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

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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.

Keywords

mPFC; prefrontal cortex; ACC; Anterior cingulate cortex; Attention; Set-shifting; Rule Learning; Behavioral Flexibility

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.

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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, 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 towards a distinct, previously unrewarded stimulus (Figure 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 disease or non-localized brain damage. This is important because PFC consists of many brain regions, each with functionally different roles critical for accurate set-shifting performance.

In the rat, mPFC is broken into two different cytoarchitectonic regions: the prelimbic (plPFC) and infralimbic (ilPFC) regions. Both the plPFC and ilPFC are the recipients of direct projections from CA1 of the hippocampus[41, 42]. The ilPFC has efferent projections to plPFC, ACC, orbitofrontal cortex (OFC), dorsal and ventral striatum, central and basolateral amygdala, Medial Dorsal (MD) thalamus and ventral tegmental area/substantia nigra pars compacta (VTA/SNc), and shares many of the same projections as plPFC, with minor exceptions being projections to central, but not basolateral amygdala projections[43]. However, plPFC also is strongly innervated by CA1 projections and not CA2/CA3 or dentate gyrus[44], and plPFC cells can be excited by hippocampal stimulation at monosynaptic latencies[45]. Medial PFC (mPFC) as a whole is thus a strong recipient of CA1 projections, though interestingly mPFC does not reciprocally project directly to hippocampus[46, 47], but projects to hippocampus via parahippocamoal regions and the nucleus reunions [43, 48]. Rat mPFC is also strongly innervated by corticostriatal loops[49, 50] and receives direct dopaminergic projections from VTA[51, 52]. Indeed, dopamine receptor blockade in mPFC yields the same behavioral deficits as direct inactivation[53, 54]. Thus, rat mPFC is situated to effectively integrate context, current sensory stimuli, recent and past memories, value (both expected and unexpected) and recent motor plans.

In rodents and monkeys the ACC is often considered a sub section of the mPFC, along with the prelimbic and infralimbic cortices, however, these structures have been shown to serve different functions[55, 56], thus we will discuss them as different brain areas. In both rodents and monkeys, ACC is dorsal to plPFC (area 32 in monkeys), however, in many studies it is difficult to ascertain their dissociable roles because they are often lumped

together and share many of the same connections[47, 57-60]. ACC receives projections from ilPFC and plPFC[61, 62] as well as motor and somatosensory cortices[63, 64]. Efferent projections from ACC are to sensorimotor and visual areas, while also projecting to caudal areas within the cingulate cortex[61] and to both plPFC and ilPFC[65]. ACC also projects to more basal and lateral areas of the amygdala, medial areas of the striatum, including both dorsal and ventral areas[66].

It is generally accepted that rodent mPFC and ACC are good anatomical homologues to the same regions found in primate PFC[65, 67-69]. Unlike rodent PFC, primate PFC is generally broken down also into a more dorsolateral region that is thought to be involved in more executive and cognitive-related functions as compared to more ventromedial portions (VMPFC) that are more related to emotional content and reward associations[58, 70, 71]. While there are no perfectly compatible dorsolateral neuroanatomical regions of the rodent PFC, a great body of work suggests that some of these functions might be under the control of rodent mPFC[43, 47, 63, 65, 68, 72, 73]. Certainly, the deficits observed after DLPFC lesions in monkeys and mPFC lesions/inactivation in rodents suggests they serve similar roles, at least during set-shifting as we will discuss below.

Set-shifting tasks identify a common property of cognition: that dynamic and complex processes underlie the cognitive function of set-shifting. When viewed broadly, understanding rule learning and shifting may appear simple, yet forming and shifting an established set requires the complex coordination of multiple underlying cognitive processes. These processes include competition between two behavioral responses (conflict), error detection, reward predictions and reinforcement history[74, 75]. These underlying cognitive processes all play major roles in the formation and shifting of an attentional set. Recent research has shown that many different regions in prefrontal cortex are critical for these functions to various degrees[74, 76-81]. Below we review several tasks that examine set-shifting in monkeys, rats, and mice, and how they have pointed to specific neuroanatomical regions being related to different aspects of set-shifting. Then, we explore what functions recently attributed to these areas might be critical for these aspects.

