The role of the pre-supplementary motor area in the control of action

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Abstract

Although regions within the medial frontal cortex are known to be active during voluntary movements their precise role remains unclear. Here we combine functional imaging localisation with psychophysics to demonstrate a strikingly selective contralesional impairment in the ability to inhibit ongoing movement plans in a patient with a rare lesion involving the right pre-supplementary motor area (pre-SMA), but sparing the supplementary motor area (SMA). We find no corresponding delay in simple reaction times, and show that the inhibitory deficit is sensitive to the presence of competition between responses. The findings demonstrate that the pre-SMA plays a critical role in exerting control over voluntary actions in situations of response conflict. We discuss these findings in the context of a unified framework of pre-SMA function, and explore the degree to which extant data on this region can be explained by this function alone.

Introduction

A region within the medial frontal cortex – seemingly at the interface between pre-frontal and motor systems – has become the focus of great interest in recent years. The supplementary motor complex (SMC) occupies a rostrally ill-defined area of mesial agranular frontal cortex immediately anterior to Brodmann Area 4 (BA4)(Freund 1996; Picard and Strick 1996; Zilles, Schlaug et al. 1996). Within this region, a fractionation into at least two, functionally distinct divisions – the pre-supplementary motor area (pre-SMA) and the more caudal supplementary motor area (SMA) proper(Matsuzaka, Aizawa et al. 1992) - is strongly suggested both on grounds of cytoarchitectonics(Matelli, Luppino et al. 1991; Vorobiev, Govoni et al. 1998) and strikingly different cortical and subcortical connectivity(Luppino, Matelli et al. 1993; Inase, Tokuno et al. 1999; Johansen-Berg, Behrens et al. 2004; Morel, Liu et al. 2005; Wang, Isoda et al. 2005; Behrens, Jenkinson et al. 2006). Unlike its rostral counterpart, the SMA is somatotopically organised(He, Dum et al. 1995; Chainay, Krainik et al. 2004), has direct projections to spinal cord(Luppino, Matelli et al. 1994; He, Dum et al. 1995), and primary motor cortex(Luppino, Matelli et al. 1993), but receives no pre-frontal inputs(Luppino, Matelli et al. 1993). By contrast, the pre-SMA has extensive pre-frontal connectivity(Luppino, Matelli et al. 1993; Wang, Isoda et al. 2005), a feature shared by the supplementary eye field (SEF) (Tehovnik, Sommer et al. 2000), a region found at the pre-SMA/SMA border(Grosbras, Lobel et al. 1999; Yamamoto, Ikeda et al. 2004) with marked activity during eye movements, but

functional characteristics not dissimilar from the pre-SMA(Coe, Tomihara et al. 2002; Fujii, Mushiake et al. 2002; Husain, Parton et al. 2003; Isoda and Tanji 2003).

There are good anatomical grounds, then, for the wide range of "higher" functions in which this region – and the pre-SMA in particular – has been implicated: language generation(Wise, Chollet et al. 1991; Binder, Frost et al. 1997), movement recognition and ideation(Stephan, Fink et al. 1995; Grafton, Arbib et al. 1996), maintaining working memory(Pollmann and von Cramon 2000), establishing visuomotor associations(Sakai, Hikosaka et al. 1999), learning and performing movement sequences(Hikosaka, Sakai et al. 1996; Kawashima, Tanji et al. 1998; Nakamura, Sakai et al. 1998; Sakai, Hikosaka et al. 1998; Shima and Tanji 1998; Nakamura, Sakai et al. 1999; Shima and Tanji 2000; Isoda and Tanji 2004), time perception and discrimination(Coull, Vidal et al. 2004; Pastor, Macaluso et al. 2006), "internally"-guided action(Deiber, Passingham et al. 1991; Frith, Friston et al. 1991; Hadland, Rushworth et al. 2001; Lau, Rogers et al. 2006), representing action intentions(Lau, Rogers et al. 2004), resolving conflict resolution or monitoring(Ullsperger and von Cramon 2001; Garavan, Ross et al. 2003; Nachev, Rees et al. 2005), and switching between action sets(Matsuzaka and Tanji 1996; Shima, Mushiake et al. 1996; Rushworth, Hadland et al. 2002; Kennerley, Sakai et al. 2004). However, it is possible that the multiplicity of functions these data have been interpreted as indicating is in fact a multiplicity of aspects of a much smaller range of fundamental functions, possibly even just one: the resolution of competition between motor plans so that a unitary action may emerge.

It may be argued that such a process of resolving competition between conflicting motor plans is fundamental to action control(Botvinick, Braver et al. 2001). At any point in time we are faced with a choice of actions, the majority of which are either incompatible or likely to interact with one other. A critical question is therefore how one action is selected in favour of another. Positing a brain area that *chooses* the specific neural circuit required to execute the action leads to an infinite regress: one would have to explain what chooses its choice, and so on *ad infinitum*. Much more plausibly, the action ultimately performed is the outcome of a competition within a space of contingent *condition-action associations* whose neural representations are variously activated by current external stimuli as well as internal biases.

We use the term condition-action associations rather than the more conventionally used 'stimulus-response (S-R) associations' for a specific reason. S-R associations refer to the links between an action and a particular stimulus in the environment, e.g. stop at a red light. In experimental situations, animals are often required to learn, by trial and error, the appropriate response for a particular arbitrary stimulus, e.g. move hand to top right when there is a red circle but to bottom left when there is a blue square. Positive or negative feedback following the animal's response to each of these stimuli leads to the development of strong S-R associations. These associations need not only involve external stimuli, but also an internal state or combinations of many external stimuli and internal states, making the term condition-action associations more appropriate.

