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Review

# Neural structures underlying set-shifting: Roles of medial prefrontal cortex and anterior cingulate cortex

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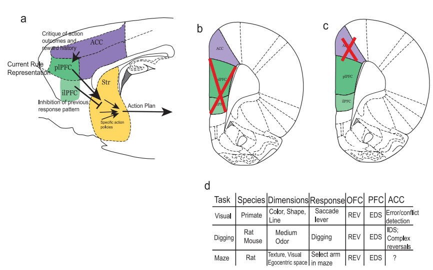
## HIGHLIGHTS

- Thoroughly outline attentional set-shifting tasks across many animal models.
- Summarize research findings in set-shifting literature.
- Propose new directions and necessary experiments to fill in important gaps in literature.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Impaired attentional set-shifting and inflexible decision-making are problems frequently observed during normal aging and in several psychiatric disorders. To understand the neuropathophysiology of underlying inflexible behavior, animal models of attentional set-shifting have been developed to mimic tasks such as the Wisconsin Card Sorting Task (WCST), which tap into a number of cognitive functions including stimulus–response encoding, working memory, attention, error detection, and conflict resolution. Here, we review many of these tasks in several different species and speculate on how prefrontal cortex and anterior cingulate cortex might contribute to normal performance during set-shifting.


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## 1. Introduction

Cognitive rigidity is a hallmark of many human psychiatric disorders and is a frequent result of traumatic brain events [1–7]. Patients who suffer from deficits with behavioral flexibility are generally able to learn information and rules to guide behavior, but lack the ability to modify responding when the situation warrants such a change. One of the ways in which people assess deficits with behavioral flexibility is by studying selective attention. Attention is a cognitive process by which the brain dedicates sensory resources to particularly relevant stimuli, necessary to motivate behavior, and ignores other sensory input irrelevant to the current motivated goal [8–11]. Attention is context-dependent, and is an emergent property of semantic memory, working memory and reward related assessments of recent behaviors. Appropriate control and use of attention can lead to effective behavioral flexibility, enabling animals to successfully navigate in an ever changing world.

Rule learning and executive function in humans has been assessed successfully through several different behavioral methods, most notably the Wisconsin Card Sorting Task (WCST) [7,12]. In the WCST, participants are presented with a series of cards with different shapes that vary in type, number, and color, and asked to sort them. Participants are not told how to sort the cards, but only to categorize them based on one of these dimensions in order to receive reward. Generally, people will quickly learn rules governing their card sorting and rapidly progress with effective sorting measures [11,13]. Over time, the rule for sorting parameters is changed (unbeknownst to the participant) who then will need to determine the correct sorting parameters and shift their behavior from the previous rule to the current rule. The WCST test has proven to be an effective test of flexible learning and category learning in humans [14].

While the main strength of the WCST rests on its usability in assessing prefrontal damage in humans [7], both the WCST and other set-shifting paradigms are also highly effective at testing executive function in humans with psychiatric disorders [7,15–17]. Impairments on the WCST in psychiatric patients and after brain damage have pointed to PFC as being critical for behavioral flexibility [16]. These deficits exist for disorders ranging from Alzheimer's disease to schizophrenia, and even include individuals exposed to severe bouts of stress [2,13,18–28]. Although the proposed mechanisms of deficits in each of these disorders differ, deficits with behavioral flexibility regarding rule shifting likely originates, at least in part, from changes to the prefrontal cortex (PFC).

For example, it is thought that with patients who have schizophrenia, altered prefrontal gamma oscillations from deficits in parvalbumin expressing cortical interneurons may underlie the associated problems with behavioral flexibility [29,30]. In people with a genetic risk factor for Alzheimer's disease, the apolipoprotein E type 4 allele (ApoE4), there is a link between prefrontal cerebrovascular risk and degeneration due by blood pressure [31] which may lead to set-shifting deficits. Individuals with frontal lobe epilepsy also show deficits in set-shifting [3,32–34]. Thus, it is of broad importance to try to understand the nature of the anatomy and circuitry behind set-shifting, and it is clear that we should be focusing on prefrontal cortex and its associated areas.

Animal variants are needed so that we can elucidate the neuroanatomical areas, connections and pharmacology that underlie particular cognitive functions and how these different neural substrates generate these cognitive functions [35]. One common behavioral method for assessing this is to use an attentional set-shifting paradigm from rodent to primate, which requires an initially learned rule to be shifted. Such tasks vary in their design, though they all maintain the same general principle requiring the learning of abstract rules to guide behavior, followed by a shift between available rules [11,36,37].

While the human WCST uses dimensions in which humans are well skilled to distinguish between, animal variants use dimensions from modalities that are readily sensed and learned by the animal of interest. Primate tests generally take advantage of their advanced visual and spatial systems [38], and rodent tests use olfactory and texture cues or sets of simple visual cues that are easily dissociable and highly visible [36,39,40].

Key elements of set-shifting include intra-dimensional shifts (IDSs) and extra-dimensional shifts (EDSs). All set-shifting paradigms start with the formation of a rule (Fig. 1a; initial discrimination). For example, subjects may be presented with differently shaped stimuli of different colors and they must learn which object, when selected, produces a reward (e.g. money; food). In the example illustrated in Fig. 1a, during the initial discrimination, subjects learn that selection of the pentagon produces reward. This is true regardless of the color. Thus, subjects need to ignore the *irrelevant dimension* (color) and pay attention to the *relevant dimension* (shape), while following the *rule* of responding to the pentagon to obtain reward.

For an IDS, the relevant dimension stays the same, but the exemplars change. In this case, participants must still focus on the same relevant dimension (shape) and ignore the irrelevant dimension (color). If participants are following the previously learned rule, performance on the IDS will include few errors. Thus, attention is still focused on the shape dimension while ignoring the irrelevant dimension (i.e. color). However, during an EDS, subjects must switch the dimension they are paying attention to because the relevant rule now resides in another dimension. In the example above, on EDS trials the shape of the object has no predictive power. Instead, one of the other exemplars from the other dimensions predicts reward, providing the new rule (Fig. 1a). Across tasks, dimensions vary (i.e. colors, shapes, space, textures, etc.) depending on the subject being studied (i.e., rat, mouse, human, monkey, etc.), but the general idea stays the same; rules are learned and reinforced within a dimension on IDS trials and rules are shifted across dimensions on EDS trials.

The IDS and EDS tasks differ from other classical reversal tasks, in that a reversal requires an animal to inhibit responding to a distinct stimulus which previously was instructive of a reward, and to drive responding toward a distinct, previously unrewarded stimulus (Fig. 1). Reversals, therefore, test a more discrete form of cognition, whereas the IDS and especially the EDS test more abstract, rule-based learning. Animal models of set shifting are extremely powerful, as they combine elements of sensory perception, attention, and working memory to provide a more accurate representation of complex real life decisions. Set-shifting tasks have allowed animal researchers to test and tease apart prefrontal cognitive function, something that is difficult to do in humans with