Cortical control and performance monitoring of interrupting and redirecting movements

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Voluntary behaviour requires control mechanisms that ensure our ability to act independently of habitual and innate response tendencies. Electrophysiological experiments, using the stop-signal task in humans, monkeys and rats, have uncovered a core network of brain structures that is essential for response inhibition. This network is shared across mammals and seems to be conserved throughout their evolution. Recently, new research building on these earlier findings has started to investigate the interaction between response inhibition and other control mechanisms in the brain. Here we describe recent progress in three different areas: selectivity of movement inhibition across different motor systems, re-orientation of motor actions and action evaluation.

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1. The cortical networks for interrupting eye and limb movements

The specificity of control for the eye compared with other skeletal movements has been and still is a subject of debate. Theoretically, both eyes and skeletal movements have been described as relying on common code or signal for execution, but on different and/or independent processes for inhibition [1]. Experimentally, the neuronal activity recorded by electromyograms (EMGs) reveals similar activation prior to movement execution. However, while partial EMG activation remains present when subjects successfully withhold limb movement responses, no such significant activation is detected when saccades are inhibited (see fig. 1 from [2]). By themselves, these observations have confirmed and highlighted similarities, but also potential important differences, between the control of the spinal motor and the saccade systems when studying inhibition of movements (figure 1).

(a) Selectivity of movement inhibition

Whether any suppressions of movement inhibition exert a global inhibitory effect on other motor systems is still not totally known. Several research studies, using stop tasks for limb movements (hand, leg) as well as orofacial movements (speech), have shown that in certain contexts rapidly stopping actions can lead to global suppression of various motor systems [3–5]. Some of these conclusions have been reached by recording corticospinal excitability (CSE) indices in studies with transcranial magnetic stimulation (TMS), but also event related potentials (ERPs) during tasks combining the recording of one targeted and one unrelated effector. Similar global inhibition effects were also described when CSE was measured from the hand while participants successfully stopped their eye movement compared...
with unsuccessful movement inhibition. More precisely, the results have shown that around 50 ms before the estimated time at which a saccade is successfully stopped the CSE of other skeleton effectors was reduced even if those effectors were task irrelevant. Together, these results were interpreted as showing that rapidly stopping eye movements exerts a global motor inhibitory effect [6].

Beyond these observations, other studies rendered this feature of partial selectivity of the inhibitory process more complex than previously thought. Recent works have shown that inhibition of bilateral index finger extension or thumb abduction supports a model of inhibition of a unitary response and selective re-initiation, rather than selective inhibition [7]. These studies indicated that successful performance in the selective condition occurred via suppression of the entire prepared response and subsequent selective re-initiation of the remaining component. Importantly, the delayed re-initiation of motor output was sensitive to the degree of similarity between responses, occurring later but at a faster rate with similar digits with homologous muscles. Furthermore, there were persistent after effects from the selective condition on the motor system, which suggested greater levels of inhibition and a higher gain was necessary to successfully perform selective trials with homogeneous pairings [7]. In the same vein, using a bimanual (with the two index fingers or the two middle fingers) inhibition task in which one of the two finger responses should be withheld, gave results indicating that a given response was slower when the response on the other hand was stopped compared with the no-stop condition. In addition, the given response was also made more forcefully, indicating that the requirement to stop one activated response was contaminated by the irrelevant inhibition [8]. Also contradicting or moderating the view of necessary broad contamination owing to inhibition activity over a large spectrum of motor effectors, some studies have shown evidence for possible selectivity of the inhibition processes [9]. In particular, when subjects were asked to detect suppression in the leg when the hand is being stopped, some results indicated that if subjects prepared to stop, then they were capable of doing so without global effects on the motor system. Thus, with sufficient preparation time, human subjects appear to able to stop more selectively one or the other of the motor effectors [3–5,9]. Some few studies go even beyond a modest selective effect by indicating that with a limited amount of training and highly compatible stimulus–response mappings, people can successfully perform a selective-stop task without any cost on the non-aborted component. Other recent studies also suggest that when participants used a global inhibition mechanism (acting alone), the selectivity is poorly active; however, participants can recruit a more selective and slower suppression mechanism when acting in a social or multiple actors environment [10]. These results demonstrate that under certain constraints, inhibition can be selectively controlled and present a challenge for models of inhibitory control that posit the operation of generic processes [11]. However, and as discussed in §2, all these results also suggest that a common interrupting signal may also be at play for reach movements, at least when saccadic eye movements co-occur and are strongly correlated in their reaction times. In the presence of weak eye–hand correlations, eye and hand control may thus become more specific. Anatomically, these abilities to produce a global selective inhibition have been described in association with some basic anatomical constraints attributed to the recruitment of cortico-basal ganglia pathways that allow the rapid inhibition of action but operate in a relatively generic manner. The refined and selective inhibition pathways have been less studied.

