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Action sets and decisions in the medial frontal cortex

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Activations in human dorsomedial frontal and cingulate cortices are often present in neuroimaging studies of decision making and action selection. Interpretations have emphasized executive control, movement sequencing, error detection and conflict monitoring. Recently, however, experimental approaches, using lesions, inactivation, and cell recording, have suggested that these are just components of the areas' functions. Here we review these results and integrate them with those from neuroimaging. A medial superior frontal gyrus (SFG) region centred on the pre-supplementary motor area (pre-SMA) is involved in the selection of action sets whereas the anterior cingulate cortex (ACC) has a fundamental role in relating actions to their consequences, both positive reinforcement outcomes and errors, and in guiding decisions about which actions are worth making.

Although a functional dichotomy between the subcallosal and dorsal supracallosal human ACC is well-established [1], distinguishing the functions of the dorsal ACC and adjacent SFG (Figure 1) is difficult. Anatomical considerations suggest the two regions have similar functional roles. In the macaque, the areas are not just interconnected with one another but they also share connexions with the prefrontal cortex (PFC) [2]. Moreover, their proximity means that activations in the areas can only be distinguished with care in human neuroimaging experiments [3]. The two areas are difficult to differentiate in standard brain templates in which the medial frontal cortex is unusually shallow [4]. Finally, variability in the positioning and continuity of the human cingulate and paracingulate sulci is associated with variation in the location of functional regions with respect to anatomical landmarks [5,6]. The anatomical organization of the medial frontal region is more consistent in other species and behavioural results are easily and directly related to a set of known anatomical connexions (Figure 1).

The ACC and lateral PFC: working memory and task switching

It has been argued on the basis of meta-analyses of human imaging results that the ACC, like the lateral PFC, has a role in executive control [7,8]. Although it is true that humans activate both regions during working memory tasks [9] lesions of their homologues in the macaque brain have different effects. Whereas dorsolateral PFC lesions cause a profound working memory impairment [10] ACC lesions have little effect [11–13]. Procyk and Joseph [14] have also questioned the degree to which macaque ACC sulcal cells hold information in working memory over delays. ACC activation in the delay period may reflect the preparation of a motor response [15].

Manipulations which induce task interference, such as the Stroop or flanker procedures, and task switching paradigms result in activity in both human ACC and lateral PFC [16–18]. The ACC is distinguished, however, by having a later, narrower, and less central role in task switching. If a long delay separates the initial instruction to switch and subsequent performance of the new task then human ACC activation, unlike PFC activation, only begins at the later time with performance of the new task [19]. Unlike lateral PFC, ACC is activated only when there is a change in response set or when there is conflict between possible responses but it is not active when only stimulus selection is at issue [20,21]. The more central role of the lateral PFC is underlined by lesion evidence in monkeys; lateral PFC lesions impair task switching [22] whereas ACC lesions cause little disruption [11].

ACC lesions cause a slight increase in errors but the increase is not related to task switching *per se* [11]. The only pattern to the errors is that they occur one after the other whereas the realization that an error has been made prevents a normal monkey from making more mistakes. A patient with an ACC lesion has also been reported to be less likely than healthy controls to correct his own mistakes [23]. Related observations have also been made in rats with ACC lesions [24,25]. In summary the ACC involvement in task switching and interference might be a consequence of a role that it has in monitoring performance for mistakes which are just more likely in such situations. It may be more difficult to distinguish functions of the SFG and lateral PFC. Like the lateral PFC, the SFG is important in task switching [21,26] and this is discussed in the final two sections.

Errors and conflict in the ACC and SFG

Niki and Watanabe [27] first recorded changes in the activity of single ACC neurons when a monkey made errors. An error-correlated change is also present in the