Monkey Visual Tasks

Primate research generally requires subjects to make visual saccades, or to manipulate objects to make selections. Primates possess great visual acuity, and attentional set-shifting tests for primates make use of this, generally presenting two complex and colorful visual cues, and requiring the monkey to make a response to one for a juice reward[38, 74, 82, 83]. The visual task is similar to the human set shifting tasks, in that it uses visual cues as the dimensions, including different colors, patterns and shapes which are frequently used as response options. Using a rule to guide behavior, the monkey must ignore the irrelevant stimulus dimension, but focus on the correct dimension.

Dias et al (1996) demonstrates in marmosets that lesions to OFC resulted in reversal deficits, while lesions to the lateral PFC lead to set-shifting deficits on EDS[38, 83] . These data utilized complex visual cues which shifted between using shape or lines to guide their behavior. Subsequent work demonstrated that inhibition of the serotonergic system in the cortex leads to reversal, but not attentional set-shifting deficits[38]. The learning of abstract categories relates to learning rules in that generalizable behavioral responses are created, based on rules that relate to future circumstances. Antzoulatos and Miller (2011) demonstrated that correlates of Stimulus-Response (S-R) learning occur earliest in the striatum of primates as they perform a categorization task, while the dorsolateral prefrontal cortex DLPFC more slowly encodes the developing associations[74]. Changes in activity in DLPFC predicted the shift in rules or responses better during category learning than S-R

learning, which were better predicted by striatal activity. These data suggest that DLPFC is necessary for holding online a current and abstract rule to guide responding, while the striatum is more essential for behaving in a more stereotyped S-R manner, consistent with much previous literature[80, 82, 84, 85].

Unlike lateral PFC, lesions to ACC in monkeys do not yield large deficits on a set-shifting-like task per se, but rather a deficit related to error monitoring and sustaining attention to the task[86]. These data suggest that there are reliably dissociable functions of DLPFC and ACC in primates, whereby DLPFC has a more dedicated function towards forming attentional sets, and ACC is more directly activated under changing circumstances, such as altered response sets, changing rules or when there is conflict between responses. Notably, primate research on set-shifting has focused on dorsal and lateral parts of PFC, with few interference studies examining the role that mPFC (Brodmann areas 32 and 25) and ACC (Brodmann area 24) play in set-shifting [38, 56, 74, 85, 87] .

Digging Tasks

One method of testing rodents has been to use of a digging task as illustrated in Fig. 1b which combines attentional set-shifting with reversal learning [36]. Rodents are trained to dig in one of two bowls based on either an olfactory cue, or a media/texture cue, in cases where the two cues are presented together in random locations and combinations. Both rats and mice will readily dig for a food reward and quickly learn the associated rules, using either odors or digging media to guide decisions. In order to teach rodents a generalizable rule, different digging media and olfactory cues are used for multiple IDS tasks. Increased performance, measured as an enhanced learning rate, on new IDS tasks is generally taken as a measure of the rodent learning the ‘rule’ and applying this characterization rule to novel sets of exemplars in which the overarching ‘rule’ (ie, follow the odor, ignore the digging media) is followed. To avoid a potential confound with reversal learning on a known set of exemplars, new sets of exemplars are used for the EDS portion of the task, requiring animals to appropriately shift their response strategies on a novel set of discriminants, though the rule has shifted.

This is a robust task, allowing the testing of multiple rodent models for the purpose of examining multiple different topics. With the initial examination in rats, Birrell and Brown (2000) demonstrated that OFC and mPFC are necessary to effectively resolve reversal and set-shifting digging problems, respectively[36]. They demonstrated that rodent OFC and mPFC have independent and distinct roles during situations requiring flexible behavior, as described in primates.

Subsequent work demonstrated that not only rats, but mice, had similar functional neuroconnectivity[39]. Bissonette *et* al demonstrated that excitotoxic lesions to OFC disrupted performance on a reversal digging task, while lesions to mPFC impaired performance on the EDS portion of the task (Fig. 2a). By demonstrating that mice had the capabilities to perform attentional set-shifting in a manner dissociable from reversal learning, Bissonette *et al.* opened the door for a myriad of transgenic testing[88-91]. Recently, they investigated the role of topiramate, an anti-seizure medication with mechanisms of action on $GABA_A$ receptors known to lead to impairments in humans[92] on set shifting in mice. Further research from their lab investigated the role of impaired cortico-striatal GABAergic inhibition on the digging task using a mutant of the autism associated gene, *MET*- and uncovered a reversal deficit similar to previous lesion work. Remarkably, they found that a loss of only 30% of the parvalbumin interneurons was sufficient to impair reversal learning[93]. The wealth of data originating in both the rat and mouse reports from

this digging task should not be understated, as it remains a simple and relatively cost-effective task to perform, during which time many animals can be evaluated.