(b) Anatomical network supporting inhibition of movements

What are the potential sources for cortical top-down signals capable of globally or selectively interrupting a movement? Anatomically, it has been proposed that the global inhibition may arise, because rapidly stopping movements are achieved via input to the subthalamic nucleus of the basal ganglia, with a putatively broad suppressive effect on thalamocortical drive. Within these anatomical constraints, an abrupt-onset stimulus is going to interrupt any ongoing processes by generating global inhibitory motor and non-motor effects [6]. In addition, to act on a more specific and selective inhibition process, a slower frontostriatal network activity is capable of generating activity for finely tuned control of action. Experimentally, to examine the dynamic role of each of these cortical and subcortical areas in the inhibition processes, the countermanding paradigm still provides a clear criterion for determining whether a given neuronal activity generates signals sufficient to control the production of movements [12]. In neurophysiological practice, the key test is whether the activity of neurons is different between trials with a movement (no-stop-signal or non-cancelled trials) and trials with no movement (cancelled trials) and, critically, whether such a difference occurs before the stop-signal reaction time (SSRT). If some neural modulation occurs after SSRT, then according to the race model that identifies SSRT with the time of inhibition of the movement, then the modulation is too late to contribute to controlling response initiation [13,14]. Specifically, if a neural signal is to be sufficient to control movement, then a significant difference in the activity in cancelled trials versus the activity on no-stop trials must occur before SSRT. Within the frontal cortex, the supplementary motor area (SMA) and pre-SMA are widely considered to be of central importance for control ability because of their role in movement initiation and inhibition. A large majority, if not all, movement-related neurons in SMA and pre-SMA failed to exhibit time-locked
activity changes predictive of movement initiation in the context of the countermanding task. Similarly, a few inhibitory cells responded early enough to be able to influence the cancellation of the movement. Together, these studies have suggested that the movement-related activity in pre-SMA and SMA might be representing the motivation for a specific action but not whether or not that action is performed [15]. Many supplementary eye field (SEF) neurons are active during the preparation and execution of saccades, in the saccade stop-signal task; however, these neurons with apparent movement-related activity fail to produce signals sufficient to control gaze [16]. In the same vein, previous work has reported that subthreshold microstimulation of the SEF improves stop-signal task performance in monkeys by delaying saccade initiation [17]. These results provide a useful perspective on a recent hypothesis that identifies the stopping process with a circuit between the SMA, the inferior frontal gyrus and the subthalamic nucleus [18,19]. In fact, damage to the inferior frontal gyrus impairs inhibition in stop-signal trials of a countermanding task [20,21].