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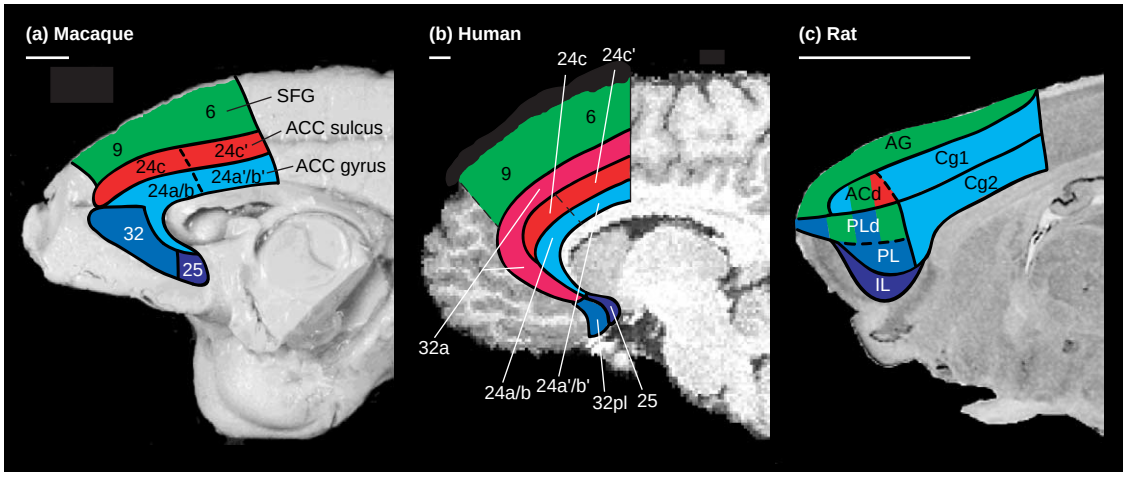

Figure 1. **(a)** Three broad divisions can be distinguished within the medial frontal cortex of the macaque monkey. The ACC gyrus (blue) is dorsal and rostral to the corpus callosum. Subdivisions of area 24 (24a, 24b, 24a′, 24b′) constitute the dorsal part and areas 32 and 25 are more rostral and ventral. The ACC sulcus (red) consists of a further subdivision of area 24, 24c. Its caudal part, 24c′, contains the rostral cingulate motor area (CMAr). The even more caudal sulcus contains one or two more motor areas [69]. The SFG (green) consists of areas 9 and 6. The pre-SMA is a part of the SFG that lies rostral to the level of the anterior commissure [69]. **(b)** Three broad regions can be discerned within the human medial frontal cortex. ACC gyrus areas 32pl, 25, 24a and 24b resemble the macaque ACC gyrus [6,70]. Human areas 24c, 24c′, and 32ac in the ACC sulcus and the second superior cingulate gyrus bear similarities with the macaque ACC sulcus and include CMAr [6,70]. The SFG region is similar in the two species. **(c)** The identification of homologous structures in the brains of rodents is more controversial. There is a good case for thinking that some parts (Cg2, posterior Cg1, infralimbic cortex [IL] and prelimbic cortex [PL]) resemble the primate ACC gyrus. There is no equivalent of the primate ACC sulcus in the rat but it might be argued tentatively that rat rostral ACd bears some resemblance in its anatomical connexions. The anatomical connexions of dorsal PL (PLd) make it distinct from ventral PL and it may have some functional similarities with both the ACC sulcus and SFG regions of the primate brain. The AGm cortex resembles primate SFG areas such as the SMA but it also shares characteristics of other adjacent primate areas such as the premotor cortex and adjacent eye fields. The white scale bar in the top left corner of each panel indicates an approximate length of 5 mm.

aggregate activity of many ACC neurons and can be recorded as a surface negative field potential when electrodes are placed beneath the dura of the macaque ACC [28]. An event related potential (ERP), called the error related negativity (ERN), can be recorded with electrodes on the human scalp, with a similar time course, peaking between 80 and 130 ms after an erroneous response [29]. A combined ERP and event related fMRI study demonstrated that errors which are associated with ERNs are also associated with activity centred on the ACC sulcus probably in CMAr in area 24c′ [30]. Consistent with such a localization, reductions in reward have been associated with activation in the ACC sulcus and, when present, the superior cingulate gyrus [31]. The firing rates of cells in the homologous region of the macaque ACC sulcus also change when rewards are reduced [32]. Systematic comparisons of the error related responses of single cells in the ACC sulcus and gyrus have yet to be reported.

Although the most straightforward interpretation of the ERN is that it reflects the detection of an error after the intended and actual movement are compared, it has been suggested that the waveform may instead reflect response conflict [17]. The response conflict account argues that errors tend to occur on trials when representations of more than one response are co-activated. The wrong response might be made because its representation is more quickly activated, perhaps as a result of the greater frequency of its use or simpler stimulus response mapping or because of the subject's uncertainty about how to respond, but representations of other responses, including the correct response, are also likely to be activated on the same trial. Crucially it is argued that response conflict alone, even if it does not lead to an actual error, is sufficient to cause a change in ACC activity. An attractive feature of the hypothesis is that it provides an account of how the need for cognitive control might be detected even before mistakes are made. Moreover response conflict can be clearly and quantitatively defined as the product of the activity associated with each response in a neural network model. Demonstrations of ACC activation on high conflict trials that are performed without error and reports that the ERN is affected by manipulations of response conflict have supported the theory [16,17,33].

