Functional role of the supplementary and pre-supplementary motor areas

Parashkev Nachev[*‡], *Christopher Kennard*[‡] *and Masud Husain*[*]

Abstract | The supplementary motor complex consists of the supplementary motor area, the supplementary eye field and the pre-supplementary motor area. In recent years, these areas have come under increasing scrutiny from cognitive neuroscientists, motor physiologists and clinicians because they seem to be crucial for linking cognition to action. However, theories regarding their function vary widely. This Review brings together the data regarding the supplementary motor regions, highlighting outstanding issues and providing new perspectives for understanding their functions.

Ever since they were first identified, the regions that comprise the supplementary motor complex (SMC) have remained, in large part, a mystery. Most investigators now appreciate that these brain regions are far from 'supplementary' to requirements[1–7]. Without them, there are profound alterations in behaviour. For example, lesions to these areas in humans can lead to alien-limb syndrome, with patients demonstrating involuntary actions such as grasping nearby objects — even other people — without ever intending to do so[8,9]. Some individuals demonstrate utilization behaviour: unable to resist the impulse to use an object that has been placed within their reach, even when the object is not needed[10]. Paradoxically, other patients show the converse behaviour: neglecting to use the affected limb when it would be appropriate to do so or, in extreme cases, showing no spontaneous actions unless prompted[11]. Recent studies have also implicated the SMC in the deficits that are associated with Parkinson's disease (PD)[12], with one investigation even claiming improvements in motor function following transcranial magnetic stimulation (TMS) of this region[13].

How can we begin to understand the role of regions that, when damaged, lead to such a range of behaviour? In the past decade, advances in recordings from awake, behaving monkeys using sophisticated behavioural paradigms, and functional-imaging studies in healthy humans, have led to a wealth of findings. Indeed, there is no shortage of hypotheses regarding the possible roles of the SMC, ranging from a crucial role in voluntary action to having a key function in cognitive control. How this region contributes to the capacities that make voluntary behaviour possible is now a matter of great debate.

In this Review, we first provide an overview of the key findings from studies in humans and monkeys. Then we provide a critique of current theories of SMC function, which we hope will stimulate the development of conceptual frameworks for a better understanding of this region.

*Institute of Cognitive Neuroscience and Institute of Neurology, University College London, Alexandra House, 17 Queen Square, London, WC1N 3AR, UK.
‡Department of Clinical Neuroscience, Imperial College London, St Dunstan's Road, London, W6 8RP, UK.
Correspondence to M.H.
e-mail:
m.husain@ion.ucl.ac.uk
doi:10.1038/nrn2478
Published online
9 October 2008

Anatomy and connections

The supplementary motor area (SMA) and pre-supplementary motor area (pre-SMA) are, in humans, located on the medial aspect of the brain: in the dorsomedial frontal cortex[3,14], anterior to the leg representation of the primary motor cortex (FIG. 1). Both areas lie in the superior frontal gyrus and constitute the medial part of Brodmann's area 6c (later divided into two areas: mesial 6aα and 6aβ). The supplementary eye field (SEF) lies at the border of the SMA and the pre-SMA, close to the paracentral sulcus[15,16]. Just ventral to the SMC are the cingulate sulcus and gyrus, including the cingulate motor areas and the regions that are often subsumed in the recent cognitive literature under the terminology of the 'anterior cingulate cortex' (ACC)[17].

In the macaque monkey, a caudal (posterior) area 6aα and a rostral (anterior) area 6aβ on the medial surface of the brain correspond reasonably well to the human SMA and pre-SMA, respectively[18]. More-recent histochemical and cytoarchitectonic studies have parcellated the medial frontal region (FIG. 1) into area F1 (the primary motor cortex), area F3 (corresponding broadly to the SMA) and area F6 (the pre-SMA)[19,20]. Importantly, unlike in humans, the SEF in the macaque lies high on the dorsolateral convexity[5,21] — not on the medial surface — in a zone that corresponds to the most dorsomedial aspect of area F7.

Stimulation studies. But what do these areas do? Importantly, stimulation of this region was observed to evoke both movements (consisting of slow postural

changes involving several muscle groups, complex manoeuvres such as stepping, or even merely the urge to move) and inhibition of action (for example, speech arrest)[22,23].

The current that is needed to evoke movements or inhibit actions becomes higher as one proceeds rostrally from the zone that we now call the SMA, and in 1992 the term 'pre-supplementary motor area' was introduced to distinguish this more anterior region from the SMA proper[24]. The SMA holds a somatotopically arranged map of the body: movements of the hindlimb are evoked from caudal sites, whereas forelimb and orofacial movements are evoked from more-rostral sites, closer to the border with the pre-SMA[23–26]. Stimulation of the SEF can elicit saccadic eye movements[5] as well as combined eye–head movements[27]. By contrast, the findings from the pre-SMA are more variable: whereas stimulation of some sites can produce movements, mostly of the forelimb, at other locations even high currents will not evoke movements.

Connectivity. Most of our knowledge about the connections of the SMC comes from studies in monkeys, although there are some recent diffusion-weighted imaging findings from humans[28]. In keeping with the findings that the electrical excitability of the SMA is greater than that of the pre-SMA (movements are evoked more easily in the SMA), anatomical studies using retrograde tracing methods have shown that the SMA makes a direct and substantial contribution to the corticospinal tract: it comprises ~10% of all corticospinal cells[29–31]. Moreover, the pattern of termination of SMA corticospinal cells resembles that of primary motor cortex projections, suggesting that these SMA cells make direct connections

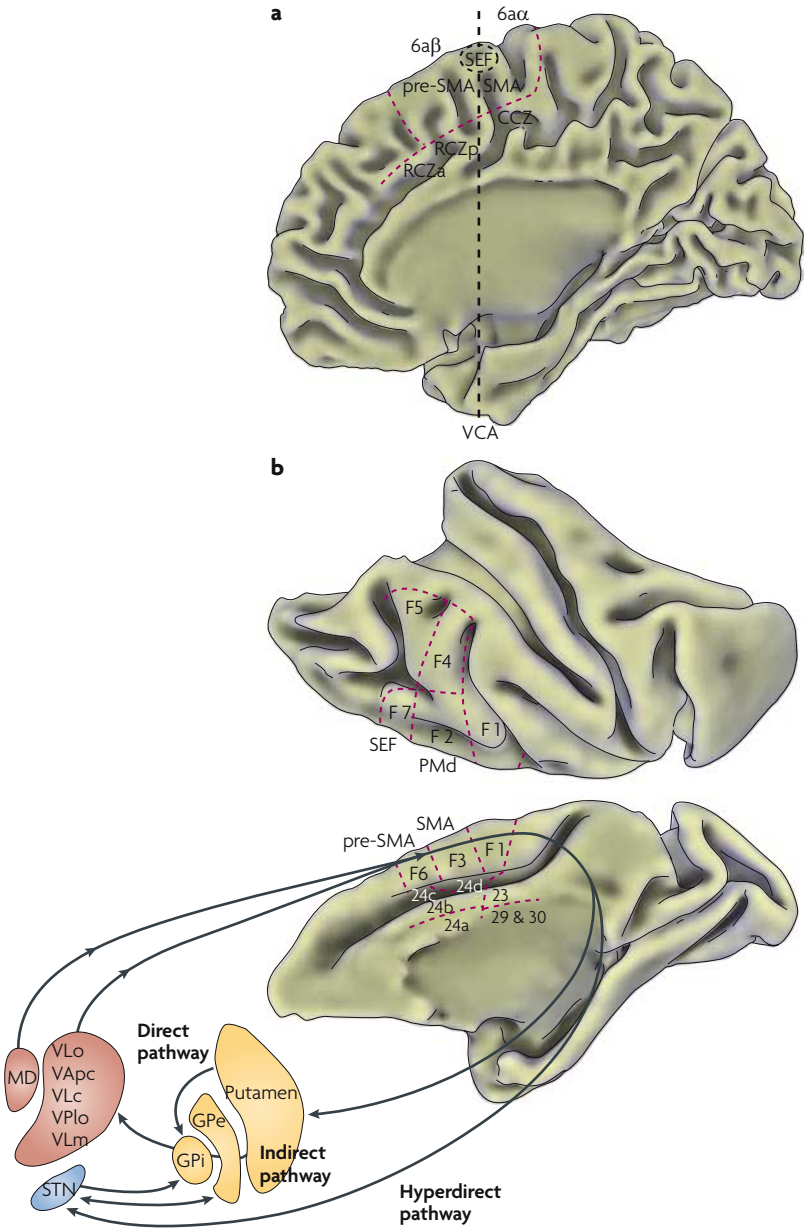


Figure 1 | **Anatomy of the supplementary motor complex (SMC). a** | The medial surface of the human brain, with the supplementary motor area (SMA) shown caudally (posteriorly), the supplementary eye field (SEF) in the middle and the pre-SMA shown rostrally (anteriorly). The SMA occupies mesial area 6aα, whereas the pre-SMA is located in mesial area 6aβ. The VCA (vertical commissure anterior) line is often used in imaging studies to differentiate pre-SMA from SMA activations. Ventral to (below) the SMC are the cingulate motor zones, including areas RCZa and RCZp (anterior and posterior rostral cingulate zones) and area CCZ (caudal cingulate zone). **b** | Medial and lateral views of the macaque monkey brain with some of the projections to the basal ganglia (shown in yellow), which in turn project back to cortical areas through thalamic nuclei (shown in orange). Area F3 corresponds to the SMA, whereas area F6 corresponds to the pre-SMA. The SEF is part of area F7. Area F1 is the primary motor cortex (M1) and area F2 corresponds to the dorsal premotor cortex (PMd). The SMC sends efferents to the putamen and the caudate (not shown), which then project to the internal segment of the globus pallidus (GPi), either through a direct pathway or through a longer, indirect pathway that runs through the external segment of the globus pallidus (GPe). There is also a hyperdirect pathway from the SMC to the subthalamic nucleus (STN) (shown in blue), which affects GPi activity and might thereby modulate the return flow of information to the cortex in the corticostriatal circuitry. Areas F1, F3 and F6 each have direct projections to the striatum and the STN, and each of these areas receives separate inputs from the thalamus. The single loop shown here is simply for illustrative purposes. Note that the input from the thalamus to areas F3 and F6 originates in different parts of the GPi. Cingulate cortical areas (Brodmann's areas 23, 24, 29 and 30) are located ventral to the SMC. MD, nucleus medialis dorsalis; VApc, nucleus ventralis anterior, pars parvocellularis; VLc, nucleus ventralis lateralis, pars caudalis; VLm, nucleus ventralis lateralis, pars medialis; VLo, nucleus ventralis lateralis, pars oralis; VPlo, nucleus ventralis posterior lateralis, pars oralis. The macaque figures were generated from subject F99 using the Caret software[135]. The human brain figure was generated using Colin27 of the Montreal Neurological Institute.

to motor neurons[32]. By comparison, the pre-SMA has a sparse projection in the corticospinal system[31,33]. Similarly, whereas the SMA has reciprocal connections with the primary motor cortex, the pre-SMA does not[34]. Instead, the pre-SMA and the SEF project to the dorsolateral prefrontal cortex[34–36] (but see REF. 37). One interpretation of these findings has been that the SMA is directly related to motor output, whereas the pre-SMA, and to some extent the SEF, are more distant from such a role. There are also other differences in cortical and subcortical connections between these SMC subregions[5,36,38,39] but, as we discuss later, the differences and similarities are harder to capture than this simple sketch might imply.