Most recent research in rodents or primates suggests that the success in countermanding a movement is achieved via a hyper-direct pathway from frontal areas to the subthalamic nucleus (STN) of the basal ganglia, which then activates the internal globus pallidus (GPI) and suppresses thalamocortical drive. Recent subparcellated regions of STN have also been confirmed in humans using a driven method with diffusion-weighted imaging (figure 2). The broad skeletonmotor suppression that occurs for outright stoppage could reflect the putative divergent innervation of the GPI by the STN, for which there is some evidence from neuronal tracing studies [22,23]. The engagement of this mechanism may also explain the broad skeletonmotor suppression that occurs after surprise or even cognition via the same brain mechanism [24]. One possibility is that the STN-mediated impact on GPI is so divergent as to also interrupt cognitive information that is putatively maintained in the ‘associative’ corticobasal ganglia loops. Contradictory evidence of STN being a unique node for activation to directly stop action has also been published. Recent neurophysiological studies have demonstrated that in the context of the countermanding task, STN neurons respond to the stop signal equally on both cancelled and non-cancelled trials [25,26]. Furthermore, greater activation within these corticobasal loops, outside STN, in regions including frontal eye fields and SEFs, and the striatum has also been observed during correctly executed redirect trials, a paradigm in which the target location jumps to different places while the subject is producing its movement towards it [27].

These results obtained with re-orienting paradigms will be discussed in detail in §2.

2. Cortical networks for re-orienting eye and limb movements

Although online inhibitory control is most often studied with the countermanding task, a more common behaviour that involves online control is one that entails changing motor plans in dynamic environments. In this context, the double-step task has been successfully used to probe the ability to modify saccade plans [28,29] and reach movements [30–32]. In this task, on some random fraction of trials a second final target appears in another location from the initial target (figure 3a,b). Subjects have to modify the saccade/reach plans to the initial target to make another plan to the new target. Analogously to the non-cancelled trials, in some trials subjects are unable to modify the saccade/reach plan to the initial target, leading to an erroneous response. The probability of error, which is an index of the ability to modify the initial response, increases with the delay in the appearance of the new stimulus, and describes the compensation performance of the subject; it is analogous to the inhibition function observed in the countermanding task.

(a) Race model approach to studying changing plans

Theoretically, the simplest model that can account for performance in a redirect task involves the use of two independent integrators—two GO-accumulators—GO1 and GO2, which represent saccade preparation to initiate an action following the onset of the initial and final target, respectively [28,30]. However, GO–GO models fail to explain the compensation function in the redirect task [34] in the context of switching saccade between plans. This is because such a model does not allow for the cancellation of saccade preparation to the first target and therefore the proportion of error trials is much more than expected. GO–GO models also predict the existence of averaging or midway saccades, that are not typically observed in the proportion expected based on the reaction time distributions of no-step trials [35]. Instead, a larger fraction of averaged saccades display prominent undershoot (hypometry) [36,37], suggesting the presence of a STOP signal, analogous to the countermanding signal [38]. In addition, recent modelling work suggests the presence of a dedicated fast-stop unit for fast action cancellation [39].

Although the control of reach plans has not been studied in the race model framework as have saccades, an implicit...
GO-GO model continues to be the dominant framework used to understand how reach plans can switch in real time [40,41]. The basis for this position appears to be the absence of a clear refractory period in terms of the reaction time of the second movement together with the observation of a gradual change in the reach trajectory and in the EMG responses. In addition, and rather surprisingly, there have been no studies testing alternative hypotheses concerning the architecture underlying switching reach plans in the framework of the race model as has been done in the context of saccades [34,35,42] or button presses [14]. Therefore, it remains unresolved at this point whether there are fundamentally different algorithms and neural mechanisms being used in eye versus hand switching.

One difference is that hand movements are slow and sensory feedback is a prominent aspect of motor control, unlike saccades that are driven predominantly by feed-forward mechanisms. This notwithstanding, most of our ethologically valid reaching behaviours do not occur in isolation but co-occur with saccadic eye movements whose reaction times are highly coordinated [31,32]. Thus, in corresponding dynamic environments, it seems natural to think that the control of eye and hand movements should invoke similar mechanisms. This hypothesis was tested in a recent study by Gopal et al. [43], who found that performance curves were distinct for the eye and hand when these movements were executed in isolation, but were comparable when they were executed together. Second, the time to switch motor plans, called the target-step reaction time (TSRT) and analogous to the SSRT, was different in the eye-alone and hand-alone conditions, but was similar in the coordinated condition under the assumption of a ballistic stage of 40 ms, on average. Interestingly, the duration of this ballistic stage could predict the extent of eye–hand dissociations seen in individual subjects. Finally, when subjects were explicitly instructed to control specifically a single effector (eye or hand), redirecting one effector had a strong effect on the performance of the other effector. These results suggest that a common STOP signal similar to the countermanding task may also be at play for reach movements, at least when saccadic eye movements co-occur, and strongly correlated in their reaction times. In the presence of weak eye–hand correlations, however, it appears that eye and hand control may be distinct [1,13,44], suggesting the need for flexible circuits to instantiate such specific behaviours.