Recent debate has centred on whether the ACC detects errors or response conflict. The controversy may have arisen because different researchers are discussing separate parts of the medial frontal cortex. Human ACC activation increases when errors are made in many situations including go/no-go [34,35], flanker [30], oddball target detection [34], and motion prediction [36] tasks. The activation coordinates ($18<y<21$; $z<35$) in all these studies place them far from human SFG and make their attribution to ACC unambiguous. Activation in this region is not modulated by response conflict in the absence of errors to the same degree [30,34,35]. Although there might be some overlap, response conflict is better associated with activations at a more dorsal level ($z>45$) in the SFG [30,34,35]. Even proponents of ACC conflict monitoring report caudal and dorsal activations that are close to the SFG and some distance from the rostral and ventral region that is unambiguously ACC [16,17].

A study of the effects of lesions on response conflict in 51 patients also emphasized the SFG at the expense of the ACC [37]. Although there are some single case reports of increased response competition effects on incongruent Stroop trials after ACC lesions the evidence has not been

consistent [15,23,38,39]. Data from one patient with an ACC lesion, like the neuroimaging data, emphasized the dissociation between error detection and conflict monitoring [23]; although the lesion was associated with changes in both behavioural and ERP indices of error detection, other electrophysiological measures of the N450 potential indicated intact or enhanced response conflict detection. Complete bilateral ACC lesions in macaques do not cause any special impairment on task switching trials when response conflict is at a maximum [11]. Single neuron recording studies in macaques are also consistent with an involvement of the ACC sulcus in error detection but not in conflict monitoring [40]. There is, however, evidence for conflict related modulation of firing rates, even in the absence of errors, when recordings are made in the macaque supplementary eye field (SEF), an SFG area just lateral to the pre-SMA in which oculomotor as opposed to motor activity predominates [41].

In summary, it is difficult to explain human medial frontal activation on trials that are performed correctly by reference to error detection alone. Instead it may be necessary to invoke the detection of response conflict even before any error is committed [16,42]. Nevertheless human neuroimaging, macaque single cell recording, and lesion studies in both species suggest that a caudal SFG region has the central role in encoding response conflict.

The ACC and the coding of action outcomes

Despite preoccupation with the errors vs conflict-monitoring debate it is now clear that the ACC has a broad role in encoding the relationship between an action and the reinforcement value of its outcome even when the outcome is a positive reward and not an error. It is true that macaque ACC sulcal neurons respond when actions lead to errors or when reinforcement is not delivered but similar or higher proportions of ACC sulcal neurons also respond to the delivery of positive reinforcers [40]. Although some neurons in the SFG also respond to rewards a greater proportion of ACC sulcus neurons have such properties [43].

Matsumoto and colleagues [44] recorded from neurons in the rostral ACC sulcus while monkeys performed an asymmetrically rewarded go/no-go task. Monkeys were taught to either pull a joystick (go) or to just keep hold of a joystick (no-go) in response to picture cues. Only two picture cues were used on a given day but the relationships between the cues and the responses were varied from block to block. Sometimes picture cues 1 and 2 instructed go and no-go responses but on other blocks the associations were reversed. Importantly Matsumoto and colleagues also changed the relationships between the cues and the reward and the responses and the reward (Figure 2) so that the full set of eight different visual-motor-reward combinations were assessed. Even before the response was made and the monkeys were looking at the visual cue the activity of ACC neurons depended on the expectation of reward or non-reward (25%), the intention to move or not (25%), or a combination of movement intention and reward expectation (11%). Comparatively few neurons encoded the visual cue or its relationship to reward. The learning of action outcome relationships is central to the sequence learning task used by Procyk and colleagues [45]. They reported a population of ACC cells in which activity changes were most prominent when monkeys were learning which sequence of three movements was followed by reward.