Critically, in a given context and at some level, a multitude of neural representations *must* be co-activated *automatically* by external stimuli, internal biases, and conditional associations between the two. There can be no homunculus determining which representation should be activated and which should not. Without a mechanism to resolve this competition, coherent action would fail to emerge because of interference from actions incompatible with the one being performed. Importantly, such a mechanism does not do any *selection* – as the competition itself is the selection – but merely reinforces the winners and inhibits the losers of the competition.

If such a mechanism exists, one would expect its activity to be sensitive to at least three things. First, and most obviously, it will depend on the degree of incompatibility between the possible actions whose representations are activated (degree of conflict). Second, it will depend on how greatly one action plan is biased over the others (degree of bias): where there is a pre-existing bias in favour of one action, competition would be expected to be less. Third, it will vary with number of condition-action associations concurrently activated (condition-action dimensionality) in a context-specific fashion depending on attention and other processes that may introduce bias towards specific behavioural sets.

This framework allows us to make specific and testable predictions. If the pre-SMA is indeed involved in this conflict-resolving process, we would expect its inactivation to lead to a deficit in the ability to select one movement over another when two movement plans are concurrently activated. Using a manual paradigm designed to expose such a deficit(Logan, Cowan et al. 1984; Husain, Parton et al. 2003), we therefore tested a rare patient with a unilateral lesion involving the whole of the right pre-SMA, but – as we demonstrate by functional imaging – entirely sparing the SMA proper, allowing for a dissociation between the two areas. We also show that the patient's lesion incorporates a region of the pre-SMA responsive to conflict identified by functional imaging of the same basic paradigm(Nachev, Rees et al. 2005).

Patient and methods

Patient AG, a previously fit right-handed woman, presented aged 52 following two generalised seizures. Neurological examination was unremarkable. Structural MRI revealed a right dorsomedial frontal lesion whose margins functional MRI confirmed to be anteromedial to hand primary motor cortex. A tumour (grade 2 oligoastrocytoma) was surgically completely removed in conjunction with intra-operative electrical stimulation ensuring that none of the areas designated for resection could elicit a motor response. Immediately after the operation, there was motor neglect of the left upper limb which resolved spontaneously. The experiments described here were performed 22 months after surgery when the patient was entirely asymptomatic. At this stage routine clinical examination was normal, including simple bimanual tasks such as in-phase and out-of-phase hand tapping with vision occluded(Stephan, Binkofski et al. 1999). However, the patient showed some subtle left-sided abnormalities when performing out-of-phase sequential hand movements on Luria's bimanual hand co-ordination task, also with vision occluded(Luria 1966). Follow-up imaging 4 years after diagnosis has failed to show any evidence of recurrence.

Ten right-handed normal subjects with comparable performance on simple reaction task measures were used as controls. The study was approved by the local ethics committee and all subjects gave informed, written consent.

Imaging

The lesion was manually traced on what was an otherwise normal T1-weighted $1\times1\times2$mm MPRAGE sequence at $1\times1\times2$ resolution obtained 22 months after surgery on a 1.5T Siemens Magnetom Vision system (see Fig 1). The brain volume image was then transformed to the standard Montreal Neurological Institute T1 template using SPM2 (http://www.fil.ion.ac.uk/spm) non-linear coregistration routines. So as to avoid lesion-induced distortion, the normalisation parameters were derived only from normal brain regions (Brett, Leff et al. 2001).

The border between the pre-SMA and the SMA proper has been found to correspond reasonably well to the VCA line(Zilles, Schlaug et al. 1996); however, there is considerable inter-individual variation to which local sulcal patterns offer no reliable(Picard and Strick 1996) clues, making it hard to differentiate between these two areas with conventional imaging

(Behrens, Jenkinson et al. 2006). We wanted to establish whether the area of the SMA representing the hand was intact. Since manual movements can cause pre-SMA and SEF activation (the latter as a result of actual or suppressed gaze shifts) instead of imaging hand movements we used eye movements to localise the SEF which is rostral to the hand area of the somatopically organised SMA(Grosbras, Lobel et al. 1999; Yamamoto, Ikeda et al. 2004). We did this by running a functional series of images contrasting blocks of saccades performed in the dark with blocks of rest (see Fig 1A, orange). These data were collected with a T2*-weighted echoplanar sequence (TR=4.3s, 40 axial slices, resolution 3.5×3.5×3.5mm) in one session of 85 volumes. The first 5 volumes were discarded to allow for magnetic saturation effects. For the remainder of the run, the patient was aurally cued to perform free saccades in the dark or to rest in alternating blocks lasting 10 volumes each. Using SPM2, the functional images were realigned, normalised to the same stereotactic space as the T1 image, and smoothed with a Gaussian kernel of 7 mm full-width at half-maximum. The data were high-pass filtered (0.0078 Hz cutoff) to remove low frequency signal drifts. To test for eye-movement-related activation the data were entered into a voxel-wise general linear model that included the experimental conditions, and head movement parameters derived from the realignment as effects of no interest. An appropriately weighted linear t contrast with a threshold of $p < 0.05$, corrected for multiple comparisons across the brain, was used to identify voxels in the region of the medial frontal wall corresponding to the patient's SEF. Eye movements were monitored using an ASL model 504 LRO infrared video-based eye tracker (Applied Science Laboratories, Bedford, MA) sampling at 240Hz.

The co-registered statistical parametric map derived from this series was superimposed on the anatomical scan to localise the SEF in relation to the lesion. Since the images are in normalised stereotactic space we can also demonstrate that the region of the pre-SMA that we have previously shown to be activated by conflict between motor plans(Nachev, Rees et al. 2005) falls well within the lesion (see Fig 1A, purple).

Psychophysics

All subjects viewed a computer screen placed 60 cm in front of them and responded with either forefinger on a button box. They performed 800 pseudorandomly ordered trials of a change-of-plan paradigm in one session, consisting of 8 blocks (see Fig 2).