All parts of the SMC connect with the basal ganglia (FIG. 1), which is one of the reasons for the interest in these areas from the perspective of PD. In fact, a recent investigation revealed that the number of cells that project from the internal segment of the globus pallidus (GPi) of the basal ganglia to both the SMA and the pre-SMA, through the thalamus, is ~3–4 times the number that project from the cerebellum, quite unlike the pattern for other cortical motor areas[40]. The SMA, the pre-SMA and the SEF all send efferents to the striatum[41,42], which projects onto the GPi both directly and indirectly. Thus, these pathways complete a key cortico–subcortical loop. In addition, both the SMA and the pre-SMA have a 'hyperdirect' connection to the subthalamic nucleus (STN)[43] (FIG. 1); this is considered by some to be an important route through which ongoing activity in cortical–basal ganglia circuits can be rapidly 'braked' by the SMC[44].

Neurophysiology and functional imaging

Several lines of evidence show that regions in the SMC are active before movements occur, but the precise role of such activity is controversial.

Self-initiated versus externally triggered movements. Recordings from monkeys have demonstrated that many SMC neurons discharge before movements in an effector-specific manner; for example, SMA neurons fire before hand or foot movements[45,46], and SEF neurons fire before eye movements[5,21]. Moreover, scalp recordings from humans have revealed a slowly increasing negative potential, known as the *Bereitschaftspotential,* that is centred over the SMC before movement onset[47] (FIG. 2a). The latter part of this 'readiness potential' is greater when it precedes self-initiated movements than when it precedes externally cued movements[12]. Furthermore, the *Bereitschaftspotential* is significantly less prominent in patients with PD than in healthy controls[12]. These findings might be considered to be consistent with the proposal that the SMC has a key role in voluntary action (self-initiated movements) rather than in responses to external events[2,48], and that this role might be particularly disrupted in PD.

In accord with this view, imaging studies have reported greater activity in the pre-SMA when participants are free to choose their actions than when they are instructed by external signals[49–52]. One investigation has also reported greater pre-SMA activation when participants "pay attention to their intentions" (REF. 53), although exactly what such a process might have to do with voluntary action is unclear.

In one event-related functional MRI (fMRI) study, SMA activity before internally generated and externally triggered actions was similar, but there was earlier activation of the pre-SMA for internally generated movements than for externally generated movements[54]. In general, the association with internally generated movements seems to be stronger for the pre-SMA than for the SMA, but it needs to be borne in mind that the difference between self-initiated actions and those triggered by sensory cues might also relate to differences in task complexity. The dichotomy between 'internal' and 'external' might not simply relate to whether or not the subject was instructed to perform an action. Note also that matching the number of possible internal and external responses does not eliminate the differences in the complexity of the conditions that determine which action is taken. When the conditions are not externally specified they remain opaque to the experimenter, making any differences between internally and externally specified movements impossible to gauge. However, because internal conditions inevitably involve integrating information from past responses, they are likely to be associated with greater complexity than external ones.

A related finding that is of relevance here is that the human SMA is also active even when people simply observe graspable objects, without being required to hold them[55]. In this situation there is no generation of movement, but the external object might implicitly activate a motor plan in the brain, underlying the phenomenon of 'object affordance' — that is, the facilitation or speeding up of behavioural responses to an object. Of course, it is essential for successful behaviour that not all possible actions are executed when objects come into view, so it is important to also have mechanisms that inhibit such activation if a directed action to an object is not in fact required. Lesion evidence[56], which we review later, suggests that the SMC normally makes a contribution to such an inhibitory process.

In monkeys, SMA neurons respond to both self-initiated and externally cued movements[57,58], which is inconsistent with a clear dichotomy between responses to internally and externally triggered actions. Indeed, some neurons in the SMA respond before a movement only when the movement is cued by a specific sensory cue (for example, a visual cue) and not if it is cued by a different signal (for example, a tactile or auditory cue)[46,59] (FIG. 2b). Simply presenting the preferred cue alone is not sufficient to evoke a discharge — the monkey also has to make the appropriate movement. Thus, it is the combination of specific cues (defining a set of conditions) and motor responses (actions) that is necessary for activity in these cells. Other neurons in the SMA or in the SEF display a slow build-up of activity in response to a preparatory cue that informs the monkey to make an arm or an eye movement, respectively, if a second cue is given[59,60] (FIG. 2c), but their activity can be suppressed if the second cue signals withholding a movement[59]. By contrast, yet other neurons in the

Effector
An organ (a gland or, in the context of this article, a muscle) that becomes active in response to nerve impulses.

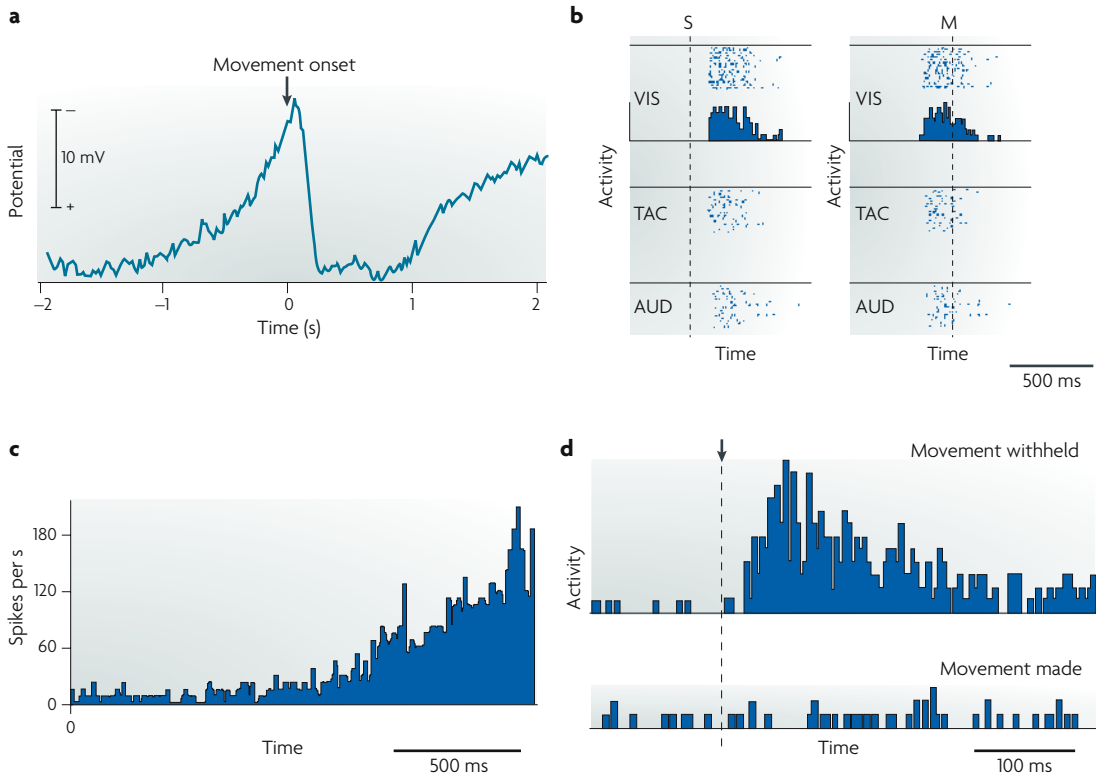


Figure 2 | **Electrophysiological responses in the supplementary motor complex. a** | The *Bereitschaftspotential*, or readiness potential, is a negative wave that can be recorded over the medial frontal lobe of humans during the second before movement onset (at time 0 s). **b** | A recording from a neuron in the supplementary motor area (SMA) that responds to a visual signal (VIS) for making a wrist extension movement but not to tactile (TAC) or auditory signals (AUD) to make the same movement. The activity is shown time-locked to the signal (S) or to the movement onset (M). **c** | Discharge of an SMA neuron following a tactile signal (at time 0 s) informing the monkey that it needs to be prepared to make a key press when it receives another sensory signal. Note the build-up in activity during the preparatory period. **d** | Activity of an SMA neuron in response to a tactile stimulus (at the time indicated by the arrow) when a movement was withheld (upper panel) and when a movement was made (lower panel). Part **a** reproduced, with permission, from REF. 136 © (1965) Springer. Part **b** reproduced, with permission, from REF. 46 © (1982) American Physiological Society. Part **c** reproduced, with permission, from REF. 59 © (1985) American Physiological Society. Part **d** reproduced, with permission, from REF. 61 © (1985) American Physiological Society.

SMA and in the SEF show brisk activity in response to a sensory cue that signals that the monkey should withhold a movement, but not if the animal is cued to make a response[60,61] (FIG. 2d).

The complexity of responses in the SMC — to signals that instruct a particular rule, to signals that trigger a response or that trigger withholding movement, and to making the movement itself — is quite unlike that which is observed in the primary motor cortex; there, responses are more stereotypically related simply to movement execution[61]. In fact, as we shall see later, the contribution of SMC regions in linking conditions — whether internal or external — to actions is a recurring theme in many lines of investigation. By 'conditions' we here refer to both environmental triggers (such as visual cues) and internal states (such as memory of previous responses and the outcomes that are associated with them, or reward contingencies).

Movement sequences. Rather than claiming a special role for the SMC in internally versus externally generated movements, some researchers have considered the possibility that it makes an important contribution to action sequences[62]. SMA and pre-SMA neurons respond before some sequences (for example, turn–pull–push a lever) but not others (for example, turn–push–pull)[63,64] (FIG. 3a). They also respond in a specific manner in the interval between actions, so they might respond before a pull movement but only following a push. Thus, the response that is associated with the pull movement is conditional on the prior movement; that is, there is a conditional response–response association. Remarkably, some neurons respond only to the rank order of a movement in the sequence[64,65]; for example, they might respond only before the third movement, regardless of what that movement actually is — either turn or pull or push (FIG. 3b). Although these responses are more frequently found in the pre-SMA than in the SMA, the difference is one of degree rather than being an absolute distinction between the two areas[64]. Some pre-SMA neurons also show consistent activity just before the next sequence has to be executed, irrespective of the motor components of the sequence[66].