Digging tasks have also been used to make dissociations between mPFC and ACC. Ng and colleagues demonstrated that ACC was critical when shifting attention between closely related meaning cues (ie, between two odors) within a perceptual dimension[37] on an IDS, whereas the mPFC was critical for shifting attention between disparate sets of meaningful cues (ie from odors to digging media) between perceptual dimensions on an EDS. This suggests that ACC is more critical for flexibility when cues are more closely related during IDS[37]. Although Ng *et al.* found that ACC was not critical for simple reversals, other groups have tested ACC inactivated rats on a 4-choice odor discrimination task with reversals and found impairments[94, 95]. Thus, unlike OFC, ACC is not critical for simple reversals but is necessary when reversals are more challenging, and unlike mPFC, ACC is necessary for discriminating between closely related cues, such as those found during an IDS, but not for more distinctly different cues, such as would be encountered on an EDS.

Maze Tasks

Strategy set-shifting is generally completed in an operant chamber or maze environment, typically a cross or Y maze[96, 97]. These tasks require animals to shift, on egocentric (left/right) or visual responses, though some tasks do use mazes contrasting visual brightness with tactile stimuli[98]. Operant tasks have the added advantage of using the same types of exemplars (egocentric direction and visual cues)[53, 96, 99, 100]. Errors in attentional set-shift paradigms are difficult to parse out, as they may be due to confounding sensory processing issues with novel stimuli. In a maze or operant task, since the stimuli are constant, the behavior tests conflict resolution more than investigative behaviors behind seeking a novel and successful behavioral strategy to solve a current problem.

Ghods-Sharifi et al, 2008, demonstrated the effectiveness of this type of task, by inactivating OFC and demonstrating impaired behavior on reversal trials, compared to strategy set-shifting trials for rats shifting between visual cued responses or egocentric responses[97]. These data continued to support dissociable roles for OFC and mPFC in mediating reversal or set-shifting type behaviors, respectively.

However, recent work has now suggested that OFC may play some role in mediating the formation of attentional sets on a rodent digging task. Worse performance on a repeated IDS task (using 4 ID tasks) correlated with severity of EDS deficit in an OFC lesioned animal[101]. This finding was replicated in a 7IDS task that included a reversal trial. OFC lesioned rats had a robust reversal deficit and reduced shift-costs, suggesting OFC plays an important role in clearly identifying the important relevant cues after a shift occurs, which generally leads to unexpected outcomes in performance during behavior. A deficit in identifying a relevant cue in an ambiguous situation may lead to an initial delay in determining what new rules may be important to guide behavior[101].

These maze tasks have allowed the testing of the role of many neuromodulators and have also revealed the functionality of different receptor subtypes. For example, Dalton et al (2011) demonstrated a set-shifting deficit stemming from the inactivation of the GluN2B subunit of the NMDA receptor in the PFC, while Floresco et al (2006) highlighted the fact that inhibiting multiple dopamine receptors (D1, D2 and D4) impaired performance in set-shifting tasks[53, 102]. Others have demonstrated the role of NMDA receptors in forming and assisting behavioral flexibility, where systemic injections MK801 disrupted both the formation and shifting of behavioral sets from egocentric to light rules[100] while local mPFC infusion MK801 just disrupted the set-shifting portion of the task.

Others have used similar tasks to examine specific subregions of mPFC. Oualian and Gisquet-Verrier (2010) found that lesions to either plPFC or ilPFC led to perseverative responding to previous rules during a necessary shift in strategy[103], reinforcing a role for ilPFC directly in mediating these shifts[96, 97]. Indeed, they also found that lesions encompassing both plPFC and ilPFC showed robust strategy set-shifting deficits, whereas lesions to plPFC or ilPFC yielded more moderate deficits. They go on to suggest that an intact ilPFC may assist animals in choosing a previous unrewarded strategy, whereas in an inactivation or lesion situation, a loss of the ilPFC region of the mPFC may inhibit their ability to directly choose a novel option[103].