Each trial began with a central fixation cross presented for 500-800 ms followed by a green arrow (GO cue) of 200 ms duration which instructed the subject to make a speeded response with the corresponding hand. On 20% of trials, the green arrow was accompanied or succeeded by a pair of white bars (CHANGE cue), appearing above and below it and also lasting 200 ms, which instructed the subject to cancel the planned movement and execute a response with the opposite hand. The interval between the two cues (SOA) was automatically adjusted, depending on performance, by a staircase algorithm that increased it by 50ms after every successful CHANGE trial, and reduced it by the same amount after every failed CHANGE trial. So as to eliminate the confounding effects of slowing following CHANGE trials, such trials were always succeeded by a GO trial which was removed from the final analysis. Subjects were asked not to correct their errors but were not penalised for doing so. On the remaining 80% of trials, subjects simply executed the movement indicated by the GO cue (NO CHANGE trials). All stimuli were controlled using Presentation software (http://nbs.neuro-bs.com/) running with real-time priority under Microsoft Windows 98SE on a Toshiba SatPro 6000 laptop computer.

On a separate occasion, AG was tested on a manual 'countermanding' (or 'stop-signal') paradigm. She performed 900 trials exactly as in the change-of-plan task except that she was asked to withhold *any* response when she saw the CHANGE cue. Thus, in this task, control can be evaluated in the absence of competition from contralateral responses.

The measure of interest was the relation between the SOA and the probability of successfully withholding the first response. The staircase adjustment of the SOA ensured that we could counteract any strategic slowing and thereby accurately evaluate subjects' inhibition performance. To characterise the psychometric functions we used Bayesian methods in conjunction with Markov chain Monte Carlo (MCMC) sampling(Neal 1993). These methods have been shown to provide more accurate estimates of the parameters than analogous frequentist approaches(Kuss, Jakel et al. 2005), especially when the number of observations is small as is necessarily the case in psychophysical studies involving patients. The psychometric functions were parameterised as a logistic functions and maximum *a posteriori* (MAP) estimates were derived as follows. For each psychometric function, a binomial mixture model describing the threshold, slope, and lapse rate was generated using the following very broad prior distributions (parameters in brackets): lapse rate: beta (2, 50), threshold: normal (200, 200), slope lognormal (4,1). The same prior was used for all functions. MCMC sampling was used to derive 5000 samples from the posterior of which the last 4800 were used to generate the MAP estimate and approximate Bayesian confidence intervals for the threshold.

Results

Functional localisation of the SEF (coordinates 6, −15, 52, t = 8.00, p < 0.001) demonstrated the posterior extent of the lesion to be just anterior to the SMA/pre-SMA border. Thus the lesion spared the SMA.

On the change-of-plan task, AG's performance revealed a marked deficit in her ability to inhibit a response of the left hand specifically on CHANGE trials, i.e. when she was instructed to change her ongoing plan to make a left hand button-press and instead instructed to move her right hand (See figure 3A). Inhibitory performance here is best described by the probability of inhibiting the first response on CHANGE trials as a function of the SOA adjusted for the median reaction time. MCMC estimates of the threshold (50% performance) of this function were significantly higher for the left compared with right hand (278 ms vs 230 ms, Bayesian p = 0.002 based on MCMC sampling), a finding that was not observed in any of the controls. Furthermore these values differed from the controls only for the left hand (two sample t test, left p = 0.011, right p = 0.39, see figure 3B).

By contrast, the threshold asymmetry in the pure countermanding condition (in which either one or no responses were made) was much less pronounced (216 ms for left hand vs 198 ms, for the right, Bayesian p = 0.053 based on MCMC sampling), demonstrating that the lateralised deficit observed in AG was sensitive to the presence of competition between two alternative responses, i.e. as in the change-of-plan task.

Critically, this difference between the hands was not present on simple GO reaction times (median values: left = 458 ms, right = 440 ms, two-sample Kolmogorov-Smirnov test asymptotic p = 0.22). These reaction times did not differ significantly from controls on either side (two sample t test, left p = 0.16, right p = 0.18), suggesting the deficit is specific to situations where competition between actions occurs.

Discussion

This study provides the first evidence that the human pre-SMA may be *necessary* for inhibiting competing single motor plans in situations of response conflict. It is a direct test of a previous study which found activation in a medial frontal area well within the borders of this patient's lesion in response to conflict generated by the same paradigm, but in the oculomotor domain (Nachev, Rees et al. 2005). These results cannot be explained by damage to the SMA proper

as functional imaging demonstrated that this patient's lesion must be rostral to it.[*] Although involvement of other anterior motor areas in the periphery of the lesion, particularly the dorsal cingulate, is possible, medial activation anterior to the VCA line in our imaging version of this task was confined to the pre-SMA(Nachev, Rees et al. 2005). Moreover, no adequately controlled lesion study to date has convincingly associated damage to the cingulate with deficits interpretable as a failure of control over immediate action(Fellows and Farah 2005; Baird, Dewar et al. 2006; Kennerley, Walton et al. 2006).

The pre-SMA is consistently activated in paradigms in which conflict is explicitly induced by requiring subjects to inhibit an established response rule in favour of another(Ullsperger and von Cramon 2001; Rushworth, Hadland et al. 2002; Garavan, Ross et al. 2003; Miller, Sun et al. 2005; Nachev, Rees et al. 2005; Wittfoth, Buck et al. 2006; Wolbers, Schoell et al. 2006). Although such paradigms have sometimes used sequences, similar activation profiles are generated with single responses. Indeed, the most elemental paradigm - a race between two incompatible actions is sufficient to produce robust pre-SMA activity(Ullsperger and von Cramon 2001; Garavan, Ross et al. 2003; Nachev, Rees et al. 2005), which is not even dependent on the subjects' having any conscious awareness of conflict(Wolbers, Schoell et al. 2006).