Not only do ACC neurons encode action outcome associations but lesions of macaque ACC disrupt reward-related action selection (Figure 2). Hadland *et al.* [46] taught monkeys to select one of two joystick movements after free delivery of one of two rewards. Correct movements were rewarded with a second similar reward. ACC lesions disrupted performance on the reward guided action selection task without affecting visual stimulus selection. It is not clear if actions are selected on the basis of the experienced or the anticipated reward in this paradigm. Nevertheless it is known, first, that selecting actions on the basis of received rewards does not depend on parts of the lateral frontal circuit used when actions are instructed by external sensory cues [47]. Second, learning is quicker if actions are not just instructed by distinct cues but if they are also followed by distinct outcomes [44]. The reward guided action selection deficit should also be contrasted with the preservation of action selection when it is guided by external sensory cues after ACC inactivation [32]. A direct comparison of the two types of action selection, externally guided and reward guided, however, has not been carried out in the same set of animals with ACC lesions.

It might be harder to sustain an association between an action and outcome when the action does not lead to the outcome on every occasion that it is made, for example when the action has to be performed repeatedly on a fixed ratio schedule before the reward is delivered. The ACC may have an important role in maintaining action outcome associations when they might otherwise be vitiated by such schedules. Medial frontal lesions that include the ACC impair marmoset monkeys' ability to sustain responding for primary reinforcers in fixed ratio schedules [48]. The deficit is different from the stimulus reward association impairment seen after orbitofrontal lesions [48].

Recent studies demonstrate that the primate ACC has a fundamental role in mediating action outcome associations, even when the outcome is positive and not an error. In this respect our understanding of the primate medial frontal cortex is beginning to catch up with our knowledge of related regions of the rodent brain. After damage to the prelimbic cortex rats' actions are no longer sustained by the prospect of particular outcomes, but merely by habit [49,50]. Medial frontal lesions can have a fundamental effect on the ability to generate voluntary goal-directed behaviour.

Several studies have reported ACC activation when people perform 'willed action' or 'self initiated movement' tasks [51]. Such tasks require subjects to generate random responses, such as finger movements or spoken words, in the absence of cues and prompts. According to the conflict monitoring hypothesis ACC activation in such situations reflects the monitoring of competition between representations of the many different responses that are possible in