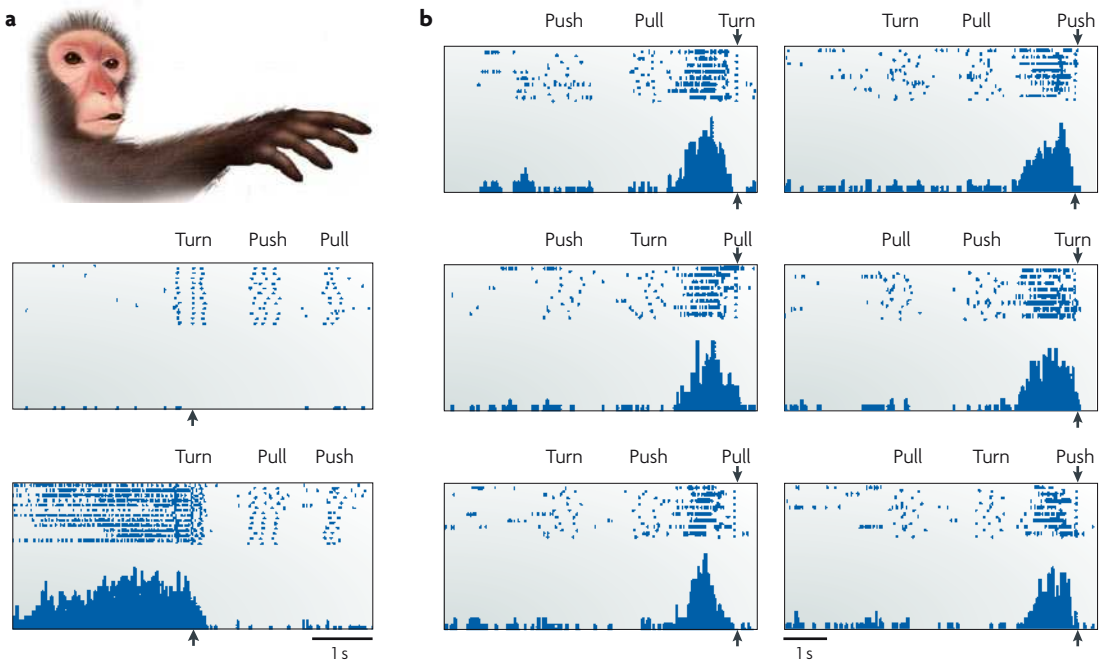


Figure 3 | **Neuronal activity in the supplementary motor cortex related to movement sequences. a** | Recordings from a neuron in the supplementary motor area reveal that it responds before turning movements, but only if they are followed by a push and not a pull movement. **b** | This pre-SMA neuron fires only before the third movement, regardless of whether the third movement is a push, a pull or a turn and regardless of the type of movement that precedes it. Monkey image in part **a** reproduced, with permission, from REF. 137 © (2004) American Association for the Advancement of Science. Recording plots in part **a** reproduced, with permission, from REF. 63 © (1994) Macmillan Publishers Ltd. All rights reserved. Part **b** reproduced, with permission, from REF. 64 © (2000) American Physiological Society.

SMA and pre-SMA cells also encode the number of movements that remain to be made to complete a sequence and obtain a reward[67], while SEF neurons can respond to one particular element in a sequence of eye movements[68]. Some pre-SMA neurons and, less frequently, SMA neurons also respond differentially to whether the monkey is on an odd- or even-numbered trial[69]. The different types of neuron in the SMC might therefore help to encode not only where in a sequence the monkey is but also the conditional links between the previous response and the upcoming response[7], often in a highly specific manner. In humans, positron emission tomography (PET) studies have shown activation of the SMC during movement sequences. Importantly, such activation was also observed when subjects 'internally' simulated the motor sequence without actually executing the movements[70].

Learning. Several investigators have reported that the activity of SMC regions can be modulated by learning new associations between stimuli and responses, or during the learning of movement sequences. Chen and Wise recorded from SEF neurons while monkeys learnt, by trial and error, the correct saccade to make in response to an arbitrary visual stimulus (for example, an upward eye movement in response to a rectangle but a leftward one to a circle). They found that different types of cells showed increased activity during the learning phase and when a novel association had to be learned[71]. Importantly, the preferred direction of some of these neurons was not fixed — rather, it evolved during learning, demonstrating that the SEF is a highly labile network that can flexibly map new stimulus–response associations, which is essential for conditional behavioural learning[72].

Hikosaka and colleagues also reported cells that show learning-related activity, this time for a complex sequence of hand movements[73]. Such activity was more prominent in the pre-SMA than in the SMA. These effects were not tied to the muscles or kinematics of the actions performed, because similar responses were observed with each arm. Moreover, although the activity was related to sequence learning, the paradigm required monkeys to learn which of two illuminated keys to press first at each phase of a sequence; in other words, they learnt to associate stimulus with response in a conditional manner, analogous to the requirements of the Chen and Wise paradigm. SMC activation has also been demonstrated, using neuroimaging, during sequence learning in humans[74], but importantly this activity is most likely due to learning associations between — or paying attention to — visual cues and the responses required, and not to learning sequences *per se*[75]. One recent PET study also revealed increased dopamine release in the pre-SMA, and corresponding reduced dopamine release in the GPi of the basal ganglia, during learning[76]. Such a link emphasizes once again the strong connectivity between the SMC and the basal ganglia, but this time reveals how such a link is functionally relevant, namely through dopaminergic modulation.

Saccade
Quick, simultaneous movements of both eyes in the same direction, allowing one to fixate rapidly on elements of a visual scene.

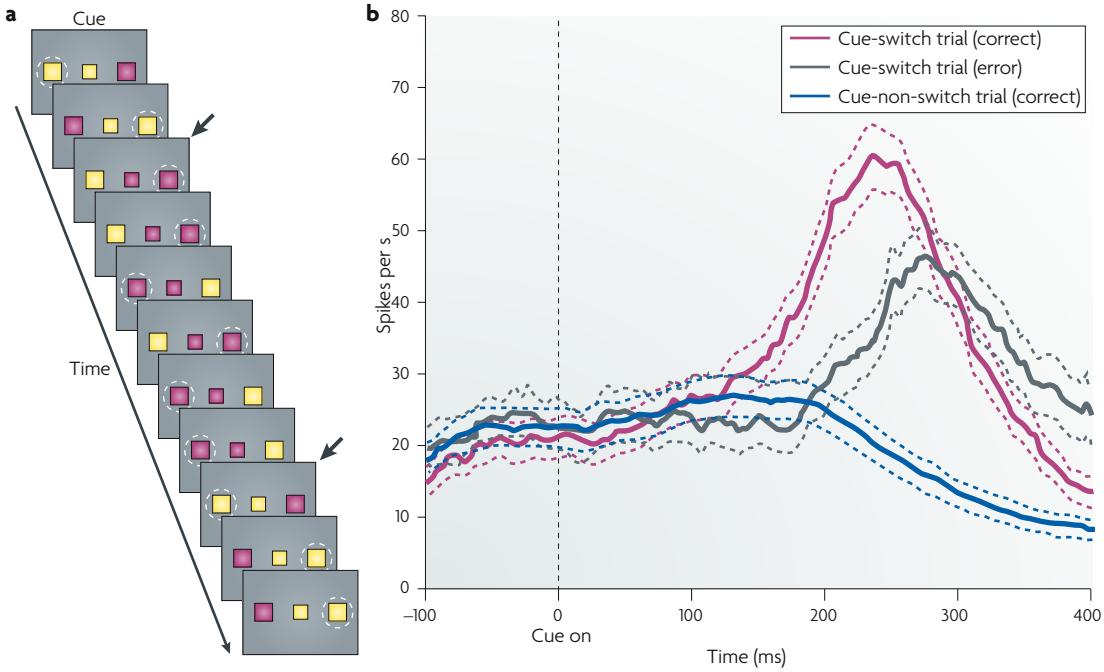


Figure 4 | **Neuronal activity in the pre-supplementary motor area related to switching responses. a** | Monkeys were trained to make a saccadic eye movement to the peripheral target that matched the colour of the central cue. Correct targets are shown by the dashed circles in each panel. Switch trials, when the central cue colour changed, are indicated by the arrows. **b** | The firing of a population of neurons with activity that was related to switching responses. There was greater discharge when the monkey correctly switched (pink trace) than when it made an error and did not switch (grey trace). Baseline discharge rates on non-switch trials for these neurons is shown in blue. Part **b** reproduced, with permission, from REF. 91 © (2007) Macmillan Publishers Ltd. All rights reserved.

Cognitive control. For better or worse, the term cognitive control[77] has come to be associated with a series of processes that are considered to be essential to successful behaviour. Also known as 'executive-control' functions[78], these processes have been proposed to come into operation when we need to initiate a new action or, alternatively, inhibit a response plan. They are considered to be critical for our ability to flexibly switch from one plan — or one rule linking a stimulus to a response — to another, and also for our ability to reduce interference from irrelevant, distracting features in the environment, which compete with current task goals and thereby produce conflict. Some researchers also consider performance- or error-monitoring to be a key control function, one that allows adjustments to be made so that future responses can be optimized. As discussed before, initiation of movement is considered to be an important function of the SMC by some investigators who approach it from a motor perspective. Cognitive neuroscientists too have been interested in how the SMC responds to situations in which cognitive control is invoked.

What happens, for example, when current plans have to be altered? We have known for some time that neurons in the pre-SMA and, less frequently, in the SMA respond when monkeys have to change a reaching-movement plan[79]. Functional-imaging studies in humans have now also implicated the pre-SMA in such a process. Many of these studies used a countermanding task, in which a participant is instructed to make a movement on at least half of the trials, but on the rest of the trials this request is countermanded while the subject is preparing to make a response. In some experiments the participant's task on these trials was to withhold the movement altogether ('stop signal' paradigm), whereas in other studies the subject was required to make a movement in the direction opposite to that of the first instructed action ('change-of-plan' task). By altering the time at which the stop or change cue is presented after the go signal, it is possible to compare participants' brain activity when they are making errors (failing to alter the initial plan) with their brain activity when they correctly alter plans. Both change-of-plan and stop tasks for hand and eye movements have demonstrated pre-SMA and/or SEF activity that is related specifically to altering movement plans[49,80–82]. Other tasks that require inhibiting responses or switching between tasks, or switching between rules linking stimuli to responses, also consistently activate the pre-SMA[83–88].

In the monkey SEF, neural activity can be associated either with successfully withholding movements during the performance of an oculomotor stop task or with failing to do so, with the latter type of response potentially being important for monitoring errors[6,89]. Microstimulation of the SEF altered performance on this paradigm[90]. A more recent study reported neurons in the pre-SMA that are specifically related to switching eye-movement responses[91]. In this experiment, monkeys had to saccade to one of two possible locations, coloured pink or yellow, to the left or right of the point of fixation (FIG. 4a).

The direction of movement was signalled by a colour cue at the point of fixation; this cue appeared just after the colours appeared at the peripheral locations, and the monkeys were required to saccade to the location that had the same colour as the cue. For several trials the central cue colour would be kept constant, and then it would change unpredictably. The population activity of a group of neurons in the pre-SMA showed activity on switch trials but not on non-switch trials (FIG. 4b). On switch trials on which the monkey made an error and stuck to the previous rule, activity was less prominent and appeared much later. Microstimulation of the pre-SMA reduced the frequency of incorrect fast responses and increased the frequency of slower correct ones. Crucially, switch-related neurons also responded to response inhibition or facilitation on a control go/no-go task[91]. Thus, neurons were not switch-specific. This finding has important implications for understanding the contribution of the pre-SMA to the many functions that have been attributed to it.

The human medial frontal cortex, particularly the ACC, has also been implicated in minimizing interference from irrelevant, conflicting cues, in cognitive-control experiments[92] such as the Stroop task and the Eriksen flanker task. Brain-imaging studies of humans performing such conflict paradigms have often revealed medial frontal activation[92], but many such activations actually involve the pre-SMA[93–95]. Moreover, monkey recording studies have provided no good evidence for a link between ACC activity and response conflict, although single-cell activity would be consistent with a role in error monitoring[96–98]. In our view it is likely that conflict-related activity in the medial frontal cortex is more attributable to pre-SMA, rather than nearby ACC, activation (see also REFS 7,95). When we have examined medial frontal activity in situations of response conflict, controlling for level of arousal, we did not observe any activity in the ACC, only in the pre-SMA[49]. Finally, it is also noteworthy that meta-analyses of this region demonstrate that activity in more rostral areas (the pre-SMA) is associated with more-complex control situations than activity in the more caudal end (the SMA)[3,14].