It may be objected that pre-SMA activity occurs too early in relation to active movement to account for the kind of inhibitory process we describe(Alexander and Crutcher 1990; Matsuzaka, Aizawa et al. 1992). However, all that is required is that the timing of activity should be within the period when competing condition-action associations are co-activated. This need not be at the execution stage, indeed it would seem inefficient for resolution to occur so late. In any case, there is direct evidence of pre-SMA involvement *during* the preparation or execution of action(Luppino, Matelli et al. 1991; Nakamura, Sakai et al. 1998; Isoda 2005). For example, it has been shown that when monkeys are taught to perform a simple delayed saccadic task, microstimulation of the pre-SMA in the pre-saccadic interval modulates saccadic latency in a context-dependent way(Isoda 2005). Interestingly, when microstimulation was applied in close proximity to the GO signal saccade initiation was globally delayed, whereas microstimulation earlier in the delay period led to *shorter* latency saccades for contraversive targets.

This is the kind of activity we would expect if the pre-SMA is suppressing competing plans. But even more directly, it has been shown that interfering with the function of the pre-SMA specifically alters switching from one condition-action association to another(Shima and Tanji 1998; Nakamura, Sakai et al. 1999; Rushworth, Hadland et al. 2002). Furthermore, preliminary reports have shown remarkable single cell activity in the pre-SMA that is sensitive to switches between condition-action associations in a saccadic task switch paradigm(Isoda and Hikosaka 2005). Importantly, the time point of differentiation in neuronal activity between switch and non-switch trials preceded the behavioural differentiation time by long enough to allow this activity to affect behaviour. Indeed, microstimulation following the cue to move resulted in significantly *improved* switching behaviour, with a conduction time well within the available time window.[†]

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[*]In line with the peculiarly polarised pattern of dysfunction seen after damage to large regions with medial frontal cortexLaplane, D., J. Talairach, et al. (1977). "Clinical consequences of corticectomies involving the supplementary motor area in man." J Neurol Sci **34**(3): 301-14. – either absence of spontaneous movement or disinhibited semi-purposeful movement – it is conceivable that failure of inhibition following damage to the pre-SMA requires an intact SMA in order to become manifest, as the pre-SMA may act by inhibiting the SMA in the normal state.

[†]It should be noted that the inhibitory deficit seen in our patient is in the context of competition between alternative movements rather than between a movement and no movement at all. This raises the possibility that the inhibitory failure is secondary to a failure adequately to activate the alternative response which is normally inhibitory of any other responses. However, it would be odd for the principal deficit here to involve processes plausibly dominated by the contralesional hemisphere.

Moving beyond the specific evidence, we would suggest that the results of studies not directly focussed on competition between responses can also be reconciled with the unitary function we propose for the pre-SMA. As we outline below, it seems to us that our proposal is the most parsimonious way of explaining the large corpus of data on this region.

Motor paradigms

The most general observation about pre-SMA activity in relation to overt action is that it tends to favour complex acts over simple ones(Picard and Strick 1996). A finer and largely uncontroversial classification is based on its modulation by three contrasts: internally vs externally guided, novel vs well-learned, and sequential vs single. Here we show that the conflict-related activity outlined in the introduction can account for *all* of these contrasts without the need to invoke any higher order process.

Internally vs externally-guided action—The earliest studies of voluntary action noted that when a choice between two movements is not guided by an explicit cue in the immediate external environment, pre-SMA activity is greater than when such a cue is present(Deiber, Passingham et al. 1991; Frith, Friston et al. 1991). Indeed, the contrast appeared to be strongest when subjects were not given any basis on which to choose one response over the other, and were instructed to respond "freely". It has been tacitly assumed that because the number of responses between the two conditions is equated the difference in brain activation must reflect a difference in the pathways engaged by internally and externally triggered movements.

In fact, these conditions are very poorly equated, and no such conclusion can be safely drawn. When subjects respond "freely" the circumstances that determine their responses are not simpler than when they are cued, but much more complicated, since removing an external criterion for responding does not make the response criterionless but merely hides the criterion from view. Critically, the range of criteria that might determine the subject's response – whether consciously or not – is indefinite and is likely to be substantially larger than in the explicitly directed condition because it is no longer constrained by attention to a specific set of stimuli. Thus the number of condition-action associations that are automatically activated will be much greater, leading to greater need for conflict resolution, as outlined in the introduction. In addition, this need for inhibition will be further amplified by the absence of bias in favour of any one action(Botvinick, Braver et al. 2001).

For these reasons, the apparent specialisation for internally guided action is much more simply explained by the same process of inhibiting competing motor plans being manifest to a different degree in response to differing demands. We have attempted to disprove this argument in an experiment where response "freedom" and response conflict were independently manipulated in the oculomotor domain(Nachev, Rees et al. 2005). Consistent with the hypothesis advanced here, the pre-SMA was activated by both manipulations; however, the modulation of activity was dissociable, with two close but distinct parts of the pre-SMA being responsive to either factor but not significantly to both. It is therefore conceivable that different processes were engaged by the two factors, but it is also possible that different regions within the pre-SMA were differentially engaged by the same process. Only the finding of an interaction between the two factors in the same brain region – which was not present – could be adduced as strong evidence of unitary function.

A recent sophisticated study of intention does not settle the point either(Lau, Rogers et al. 2004). Adapting Libet's paradigm(Libet, Gleason et al. 1983), subjects made freely timed movements and were asked to attend to the correspondence between an external clock and, on different trials in blocks, either the perceived time of the desire to move or the time of the movement itself. The contrast between the two revealed activation in the pre-SMA, from which the authors concluded that they had identified a "representation of intention" in the human

brain. It may be objected, however, that merely because subjects attended to the time when they believe they felt a desire to move does not imply that the areas activated in their brains represented their intention.