(b) Neurophysiology of changing plans
Although the original motivation of the behavioural studies in the double-step saccade task was to understand the mechanisms underlying switching saccade plans [45–47], interestingly, most neurophysiological investigations using the same task have been largely driven to understand different aspects of oculomotor programming, such as coordinate transformations [48–50] or the adaptive properties of the oculomotor system [51]. However, such neurophysiological investigations, using the double-step task within the framework of race models, are critical to understanding the neural mechanisms of interrupting and changing plans for three important reasons. First, what are the sources of the signals that interrupt movements? Do they reflect the same circuits that control the initiation of movements or do they reflect distinct signals from different brain regions dedicated to inhibitory control or a combination of both? Second, we need to understand the nature of the specific representations that are subject to the interruption. Are these representations of goals that reflect the outcome of visual selection, or are these representations of movement planning, or a combination of both? Given the similarity of the architectures responsible for countermanding and redirecting, it is likely that the neural basis of countermanding discussed in §2a is similar to redirection as well. Indeed, in a recent study involving search step and double step, Murthy et al. [33] showed that movement-related activity in FEF, in contrast to visual neurons, reflected more robustly the effect of inhibitory signals, similar to that which Hanes et al. [12] described for saccade countermanding. Likewise, cells in the LIP that send feed-forward projections to the FEF show little evidence of inhibitory control [52], whereas it is robustly expressed in the movement-related cells in the superior colliculus [53]. Interestingly, a similar differential expression of inhibitory control is seen among cortical cells involved in the online change of reach plans. Here, premotor cortical cells have been shown to most

Figure 3. Movement (a) and visual activity (b) during target-step trials in the double-step task in which the target stepped out of the receptive field. Compensated target-step trials (red solid) and latency-matched no-step trials (black). While movement-related activity showed countermanding (cancellation) of a partially prepared motor plan before the target-step reaction time (TSRT), visual cells did not. (Adapted from [33])

(a)

(b)
robustly express the change in motor plans before cells in the primary motor cortex as well as the parietal cortex [54] (see also [55]). Taken together, these results suggest that inhibitory signals target movement-related representations to rapidly and actively interrupt movement planning, while visually related signals continuously reflect the changing goal in a more passive manner, whereas other sensory signals, particularly in parietal cortex, play a more direct role in generating corrective movements [56,57]. In the context of switching motor plans, such a strategy allows for effective stopping, yet gives adequate time for the selection of a new accurate goal representation. This strategy effectively allows for fast and brief stopping without compromising the accuracy of the new action. Additionally, the absence of a refractory period seen in single cells coding for reach/saccade plans, as well as behaviourally in the reaction times of the compensated response [30,58], is likely to reflect an inhibitory process that is spatially selective in nature [34].

3. Cortical networks for monitoring eye movements

As described in §2, response interruption or re-orientation requires continuous monitoring of ongoing behaviour, its consequences and the environmental context, to detect situations when response inhibition is necessary. Neurons in the medial frontal cortex have long been known to carry signals related to response evaluation. SEF neurons respond to the anticipation and delivery of reward [59,60], as well as to errors and response conflict [60,61]. Similar signals reflecting positive and negative evaluations of actions have been found in the anterior cingulate cortex (ACC) [62,63]. These same cortical areas also contain neurons that participate in the control and selection of motor behaviour [17,64]. This indicates that medial frontal cortex might be an important node in the neural circuit underlying monitoring and control of behaviour. However, many aspects of this circuit and its role in behaviour are not yet well understood. In particular, it is not clear what the origin of the monitoring signals is. Furthermore, it is debated whether the role of medial frontal cortex is exclusively evaluative in nature or whether it also participates in the control of behaviour [65,66].