Action without a normal SMC

In humans, resection of the SMC (usually for tumours) often initially abolishes spontaneous movement of the contralesional limbs. Known as motor neglect[11], this condition has been claimed to be due specifically to lesions of the SMA[99]. Occasionally patients are more severely affected: they can be mute, immobile and generally unresponsive (this is known as akinetic mutism)[11]. These deficits usually improve within weeks or months. Often, however, a residual contralesional problem is still observable on detailed testing of alternating bimanual movements[11] — for example, opening and closing each hand, particularly in the absence of vision. Bimanual deficits have also been observed in monkeys with SMA lesions[100]. In addition, some reports in humans have documented deficits in gait initiation or execution (gait 'apraxia'), elements of which resemble some of the features of parkinsonian gait[101].

The effects of SMC lesions are not always simply an absence of movement: sometimes lesions cause movements that subjects find inimical to their goals. In its most striking form this presents as full-blown alien-limb syndrome, in which the affected arm sometimes makes semi-purposeful movements (for example, grasping objects in the vicinity) that are apparently outside the subject's control[8,9]. Sometimes the 'alien' limb interferes with what the other limb is doing — for example, by putting down the telephone receiver that the patient has picked up with the unaffected hand to make a call. Even more remarkably, some patients demonstrate utilization behaviour: they use nearby objects in a stimulus-driven fashion, even when they have no apparent intention to do so[10]. Thus, they might pick up a pair of spectacles and put them on, and then see another pair on the table and put those on too. The precise regions of the SMC that are involved in such behaviour have been difficult to localize, because lesions are often not focal and often also involve the corpus callosum. However, transient involuntary grasping has also been reported in monkeys with SMA lesions but without full-blown alien limb syndrome or utilization behaviour[102].

New observations from patients with highly focal lesions of the SMC have begun to provide some insights into the mechanisms that might be disrupted in these syndromes. Behavioural studies in healthy people have shown that stimuli that are briefly presented so that they are not consciously seen by observers can prime the brain, initially facilitating responses but then inhibiting them. Two patients (J.R. and C.B.) who have discrete lesions involving the SEF (J.R.) and the SEF plus SMA (C.B.) show normal facilitation but lack the subsequent inhibition[56]. Moreover, the behavioural abnormalities are effector-specific: for eye movements in J.R. and for both eye and hand movements in C.B. (FIG. 5). These observations suggest that the SMA and the SEF normally have a key role in suppressing motor programmes that might be subconsciously primed simply by viewing objects. As discussed earlier, the SMA is activated under such conditions[55]. Syndromes such as alien limb syndrome and utilization behaviour, which result from more extensive lesions, might represent an exaggeration of the effects observed in these patients, with failure to suppress making actions in response to seeing objects that implicitly activate motor programmes in our brains.

Self-initiated versus externally triggered movements. In monkeys, SMC lesions produce little visible disturbance[102,103] unless the animals are required to execute tasks that are not prompted by events in the immediate environment, leading to suggestions that the region is specialized for internally guided rather than externally cued actions. For example, Passingham and colleagues first showed that monkeys that were taught to self-initiate an arbitrary movement (raising an arm above a certain height) to receive a reward were impaired at initiating such actions following lesions involving the SMA and the pre-SMA[104]. Such a deficit could be remedied if the monkeys were given an auditory tone to act as an external prompt.

Stroop task
A behavioural task in which subjects are asked to rapidly respond to visually presented colour words by saying either the word itself or the colour of the ink in which the words are displayed. When the word is not the colour of the typeface, subjects tend to be slower and less accurate than when the two are the same.

Eriksen flanker task
A behavioural task in which subjects have to respond to a central stimulus that is flanked by distractor stimuli that code an alternative response — for example, the opposite of the response that is cued by the central stimulus.

Contralesional
The side of the body that is opposite to the side of a brain lesion.

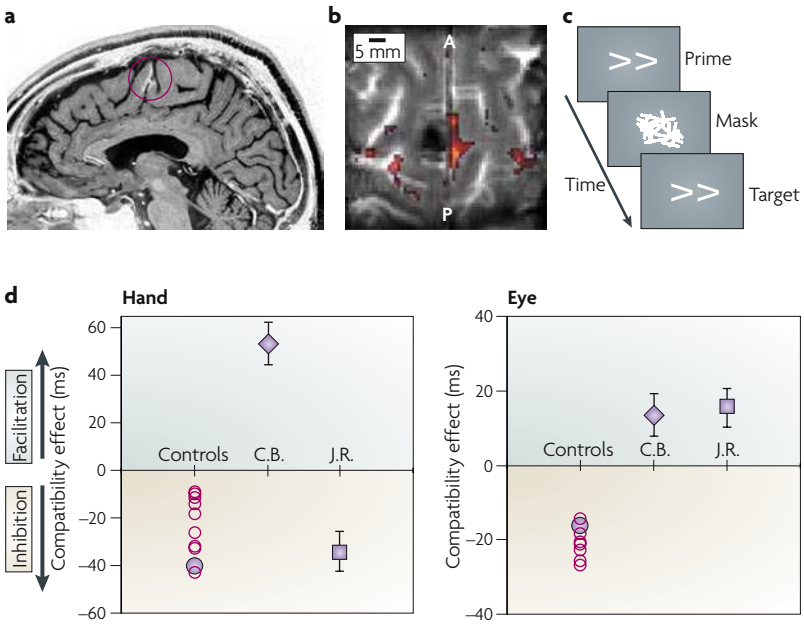


Figure 5 | **Focal human supplementary eye field (SEF) lesion. a** | Patient J.R.'s small venous stroke shown on a sagittal MRI scan. **b** | Activation of eye fields in a functional MRI experiment performed at 7 T reveals that the lesion lies in the left hemisphere, opposite the intact SEF. Activity in the frontal eye field can been seen to the left and right of the main area of activation in the middle of the scan. **c** | A masked-prime task used to test automatic motor inhibition. In this task, a target prompting the participant to make leftward or rightward movements (with either the hands or the eyes) is preceded by a masked prime, which can be congruent (pointing in same direction) or incongruent (pointing in a different direction) with the target. The presentation of the mask ensures that the prime is not consciously perceived by the subject. Nevertheless, if the mask–target interval is shorter than 100 ms, primes speed up responses to congruent targets. If the interval is longer than 100 ms, primes slow responses to congruent targets, indicating an automatic inhibition of partially activated motor plans. **d** | Control subjects show normal inhibition (slowing) on this task with congruent prime–target combinations when the mask–target interval is 150 ms. Patient C.B. (who has an SEF lesion and a hand-area lesion in the supplementary motor area) shows facilitation for both eye and hand versions of the task, whereas patient J.R. (who has an SEF lesion) shows normal inhibition for hand movements and facilitation only for eye movements. A, anterior; P, posterior. Part **a** reproduced, with permission, from REF. 111 © (2007) Pergamon Press. Parts **b** and **c** reproduced, with permission, from REF. 56 © (2007) Elsevier Science.

However, reversible inactivation of the SMA with cooling suggests that the impairments that are observed after lesioning cannot simply be explained by the SMA's involvement in internally versus externally triggered actions. Tanji and colleagues trained a monkey on a complex conditional task to either make an action or inhibit it[105]. In some trials the monkey heard a 300 Hz auditory tone that signalled it to make a rapid key press if it was subsequently presented with a (different) auditory tone; presentation of a tactile stimulus instead was the signal to withhold the movement. On other trials the monkey was given a 100 Hz tone which signalled that it should now withhold movements to a subsequent auditory tone and instead press the key in response to a tactile stimulus. The monkey's behaviour was profoundly disturbed when the SMA was cooled, with both omissions (failures to respond) and commission errors (executing movements when they should have been withheld), even though the monkey could make key presses without any difficulty. This type of deficit suggests a problem in linking conditional rules to actions (BOX 1), a theme that runs throughout this Review.

Movement sequences and learning. Just like physiological and imaging studies, the focus of several lesion studies has been the contribution of the SMC to the execution of action sequences[62]. When muscimol, a GABA (γ-aminobutyric acid) agonist, was injected bilaterally into either the SMA or the pre-SMA, monkeys that had been trained to perform movement sequences from memory (for example, push then pull then turn a handle) were greatly impaired, although if they were cued by visual signals they were able to perform the correct sequence without difficulty[106]. Importantly, the monkeys were able to perform simple reaching movements that were externally cued or self-initiated, so this deficit seems to be one of executing sequences of movements rather than one of internally generating an action. However, muscimol injected unilaterally into the pre-SMA — but not the SMA — had significant effects on learning a new sequence but did not lead to more errors on previously well-learnt sequences[107]. These findings suggest a role for the pre-SMA in putting together new sets of actions or chains of response–response associations in the correct order[7].

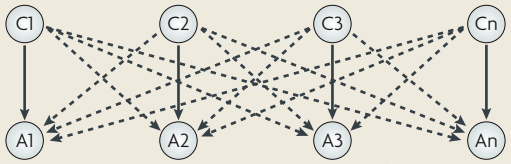
In humans too, the contribution of the SMC to movement sequences has been investigated in several studies of limb or eye movements[108,109]. However, most reports have been based on patients with quite extensive lesions that are not confined to the SMC. Patient J.R., with the highly discrete venous stroke involving the SEF[56,110] (FIG. 5), could execute saccadic eye movement sequences from memory well[111], although each movement slightly undershot the target location, much like movements executed by patients with PD[112]. However, he encountered difficulty in learning new stimulus–response associations specifically for eye (not limb) movements[111].

Cognitive control. In terms of cognitive control, task-switching has been the predominant function to come under scrutiny following disruption of the SMC. In addition to his other deficits, patient J.R. was found to be severely impaired on an oculomotor change-of-plan task. Once he had committed to making an eye movement, he was unable to change to an alternative saccade unless the signal to change plans was presented very soon (~60 ms) after the cue to make the first saccade[110]. A second patient, J.G., who had a lesion of the pre-SMA, had similar difficulties on a hand-movement version of this change-of-plan task[113]. In addition, lesions of the SMC disrupt performance on the stop-signal task[114], and TMS to this region in healthy people increases error rates on the Eriksen flanker task, which is used to index cognitive control[115].

Switching between rules that link visual cues to actions is disrupted in healthy people when TMS is applied to the SMC[85]. Similarly, patient J.R. was impaired in switching between oculomotor task rules[110]. He also

Muscimol
A $GABA_A$ receptor agonist, 3-hydroxy-5-aminomethyl-isoxazole, that can be injected into the brain to temporarily disrupt activity at the site of injection.

Box 1 | **Condition–action associations**



A key property of neurons is their capacity to instantiate a rule for the transformation of a set of inputs into an output. In simple organisms, the only rules that can be encoded are direct associations between the outside world and an action. Most of human behaviour, however, cannot be easily explained by simple stimulus–response (S–R) associations, because in identical external circumstances entirely different actions could be performed. A popular way of resolving this problem is to posit that there is an essentially autonomous supervisory (executive) system that polices lower-order S-R associations, biasing the selection of an action. There is, however, no need to invoke a discrete executive: a satisfactory model that accommodates the full complexity of human behaviour can be specified without recourse to the dichotomous hierarchical organization that executive theories imply, by considering the notion of a condition–action association.

Here, the combination of external stimuli and internal states at any point in time — a set of conditions (C1–Cn) — leads to the differential activation of neuronal ensembles that code for different possible actions (A1–An) (see figure). The action that is ultimately performed is determined by the outcome of fair competition between the ensembles, which is itself determined by the strength with which the set of conditions favours one ensemble over the others.