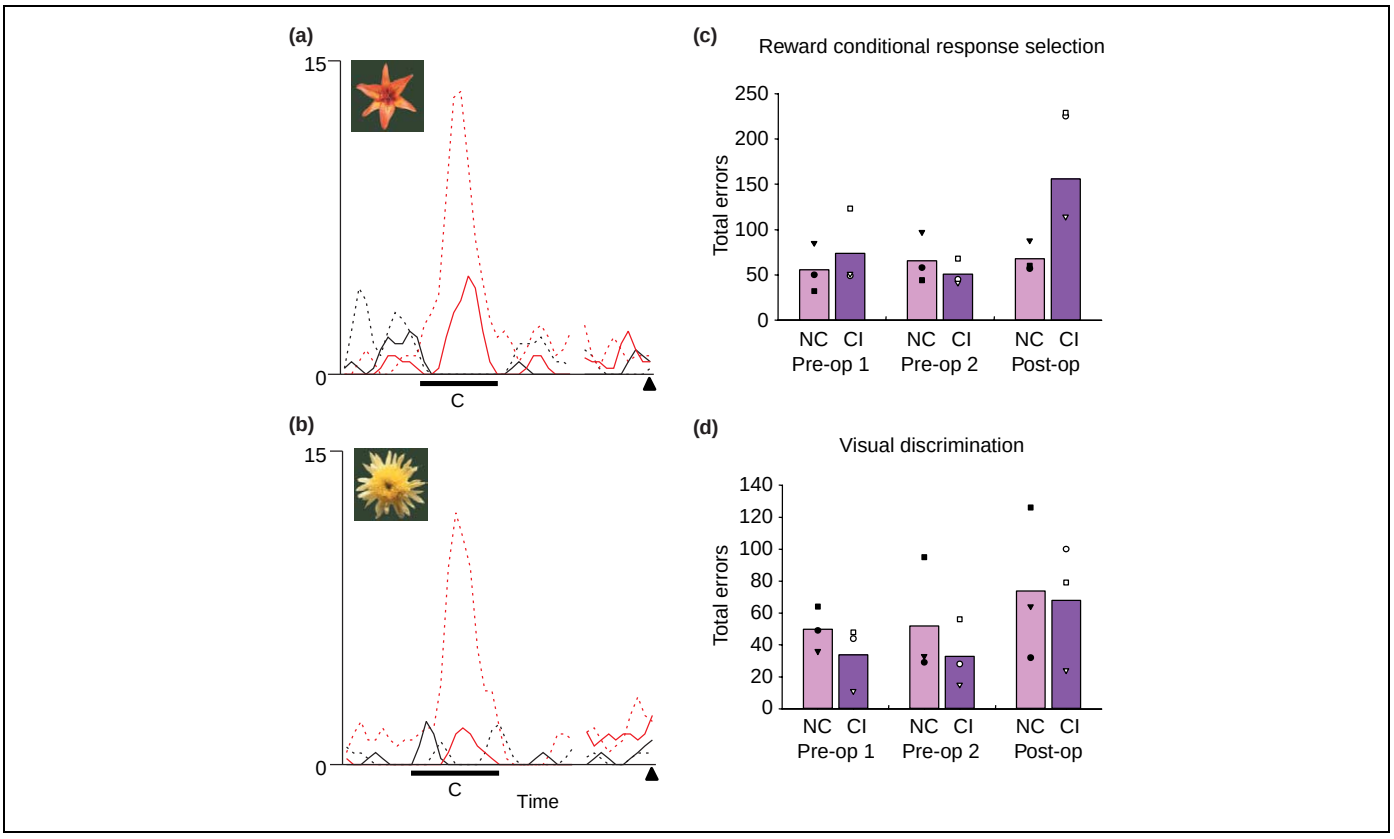

Figure 2. (a,b) An ACC neuron that encodes both a specific motor intention (No-go) and reward expectancy. Increases in activity when a visual cue, c (shown in the top left corner) is presented during the time indicated by the horizontal bar. Although the activity is time locked to the cue it is not specific to either cue (a, b) but encodes the expectation of reward delivery on a No-go trial (dotted red line) as opposed to the association of a reward on a Go trial (continuous red line) or Go or No-go trials in which no reward is expected (continuous and dotted black lines respectively). The time of reward delivery is indicated by an arrowhead. **(c)** Reward conditional response selection. The total number of errors made by the normal control animals (NC) and animals with ACC lesions (CI) on two pre-operative and one post-operative testing session. The ACC lesions were made in the CI group between the second and third tests. **(d)** The ACC lesion did not affect the ability to discriminate stimuli associated with rewards. Adapted from [44,46] with permission.

the absence of constraints. An alternative interpretation is that such tasks tax mechanisms for voluntary action generation. It is certainly true that a dearth of voluntary goal directed actions is witnessed after ACC lesions when prompting cues are not available [52]. Unlike the neuroimaging activations, the lesion deficit is hard to reconcile with either conflict monitoring or error detection accounts. Actions might not be carried out at the normal rate after an ACC lesion because there is a failure to conceive of their possible beneficial outcomes. Actions can only be prompted by cues but they are not elicited by the lure of anticipated outcomes.

The ACC and decisions about the values of actions

The ACC might not just encode *which* outcome is expected from an action and whether the action is expected to lead to an error. It might also be a crucial part of a system for encoding whether or not an action is *worth* performing given the value of the expected outcome and the cost of performing the action. Evidence that the ACC encodes the value of outcomes comes from scalp recordings of ERPs with ACC dipole sources [53]. Human subjects picked one of two numbered panels and received either a monetary loss or gain equivalent to the number on the panel. Picking the larger number was an error when the trial ended in a loss but picking the smaller number was an error when the trial ended in a gain. The size of the ERP was only influenced by whether the chosen outcome entailed a loss or a gain but not by whether the outcome could be thought an error in comparison to the other possible outcome.

ACC lesions, even when limited to just Cg1 and Cg2 fields, affect how rats make a decision about whether it is worth making an effortful action given the value of the expected outcome [24,54]. Rats performed a T-maze task [55] in which the choice of one arm was always followed by a small reward whereas choosing the other arm resulted in a large reward. The catch was that the large reward could only be obtained if the rats selected a more effortful action and climbed over an intervening barrier. Normal rats chose the effortful but high reward action but rats with ACC lesions rarely did (Figure 3). The deficit reflects an impaired ability to integrate both the expected costs and benefits of an action rather than a simple insensitivity to reward differentials, failure to remember the size or positions of rewards, or difficulty climbing the barrier. No obvious motor impairments were detected after Cg1/Cg2 removal; rats with lesions exhibited higher general activity levels and they scaled the barrier as quickly as controls. Moreover, even the rats with ACC lesions chose the high reward arm of the maze when a second identical barrier was placed in the low-reward arm of the maze. In this case there was no need to integrate the difference in rewards with the difference in costs before a decision could be made.