(a) Origin of monitoring signals

The monitoring signals represent mismatch between expected and actual outcomes of actions. This evaluation process is often described in terms of reinforcement learning models [67,68]. A key element in many of these models is the ‘reward prediction error’, i.e. the difference between the expected and the actual reward outcome [69]. An important open question is the source of the signals that need to be compared and where this comparison takes place. Outcome-related neuronal activities, such as those found in SEF and ACC, are also found in other brain structures, such as the dopaminergic midbrain neurons [70] and in the amygdala [71]. Both these subcortical areas have widespread projections into the medial frontal cortex [72,73]. It is therefore possible that the monitoring signals in SEF and ACC simply reflect input coming from these areas [73]. An alternative possibility is that the medial frontal cortex itself computes the monitoring signals. To compute a reward prediction error signal, it is necessary to represent both its precursor signals, i.e. the expected and the actual value of the outcome. If this computation takes place in medial frontal cortex, then one would expect that both the precursor and outcome signals should be present in this cortical area.

A recent study has examined this question in SEF using an oculomotor gambling task, in which monkeys choose between options with uncertain reward outcome. SEF neurons carry various monitoring signals throughout the delay, when the outcome of the choice is still unknown, and the result period [74]. In particular, SEF neurons represent the expected value of the chosen option throughout the delay and the result period. Following the result, SEF neurons represent the actual reward that was received and a reward prediction error signal, i.e. the comparison of the expected and actual reward signals. Such a reward prediction error signal is equivalent to the teaching signal that is predicted in the Rescorla–Wagner model of reinforcement learning [67], and is similar to the well-known signal carried by midbrain dopamine and habenular neurons [75,76]. Thus, these findings suggest that SEF could compute a reward prediction error signal using locally represented signals about expected and actual reward without input from other structures. Similar local computation of reward prediction error likely occurs in other cortical areas [77,78]. All these local computations are likely to be context- and effector-dependent. For example, SEF would be expected to compute reward prediction error signals only in the context of eye movements. The outcome of these local computations could be sent to the dopaminergic midbrain nuclei and the habenula via connections through the basal ganglia [79,80]. These converging inputs from multiple specialized evaluation systems might generate a more general reward prediction error representation.

In addition to the reward prediction error-related signals, the SEF contains a number of other evaluative signals [74,81,82]. A particular type of monitoring signal that has received a lot of experimental and theoretical consideration is confidence. Choices are made with varying degrees of confidence, a cognitive signal representing the subjective belief in the optimality of the choice. Confidence has been mostly studied in the context of perceptual judgements in which choice accuracy can be measured using objective criteria [83,84]. The oculomotor gambling task allows confidence to be studied in subjective value-based decisions, which have to be based on subjective criteria. The SEF contains neural signals that explicitly represent choice confidence independently from reward expectation [82]. This confidence signal appeared after the choice and diminished before the choice outcome (figure 4). Most of this neuronal activity was negatively correlated with confidence, and was strongest in trials on which the monkey spontaneously withdrew their choice. This indicates that SEF not only guides saccade selection, but also evaluates the likelihood that the choice was optimal. This internal evaluation influences decisions concerning the willingness to bear later costs that follow from the choice, or to avoid them.

