

Cognitive Neuroscience: Resolving Conflict in and over the Medial Frontal Cortex

The medial surface of the brain's frontal lobe has been implicated both in the voluntary initiation of action and in monitoring actions in situations where several conflicting responses are possible. Recent work casts light on how these functions are parcelled out in the medial frontal cortex.

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How the cognitive functions of the medial frontal cortex (MFC) might be best characterized is hotly contested. A study reported in this issue of *Current Biology* [1] suggests that while one distinct MFC sub-area is concerned with monitoring whether any of several possible competing responses might be made instead of the correct one — conflict monitoring — an adjacent MFC area is better described as being concerned with the initiation of voluntary, as opposed to instructed or reflexive, behavior.

While there has long been discussion about the functions of the prefrontal cortex, most of the relevant studies have tended to focus on the lateral surface of the frontal lobe (Figure 1). More recently, attention of researchers has been drawn to the medial surface, because human neuroimaging studies have shown that this region is consistently activated when subjects perform difficult cognitive tasks, such as the Stroop task [2,3].

In the Stroop task, subjects are shown a succession of color words printed in different colored inks and they are asked to name the color of the ink of each stimulus. The task is taxing because, while the subject is selecting the correct verbal response — the word corresponding to the ink color — a competing response — the word spelt out by the letters — is inadvertently accessed. According to the dominant hypothesis in the field [3,4], selection of the correct response

is only possible if there is a mechanism for detecting response conflict. It is argued that the MFC provides such a mechanism and that, even before any mistake is made, it triggers the operation of other control areas in the brain that oversee the selection of the correct response.

While everyone seems to agree that the MFC is active when there is response conflict, a number of issues remain contentious. First, it is not clear which of the many sub-areas within the MFC

(Figure 1) is the critical one for detecting when a conflict between responses has arisen. For some time an influential group of researchers has emphasized the importance of the anterior cingulate cortex (ACC), a region that lies relatively ventrally within the MFC [3,4]. Intersubject variability in the patterns of the major sulci in this area [5,6], and its unusual shape and size in one brain atlas, have made precise localization within this region difficult. More recently, it has been suggested that the critical regions may be in the more dorsal MFC: either the pre-supplementary motor area (pre-SMA) or the nearby supplementary eye field (SEF) [7–9].

Second, it is not clear whether MFC function is best characterized as conflict monitoring. Part of the power of the conflict monitoring hypothesis is that it offered, not just an explanation of results with the

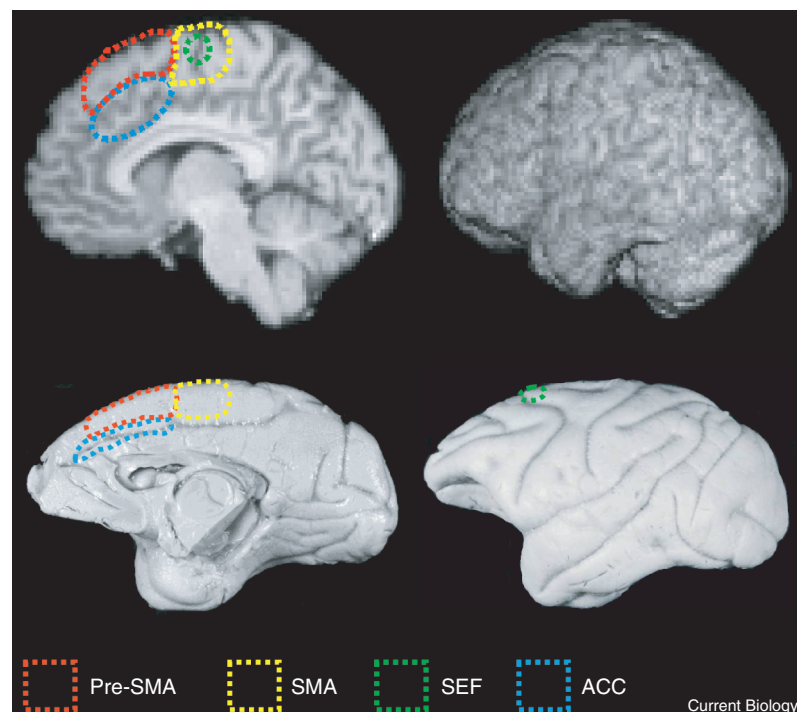


Figure 1. Medial (left) and lateral (right) views of the human (top) and macaque (bottom) brain.

There is evidence that homologous areas can be identified in the two species. The pre-supplementary motor area (pre-SMA) and the supplementary motor area (SMA) are in the anterior and posterior parts of the superior frontal gyrus. The supplementary eye field (SEF) lies in an intermediate position and in the macaque it extends over onto the lateral surface. A part of the anterior cingulate cortex (ACC) that contains the rostral cingulate motor area is also shown. (Based on [18–20].)

Stroop task, but a new way of looking at what might be happening in tasks where subjects were asked to choose freely between actions. Earlier studies had emphasized that the MFC was important when subjects voluntarily chose which action to make, rather than when they were instructed what to do [10]. Lesions of either the ACC or the more dorsal MFC areas, including the pre-SMA, cause a dearth of voluntarily initiated responses, though instructed responses are still made at the normal rate [10].

In such situations, it was argued by proponents of conflict monitoring, representations of several responses the subject might make were initially co-activated and in conflict with one another. It was possible, therefore, that the MFC role in voluntary behavior was really just a consequence of the region's involvement in conflict monitoring. On the other hand, diehard proponents of the volition hypothesis could argue that many instances of conflict monitoring required subjects to overcome reflexive-response selection tendencies (naming a word spelt out by letters) rather than choosing to make a more difficult response (naming the color of the ink used to spell a word).