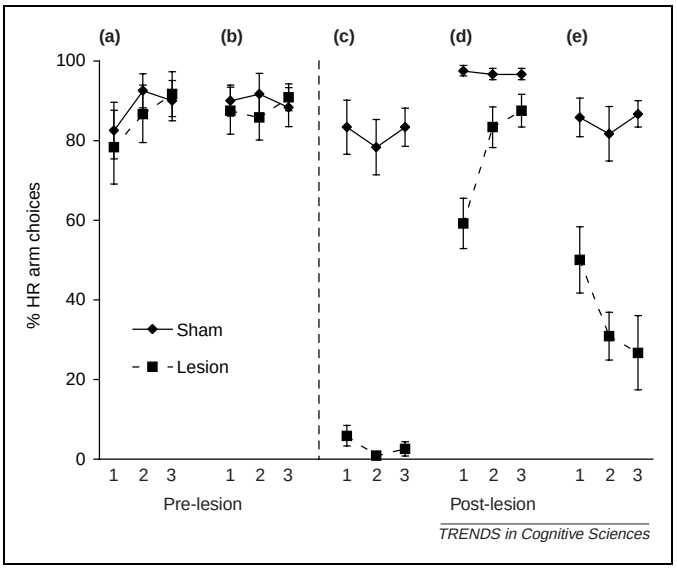

Figure 3. The number of times that two groups of 12 rats chose the high reward (HR) but high cost arm (requiring climbing over a barrier) of the T-maze on the two control tests is indicated in **(a)** and **(b)**. Lesions of the ACC and adjacent prelimbic cortex were made in one group before collecting the data shown in **(c)**. Similar deficits have been recorded with lesions of just Cg1 and Cg2 divisions of the ACC [24]. The performance of the lesion group improved dramatically when the costs of each action were equated by placing a barrier in each arm of the T-maze **(d)**. Impaired performance was clearly visible, however, as soon as the barrier was present only in the HR arm **(e)**. Adapted from [54] with permission.

The ACC works in conjunction with the interconnected ventral striatum to mediate cost benefit decisions and persistence in accomplishing a goal [55]. Shidara and colleagues taught their monkeys to persist through a series of actions to obtain rewards. Neurons in both the ACC and ventral striatum encode the monkey's position in the series of actions. The activity of some neurons in the ACC even changes as the monkey progresses towards the reward [56].

The SFG and task control

The SFG role in task control and the selection of action sets can be contrasted with that of the dorsal premotor cortex which selects single actions even in the absence of response conflict [57]. The SFG, on the other hand, may not be needed when a single action is selected but it is necessary when the set of action selection rules themselves are changed or when they are first selected. Activation centred on the pre-SMA region of human SFG can be recorded when subjects are instructed to switch between two different sets of rules for selecting finger press responses to visual shapes [21] (Figure 4). The SFG is involved in task switching when changes have to be made to the way that responses are selected but it is less important when the task switch simply entails a change in the way sensory stimuli are processed without any changes in stimulus response associations [58,59]. ERP modulations over medial frontal electrodes begin within 400 ms of a cue instructing subjects to switch response selection rules but similar modulations do not occur when the task switch requires subjects to shift between attending to either the colour or shape of stimuli.

Not only is human SFG activated when subjects change response sets but lesions or transcranial magnetic stimulation (TMS) here impair switching between response sets. TMS has been directed over the SFG during a task in which subjects switched between two opposite sets of rules for selecting manual responses (Figure 4). TMS significantly slowed subjects' responses on the trials that followed the switch instruction but it had less effect after a control cue that just instructed subjects to carry on performing the task as before [21]. A patient with a lesion restricted to the SEF region of the SFG has been tested on a related task that required alternation between two opposite sets of rules for selecting oculomotor responses (Figure 4). The patient was significantly slower and more likely to make errors on switch trials than control subjects [26]. Once again similarities between recent findings in the primate and a more extensive literature based on experiments with rats are emerging. Prelimbic lesions impair set and response strategy switching in the rat although more posterior cingulate lesions have little effect [24,25,60,61].