First, being conscious of a desire to move is neither a necessary nor a sufficient criterion for voluntary action(Bennett and Hacker 2003). One would not think of oneself as having moved involuntarily if one were not aware of a conscious desire to move just before the movement itself, and, equally, one would not call a movement voluntary solely because it was preceded by an urge to move (or else sneezing would be a voluntary act). What the subjects were attending to therefore cannot be unambiguously related to anything of consequence to voluntary action. Secondly, attending to one's intention – however conceptualised – need not necessarily activate a brain region concerned with intention, any more than attending to one's anger need identify a region representing anger. A much simpler explanation of the data in this experiment is that subjects attended more carefully to their actions in the blocks where they had to attend to the timing of the "desire to move", thereby leading to activation of a wider range of condition-action associations and consequently resulting in greater pre-SMA activity as previously described.

Novel vs well-learned action—Pre-SMA activity has been shown to be greater when novel actions are compared with well-rehearsed ones(Hikosaka, Sakai et al. 1996; Kawashima, Tanji et al. 1998; Nakamura, Sakai et al. 1998), and to decrease during motor learning(Sakai, Hikosaka et al. 1999). Disruption of the pre-SMA has been show to interfere with the acquisition of new sequences but possibly not established ones(Nakamura, Sakai et al. 1999). On this basis it has been proposed that the pre-SMA is critically involved in establishing new S-R associations(Nakamura, Sakai et al. 1998; Sakai, Hikosaka et al. 1998; Sakai, Hikosaka et al. 1999). However, none of the extant data allows us to distinguish a critical role in such learning from the role in resolving conflict between condition-action associations we have suggested.

Consider the case where an animal has to learn, by trial and error, an appropriate motor response when confronted with a particular sensory stimulus (or external condition). Positive or negative feedback helps to establish strong condition-action associations as the animal learns the correct response for each particular stimulus (or condition). But such learning necessarily entails the inhibition of competing responses. Moreover, the degree of inhibition will tend to covary tightly with learning. A poorly-learned association will inevitably generate greater competition between contingent responses than a well-learned one because there will *necessarily* be less bias in its favour. But as the association becomes better established, the increased bias towards it will reduce the need for inhibition of competing plans.

Finding a condition-action specific pattern of activation would not be decisive in making the distinction between learning vs resolving competition between motor responses, since the pattern of inhibition may well differ depending on the array of condition-action representations being inhibited.

One fact, however, is strongly against the learning account: activity in the *same* learning-related cells reappears during switching from one well-learned action to another(Nakamura, Sakai et al. 1998), which is clearly surprising for a purely learning-related role but would be entirely consistent with inhibition of competing action plans. It must nevertheless be conceded that these two accounts will always be difficult to differentiate, as successful inhibition of competing alternatives will clearly be essential to rehearsal on which learning self-evidently depends.

Single vs sequential action—Perhaps the most carefully explored aspect of the pre-SMA is its marked activity during sequences of movements(Hikosaka, Sakai et al. 1996; Shima, Mushiake et al. 1996; Kawashima, Tanji et al. 1998; Shima and Tanji 1998; Shima and Tanji 2000). This has lead to the notion that the pre-SMA has a special role in movement sequences, and, by implication, that it is part of a neural circuit specialised for various aspects of sequential action. Carefully considered, this notion is implausible. Virtually all voluntary movements involve the sequential contraction of different muscle groups that do not always operate together and are therefore unlikely to have unitary representations at a cortical level. All action is therefore sequential to some degree. If the SMC had a special function in sequencing actions we would therefore expect it to show differential activation between two "simple" movements that differ in the number of independently operable muscle groups involved: e.g. a reaching hand movement vs an eye movement. This has not been shown to be the case.

What we need to consider is the peculiar – and artificial – nature of the movement sequence paradigms used to study this phenomenon. An action is considered as a sequence of movements if it is composed of several movements that can each be – and often habitually are – made independently: e.g. a sequence of saccades. By contrast, the oculomotor pursuit of a target describing a smooth arc across the visual field is not considered a sequence even though it involves sequentially shifting changes in the contraction of the ocular muscles. Furthermore, experimental sequences usually require the subject to perform the same component movements but in a different order within the same experiment: this is obviously necessary so as to distinguish between activity due to each component from that due to their interaction as part of a sequence. Finally, the movements are considered a sequence – rather than just a series of individual trials – because they are cued at the onset of the first movement only. Thus, in these paradigms, each component movement is associated with a cue (or some other condition) and what differs across trial types is just the timing of its execution. The result is that condition-action associations are established for each component movement that initially differ only in their relative timings, if at all. At the early stages of learning, presentation of the initial cueing stimulus will therefore activate *all* condition-action associations involved to some degree, giving rise to conflict requiring appropriate inhibition. Since the variation between one sequence and another is at the time point of each component movement initiation, this is when we would expect pre-SMA activity to occur to resolve conflict between competing motor plans. Once the sequence is well learnt, the order of each component becomes part of the condition on which the response is selected and therefore there will be less requirement for conflict resolution, resulting in reduced pre-SMA activity. The pre-SMA may therefore facilitate the encoding of a sequence, but only to the extent to which it inhibits alternative responses so that the sequence may be successfully performed enough times for the encoding to take place. There is no need to suggest it *represents* sequence information for later retrieval, indeed neurons exhibiting sequence-specific activity have recently been shown to be 6 times commoner in M1 than in the SMC(Lu and Ashe 2005).

Non-motor paradigms

The pre-SMA has been implicated in functions that do not involve action by the subject. Since pre-SMA activity often precedes movement execution it is not surprising to find that it accompanies movements that are not executed but only imagined. Indeed, the most detailed study of single cell activity in the human SMC found some neurons whose activity is *greater* during imagined movements than executed ones(Amador and Fried 2004). If this region is involved in the suppression of competing motor plans this is precisely what we would expect. It would be very surprising indeed if imagining a movement did not involve suppressing a conscious desire to execute it.