In their new study, Nachev *et al.* [1] have begun to unpick the conflicting strands of the debate about conflict and volition in the MFC. Their subjects made eye movements or saccades while in a functional magnetic resonance imaging (fMRI) scanner. On some trials, arrows instructed subjects to saccade to the left or the right; on others, an upward pointing arrow meant that the subject was free to choose. In this way Nachev *et al.* [1] were able to compare brain activity associated with either voluntary or instructed responses.

Subjects did not, however, make the saccade straightaway but only after another signal told them to 'go'. Finally a third signal was presented. When it was a 'change' signal, it instructed subjects to reverse their original decision and make a saccade in the opposite

direction. On other occasions, a 'no change' signal simply instructed the subjects to continue the planned saccade. This enabled Nachev *et al.* [1] to look at high and low response conflict trials, respectively. The experimental design is elegant, because the two manipulations make it possible to look separately at conflict and volition in the same subjects in the same study.

Surprisingly, Nachev *et al.* [1] did not find that conflict and volition manipulations activated the same MFC region, as might have been predicted by proponents of either volition or conflict accounts. Instead, activity in an anterior part of the pre-SMA increased when greater response conflict was occasioned by a 'change' cue, regardless of whether the initial saccade had been voluntary. An area identified as the SEF was also more active on the change — high conflict — trials, but only when they were subsequently performed correctly. A posterior part of the pre-SMA, however, appeared more concerned with initiating voluntary behavior because it was more active when subjects decided in which direction to make a saccade regardless of whether or not the trial subsequently involved high conflict.

MFC activity during voluntary behavior is not, therefore, simply the consequence of conflict, nor is it the case that conflict monitoring is just a special instance of voluntary behavior. Other recent studies concur that the pre-SMA is more active and more vulnerable to disruption when subjects change the way they have been selecting responses than if their responses are guided by explicit cues [11,12]. As Nachev *et al.* [1] point out, response conflict cannot explain everything that the pre-SMA is doing in such situations, because pre-SMA activity begins long before the response conflict is present [13,14], suggesting instead that it may have a role in updating response sets [15].

The importance of volition in other MFC areas has also been investigated [16]. Walton *et al.* [17] found that ACC activation

levels were also dependent on whether responses were chosen voluntarily. Unlike the pre-SMA, however, ACC activation additionally reflected whether it was necessary to monitor the response's outcome to see if it was correct. ACC activation was also not explicable simply in terms of response conflict. The results suggest that the ACC division of the MFC may be using reward and error outcome information to guide voluntary response selection.

In summary, the conflict monitoring hypothesis remains an influential account of MFC function [4], but it may be the case that it provides a particularly good account of the anterior pre-SMA subdivision. Reinforcement outcome monitoring and volition are also important determinants of function in other MFC areas and will need to be accommodated within any successful comprehensive theory of MFC function.

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DOI: 10.1016/j.cub.2004.12.054

Sex: Is *Giardia* Doing It in the Dark?

The protist *Giardia* has long been considered strictly asexual. Now genes specific for meiotic recombination have been found in the *Giardia* genome, but their consequences for genetics, epidemiology and evolution remain unknown.

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Sexual reproduction is so nearly ubiquitous among vertebrates and plants that we tend to forget that many eukaryotes appear to have dispensed with meiotic sex altogether [1]. These range from parthenogenetic lizards to a wide array of eukaryotic protists, many of which are important parasites like *Giardia*. It is important to know if these organisms are truly asexual, because the answer will help determine when and how meiotic sex first evolved.

Early phylogenetic trees of eukaryotes based on sequences of the 18S ribosomal RNA gene suggested that the earliest branches are those leading to *Giardia* and some other species, such as *Euglena* and its relatives, that have been presumed to be asexual (Figure 1). If this is true, meiotic sex may have arisen after these organisms separated from the rest of the eukaryotes, and *Giardia* and its relatives may hold clues to the evolutionary origin of sex. However, recent studies

using large numbers of protein sequences, or unique events such as gene fusions, to root the tree have tended to place the root on the branch connecting the opisthokonts and amoebozoa to the rest of the eukaryotes [2]. This tree would imply that meiotic sex arose in a common ancestor of all eukaryotes.

Another reason for wanting to know which organisms truly lack sex is that they can be used in comparative studies to identify the evolutionary advantages of sex, which hitherto have been limited mainly to animals, plants and viruses [3–6]. Finally, knowing whether or not parasites like *Giardia* are having sex will have implications for their epidemiology and treatment [7].

Our failure to observe meiosis or fertilization in an organism does not, however, mean that it never occurs. An apparently asexual organism might: be having sex so infrequently that it has not yet been observed; engage in furtive sex, under conditions in which we have not yet observed it; or have cryptic sex, readily observed but

not easily recognized as sexual reproduction.

These problems are especially severe in protistan parasites such as *Giardia*, which grows and reproduces as tiny binucleated, flagellated trophozoites in the dark of animal intestines, and then forms a cyst with an opaque wall. Although all of the stages of the life cycle can be reproduced in the lab, their small size and requirement for anaerobic conditions have prevented direct observation of nuclear divisions.

When sexual reproduction cannot be observed directly, its effects can be detected using genetic markers. Unfortunately, most of these tests can show that sexual reproduction with outcrossing occurs, but cannot prove its absence. For example, observations of high levels of neutral sequence divergence between alleles — the Meselson effect — was used to demonstrate that bdelloid rotifers are anciently asexual [8–11]. Sequence heterozygosity is very low in *Giardia* [12], but the absence of the Meselson effect is not definitive evidence of sex, because allele sequences can be homogenized by mitotic recombination or by cycles of chromosome loss and duplication due to nondisjunction [13].

The advent of genomics suggested a new test for sex: screening complete genomes for