The anterior SFG role in task control involves anticipatory preparation and selection of a task set. Brass and von Cramon [62] taught human subjects to alternate between two different task sets in a paradigm in which the future task set was sometimes indicated by an earlier warning cue. On 'cue-only' trials, the cue warning subjects about which task was coming next was presented in isolation and no actual task stimuli followed. Activation was found throughout the pre-SMA region of SFG when the 'cue-only' trials were compared with a baseline. It is clear that a response conflict hypothesis, in isolation, cannot easily account for the early activity recorded as both humans and monkeys are about to change action sets in ERP [58], fMRI [62], and in single cell recording experiments [63] discussed below.

The SFG and movement sequences

Several divisions of primate SFG have a role in movement sequencing [64,65]. The initiation or changing of what might be called an 'action set', a set of rules for selecting responses, may be a common denominator to the SFG's role in both movement sequencing and task switching. In most task switching paradigms the action set is a set of stimulus–response selection rules whereas in sequence paradigms the action set is a set or order of response–response selection rules.

Shima *et al.* trained monkeys to perform several sequences of three joystick movements [63]. The monkeys performed eleven repetitions of each sequence and were then instructed to change to a new sequence. A quarter of task related neurons were active in the interval between the last repetition of the old sequence and before the first performance of the new sequence. In most cases the activity started and stopped well before the first movement was made. There was significantly less activity before the second and all further repetitions of the sequence. The activity of pre-SMA neurons is also higher when monkeys switch between movements in other contexts [66]. The early timing of activity in these paradigms, before any movement, is inconsistent with a response competition explanation. Moreover in some cases activity is specific to a particular sequence of

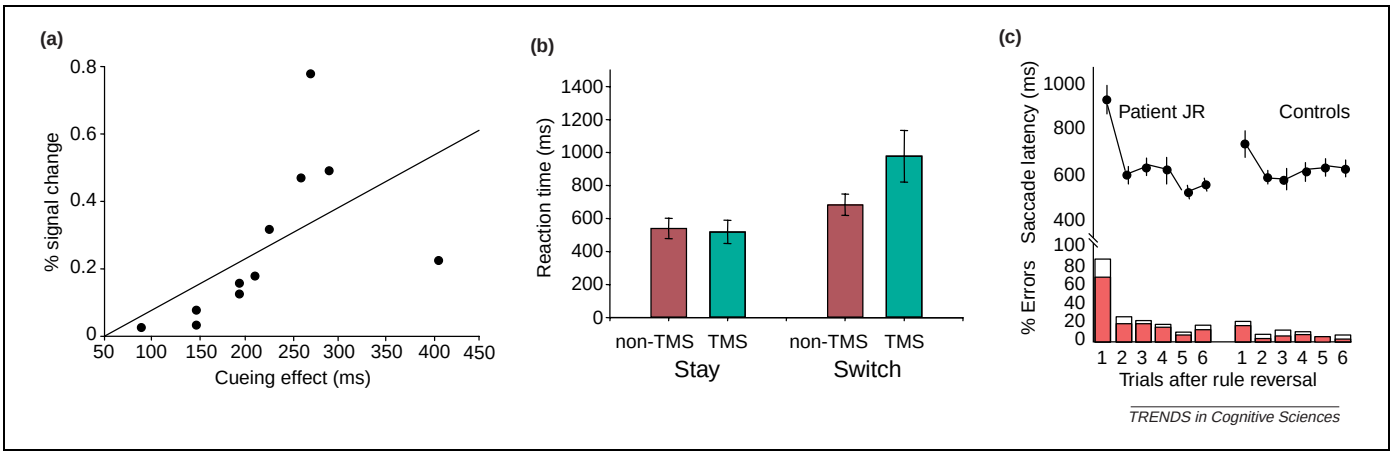

Figure 4. (a) An increase in activation was recorded in the pre-SMA region of the superior frontal gyrus (SFG) when subjects were presented with a cue warning them of an impending task. Across subjects the increases in BOLD signal change were proportional to task reaction-time savings afforded by the warning cue. **(b)** Subjects were presented with a series of at least nine task stimuli, red squares or triangles, and responded by making right and left hand responses respectively. Switch cues instructed subjects to change response set whereas stay cues instructed subjects to continue with the previous response set. TMS over the SFG disrupted performance on trials that followed a switch but not a stay cue. **(c)** Subjects have also been taught an oculomotor response switching task that required right or leftward saccades to be made to different coloured stimuli. A patient with a lesion restricted to just the supplementary eye field region of the SFG made more errors and took longer to respond on the trials that followed response switches. Adapted from [21,26,62] with permission.

movements [64]. Human SFG activation in fMRI experiments that is attributed to response competition might also be explained by the need to select or re-select partially ambiguous action sets. Sequences of movements have a microstructure that suggests that they are performed as a series of 'chunks' or action sets and the pre-SMA might be important at the transitions between chunks (Box 1).