One of the many additional advantages of these tasks is the ability to time-lock particular behaviors. With effective time-locking comes the ability to perform *in vivo* physiology with good temporal resolution to the actual behavioral occurrence. For example, Rich and Shapiro (2009) showed that plPFC and ilPFC may serve different functions related to initiating and establishing new strategies based on the dynamics of the neural response during learning[55]. Durstewitz et al (2010) investigated changes in neural ensemble firing patterns across shifts between visual and egocentric rules, and found distinct active states for neuronal ensembles during different rules[99]. Neuronal activity changed between states abruptly, suggesting that the 'switch' from one rule to the next may be more abrupt and more of an 'ah ha!' moment than a gradual process comparing previous behavioral failures and successes over time[99]. So far, such experiments have proven difficult to perform in mice. While mice readily perform digging tasks, these tasks are time consuming and require constant experimenter supervision making electrophysiological experiments more difficult (but possible) than more automated maze tasks. Implementation of mouse touchscreen tasks hold great potential to combine the power of precisely time locked behavior with specific genetic manipulations and single unit recordings[40, 104, 105].

Medial prefrontal cortex and functions related to set-shifting

From the studies described above, mPFC and ACC play different roles in set-shifting tasks than OFC, which mediates reversal learning and has been the topic of many reviews suggesting that reversal deficits are a result of lost reward expectancy signals[106-109]. Here, we focus our attention more to mPFC and ACC, and the functions that they might serve during set-shifting procedures. Set-shifting, as studied in all of these tasks, requires a number of fundamental functions to be performed accurately, all of which are thought to be under the control of mPFC and ACC to some degree. These include: 1) forming associations between stimuli, responses and outcomes, 2) detection of errors and conflict between rules, 3) tracking of reward history to determine which responses are no longer valid, and 4) enhanced attentional processes to resolve these issues when rules are violated. Unfortunately, very few studies have recorded from single neurons while animals perform set-shifting tasks, thus it is still unknown exactly how mPFC and ACC accomplish this task. Here, we speculate based on the current literature pertaining to neural correlates that likely underlie set-shifting behavior as examined in other tasks that tap into these functions.

Clearly, mPFC plays some role in forming associations between stimuli, responses and outcomes so that one can learn the contingencies necessary to perform the task initially[110, 111]. The plPFC in rats appears to be strongly associated with higher order cognition, requiring integration of past, current and future choices[43, 72, 112]. Rat plPFC mediates spatial working memory and visual object information, along with cross-modal switching involving spatial location, visual objects and spatial locations with motor responses[113-117].

Activity in mPFC has been shown to be linked to a variety of task correlates. Medial PFC appears to encode expected value, action selection, stimulus-response associations, and is spatially selective[81, 118-121]. Neural ensemble firing in mPFC reflects distinct active states during set-shifting, which is temporally related to behavioral performance[74, 79, 99]. Meanwhile, plPFC and ilPFC appear to subserve different functions in rule learning, with plPFC neurons encoding the initial learning of the rule, and ilPFC neurons lagging behind plPFC in encoding the relevant behavioral action[55]. Recordings in primate DLPFC have shown similar results, with multiple separate ensembles simultaneously representing categorization rules[79] and that DLPFC encodes, then represents abstract categories[74]. In addition to these correlates, mPFC may play an important role in monitoring performance via several functions including, maintaining information across delays, encoding correct and incorrect responses, and signaling reward-related feedback[118-120].

Lesions to mPFC do not prevent initial learning during set-shifting[36, 39, 83], suggesting that mPFC is not necessary for initial rule learning. Furthermore, the fact that performance in mPFC lesioned animals on EDS tasks is abnormal after shifts may be because mPFC cannot form new associations and that it is ‘stuck’ representing old contingencies. Recent research has demonstrated that mPFC is dependent on hippocampus for specific rule-related information. Navawongse and Eichenbaum (2013) show that inactivation of plPFC changes the location and reward based firing of hippocampal neurons, causing them to lose rule specificity[122]. Further evidence for this comes from the finding that rat mPFC contributes to maintenance of task switches, such that inactivation during a switched rule can be learned, but not recalled 24 hours later, an effect not observed when inactivating during reversals, task switching or switching between useful rules[123]. It has also been shown that primates, who have been previously trained on abstract rules, are quicker and better able to recall those familiar rules in the future[87].