Activity during the observation of action(Rizzolatti and Luppino 2001) can be explained on analogous lines. Since an action is usually tightly coupled to its goal – especially the type of actions used in observation experiments – it is inevitable that observing an action will activate neural circuits concerned with movements intended to secure the same or similar goals. Moreover, action observation experiments usually employ hand grasping gestures which the subject will generally observe when performing them himself, thereby linking the observation of an action to its execution *independently* of its goal.

That it is at no point the subject's intention to execute any of these movements is irrelevant: the brain does not *know* what the subject has been instructed to do: automatic activation will therefore occur, requiring inhibition. Thus activity here need not have anything to do with the *recognition* of action, and indeed studies showing such a perceptual deficit following interference with the pre-SMA are notably absent. Nor is there any necessity to invoke a mechanism for learning from imitation, unless it can be shown that disrupting the pre-SMA during the observation of an action subsequently impairs its learning.

Evidence that the pre-SMA is *necessary* for non-motor aspects of cognitive operations is similarly sparse. Merely correlational evidence is hard to interpret given that cognitive paradigms almost invariably involve a response of some sort. Moreover, paradigms with a spatial component usually require gaze suppression, and those with a verbal component often lead to silent or suppressed verbalisation, both of which involve motor processing. Even when these things are carefully controlled for(Hanakawa, Honda et al. 2002), one would expect tasks that are cognitively more difficult to activate the pre-SMA to a greater degree because, *necessarily*, in these situations the bias towards one response compared with another is less and/or the range of condition-action associations concurrently activated is greater, both factors to which a competition resolving mechanism would be expected to be sensitive, as we have already argued.

One case needs special consideration: the widespread belief that the pre-SMA is involved in temporal discrimination. The evidence for this rests almost entirely on functional imaging studies that have shown activation in this area when making a temporal judgment is contrasted with making some other kind of judgment(Coull, Vidal et al. 2004; Pastor, Macaluso et al. 2006). The problem is that these two conditions are never sufficiently equated in terms of the relative propensity to activate condition-action associations.

Just as imagining or observing an action may be expected automatically to activate neural substrates concerned with action, so a context more readily linked to action will result in greater activity in these areas compared with one less so. At the time scales explored in such experiments, by far the commonest reason for an object to change in the temporal dimension is because it is moving. All movement, like all action, *necessarily* takes place over time, which is not true of other properties of objects such as colour, shape or size. For this reason, we would argue, attending to the temporal aspect of a stimulus is much more likely to activate neural circuits concerned with action than attending to some other aspect of it – even if no motor act takes place.

An alternative interpretation of the activation of *any* motor area during such tasks is therefore the automatic activation of condition-action associations, and their consequent inhibition. Showing that these effects are modulated by voluntary attention does not overcome this criticism, as both motor and sensory unconscious processes are sensitive to attentional manipulations(Naccache, Blandin et al. 2002; Montaser-Kouhsari and Rajimehr 2005; Sumner, Tsai et al. 2006). Moreover, there is both behavioural(Tucker and Ellis 1998; Anderson, Yamagishi et al. 2002; Tucker and Ellis 2004) and neurophysiological(Grezes and Decety 2002) evidence of motor activation in a context more subtly related to action – the

purely passive viewing of figures with affordances – so the process we are describing here is far from hypothetical. Even highly abstract figures with minimally lateralised affordances can produce appropriately lateralised motor cortex activation.[‡]

Naturally, we are not asserting that these observations prove that the pre-SMA is not involved in temporal discrimination or any other perceptual task, but merely that *the case has not been made*. If we are to believe that an area concerned with actions – functionally and anatomically – is also involved in a highly specific aspect of perception, we need better evidence than functional imaging, and rather closer attention to confounds that may point to alternative explanations that are both simpler and more easily reconciled with the extant literature.

Conclusion

We have demonstrated that pre-SMA injury can lead to a selective deficit in the ability to inhibit a response in the context of competition between actions. These findings reflect a cardinal role for this region in the process of resolving competition between action contingencies so that coherent behaviour may emerge. We propose that this process *alone* may explain the vast bulk of extant data on this region, and that there is therefore no need to invoke less elemental functions in our description of the role of the pre-SMA in action control.

Such merit as the framework proposed here has rests on its being the most economical explanation of the facts. Naturally, the brain need not be parsimonious in its organisation, and therefore direct evidence of unitary function is required. One way of achieving this with functional imaging is to explore paradigms where two putatively dissociable processes are manipulated in a factorial manner: the presence of an interaction between the factors would suggest that they are not independent, although of course the absence would not preclude it. Alternatively, and perhaps more powerfully, imaging measures of neuronal adaptation(Grill-Spector and Malach 2001) could be used to test if neurons in the same location are dissociably activated by two potentially different processes, a technique that has shown some success in the sensory domain. In any event, it is essential that hypotheses generated on the basis of functional imaging are subsequently tested with functional interference.

More generally, we would suggest that the proliferation in functions attributed to this region should be viewed critically, and greater efforts should be made to integrate the evidence across the field, as we have attempted to do here.

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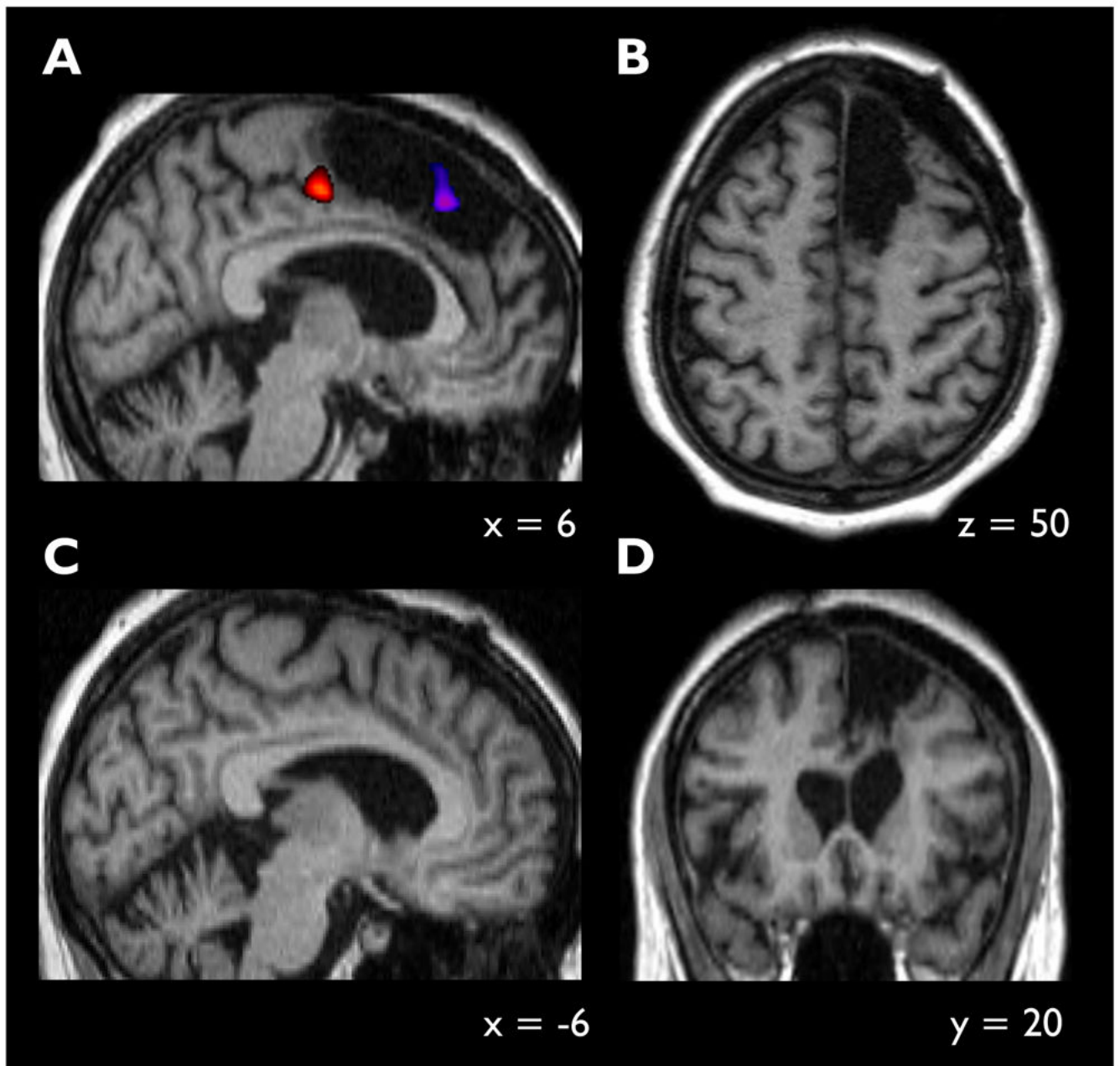
Figure 1. Lesion localisation
A. Activation in the region of the SEF – a marker for the rostral extent of the SMA –
superimposed on T1-weighted anatomical scan normalised in MNI space (orange). The purple
area identifies the location of the rostral pre-SMA region which we have previously shown to
be activated by changing oculomotor plans during conflict. **B, C & D.** Sagittal, axial and
coronal anatomical slices showing the extent of the lesion.
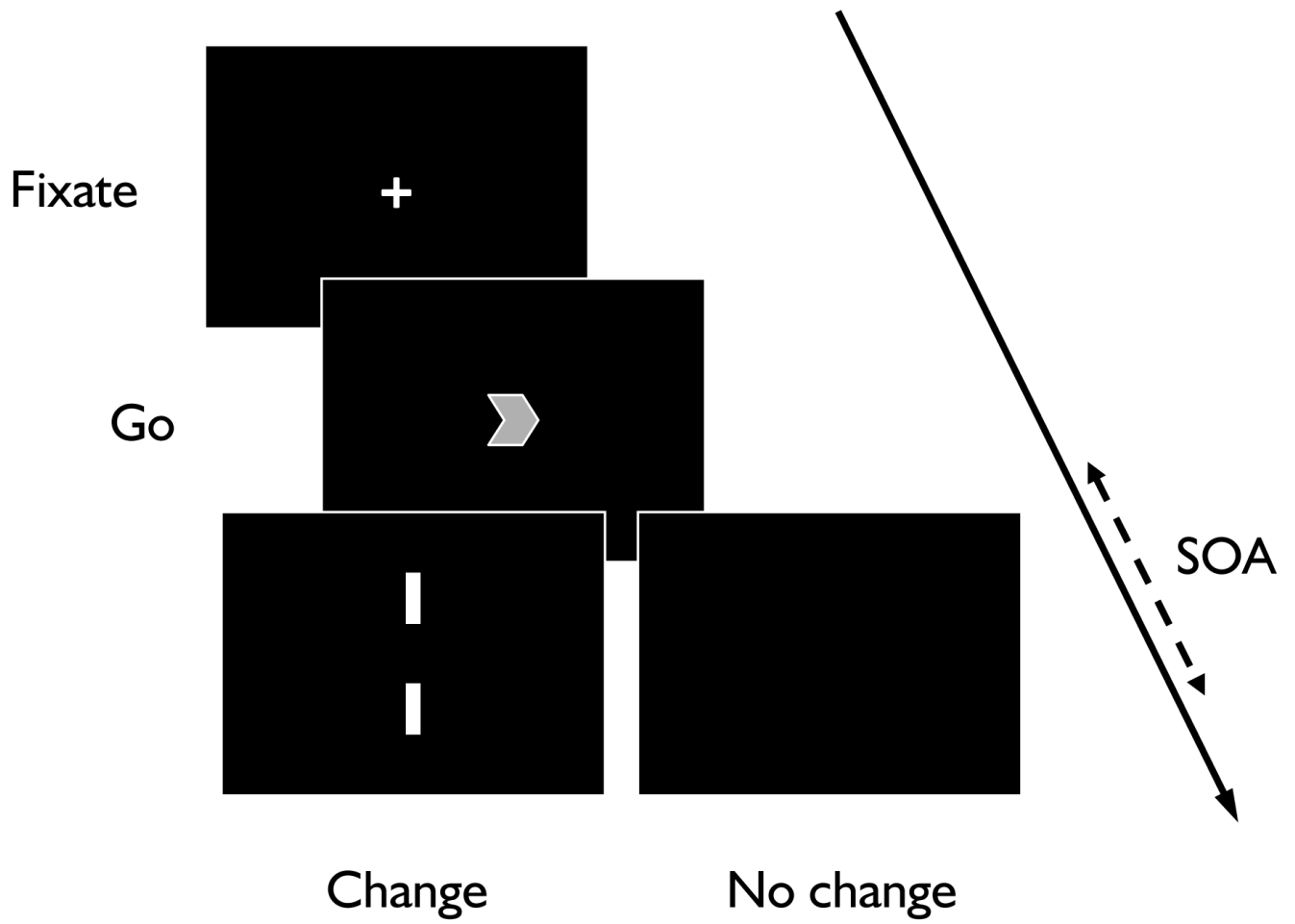
Figure 2. Schematic of the change-of-plan paradigm
Stimuli are not drawn to scale.
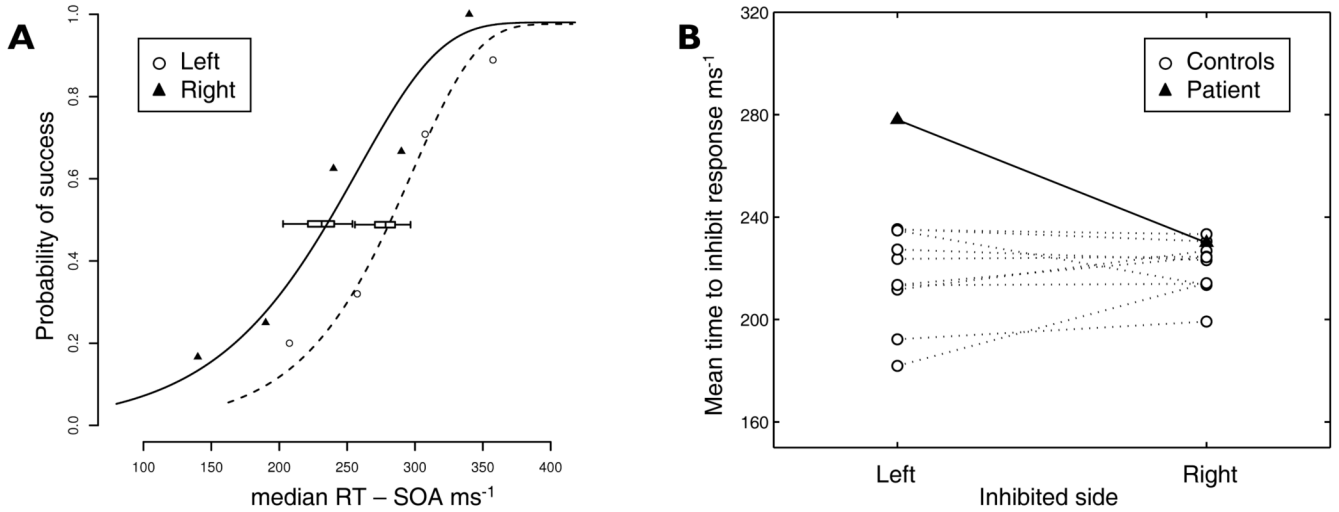
Figure 3. Behavioural data