As an example, consider a simple rule that governs the performance of a centrally guided saccade (with the eye movement direction cued by a central stimulus):

- Stimulus L → left saccade
- Stimulus R → right saccade

A more complex rule that governs the performance of either anti- (away from a visual stimulus) or pro-saccades (towards a visual stimulus) depending on the colour of the fixation point, which many suggest requires an executive system to implement, is simply the same rule but with an additional conditional term:

- Stimulus L + green fixation point → left saccade
- Stimulus R + green fixation point → right saccade
- Stimulus L + red fixation point right → right saccade
- Stimulus R + red fixation point → left saccade

It is easy to see how rules of any complexity can be so constructed. We need not distinguish between 'external' and 'internal' conditions. In some circumstances external conditions will be decisive in determining the winning ensembles, such as when eliciting a deep-tendon reflex; in others, such as when choosing a pear rather than an apple from a bowl of fruit, it will be internal conditions that are decisive.

had profound impairments when he was asked to switch from making pro-saccades (towards a visual stimulus) to making anti-saccades (in the opposite direction to a visual stimulus)[111].

Parkinson's disease. Patients with PD consistently show reduced activity of the SMC[116,117], which can be improved with L-DOPA treatment[118] or with deep brain stimulation of the STN[119]. These patients also have a loss of pyramidal neurons in the pre-SMA[120]. Together with the other links that we have reviewed between the SMC and the basal ganglia[12,40–42,44,76,112,117], these findings have led to growing interest in the contribution of SMC dysfunction to PD; a recent study has even reported improvements in motor function in patients with PD following TMS of the SMC[13]. STN stimulation can lead to impulsive decision making in PD[44], and patients off medication also show impairments in task switching[121], consistent with possible pre-SMA dysfunction.

New perspectives for understanding the SMC

Thus far, we have presented some of the data pertaining to SMC function in light of established proposals regarding its function. In reality, the data set is far more complex than might be assumed. Such complexities pose challenges for current views of the role of the SMC.

Discrete modules might not exist. Close analysis of the cytoarchitectonic data shows that the SMC has no unique individual features or invariant macroscopic landmarks: it differs from neighbouring areas of the cortex only in relative terms. Not only are the boundaries between subregions poorly defined, the variation within a putative subregion seems to be comparable to that between subregions[5]. Receptor-expression maps also elegantly show that the structural variations are best described as continuities rather than as discrete subregions[122] (FIG. 6a). Similarly, the connectivity profiles of SMC subregions reveal overlap rather than completely discrete segregation. For example, the projections to the STN from the pre-SMA and the SMA overlap just as much as they differ[41] (FIG. 6b). Few studies have investigated projections from different parts of the same subregion but, crucially, the variation within a subregion has been at least as striking as the variation between subregions. For example, the rostral and caudal parts of area F3 differ enormously with respect to their connectivity with frontal and parietal regions — this difference is comparable to the differences between area F3 and area F6 (REF. 34) (FIG. 6c). The same rostro–caudal gradient is observed in the connectivity of the SEF: rather than exhibiting the features of an 'oculomotor SMA' that a somatotopic classification would predict it to have, the SEF's connectivity patterns resemble those of the pre-SMA, to which it is closer in the rostro–caudal plane[34,36,38].

Functionally too the evidence does not favour a simple modular organization in the SMC. As we have seen, neuronal recording studies that distinguish between the SMA and the pre-SMA show relative rather than absolute differences in the number of cells that can respond to a particular parameter (for example, movement order in a sequence[64,69], altering movement plans[79] or during learning[73]) (see Supplementary information S1 (figure)). The differences are similarly relative for the distribution of saccade- and reach-related cells, as well as for the distribution of neurons that are not effector-specific but that respond to either hand or eye movements, in the SMC[123]. Thus, for example, the monkey SEF is not only involved in eye movements but also contains cells that respond differentially depending on whether there is an accompanying hand movement[123] (see Supplementary information S2 (figure)).

Whether the same is true in humans is virtually impossible to tell, because functional brain imaging produces inherently discretized pictures of the activity of the brain. This is inevitable for two reasons: first, because technical constraints require sampling of the brain at a relatively coarse resolution; and second, because the nature of the accompanying signal noise makes continuous spatial distributions difficult to distinguish from discrete ones. Investigators are forced to pick an

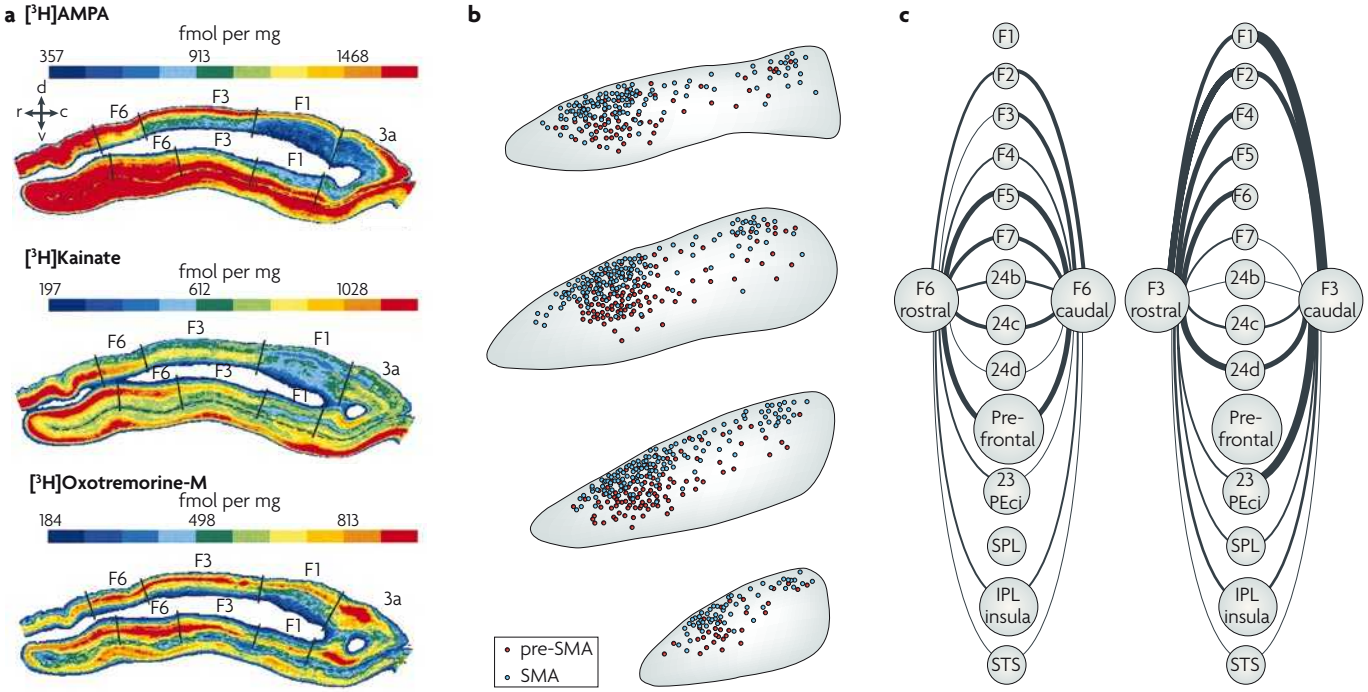


Figure 6 | **The structure and connectivity of supplementary motor cortex subregions vary in a continuous fashion. a** | Receptor expression in the medial frontal cortex shows smooth rather than abrupt changes across area F3 (the supplementary motor area (SMA)) and area F6 (the pre-SMA). AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and kainate bind to glutamate receptors, whereas oxotremorine binds to muscarinic acetylcholine receptors. **b** | SMA projections (blue) and pre-SMA projections (red) to the subthalamic nucleus (STN) show overlap as well as separation. **c** | Quantitative representation of differences between rostral and caudal cortico–cortical connections of area F6 (left) and area F3 (right). The thickness of the lines corresponds to quantitative estimates of the strength of the connection derived from REF. 34. Note that as rostral area F3 has more in common with caudal area F6 than it has in common with caudal area F3, there is no reason to think of the division between area F3 and area F6 as the decisive devision, at least on the grounds of cortico–cortical connectivity. Non-F-numbered regions refer to Brodmann's areas. ^{3}H, tritium; c, caudal; d, dorsal; IPL, inferior parietal lobule; PEci, posterior part of the cingulate sulcus; r, rostral; SPL, superior parietal lobule; STS, superior temporal sulcus; v, ventral. Part **a** reproduced, with permission, from REF. 122 © (1998) Wiley-Liss. Part **b** reproduced, with permission, from REF. 41 © (1999) Elsevier/North-Holland Biomedical Press.

arbitrary threshold above which activation is said to be significant, and this inevitably produces an artificially discretized picture. Integrating over tasks, as practised in imaging meta-analysis, however, reveals that there is both extensive variability and overlap in activations that have been reported to be associated with the SMA or the pre-SMA[124], with no distinct clustering into discrete subregions. Neither noise nor intersubject variability can be assumed to explain these findings — it could well be that the underlying distributions are continuous, just as monkey neurophysiology suggests.

Such considerations raise the possibility that, instead of discrete subregions, there might be a rostro–caudal continuum of graded change in structure and function, proceeding from the SMA through the SEF into the pre-SMA (see also REFS 3,14). This perspective of medial frontal regions echoes emerging concepts of gradients of function within lateral frontal areas, including motor and prefrontal cortices[125–130]. Indeed, some authors[127] argue that we need to move away from considering the cortex as a series of discrete modules arranged in hierarchies and instead focus on the fact that similar types of information tend to be processed in adjacent locations. Neurons within a cortical neighbourhood have clear similarities, but as one moves away there are no sharp borders to cross, just a smooth, graduated change in properties as one enters a different neighbourhood.

In sum, close examination of the data concerning the SMC suggests that either it does not support a discrete functional architecture or that no differentiation between a discrete and a continuous organization can be made. If either of these is correct, theories that depend on a modular account of the SMC, involving critical functional specialization at the subregion scale, need to be reappraised. Statements of the form 'the function of the pre-SMA is X, whereas that of the SMA is Y' must, in our view, be considered with caution. The scale of the critical functional organization seems to be much smaller, and we must look to conceptual models that adequately capture that fact.

Conditional complexity. One of the problems in trying to model the SMC is that a large array of highly disparate functions has been attributed to it, often with little concern about the nature of the mutual relations between such proposals. However, the functional pleomorphism that

Functional pleomorphism
The notion that a given area of the brain has different functions in different circumstances.

this view implies creates two difficulties. First, we would have to explain how the SMC is directed to perform one function or another in any situation. Invoking a supposedly 'higher' (for example, prefrontal) region that does this merely displaces the difficulty, as this region would also be functionally pleomorphic. Indeed, as there is no evidence for a region with the sole function of causing its subordinates to switch from one function to another, we are inevitably caught in a vicious regress. Second, we must consider whether the apparent plurality of functions is in fact merely a plurality of aspects of a single function: in essence, whether any one function is sufficient to explain all the data. Recent findings which demonstrate that the same neurons in the pre-SMA reflect both task switching and response inhibition (or indeed facilitation)[91] suggest that we might need to consider a unifying conceptual approach to the multiplicity of proposed functions.