The fact that rats with ACC lesions had no difficulty learning relevant cues or switching using different dimensions as relevant cues[37], but is critical for IDS[103], suggests that ACC might not be as critical for forming rules as does mPFC but may mediate other attentional mechanisms, especially when stimuli are perceptually similar. This behavioral deficit might reflect a deficit in a number of functions, including the inability to generalize within a dimension, increase learning sets[37], and reflect deficits in basic function such as resolving response conflict, detecting errors and attenuating attention away from the irrelevant dimension as we will discuss below.

In humans and primates, ACC is activated during scenarios of response conflict[75, 83, 86, 124-126] . Such competition requires increased attention so that engaged participants can override a stimulus-driven response in a situation where an alternative response is the more appropriate one. A classic example is the Stroop task, in which human participants are shown a word such as ‘red’ and asked to indicate the color of the font (e.g. ‘red’ written in green ink). The standard, stimulus-driven response is to read the word ‘red’, while the competing, task-imposed response is to name the color of the ink (i.e. green). On high conflict trials, participants are slower and less accurate, suggesting that it requires time and neural resources to resolve the conflict between the two competing responses. Neural activity in ACC has been shown to be positively correlated to the degree of conflict in the Stroop as well as a number of other tasks[127-138]. Thus, ACC’s role in mediating attention during set-shifting might be to signal when behaviors are in conflict with one another in terms of respective dimension, rather than identifying when a more global ‘rule’ is in conflict with current behavioral outcomes. Consistent with this idea, recent work suggests that ACC plays a role in conflict monitoring during automated retrieval of S-R maps, but not in forming or breaking S-R associations *per se*[139].

In addition to conflict monitoring function, ACC plays an important role in error detection. Originally this research focused on the role of ACC in detecting errors of commission[130, 140-142], but has also now been implicated in reporting errors in reward prediction. While the majority of this work has focused on the role of ACC in detecting errors, other studies suggest that ACC is important for signaling positive feedback[56, 111, 138].

New lines of research suggest that the role of ACC in signaling errors is related to providing an unsigned prediction error signal necessary for driving adjustments in behavior[143]. ACC neurons respond when outcomes are better and worse than expected. Hayden and colleagues demonstrated this in a task where rewards were delivered at predetermined probabilities[144]. Changes in ACC firing were observed regardless of the valence within single neurons, supporting the idea that primate ACC encodes unsigned reward prediction errors which would be important and useful for adjusting subsequent behavior[144].

We have also reported similar results as illustrated in Figure 3. As has been shown numerous times in ACC[143], we found that many neurons in rat ACC fired when there were errors in reward prediction and errors of commission. More importantly, we demonstrated that activity was increased after reward prediction errors and that these activity changes were correlated to the amount of attention exhibited on subsequent trials during which rats correctly updated behavior[143]. These results suggest that activity in ACC does not simply signal reward prediction errors, but also signals the need for increased attention on subsequent trials so that learning can occur, reflecting past reward history. These data fit nicely with primate studies, where ACC appears to direct decisions with clear and obvious reinforcement histories, rather than more abstract rule scenarios[76].

Recent theoretical work has suggested that all of these functions in mPFC and ACC - error detection, reward prediction errors and conflict monitoring may reflect the same underlying process[145]. This work considers these signals to be part of a generalized surprise/attention system. In each of these cases, activity in mPFC and ACC might reflect unexpected non-occurrence of an expected outcome. The activity caused by unexpected outcomes could explain why several studies have suggested that mPFC and ACC activity is high when there are violations in expectations[130, 146-148].

Unfortunately, few studies have dissociated mPFC and ACC functions using the same behavioral tasks, making it difficult to pinpoint and tease apart their exact roles in set-shifting, as has been done for OFC and mPFC. Anatomical limitations exist as a natural barrier to this research, as most carefully run lesions studies of mPFC will undoubtedly impact the ACC, given their close anatomical proximity. However, genetic models may emerge in which the ACC and mPFC are differentially affected, perhaps an interneuron deficit in one region or targeted deletion of a neurotransmitter receptor. While the damage to ACC is minimal in recording studies, these provide a methodological route to separating the functions of ACC and mPFC in behaving animals. Both mPFC and ACC have been implicated in encoding associations between stimuli, responses and outcomes, and both have been discussed as being involved in reporting errors and signaling response conflict, albeit, to varying degrees[118, 119]. In fact, in many papers, mPFC and ACC are not distinguished when discussing function, which might not be so surprising considering they are so well interconnected and likely function as a unitary structure in many circumstances[149, 150].