A. Psychometric inhibition functions for patient AG derived using the change-of-plan paradigm. The line plots show maximum a posteriori (MAP) estimates for the relation between the probability of inhibiting the first movement and the SOA adjusted by the median RT (effectively the time available to inhibit a response) for the left (solid line) and the right (dotted line) hands. Scatter plots of the raw data (left, white circles; right, black triangles) are also shown. The SOA values were determined by a staircase tracking algorithm that targeted the 50% performance level and therefore the sampling was slightly different between the two sides, and weighted towards the middle of the function. Only SOA values for which at least 5 data points were available were used. The SOA values were: left, 100ms (n=9), 150ms (n=24), 200ms (n=25), 250ms (n=10); right, 100ms (n=6), 150ms (n=15), 200ms (n=24), 250ms (n=20), 300ms (n=6). So as to generate functions describing the relation between the probability of changing response and the effective time available to do so, the SOAs were adjusted by subtraction from the median RT on Go trials: left = 458 ms, right = 440 ms. The horizontal box plots show 0.05, 0.25, 0.5, 0.75, and 0.95 confidence boundaries. The two functions are significantly different (Bayesian p= 0.002). **B.** Scatterplot of the left and right hand inhibition function 50% thresholds for AG (filled markers) and the ten control subjects (unfilled markers), derived as described in A. AG differed from controls only on the left (two sample t test, p=0.011), and none of the controls showed a significant difference between left and right based on Bayesian MAP estimates.