Although currently there are no established models or theories of the SMC that capture the range of functions we have reviewed, we draw attention here to a recurring theme that emerges from our review of the existing data. Whether they use monkey neurophysiology, human brain imaging, TMS or lesion studies to investigate the SMC, most researchers would seem to agree that the more rostral end of the SMC — the pre-SMA — is more likely to be active in more-complex or more-'cognitive' situations than the more caudal end (the SMA), which seems to be more tightly related to actions, and that the SEF might lie somewhere between these extremes[3,6,7,14,24,49,73,113,131]. Actions performed in experimental situations can more formally be considered to be actions that are prompted by specific conditions. Simple condition–action associations involve the mapping of one condition to a single action, but more-complex situations are captured by far more-complicated mappings between conditions and the appropriate reaction to them. BOX 1 shows how conditional complexity can explain the differences between tasks that seem to be hierarchically related. In the next paragraphs, we consider how the complexity of condition–action associations might relate to some of the functions that have been associated with the SMC.

One or many functions? First, consider the claim that the SMC is concerned with 'self-initiated', internally driven action. Such an assertion rests on comparing circumstances in which the action is specified by the immediate external environment (for example: make response A if signal X comes on, and make response B if signal Y) with circumstances when it is not (for example: if signal Z comes on, then choose the action that you want to make out of the responses that are allowed)[49–52]. Unfortunately, this contrast is subject to an ineliminable confound: whereas one can control the externally observable complexity of a stimulus–response association — for example, by manipulating the number of sensory cues — it is impossible to control the complexity of the conditions on which an internally guided response is based. Whatever 'internal state' such conditions may be grounded in is likely to integrate associations over a long period of time (including memory of past choices): the complexity of condition–action associations dominated by internal conditions is therefore likely to be higher than in the external case.

Indeed, the most internal action of all — free choice — is perhaps among the most-complex actions, because the subject is given no criteria at all and the range of condition–action associations from which the action is chosen is therefore broadest[113]. Thus, a true free choice involves a huge set of possible responses, and the subject's action would potentially be weighted by many factors, including the reward outcomes of previous choices and the need to explore new actions. The condition–action association mapping is far more complex in such situations than it is when the subject is instructed to perform an action, free-choice tasks correspondingly preferentially activate the pre-SMA over the SMA[113].

We have also seen that the SMC is sensitive to many aspects of sequential action[62], suggesting a specific role for it in ordering individual movements in time. As it is the capacity for ordering a set of movements that seems to be key here, experimenters almost universally contrast different orderings of the same component actions or sensory cues. For example, the subject might be required to execute a series of button presses in a particular sequence, and then in another sequence to make the same movements but in a different order. It is therefore inevitable that overlapping condition–action associations will be established and that this will increase the complexity of the rule that is being instantiated in the action beyond mere ordering in a sequence. In sum, the experimenter's notion of 'sequential' here differs from 'non-sequential' in at least two important respects that have little to do with order: the number of functionally distinct responses that compete at any one point in a sequence, and the extent to which they are simultaneously primed (because of overlapping condition–action associations). Thus, complexity also emerges as a key issue here.

What about the involvement of the SMC in learning new tasks[73]? In fact, learning is only one of many differences between the execution of new and well-learnt actions. One basic difference is that in the former case the subject has a greater tendency to make movements other than those that are required for the optimal performance of the task. Thus, the next response to be made in a well-learnt sequence is well specified by the previous response; there is a simple response–response coding. By contrast, in the poorly learnt case the next response is not well encoded with respect to the previous one, so there is a wider range of action possibilities than in the well-learnt case. Another difference, one that is impossible to gauge precisely, is that the conditions on which the action is based differ in complexity. To understand why this is so, consider a monkey learning the association between a combination of visual cues and the action that is required to obtain a reward. At the beginning the monkey does not know what precise aspect of the environment — including visual, auditory and tactile stimuli — or of its own movement is critical to obtaining the reward. A 'correct' action in these circumstances will therefore initially be specified by several conditions, possibly including some that are irrelevant to the task.

For example, the monkey might think that an incidental sound or the pattern of a preceding movement is crucial, whereas in fact neither is. As the monkey learns the task, the condition–action association will narrow in scope, eliminating conditional features that are inessential to it. Thus, the condition–action association that governs the action in the case of a well-learnt task will admit a narrower range of possibilities than the association in the case of a poorly learnt task, and therefore the two associations will differ correspondingly in complexity.

Importantly, this account can explain why activity in 'learning-related' cells reappears during switching from one well-learnt action to another[73]. If such cells were truly concerned with learning, no such activity would be observed. Functional imaging also shows that making arbitrary associations between visual stimuli and responses is sufficient to account for pre-SMA activation during sequence learning[75]. Furthermore, subjects with SMC lesions did not fail to learn the task, they merely made more errors when the task was still poorly learnt[107,111]. This suggests that such subjects have a problem with executing actions when a task is not yet well learnt, rather than a problem with learning itself.

Finally we turn to the issue of cognitive control. The essential feature of all paradigms that are said to necessitate such control is the presence of conflict — the activation of more than one potential response plan. For conflict to occur there must be a degree of overlap between the conditions on which each of the conflicting actions is based: if there is no overlap there can be no conflict. Thus, in the Stroop task the conflict arises from overlap between responses that might be prompted by reading the word and those prompted by seeing the colour of the ink. The presence of such overlap inevitably increases the complexity of the condition–action association that guides the behaviour relative to a control condition in which no such overlap exists. This is because each stimulus must be disambiguated by another cue — for example, in the Stroop task, 'follow the colour, not the words' or, in countermanding, 'stop the movement that the go signal prompted you to execute'. That is to say, these examples are characterized by the presence of another conditional level. Conflict is therefore, by its very nature, associated with a higher order of complexity than non-conflict situations.

These observations on the existing data show how the varying interpretations that have been placed on SMC function can be related, in conceptual terms, to the complexity of their associated condition–action associations. Thus, internally generated actions are by their nature more complex than instructed ones, situations of conflict are associated with higher levels of complexity than non-conflict situations, and complexity of condition–action associations is also a key issue in the execution of sequences or learning. However, the problem with considering condition–action associations is that one could argue that making such associations is a function of many brain areas[132,133]. Indeed, rule-based behaviour is increasingly considered to be the province of several regions, including some in the frontal cortex and in the basal ganglia[2,125,132–134]. Thus, it will be important to establish what characteristics of conditional complexity, if any, are unique to the SMC. What is clear, however, is that all of the current theories of the region are undercut by a critical confound that offers a simpler and more general explanation for the data: the complexity of the condition–action associations.

Future directions

These considerations reveal just how complex the functional attributes of the SMC are. Although there is no doubt that we have learnt an enormous amount about this region, it is evident that much remains to be established about the precise contributions that it makes to cognition, action and conditions such as PD. It is clear that in the next few years we need to relate these processes to neighbouring cortical areas, as well as to the basal ganglia; viewing the function of the SMC in isolation will probably not help us to discover its specific contributions. Uncovering these presents a formidable — but potentially surmountable — challenge. A crucial aspect of future developments will be the rigor with which new conceptual frameworks can be evaluated, refined or rejected by empirical testing.

1. Tanji, J. & Shima, K. Supplementary motor cortex in organization of movement. *Eur. Neurol.* **36** (Suppl. 1), 13–19 (1996).
2. Passingham, R. E. *The Frontal Lobes and Voluntary Action* (Oxford Univ. Press, Oxford, 1995).
3. Picard, N. & Strick, P. L. Motor areas of the medial wall: a review of their location and functional activation. *Cereb. Cortex* **6**, 342–353 (1996). **This seminal review includes a meta-analysis which shows the relation between task complexity and the location of activation in the rostro–caudal plane.**
4. Rizzolatti, G. & Luppino, G. The cortical motor system. *Neuron* 31, 889–901 (2001).
5. Tehovnik, E. J., Sommer, M. A., Chou, I. H., Slocum, W. M. & Schiller, P. H. Eye fields in the frontal lobes of primates. *Brain Res. Rev.* **32**, 413–448 (2000).
6. Schall, J. D., Stuphorn, V. & Brown, J. W. Monitoring and control of action by the frontal lobes. *Neuron* **36**, 309–322 (2002).
7. Rushworth, M. F., Walton, M. E., Kennerley, S. W. & Bannerman, D. M. Action sets and decisions in the medial frontal cortex. *Trends Cogn. Sci.* **8**, 410–417 (2004).
8. Della Sala, S., Marchetti, C. & Spinnler, H. Right-sided anarchic (alien) hand: a longitudinal study. *Neuropsychologia* **29**, 1113–1127 (1991).
9. Feinberg, T. E., Schindler, R. J., Flanagan, N. G. & Haber, L. D. Two alien hand syndromes. *Neurology* **42**, 19–24 (1992).
10. Boccardi, E., Della Sala, S., Motto, C. & Spinnler, H. Utilisation behaviour consequent to bilateral SMA softening. *Cortex* **38**, 289–308 (2002).
11. Laplane, D., Talairach, J., Meininger, V., Bancaud, J. & Orgogozo, J. M. Clinical consequences of corticectomies involving the supplementary motor area in man. *J. Neurol. Sci.* **34**, 301–314 (1977).
12. Jahanshahi, M. *et al.* Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. *Brain* **118**, 913–933 (1995).
13. Hamada, M., Ugawa, Y. & Tsuji, S. High-frequency rTMS over the supplementary motor area for treatment of Parkinson's disease. *Mov. Disord.* **23**, 1524–1531 (2008).
14. Picard, N. & Strick, P. L. Imaging the premotor areas. *Curr. Opin. Neurobiol.* **11**, 663–672 (2001).
15. Grosbras, M. H., Lobel, E., Van de Moortele, P. F., LeBihan, D. & Berthoz, A. An anatomical landmark for the supplementary eye fields in human revealed with functional magnetic resonance imaging. *Cereb. Cortex* **9**, 705–711 (1999).
16. Yamamoto, J. *et al.* Human eye fields in the frontal lobe as studied by epicortical recording of movement-related cortical potentials. *Brain* **127**, 873–887 (2004).
17. Paus, T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nature Rev. Neurosci.* **2**, 417–424 (2001).
18. Vogt, C. & Vogt, O. *Allgemeine Ergebnisse unserer Hirnforschung* (Barth, 1919).
19. Matelli, M., Luppino, G. & Rizzolatti, G. Architecture of superior and mesial area 6 and the adjacent cingulate cortex in the macaque monkey. *J. Comp. Neurol.* **311**, 445–462 (1991).
20. Rizzolatti, G., Luppino, G. & Matelli, M. The organization of the cortical motor system: new concepts. *Electroencephalogr. Clin. Neurophysiol.* **106**, 283–296 (1998).
21. Schlag, J. & Schlag-Rey, M. Evidence for a supplementary eye field. *J. Neurophysiol.* **57**, 179–200 (1987).