Conclusions

The ACC does not exert supervisory executive control over behaviour in the same manner as lateral PFC but it does detect when actions have led to errors. In addition, any account of medial frontal function is incomplete without reference to the monitoring of response conflict before error commission but the crucial region might be in the

Box 1. The organization of action sequences and the pre-SMA

The microstructure of long sequences of movements suggests that they require the selection of more than one action set. The first movement of a sequence is characterized by a long reaction time (RT) and this has been taken as evidence that several of the sequence's movements, not just the first, are being planned before the first movement is executed. There is often, however, another movement part way through a sequence that is executed with a significantly longer RT, as if there is a need to plan and select a subsequent set of movements. This point in the sequence has been referred to as the 'chunk point' [67]. At the chunk point there is a transition from one 'chunk' of movements to another that involves changing from one action set to another (Figure I). Although the position of the transition or 'chunk point' can vary between subjects it is often a very consistent feature of each individual's performance [67,68], re-occurring in the same position over several blocks when a given sequence is repeated. Applying TMS to the superior frontal gyrus, centred over human pre-SMA, disrupts sequence performance when it is delivered at a chunk point or at the beginning of a sequence but not when it is delivered at other points in a sequence. Monkeys have been taught long sequences of ten movements by training them to perform five consecutive component sets of two movements. Pre-SMA activity is most prominent for the first movement of each of component set [65].

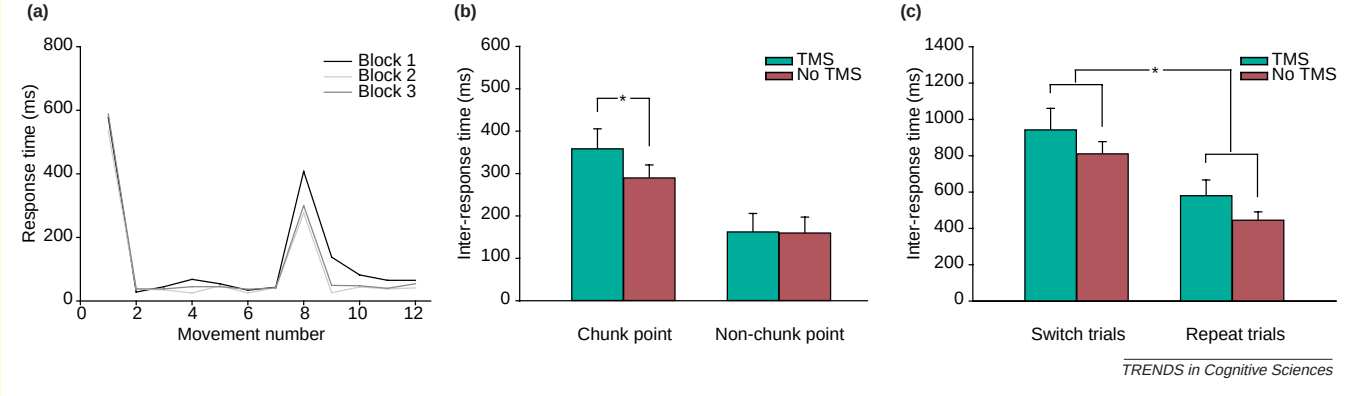

Figure I. (a) Median response and inter-response times (RTs) of a single subject performing a sequence of 12 movements. Each median value is based on 20 repetitions of the sequence and three blocks of 20 repetitions were performed. Medial frontal TMS caused an increase in RT at the chunk point but not at the non-chunk point **(b)**, and when subjects started a new sequence **(c)**. Adapted from [67] with permission.

SFG. It is clear, however, that error detection is just one aspect of a more general ACC role in associating actions with their reinforcement consequences even when these are positive rewards. The ACC's most crucial contribution in the domain of action–outcome associations may be in guiding decisions about whether the expected value of a reward means that it is worth acting.

The rostral SFG might not select individual actions but instead select superordinate sets of action-selection rules that we have referred to as action sets. The SFG is most important whenever actions sets are initiated or changed regardless of whether each action set is a set of stimulus–response selection rules, as in a task switching paradigm, or a set of response–response selection rules, as in a sequencing paradigm.

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