With that said, the majority of the research into conflict monitoring and error detection processes have been directed towards ACC, rather than mPFC[75, 86, 140, 151] and some single unit studies suggested that ACC is more involved in detecting errors and is more strongly modulated during tasks switches relative to mPFC[147, 152]. Furthermore single unit studies in mPFC in rats and DLPFC in monkeys have shown clear correlations with

rule-based decision-making and stimulus categorization [80-82, 87], and neural ensemble firing in mPFC is clearly related to shifts in behavioral performance during set-shifting tasks.

Together this suggests that mPFC may function solely to signal the rule and guide attention toward relevant dimensions as done in EDS, rather than representing error information, whereas ACC is most likely involved when a rule is violated and is critical for signaling the need for attentional shifts. In this model, mPFC functions as the region which sets the rule and ACC monitors the behavioral outcomes for favorable and unfavorable outcomes which have resulted from a behavioral action, guided by a particular rule. Although this model sits well with what happens after mPFC lesions, it does not fully explain why ACC is only critical for IDS and not EDS. Both would elicit errors and an induce response conflict. One possible remedy is that ACC is critical for reducing attention to irrelevant stimuli when contingencies change. When expected outcomes are violated, two processing are thought to occur; attention must be paid to the relevant dimension so that new association can be formed and attention to the irrelevant dimension is weakened. If attention to the irrelevant dimension is not weakened during the initial discrimination, then rats will still be equally attending to both dimensions, which might lead to impairment on IDS, but would not impact EDS[37]. Such a function fits with increased activity during conflict, on errors and on trials after errors. Typically, we think that this activity is critical for directing attention to stimuli so that new associations can be formed, but it might be equally necessary to weaken attention from irrelevant information.

Beyond this model and our knowledge obtained from single unit recordings, ACC and mPFC might encode different aspects of rules and sets. If ACC encodes the recent reward history, it could provide weighted information about which current rule possibilities will most likely yield a most desired outcome. In this regard, mPFC could store previously learned abstract rules and in the present, represent the current rule driving behavior. While mPFC represents the current rule, it would also be integrating the success of previous actions using reward history values from ACC. In this model, mPFC rule representations hold online the current rule that is the most effective, while receiving judgment advice from ACC regarding recent history and present behavioral choices. Familiar rules are stored in mPFC, making the recall of abstract rules easier for trained animals and leaving ACC to provide the information about which possible stored rule may provide the greatest maximal beneficial outcome[87]. Meanwhile, mPFC provides the rule instructions to hippocampus[122] to build the necessary spatial map required to engage the appropriate rule, as well as provides the correct rule to dorsal striatum, which enacts specific action policies when the animal encounters the necessary behavioral cues.

It is critical that we understand these functions in mPFC and ACC, and how they govern flexible and adaptive behavior because so many disorders impact this function though PFC/ACC pathophysiology. For example, in animal models of schizophrenia-like dysfunction, one mechanism by which disruption of set shifting may occur is through impairments of inhibitory neurons, in agreement with postmortem studies of patients with schizophrenia, which might lead to disorganized information processing in mPFC and ACC[21, 29, 30]. If inhibitory interneuron deficits in mPFC inappropriately tune the mPFC projection neurons that carry rule information to dorsal striatum, inflexibility may originate from a disorganized and weak rule signal emanating from mPFC. Conversely, if there is an enhancement of GABAergic inhibition tuning the local mPFC circuit, inflexible behavior may result from an overly strong and sustained rule signal. Similarly, if ACC suffers from weak tuning and organization from a deficit in cortical inhibition, weak or inaccurate information about recent reward history[153] would leave mPFC in a position to incorrectly continue to drive a rule that no longer corresponds to the desired outcome based on recent outcomes. All of

these possibilities can lead to perseverative rule responding observed in set shifting deficits in animal models[154, 155], and would have strong implications for human disorders where reduced cortical synchrony is thought to underlie cognitive deficits, notable among them, schizophrenia[21, 29, 30, 156]. In the future, more precise testing and use of appropriate animal models will be necessary to help not only tease apart the roles of mPFC and ACC, but also the proposed underlying mechanisms behind cortical dysfunction in diseases which affect the human condition.

Conclusion

The study of attention and set-shifting is important on many fronts. Such elements of cognition are disturbed in both normal aging and in a myriad of disorders which affect both frontal and limbic structures, such as schizophrenia, bipolar disorder, affective and anxiety disorders [3, 29-34]. Although research has rapidly progressed on many fronts regarding the general circuitry involved in functions underlying learning and attention, there remains a good deal of unanswered questions. Multiple lines of evidence have robustly linked mPFC and ACC to different aspects of attention and set-shifting in several animal systems. The challenges, now, are determining exactly what is being represented by these critical regions during flexible decision-making and adaptive behavior. We must consider several functions, including error detection, conflict monitoring, stimulus-response learning and abstract rule representation. Furthermore, there has been surprising little work on understanding the role of prefrontal cortex modulation of downstream areas, such as striatum, during performance of these tasks. With such data in hand, we will gain a better understanding of the effects which occur in human disease states.

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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

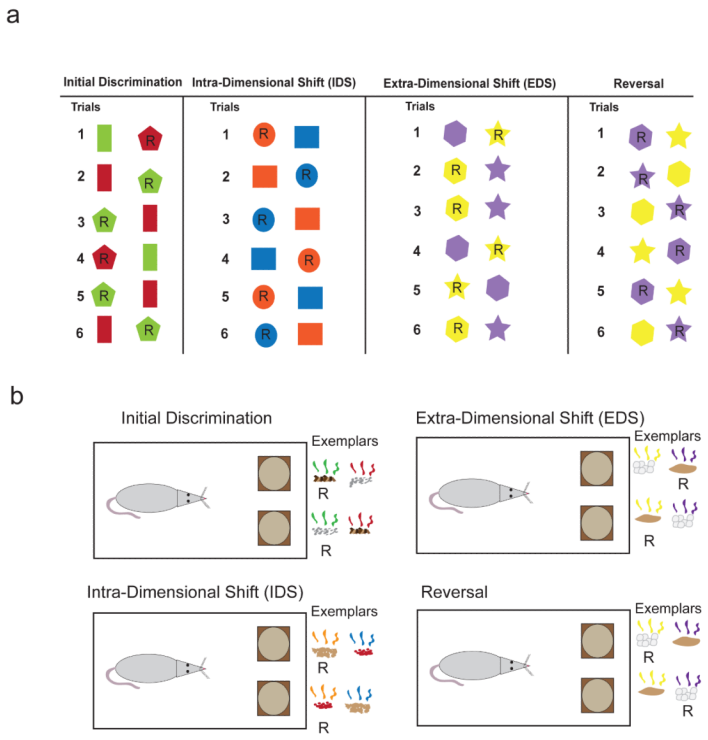


Figure 1.

Examples of set shifting tasks. **a**. Examples of different types of trials for a set shifting task between color and shape. Shapes with 'R' represent the 'correct' response, or a 'reward'. Under the initial discrimination, the rewarded dimension is 'shape', not color, where pentagons are rewarded but never rectangles. During the IDS, the exemplar options are changed, but the rule remains the same, 'shape', where circles are rewarded but squares are not. The reversal trial reverses the previously correct stimuli, but keeping the rule the same 'ie, follow shape'. For the EDS, the rewarded dimension shifts from the previous rule of 'shape' to the now correct 'color', rewarding yellow choices. **b**. A rodent version of this task, showing the same progression from a discrimination, through an IDS, reversal and an EDS. Exemplars are shown in the form of stylized digging media and odors, and correct pairings are shown with an 'R' under them. In this case, the rodent is trained to follow the rule 'odor', until the EDS, when the rodent has to shift from this rule to 'media'.

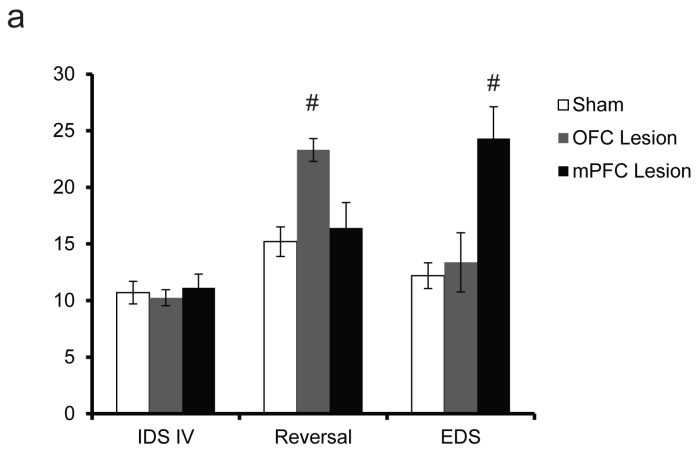


Figure 2.