(b) Role of medial frontal cortex in response evaluation and response control

Lack of confidence in the choice is conceptually similar to conflict, another type of monitoring signal that has been suggested to be represented by the medial frontal cortex, specifically in the ACC [85–90]. Both low choice confidence and conflict are driven by equally strong evidence in favour of choosing among mutually exclusive actions. The main difference is
that confidence evaluates the quality of the choice and therefore can only be computed following the action, while conflict monitors the ongoing degree of co-activation of mutually exclusive action preparation processes. Thus, conflict could, in principle, detect early signs of potential problems in ongoing action selection and be used to recruit executive control processes to resolve the problems and to avoid errors. This original conflict monitoring hypothesis has been very influential [85,88,89]. However, almost all the supportive evidence is based on human neuroimaging experiments. In practically all of the experimental paradigms that are used in these experiments, the actual error rate in ‘high conflict’ conditions is typically low (5–8%). Instead, what is typically seen is a lengthening of reaction times, which is interpreted as being caused by the conflict and the need to suppress it. This interpretation is not unreasonable, but it confounds the interpretation of neuronal activity modulations that are observed during high conflict trials. This activity could represent conflict monitoring, increased control efforts, or both. Unfortunately, this problem also affects recent studies that claimed to have found explicit conflict signals represented by single neurons recorded in human ACC [91].

An additional problem for the conflict hypothesis is the fact that single unit recording and lesion studies in monkeys have shown no evidence for response conflict representation in ACC [61,62,92]. A recent study described ACC neurons that were active whenever a behaviourally highly relevant distractor (the image of a monkey face) was present during a simple visual discrimination task [93]. These signals were independent of the conflict between mutually exclusive actions, confirming the earlier results in the ACC of monkeys. The authors of this study interpreted the neuronal signal as evidence for ‘task conflict’, i.e. conflict between different potential behavioural goals.

However, alternative interpretations seem possible, such as increased attention to suppress the interfering visual stimulus, or increased autonomic arousal as indicated by modulations in pupil size.

One possibility for this discrepancy could be a species difference [94,95]. While possible, it would stand in stark contrast to a large amount of similarity that has been found in other in cognitive domains, even including metacognitive signals such as confidence. Alternatively, it might be that conflict monitoring is not a function of ACC, but of other parts of the medial frontal cortex. Potential conflict signals have been found in SEF [60], but not ACC [62], using an identical stop-signal paradigm. Recent human recording studies have shown that monitoring signals appear earlier in the SMA than in the ACC [96].

Lastly, it might be that the conflict hypothesis, at least in its original conception, is not the best conceptual framework for describing the function of medial frontal cortex. The conflict monitoring theory has been further developed in recent years to address in more detail how monitoring signals are used to allocate control [66]. In this updated theory, the medial frontal cortex, in particular the ACC, uses a number of monitoring signals, including conflict, to compute the costs and benefits of exerting control over response selection processes. The resulting expected value of control (EVC) signal is used to adjust the level of control or to select the control strategy that maximizes EVC [97]. The EVC theory is more flexible with respect to the nature of monitoring signals and does not rely exclusively on conflict signals; it is therefore in better agreement with the monkey recording data. However, critical predictions of the EVC theory have not yet been tested in electrophysiological experiments. In particular, it will be important to demonstrate the existence of EVC.
signals. In practice, it will be difficult to distinguish such signals from simple expected reward signals. A weak point of the EVC theory from the view of monkey electrophysiology is the difficulty in quantitatively predicting the ‘costs of cognitive control’ that an animal experiences in an experimental paradigm. Further effort along these lines is necessary to test the EVC theory more thoroughly.

In addition, alternative explanations for the neuroimaging findings have been suggested [98,99]. The debate about the functional merit of the conflict hypothesis is on-going, and more experiments are necessary to clarify the issue.

4. Conclusions

Recent experiments have started to connect our understanding of response inhibition with many other aspects of behavioural control. This research will be important in understanding how response inhibition is used and controlled to achieve the overall goals of an agent in its day-to-day behaviour. However, many questions are still unanswered. Making progress will require further investigations using the stop-signal paradigm. New rodent models will allow one to investigate and manipulate neural circuits in unprecedented detail [100]. Nevertheless, experiments in behaving monkeys will likely stay at the core of this enterprise. Monkeys have exceptional behavioural flexibility, which makes them ideal models to study complex control processes that are recruited as a consequence. They are also the closest model of human behaviour and physiology that is available. Together, these different animal models will add their different strengths and offer a bright future for this exciting field of neuroscience.

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