22. Freund, H. J. Historical overview. *Adv. Neurol.* **70**, 17–27 (1996).
23. Fried, I. *et al.* Functional organization of human supplementary motor cortex studied by electrical stimulation. *J. Neurosci.* **11**, 3656–3666 (1991).
24. Matsuzaka, Y., Aizawa, H. & Tanji, J. A motor area rostral to the supplementary motor area (presupplementary motor area) in the monkey: neuronal activity during a learned motor task. *J. Neurophysiol.* **68**, 653–662 (1992).
25. Mitz, A. R. & Wise, S. P. The somatotopic organization of the supplementary motor area: intracortical microstimulation mapping. *J. Neurosci.* **7**, 1010–1021 (1987).
26. Luppino, G., Matelli, M., Camarda, R. M., Gallese, V. & Rizzolatti, G. Multiple representations of body movements in mesial area 6 and the adjacent cingulate cortex: an intracortical microstimulation study in the macaque monkey. *J. Comp. Neurol.* **311**, 463–482 (1991).
27. Martinez-Trujillo, J. C., Medendorp, W. P., Wang, H. & Crawford, J. D. Frames of reference for eye-head gaze commands in primate supplementary eye fields. *Neuron* **44**, 1057–1066 (2004).
28. Johansen-Berg, H. *et al.* Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. *Proc. Natl Acad. Sci. USA* **101**, 13335–13340 (2004).
29. He, S. Q., Dum, R. P. & Strick, P. L. Topographic organization of corticospinal projections from the frontal-lobe - motor areas on the medial surface of the hemisphere. *J. Neurosci.* **15**, 3284–3306 (1995).
30. Wise, S. P. Corticospinal efferents of the supplementary sensorimotor area in relation to the primary motor area. *Adv. Neurol.* **70**, 57–69 (1996).
31. Dum, R. P. & Strick, P. L. The origin of corticospinal projections from the premotor areas in the frontal lobe. *J. Neurosci.* **11**, 667–689 (1991).
32. Dum, R. P. & Strick, P. L. Spinal cord terminations of the medial wall motor areas in macaque monkeys. *J. Neurosci.* **16**, 6513–6525 (1996).
33. Luppino, G., Matelli, M., Camarda, R. & Rizzolatti, G. Corticospinal projections from mesial frontal and cingulate areas in the monkey. *Neuroreport* **5**, 2545–2548 (1994).
34. Luppino, G., Matelli, M., Camarda, R. & Rizzolatti, G. Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *J. Comp. Neurol.* **338**, 114–140 (1993).
35. Lu, M. T., Preston, J. B. & Strick, P. L. Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. *J. Comp. Neurol.* **341**, 375–392 (1994).
36. Wang, Y., Isoda, M., Matsuzaka, Y., Shima, K. & Tanji, J. Prefrontal cortical cells projecting to the supplementary eye field and presupplementary motor area in the monkey. *Neurosci. Res.* **53**, 1–7 (2005).
37. Takada, M. *et al.* Organization of prefrontal outflow toward frontal motor-related areas in macaque monkeys. *Eur. J. Neurosci.* **19**, 3328–3342 (2004).
38. Huerta, M. F. & Kaas, J. H. Supplementary eye field as defined by intracortical microstimulation - connections in macaques. *J. Comp. Neurol.* **293**, 299–330 (1990).
39. Luppino, G., Rozzi, S., Calzavara, R. & Matelli, M. Prefrontal and agranular cingulate projections to the dorsal premotor areas F2 and F7 in the macaque monkey. *Eur. J. Neurosci.* **17**, 559–578 (2003).
40. Akkal, D., Dum, R. P. & Strick, P. L. Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. *J. Neurosci.* **27**, 10659–10673 (2007).
41. Inase, M., Tokuno, H., Nambu, A., Akazawa, T. & Takada, M. Corticostriatal and corticosubthalamic input zones from the presupplementary motor area in the macaque monkey: comparison with the input zones from the supplementary motor area. *Brain Res.* **833**, 191–201 (1999).
42. Parthasarathy, H. B., Schall, J. D. & Graybiel, A. M. Distributed but convergent ordering of corticostriatal projections: analysis of the frontal eye field and the supplementary eye field in the macaque monkey. *J. Neurosci.* **12**, 4468–4488 (1992).
43. Nambu, A., Takada, M., Inase, M. & Tokuno, H. Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. *J. Neurosci.* **16**, 2671–2683 (1996).
44. Frank, M. J., Samanta, J., Moustafa, A. A. & Sherman, S. J. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. *Science* **318**, 1309–1312 (2007).
45. Brinkman, C. & Porter, R. Supplementary motor area in the monkey: activity of neurons during performance of a learned motor task. *J. Neurophysiol.* **42**, 681–709 (1979).
46. Tanji, J. & Kurata, K. Comparison of movement-related activity in two cortical motor areas of primates. *J. Neurophysiol.* **48**, 633–653 (1982).
47. Deecke, L. & Kornhuber, H. H. An electrical sign of participation of the mesial 'supplementary' motor cortex in human voluntary finger movement. *Brain Res.* **159**, 473–476 (1978).
48. Goldberg, G. Supplementary motor area structure and function - review and hypotheses. *Behav. Brain Sci.* **8**, 567–588 (1985).
49. Nachev, P., Rees, G., Parton, A., Kennard, C. & Husain, M. Volition and conflict in human medial frontal cortex. *Curr. Biol.* **15**, 122–128 (2005).
50. Jenkins, I. H., Jahanshahi, M., Jueptner, M., Passingham, R. E. & Brooks, D. J. Self-initiated versus externally triggered movements. II. The effect of movement predictability on regional cerebral blood flow. *Brain* **123**, 1216–1228 (2000).
51. Deiber, M. P., Honda, M., Ibanez, V., Sadato, N. & Hallett, M. Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: effect of movement type and rate. *J. Neurophysiol.* **81**, 3065–3077 (1999).
52. Deiber, M. P. *et al.* Cortical areas and the selection of movement: a study with positron emission tomography. *Exp. Brain Res.* **84**, 393–402 (1991).
53. Lau, H. C., Rogers, R. D., Haggard, P. & Passingham, R. E. Attention to intention. *Science* **303**, 1208–1210 (2004).
54. Cunnington, R., Windischberger, C., Deecke, L. & Moser, E. The preparation and execution of self-initiated and externally-triggered movement: a study of event-related fMRI. *Neuroimage* **15**, 373–385 (2002).
55. Grezes, J. & Decety, J. Does visual perception of object afford action? Evidence from a neuroimaging study. *Neuropsychologia* **40**, 212–222 (2002).
56. Sumner, P. *et al.* Human medial frontal cortex mediates unconscious inhibition of voluntary action. *Neuron* **54**, 697–711 (2007).
Unusully focal lesion evidence of involvement of the SMC in a wholly unconscious process related to voluntary action. The data undermine the notion that the SMC has a key role in 'volition'.
57. Romo, R. & Schultz, W. Neuronal activity preceding self-initiated or externally timed arm movements in area 6 of monkey cortex. *Exp. Brain Res.* **67**, 656–662 (1987).
58. Kurata, K. & Wise, S. P. Premotor and supplementary motor cortex in rhesus monkeys: neuronal activity during externally- and internally-instructed motor tasks. *Exp. Brain Res.* **72**, 237–248 (1988).
59. Tanji, J. & Kurata, K. Contrasting neuronal activity in supplementary and precentral motor cortex of monkeys. I. Responses to instructions determining motor responses to forthcoming signals of different modalities. *J. Neurophysiol.* **53**, 129–141 (1985).
60. Schall, J. D. Neuronal activity related to visually guided saccadic eye movements in the supplementary motor area of rhesus monkeys. *J. Neurophysiol.* **66**, 530–558 (1991).
61. Kurata, K. & Tanji, J. Contrasting neuronal activity in supplementary and precentral motor cortex of monkeys. II. Responses to movement triggering vs. nontriggering sensory signals. *J. Neurophysiol.* **53**, 142–152 (1985).
62. Tanji, J. Sequential organization of multiple movements: involvement of cortical motor areas. *Annu. Rev. Neurosci.* **24**, 631–651 (2001).
63. Tanji, J. & Shima, K. Role for supplementary motor area cells in planning several movements ahead. *Nature* **371**, 413–416 (1994).
This study provided the first neurophysiological evidence that sequential movements are coded in the SMC.
64. Shima, K. & Tanji, J. Neuronal activity in the supplementary and presupplementary motor areas for temporal organization of multiple movements. *J. Neurophysiol.* **84**, 2148–2160 (2000).
65. Clower, W. T. & Alexander, G. E. Movement sequence-related activity reflecting numerical order of components in supplementary and presupplementary motor areas. *J. Neurophysiol.* **80**, 1562–1566 (1998).
66. Shima, K., Mushiake, H., Saito, N. & Tanji, J. Role for cells in the presupplementary motor area in updating motor plans. *Proc. Natl Acad. Sci. USA* **93**, 8694–8698 (1996).
67. Sohn, J. W. & Lee, D. Order-dependent modulation of directional signals in the supplementary and presupplementary motor areas. *J. Neurosci.* **27**, 13655–13666 (2007).
68. Lu, X., Matsuzawa, M. & Hikosaka, O. A neural correlate of oculomotor sequences in supplementary eye field. *Neuron* **34**, 317–325 (2002).
69. Shima, K. & Tanji, J. Binary-coded monitoring of a behavioral sequence by cells in the pre-supplementary motor area. *J. Neurosci.* **26**, 2579–2582 (2006).
70. Roland, P. E., Larsen, B., Lassen, N. A. & Skinhoj, E. Supplementary motor area and other cortical areas in organization of voluntary movements in man. *J. Neurophysiol.* **43**, 118–136 (1980).
71. Chen, L. L. & Wise, S. P. Supplementary eye field contrasted with the frontal eye field during acquisition of conditional oculomotor associations. *J. Neurophysiol.* **73**, 1122–1134 (1995).
72. Chen, L. L. & Wise, S. P. Evolution of directional preferences in the supplementary eye field during acquisition of conditional oculomotor associations. *J. Neurosci.* **16**, 3067–3081 (1996).
73. Nakamura, K., Sakai, K. & Hikosaka, O. Neuronal activity in medial frontal cortex during learning of sequential procedures. *J. Neurophysiol.* **80**, 2671–2687 (1998).
A landmark neurophysiological study of the effects of disrupting the SMC on the learning of sequential tasks.
74. Hikosaka, O. *et al.* Activation of human presupplementary motor area in learning of sequential procedures: a functional MRI study. *J. Neurophysiol.* **76**, 617–621 (1996).
75. Sakai, K. *et al.* Presupplementary motor area activation during sequence learning reflects visuo-motor association. *J. Neurosci.* **19**, RC1 (1999).
76. Garraux, G., Peigneux, P., Carson, R. E. & Hallett, M. Task-related interaction between basal ganglia and cortical dopamine release. *J. Neurosci.* **27**, 14434–14441 (2007).
77. Miller, E. K. The prefrontal cortex and cognitive control. *Nature Rev. Neurosci.* **1**, 59–65 (2000).
78. Gilbert, S. J. & Burgess, P. W. Executive function. *Curr. Biol.* **18**, R110–R114 (2008).
79. Matsuzaka, Y. & Tanji, J. Changing directions of forthcoming arm movements: neuronal activity in the presupplementary and supplementary motor area of monkey cerebral cortex. *J. Neurophysiol.* **76**, 2327–2342 (1996).
An elegant demonstration of rostro–caudal population differences in cells concerned with switching between movements.
80. Li, C. S., Huang, C., Constable, R. T. & Sinha, R. Imaging response inhibition in a stop-signal task: neural correlates independent of signal monitoring and post-response processing. *J. Neurosci.* **26**, 186–192 (2006).
81. Curtis, C. E., Cole, M. W., Rao, V. Y. & D'Esposito, M. Canceling planned action: an fMRI study of countermanding saccades. *Cereb. Cortex* **15**, 1281–1289 (2005).
82. Aron, A. R. & Poldrack, R. A. Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. *J. Neurosci.* **26**, 2424–2433 (2006).
83. Wager, T. D., Jonides, J. & Reading, S. Neuroimaging studies of shifting attention: a meta-analysis. *Neuroimage* **22**, 1679–1693 (2004).
84. Crone, E. A., Wendelken, C., Donohue, S. E. & Bunge, S. A. Neural evidence for dissociable components of task-switching. *Cereb. Cortex* **16**, 475–486 (2006).
85. Rushworth, M. F., Hadland, K. A., Paus, T. & Sipila, P. K. Role of the human medial frontal cortex in task switching: a combined fMRI and TMS study. *J. Neurophysiol.* **87**, 2577–2592 (2002).
This seminal study of task switching combined TMS with fMRI to show a dissociation between rostral and caudal regions of the SMC.
86. Brass, M. & von Cramon, D. Y. The role of the frontal cortex in task preparation. *Cereb. Cortex* **12**, 908–914 (2002).
87. Garavan, H., Ross, T. J., Kaufman, J. & Stein, E. A. A midline dissociation between error-processing and response-conflict monitoring. *Neuroimage* **20**, 1132–1139 (2003).

