in conditions such as depression, dementia and psychosis. All of these conditions have impairments of so-called 'executive functions' of the frontal lobes, the severity of which are associated with poor functional outcome. Cognitive flexibility – "the ability to switch thought and/or response patterns" (Powell and Ragozzino, 2017) – is one such function: how the brain solves the problem of being, simultaneously, consistent and efficient (able to learn and generalise that learning to new situations) and yet also flexible (able to know that 'things change' and that 'rules have exceptions').

The early psychology literature is replete with a great variety of demonstrations of cognitive flexibility in many different contexts and in many species, ranging from fish to rodents and humans. Reversal learning has been called a "pre-eminent test of cognitive flexibility" (Izquierdo et al., 2017), not least because it is observed ubiquitously and is also easily quantified in different species. Other demonstrations of cognitive flexibility include task switching (Jersild, 1927), when response strategies need to change, and the shifting of attention as the relevance of perceptual features changes (demonstrated, for example, in the Wisconsin Card Sorting Test (Berg, 1948) and the intra/extra-dimensional (ID/ED) attentional set-shifting task (Lawrence, 1949)).

We have previously argued that task switching, attentional shifting and reversal learning are unlikely to reflect a unitary function called 'cognitive flexibility' (Brown and Tait, 2015). Shifting and switching tasks have in common the idea that prior experience causes the cognitive system to be dynamically set, or prepared, to perform particular mental operations or process particular information. This cognitive preparedness – also known as 'mental set' – confers a processing advantage (either stimulus processing in the case of a perceptual attentional set, or response selection in the case of a task or learning set) for as long as the preparation is appropriate. When the set of the system is not appropriate, the model-based processing will be disadvantageous, thus the system must be flexible and able to reset. The ID/ED task (Lawrence, 1949) enables this to be demonstrated by comparing new learning in two different states of mental set. At the ID stage, novel

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stimuli are presented but prior experience of particular perceptual features being relevant (*e.g.*, colour) ensures that the processing of those features are prioritised, which confers an advantage for learning. At the ED stage, different perceptual features of novel stimuli (*e.g.*, shape) are now relevant to solve the task, but as they are not the features prioritised, this results in a learning decrement. A comparison of learning rates in these two different states thus provides inference of the state of the mental set.

It is possible that the process or mechanisms that enable reversal learning may have been repurposed to support cognitive flexibility. In other words, cognitive (covert) flexibility could be a special case of behavioural (overt) flexibility. On the other hand, it seems more likely that reversal learning – like any learning – can occur in the context of various states of cognitive preparedness, ranging from model-free (no prior set) to entirely model-based, and this will probably be determined by the context or task variant (Izquierdo et al., 2017). 'Learning set' (Harlow, 1949) describes an increase in the rate of reversal learning as a function of experience of learning reversals, and it indicates that mental set (and its corollary, cognitive flexibility) is not an intrinsic, let alone necessary, aspect of adaptive behaviour resulting from learning processes (which includes reversal learning), but rather is additional to it. In other words, having a mental set (a model) can influence the rate of any learning, including reversal learning, but the nature of the mental set cannot be known by observing an isolated instance of learning. The mental set is only revealed by assessing the relative advantage or disadvantage that the model confers. This is one of the reasons we suggested that it is important that a task does not conflate reversal learning with either switching or shifting (Brown and Tait, 2015). This is particularly problematic in rule- or strategy-switching tasks for rats that employ mazes or operant chambers (see Floresco and Jentsch, 2011) because the responses to the different rules are not unique. On 50% of trials, the response to a new rule (*e.g.*, "turn left") will be the same as when an old rule (*e.g.*, "approach the light") is applied. This partial reinforcement effect, which is the result of a learning process, cannot be distinguished from the effects of cognitive flexibility. In shifting tasks, this problem can be overcome by having a sufficiently large number of stimulus exemplars so that it is possible to have a 'total change design': previously rewarded stimuli are no longer present and therefore not partially reinforced (Slamecka, 1968).

In summary, although we acknowledge that aspects of cognitive flexibility are undoubtedly relevant to, and can be assessed in the context of, reversal learning (see also Dhawan et al., in press), we do not think that all examples of reversal learning are relevant or that it is a simple way to measure cognitively flexibility. We think it is yet to be determined whether shifting and switching represent a unitary executive function, although the involvement of prefrontal cortex in both seems a compelling reason to suggest that these behaviours have aspects in common. The purpose of this paper is to describe our methods and protocol for assessing cognitive flexibility and our rationale for these. We do not intend to imply that we think this is the only, or even the best, way to assess these psychological constructs. Rather, we hope to provide helpful information for other researchers' who might consider adopting or adapting the ID/ED attentional set-shifting task (ASST) for the rat.

1.1. The ID/ED ASST

The ID/ED ASST is a well-established behavioural assay which is used in humans, primates and rodents (for review see Brown and Tait, 2016). Performance in this task specifically is impaired in neurodegenerative diseases (*e.g.*, Parkinson's disease; Downes et al., 1989) and neurological disorders (*e.g.*, schizophrenia; Elliott et al., 1995) with frontocortical neuropathology, and in rodent models of these disorders (*e.g.*, subchronic phencyclidine as a model of schizophrenia; Rodefer et al., 2005). We believe that the particular value of the task is that, regardless of species, the ID/ED ASST is formally the same: it requires the participant/subject to learn a series of two-choice compound discriminations with (typically) two systematically varied, uncorrelated stimulus dimensions – one is relevant to solving the discrimination (*i.e.*, predicts reward), the other is irrelevant. Over multiple ASST stages, an attentional set is formed to the persistently relevant dimension, and then the participant/subjects' ability to flexibly shift attention from that dimension to the previously irrelevant dimension is tested. The trials required to learn the discrimination at the ED stage is compared to learning at the ID stage and the difference is assumed to reflect the strength of the set and the cognitive cost ('shift-cost') of flexibility. Manipulations that increase shift-cost relative to control performance (which is generally expressed as additional trials at the ED stage, because there is often little room for improvement in ID acquisition) are typically interpreted as reflecting an impairment in cognitive flexibility, although the specific latent mechanisms can only be inferred. A reduced shift-cost is more difficult to interpret, as it could result from performance change at either ID (increased trials) or ED (decreased trials) or both (changes to shift-cost are discussed in more detail in Section 4.2.2).

An ID/ED ASST that is suitable for testing humans or monkeys typically uses compound (multidimensional) visual stimuli presented on a computerised touchscreen (Roberts et al., 1988). For example, the ID/ED ASST in the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, Ltd) uses stimuli which are opaque shapes with superimposed line-configurations. An ID/ED ASST employing a total-change design suitable for testing rodents was described by Birrell and Brown (2000). This approach relies on the natural propensity of rats and mice to forage for food, with subjects digging for food bait in small bowls which are discriminable by the digging media, or the scent, or the bowl itself may even have a different appearance or texture. This adaptation of the ASST for rodents, allows researchers to understand the same mechanisms governing attentional set-shifting in mammals, but using species-appropriate stimuli and responses. There is a common standard in the stages of the rat ASST: the majority of published designs use seven stages (Tait et al., 2014) – a simple discrimination (SD); a compound discrimination (CD); a reversal of the CD (REV1); the ID; a reversal of the ID (REV2); the ED; and finally a reversal of the ED (REV3) – which we refer to as the standard 7-stage task (Chase et al., 2012; Tait et al., 2014).

It does not seem to be important that the apparatus and materials are standardised for the rat ID/ED ASST: research groups typically construct their own testing chamber or arena, and the various elements of the stimuli (odours and digging media) are largely determined by local availability. On the one hand, this variability indicates the robustness of the task, nevertheless there are aspects that are important to consider when selecting materials. Here we will, therefore, discuss some of the reasoning behind choices made during the development of the rat ID/ED task, including changes made since the original Birrell and Brown publication so that researchers wishing to adopt or adapt the task in the future are informed by our experience of what worked or did not work. We will focus on designs for use with rats, as mouse ASSTs, although often similar in design to the rat ASST, have their own requirements (see Tait et al., 2014 for review). In this methods paper, we will discuss rat strain; the apparatus; the choice of stimulus exemplars; stage and trial order; counterbalancing; and data analysis.

2. Rats

ASST data have been collected in many different rat strains – including Lister Hooded (Birrell and Brown, 2000); Long Evans (Rodefer et al., 2008); Sprague Dawley (Tunbridge et al., 2004); Wistar Kyoto (Cao et al., 2012); Fischer 344/Brown Norway cross (McCoy et al., 2007) – and although the majority of the published work has used male rats, there are also data from female rats (Lovic and Fleming, 2004; McLean et al., 2012). Whereas there may be some strain or sex differences in willingness to perform the task, the pattern of data in terms of