Excitotoxic lesions to mouse OFC and mPFC yield different cognitive deficits. **a**, Lesions to mouse OFC drive reversal, but not set-shifting deficits, whereas mPFC lesions yield set-shifting, but not reversal deficits, when compared to sham animals (pound sign denotes $p<0.05$). N for Sham, OFC lesion and mPFC lesion were 10, 8 and 8, respectively. Modified from Bissonette *et al*, 2008[39]

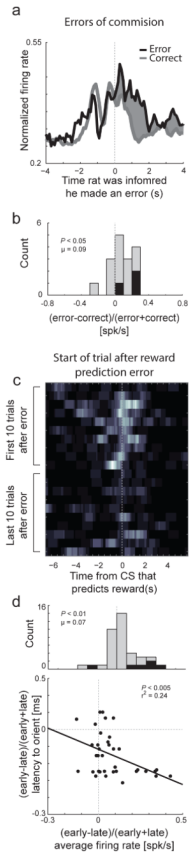
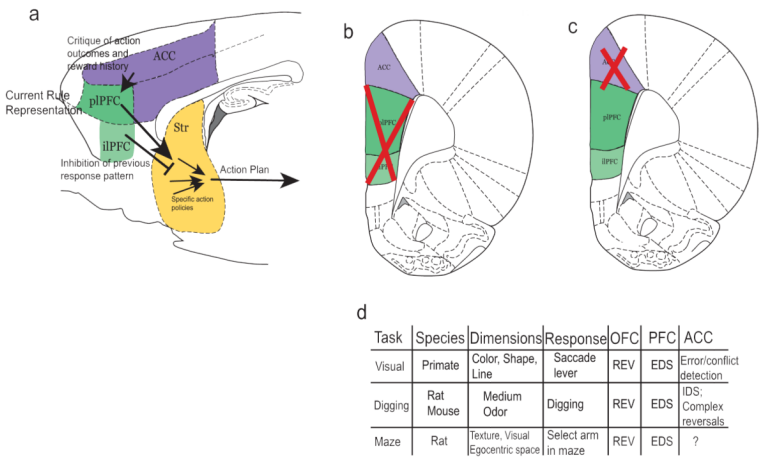


Figure 3.

Activity in ACC was high after errors of commission, errors in reward prediction, and was high at the beginning of trials that followed errors. **a**, Average activity of error related (1s following well entry) neurons upon errors of commission. **b**, Distribution reflecting the difference in activity between forced-choice errors and forced-choice correct trials ((error −correct) /(error + correct)). Black bars represent the number of neurons that showed a significant difference between these responses (t-test; $p < 0.05$). **c,** Heat plot shows the average firing of a single ACC neuron when reward contingences unexpectedly change (reward prediction error). d. Activity of ACC neurons fire more strongly after reward prediction errors and was correlated with attention. Correlation between latency to initiate behavioral trial and firing rate (x-axis) either early or late during learning ((early-late)/(early +late)). N = 4 rats. Modified from Bryden *et al*, 2011[143]



Task	Species	Dimensions	Response	OFC	PFC	ACC
Visual	Primate	Color, Shape, Line	Saccade lever	REV	EDS	Error/conflict detection
Digging	Rat Mouse	Medium Odor	Digging	REV	EDS	IDS; Complex reversals
Maze	Rat	Texture, Visual Egocentric space	Select arm in maze	REV	EDS	?

Figure 4.

Circuit diagram highlighting main set-shifting pathways. a) Overall rule circuit, demonstrating running behavioral performance updates from ACC to mPFC, current best Rule strategy from dorsal mPFC (plPFC) to striatum, inhibitory input from ventral mPFC (ilPFC) to striatum and on to behavioral action. b) Atlas coronal slice of rat brain depicting representative areas destroyed in most mPFC lesion studies. c) Atlas section depicting representative region destroyed in ACC lesion studies. d) Summary table of behavioral designs across species and the general behavioral outcome of OFC, PFC or ACC lesions.