88. Simmonds, D. J., Pekar, J. J. & Mostofsky, S. H. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia* **46**, 224–232 (2008).
89. Stuphorn, V., Taylor, T. L. & Schall, J. D. Performance monitoring by the supplementary eye field. *Nature* **408**, 857–860 (2000).
90. Stuphorn, V. & Schall, J. D. Executive control of countermanding saccades by the supplementary eye field. *Nature Neurosci.* **9**, 925–931 (2006).
This paper provided evidence that microstimulation of the SEF modulates saccade countermanding performance.
91. Isoda, M. & Hikosaka, O. Switching from automatic to controlled action by monkey medial frontal cortex. *Nature Neurosci.* **10**, 240–248 (2007).
Compelling evidence, from single-cell recordings combined with microstimulation, that the preSMA is involved in tasks that require switching between simple visuo-motor assocations.
92. Botvinick, M. M., Cohen, J. D. & Carter, C. S. Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn. Sci.* **8**, 539–546 (2004).
93. Ridderinkhof, K. R., Ullsperger, M., Crone, E. A. & Nieuwenhuis, S. The role of the medial frontal cortex in cognitive control. *Science* **306**, 443–447 (2004).
94. Ullsperger, M. & von Cramon, D. Y. Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage* **14**, 1387–1401 (2001).
95. Rushworth, M. F. S., Croxson, P. L., Buckley, M. J. & Walton, M. E. in *Neuroscience of Rule-Guided Behavior* (eds Bunge, S. A. & Wallis, J. D.) 129–157 (Oxford Univ. Press, Oxford, 2008).
96. Ito, S., Stuphorn, V., Brown, J. W. & Schall, J. D. Performance monitoring by the anterior cingulate cortex during saccade countermanding. *Science* **302**, 120–122 (2003).
97. Emeric, E. E. *et al.* Performance monitoring local field potentials in the medial frontal cortex of primates: anterior cingulate cortex. *J. Neurophysiol.* **99**, 759–772 (2008).
98. Nakamura, K., Roesch, M. R. & Olson, C. R. Neuronal activity in macaque SEF and ACC during performance of tasks involving conflict. *J. Neurophysiol.* **93**, 884–908 (2004).
A meticulous neurophysiological study that elegantly showed the absence of any single-cell activity in the dorsal cingulate cortex or in the SEF indicating "conflict monitoring" or task-nonspecific "conflict resolution".
99. Krainik, A. *et al.* Role of the supplementary motor area in motor deficit following medial frontal lobe surgery. *Neurology* **57**, 871–878 (2001).
100. Brinkman, C. Supplementary motor area of the monkey's cerebral cortex: short- and long-term deficits after unilateral ablation and the effects of subsequent callosal section. *J. Neurosci.* **4**, 918–929 (1984).
101. Della Sala, S., Francescani, A. & Spinnler, H. Gait apraxia after bilateral supplementary motor area lesion. *J. Neurol. Neurosurg. Psychiatry* **72**, 77–85 (2002).
102. Travis, A. M. Neurological deficiencies following supplementary motor area lesions in *Macaca mulatta*. *Brain* **78**, 174–198 (1955).
103. Schiller, P. H. & Chou, I. The effects of frontal eye field and dorsomedial frontal cortex lesions on visually guided eye movements. *Nature Neurosci.* **1**, 248–253 (1998).
104. Thaler, D., Chen, Y. C., Nixon, P. D., Stern, C. E. & Passingham, R. E. The functions of the medial premotor cortex. I. Simple learned movements. *Exp. Brain Res.* **102**, 445–460 (1995).
105. Tanji, J., Kurata, K. & Okano, K. The effect of cooling of the supplementary motor cortex and adjacent cortical areas. *Exp. Brain Res.* **60**, 423–426 (1985).
A fascinating — and prescient — neurophysiological study that used a novel method of disrupting activity in the SMC, in combination with a sophisticated behavioural paradigm involving go/no go with S–R reversal.
106. Shima, K. & Tanji, J. Both supplementary and presupplementary motor areas are crucial for the temporal organization of multiple movements. *J. Neurophysiol.* **80**, 3247–3260 (1998).
This paper provided the first evidence that disrupting the SMC interferes with sequences of movements but not with simpler, single movements.
107. Nakamura, K., Sakai, K. & Hikosaka, O. Effects of local inactivation of monkey medial frontal cortex in learning of sequential procedures. *J. Neurophysiol.* **82**, 1063–1068 (1999).
108. Halsband, U., Ito, N., Tanji, J. & Freund, H. J. The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain* **116**, 243–266 (1993).
109. Gaymard, B., Rivaud, S. & Pierrot-Deseilligny, C. Role of the left and right supplementary motor areas in memory-guided saccade sequences. *Ann. Neurol.* **34**, 404–406 (1993).
110. Husain, M., Parton, A., Hodgson, T. L., Mort, D. & Rees, G. Self-control during response conflict by human supplementary eye field. *Nature Neurosci.* **6**, 117–118 (2003).
111. Parton, A. *et al.* Role of the human supplementary eye field in the control of saccadic eye movements. *Neuropsychologia* **45**, 997–1008 (2007).
112. Hodgson, T. L., Dittrich, W. H., Henderson, L. & Kennard, C. Eye movements and spatial working memory in Parkinson's disease. *Neuropsychologia* **37**, 927–938 (1999).
113. Nachev, P., Wydell, H., O'Neill, K., Husain, M. & Kennard, C. The role of the pre-supplementary motor area in the control of action. *Neuroimage* **36**, T155–T163 (2007).
114. Floden, D. & Stuss, D. T. Inhibitory control is slowed in patients with right superior medial frontal damage. *J. Cogn. Neurosci.* **18**, 1843–1849 (2006).
115. Taylor, P. C., Nobre, A. C. & Rushworth, M. F. Subsecond changes in top–down control exerted by human medial frontal cortex during conflict and action selection: a combined transcranial magnetic stimulation–electroencephalography study. *J. Neurosci.* **27**, 11343–11353 (2007).
116. Grafton, S. T. Contributions of functional imaging to understanding parkinsonian symptoms. *Curr. Opin. Neurobiol.* **14**, 715–719 (2004).
117. Playford, E. D. *et al.* Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. *Ann. Neurol.* **32**, 151–161 (1992).
118. Haslinger, B. *et al.* Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. *Brain* **124**, 558–570 (2001).
119. Grafton, S. T. *et al.* Normalizing motor-related brain activity: subthalamic nucleus stimulation in Parkinson disease. *Neurology* **66**, 1192–1199 (2006).
120. MacDonald, V. & Halliday, G. M. Selective loss of pyramidal neurons in the pre-supplementary motor cortex in Parkinson's disease. *Mov. Disord.* **17**, 1166–1173 (2002).
121. Cools, R., Barker, R. A., Sahakian, B. J. & Robbins, T. W. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia* **41**, 1431–1441 (2003).
122. Geyer, S. *et al.* Receptor autoradiographic mapping of the mesial motor and premotor cortex of the macaque monkey. *J. Comp. Neurol.* **397**, 231–250 (1998).
A map of the mesial cortex that was based on neurotransmitter binding data, and showed an absence of sharp demarcations between sub-areas of the SMC and evidence of a rostro–caudal gradient of change.
123. Fujii, N., Mushiake, H. & Tanji, J. Distribution of eye- and arm-movement-related neuronal activity in the SEF and in the SMA and Pre-SMA of monkeys. *J. Neurophysiol.* **87**, 2158–2166 (2002).
124. Mayka, M. A., Corcos, D. M., Leurgans, S. E. & Vaillancourt, D. E. Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. *Neuroimage* **31**, 1453–1474 (2006).
125. Petrides, M. in *From Monkey Brain to Human Brain. A Fyssen Foundation Symposium.* (eds Dehaene, S., Duhamel, J.-R., Hauser, M. & Rizzolatti, G.) 293–314 (MIT Press, Cambridge, Massachusetts, 2005).
126. Graziano, M. S. & Aflalo, T. N. Mapping behavioral repertoire onto the cortex. *Neuron* **56**, 239–251 (2007).
127. Graziano, M. S. & Aflalo, T. N. Rethinking cortical organization: moving away from discrete areas arranged in hierarchies. *Neuroscientist* **13**, 138–147 (2007).
128. Badre, D. Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends Cogn. Sci.* **12**, 193–200 (2008).
129. Koechlin, E. & Summerfield, C. An information theoretical approach to prefrontal executive function. *Trends Cogn. Sci.* **11**, 229–235 (2007).
130. Hoshi, E. & Tanji, J. Differential involvement of neurons in the dorsal and ventral premotor cortex during processing of visual signals for action planning. *J. Neurophysiol.* **95**, 3596–3616 (2006).
131. Tanji, J. New concepts of the supplementary motor area. *Curr. Opin. Neurobiol.* **6**, 782–787 (1996).
132. Wise, S. P. & Murray, E. A. Arbitrary associations between antecedents and actions. *Trends Neurosci.* **23**, 271–276 (2000).
133. Murray, E. A., Bussey, T. J. & Wise, S. P. Role of prefrontal cortex in a network for arbitrary visuomotor mapping. *Exp. Brain Res.* **133**, 114–129 (2000).
134. Bunge, S. A. & Wallis, J. D. *Neuroscience of Rule-Guided Behavior* (Oxford Univ. Press, Oxford, 2008).
135. Van Essen, D. C. *et al.* An integrated software suite for surface-based analyses of cerebral cortex. *J. Am. Med. Inform. Assoc.* **8**, 443–459 (2001).
136. Kornhuber, H. H. & Deecke, L. Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente Potentiale. *Pflügers Arch.* **284**, 1–17 (1965).
137. Wickelgren, I. Monkey see, monkey think about doing. *Science* **305**, 162–163 (2004).

Acknowledgements
This work was supported by the Wellcome Trust (Programme Grant WT073735AIA), the National Institute for Health Research Clinical Biomedical Research Centre at University College London/University College London Hospital and Imperial College Healthcare National Health Service Trust.

DATABASES
OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
PD

FURTHER INFORMATION
Masud Husain's homepage: www.icn.ucl.ac.uk/husainlab
Caret: http://brainmap.wustl.edu/caret
Montreal Neurological Institute: http://www.mni.mcgill.ca/

SUPPLEMENTARY INFORMATION
See online article: S1 (figure) | S2 (figure)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF