LOOK AWAY: THE ANTI-SACCADE TASK AND THE VOLUNTARY CONTROL OF EYE MOVEMENT

Douglas P. Munoz and Stefan Everling[‡§]*

The anti-saccade task has emerged as an important task for investigating the flexible control that we have over behaviour. In this task, participants must suppress the reflexive urge to look at a visual target that appears suddenly in the peripheral visual field and must instead look away from the target in the opposite direction. A crucial step involved in performing this task is the top-down inhibition of a reflexive, automatic saccade. Here, we describe recent neurophysiological evidence demonstrating the presence of this inhibitory function in single-cell activity in the frontal eye fields and superior colliculus. Patients diagnosed with various neurological and/or psychiatric disorders that affect the frontal lobes or basal ganglia find it difficult to suppress the automatic pro-saccade, revealing a deficit in top-down inhibition.

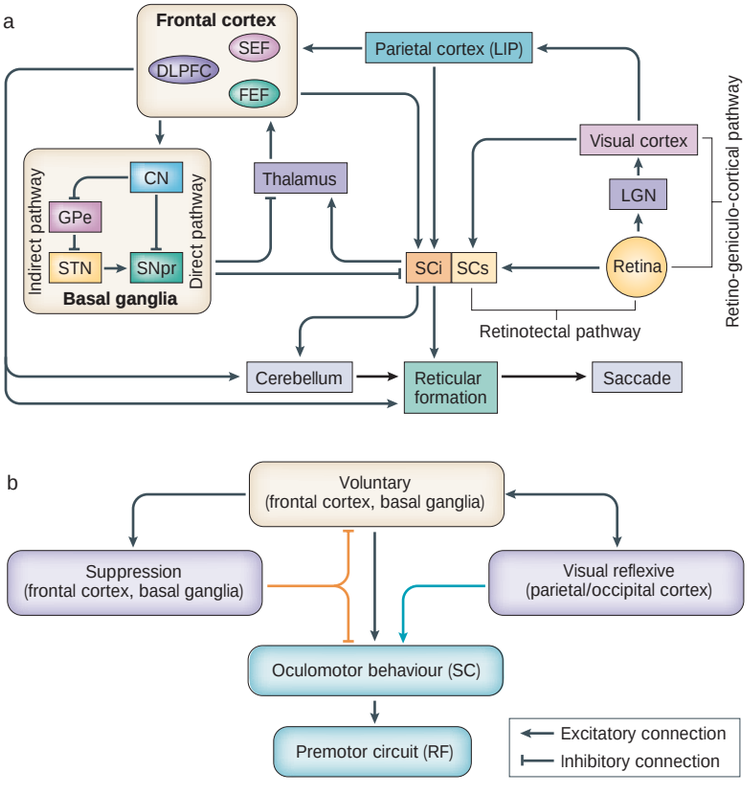
**Centre for Neuroscience Studies, Department of Physiology, CIHR Group in Sensory Motor Systems, Queen's University, Kingston,Ontario K7L 3N6, Canada.*
[‡]Departments of Physiology & Pharmacology and Psychology, University of Western Ontario, London, Ontario N6A 5C1, Canada.
[§]Robarts Research Institute, PO Box 5015, 100 Perth Drive, London, Ontario N6A 5K8, Canada.
Correspondence to D.P.M.
e-mail: doug@eyeml.queensu.ca
doi:10.1038/nrn1345

One characteristic feature of human behaviour is our ability to act flexibly in response to environmental events. For example, while strolling down a crowded sidewalk, you might notice an attractive person in the distance. Under most circumstances, an admiring glance towards that person would be appropriate. Except, however, when you are with your partner. In this instance, it might be wise to avoid looking in that direction and instead to orient in the opposite direction. This ability to control behaviour flexibly, responding automatically to stimuli in one situation and suppressing this automatic response in favour of an alternative response in a different situation, is the hallmark of executive control. The SACCADIC EYE MOVEMENT system provides an excellent model for investigating this ability of the brain because eye movements are easy to measure in the laboratory and because we have considerable knowledge of the neural networks that participate in controlling gaze (BOX 1). In this review, we describe how the anti-saccade task can be used to investigate the volitional control of action and how this task can be used to understand the pathophysiology that underlies various neurological and psychiatric disorders.

The anti-saccade task

In the laboratory, behavioural paradigms have been developed to study the ability of the brain to respond flexibly to our environment (BOX 2). The anti-saccade task[1] has become one of the most popular tasks because it contains a manipulation of stimulus–response compatibility that decouples stimulus encoding and response preparation. In this task, the participant is instructed that, after presentation of a peripheral target, they must look away to its mirror position. Correct performance on this task requires two steps. The subject must first suppress the automatic response to look at the target (pro-saccade) and then transform the location of the stimulus into a voluntary motor command to look away from the target (anti-saccade). Performance on the anti-saccade task can be contrasted with performance on the pro-saccade task in which the location of the sensory stimulus and the goal of the saccade are compatible (FIG. 1a, left), requiring a direct sensory–motor transformation. In the anti-saccade task (FIG. 1a, right), stimulus location and saccade goal are decoupled: the direct response must be suppressed and the stimulus vector must be inverted into the saccade vector. We review the neural mechanisms related

Box 1 | Neural circuitry controlling saccadic eye movements



An extensive body of literature describing lesion studies, human behavioural testing, functional neuroimaging, animal neurophysiology and detailed anatomy has identified several brain areas that are involved in controlling visual fixation and saccadic eye movements, including regions in the cerebral cortex, basal ganglia, thalamus, superior colliculus (SC), brainstem reticular formation and cerebellum[48,49,56,96,114–116] (see panels **a** and **b**). Visual inputs to the system arise from the retino-geniculo-cortical pathway to the primary visual cortex and from the retinotectal pathway to the superficial layers of the SC. Visual information is processed through several extrastriate visual areas[117] before it impinges on motor structures to affect action. The lateral intraparietal area (LIP) in the posterior parietal cortex is at the interface between sensory and motor processing[118,119]. The LIP projects to both the intermediate layers of the SC[120] and the frontal cortical oculomotor areas[121,122], including the frontal eye fields (FEF), the supplementary eye fields (SEF) and the dorsolateral prefrontal cortex (DLPFC). The FEF has a crucial role in executing voluntary saccades[98,123–125]. The SEF is important for internally guided decision-making and sequencing of saccades[126,127]. The DLPFC is involved in executive function, spatial working memory and suppressing automatic, reflexive responses[91–93]. All of these frontal regions project to the SC[28,59,62,128–130], which is a vital node in the premotor circuit where cortical and subcortical signals converge and are integrated[56,131]. The FEF, SEF and SC project directly to the paramedian pontine reticular formation to provide the necessary input to the saccadic premotor circuit so that a saccade is initiated or suppressed[59,132,133].

Frontal cortical oculomotor areas also project to the caudate nucleus (CN)[66,134,135]. GABA (γ-aminobutyric acid) neurons in the CN project through the direct pathway to the substantia nigra pars reticulata (SNpr). Neurons in the SNpr form the main output of the basal ganglia circuit: they contain GABA and project to the intermediate layers of the SC and to nuclei in the thalamus that project to the frontal cortex. Cortical inputs to the direct pathway lead to disinhibition of the SC and thalamus because these signals pass through two inhibitory synapses. There is also an indirect pathway through the basal ganglia, in which a separate set of GABA neurons in the CN project to the external segment of the globus pallidus (GPe). GABA neurons in GPe then project to the subthalamic nucleus (STN). Neurons in the STN send excitatory projections to neurons in the SNpr, which in turn project to the SC and thalamus. Cortical inputs to the indirect pathway lead to inhibition of the SC and thalamus because these signals pass through three inhibitory synapses[134,136]. LGN, lateral geniculate nucleus; SCi, superior colliculus intermediate layers; SCs, superior colliculus superficial layers.

to these two processes: suppression of the automatic response and vector inversion.

Monkeys can be trained to perform the anti-saccade task and therefore provide an important animal model[2,3] in which to investigate neural processing related to saccadic suppression and sensory–motor transformation. Pro-saccade and anti-saccade trials can be randomly interleaved in a block of trials and the instruction as to which type of movement to generate can be conveyed by the colour or shape of the initial fixation marker. In this configuration, human[4–6] and monkey[2,3] subjects produce a qualitatively similar pattern of behaviour. FIGURE 1b illustrates the distribution of reaction times obtained from a monkey generating correct pro- and anti-saccades and the reaction times of direction errors (saccades triggered in the wrong direction: towards the target in the anti-saccade task; away from the target in the pro-saccade task). There are two important observations. First, if the peripheral target appears suddenly and participants are allowed to move immediately, correct pro-saccades are initiated earlier than correct anti-saccades. Second, most direction errors are confined to

SACCADIC EYE MOVEMENT
A rapid eye movement (with speeds of up to 800 degrees per second) that brings the point of maximal visual acuity — the fovea — to the image of interest.

Box 2 | Stimulus–response mapping

The anti-saccade task requires the suppression of a saccade towards a peripheral stimulus and the generation of a saccade in the opposite direction. As such, the anti-saccade task can be regarded as a classical example of an arbitrary stimulus–response (SR) mapping task[137,138]. In particular, the anti-saccade task is a special case of an SR compatibility task. A saccade towards a flashed visual stimulus (pro-saccade) represents congruent SR mapping, whereas an anti-saccade requires incongruent SR mapping. It is well known from manual SR compatibility tasks that involve spatial stimuli and spatial responses that reaction times are faster and responses are more accurate when the stimulus and the response are compatible rather than incompatible[139–141]. A related task is the Simon task[142,143], in which subjects are presented with different tones in the left or right ear and are instructed to press a left or right key depending on the pitch of the tone. Reaction times are faster in this task when the tone and the key are compatible in sides. Kornblum[137] proposed that the reaction time benefit for congruent versus incongruent mapping rules occurs at the response stage. When the stimulus overlaps with the response, the presentation of the stimulus will automatically activate its corresponding response. If the automatically activated response is correct then it is executed. When the SR mapping instruction requires an incompatible response, this automatic response is aborted and the correct response is prepared and executed. This abort process is time-consuming and leads to the longer reaction times for incongruent responses. Support for this hypothesis has come from single neuron recordings in the primary motor cortex[144,145] and premotor cortex[146] in monkeys that show automatic activation of the congruent, but erroneous, response on incongruent SR trials. Similarily, the initial responses of visuomotor neurons in the superior colliculus and frontal eye fields on anti-saccade trials could be regarded as automatic activation of the congruent, but incorrect, pro-saccade.

There are also parallels between these spatial SR mapping tasks and tasks that require an arbitrary SR mapping. In the Stroop task[147], subjects are presented with the names of colours printed in colours and are instructed to name the print colours and ignore the words. Reaction times are faster when the print colours and colour names are compatible rather than incompatible[148,149]. In the Eriksen flanker task[150], subjects are shown a letter string with the instruction to press a key based on the central letter. Reaction times are faster when the central letter and the flanking letters are compatible.

the anti-saccade task and these errors are initiated earlier than correct responses.

Saccadic suppression ability can be challenged in these tasks by altering the fixation state at the time of target appearance. Removal of the fixation marker at least 200 ms before the target appears forces disengagement of active fixation before target appearance[7] and leads to reductions in reaction time for both pro- and anti-saccades and to an increase in direction errors in the anti-saccade task[4,8].

Closer examination of the distribution of reaction times (FIG. 1b) reveals that, in the pro-saccade task, there is a bimodal distribution. The initial peak of short-latency saccades, termed express saccades[9–11], is significantly elevated in the gap condition and represents the behavioural manifestation of the VISUAL GRASP REFLEX[12]. The latency of these express saccades approaches the minimum afferent and efferent conduction delays[13]. Express saccades are believed to be triggered by the direct transformation of the incoming visual signal into the motor command to drive the eyes to the stimulus[14–16]. However, it would not be helpful for every visual signal to trigger a saccade, and so time is required between sensory and motor processing to make a decision regarding whether a saccade is warranted. Therefore, most saccades are triggered at regular latencies.

In the anti-saccade task, the pattern of bimodality has a different shape. The initial peak of express saccades comprises, almost exclusively, direction errors and the correct responses have longer reaction times. Direction errors are most prevalent in the anti-gap condition, when the exogenous fixation marker has been removed before target appearance (FIG. 1c). Most direction errors are corrected after short intersaccadic intervals[17], revealing that errors are not the result of an inability to generate the voluntary anti-saccade. Rather, direction errors are the result of a failure to suppress the visual grasp reflex[3,18]. They result from the incoming sensory signal triggering an immediate orienting saccade to the target.

Models have been developed to account for the stochastic variability in reaction times[19–21]. Among them, the accumulator model has been particularly useful for interpreting neurophysiological and behavioural data that are related to saccadic eye movements[13,22–25]. These models suppose that, to initiate a movement, neural activity must accumulate at some rate from a baseline until it surpasses a threshold, thereby triggering the movement. Variations in baseline, threshold or the rate of rise can theoretically influence reaction time. Neurophysiological studies have determined that the rate of rise of activity among saccade neurons in the FRONTAL EYE FIELDS (FEF) and superior colliculus (SC) that occurs after target appearance can account for at least some of the stochastic variability in saccadic reaction times[23,24,26]. Other studies have revealed that the activity level of saccade neurons in the FEF and SC at the time of target appearance (the baseline level) can also account for variability in saccadic reaction times[15,27,28]. From these observations we can conclude that both pre- and post-target processing influences the accumulation of activity towards threshold to trigger a movement.

In the anti-saccade task, there are two processes racing towards threshold[1]: a process that is initiated by the appearance of the target that serves to initiate the automatic prepotent response and another process that is initiated by the inversion of the stimulus vector to initiate a voluntary anti-saccade. To perform the task correctly, processes related to the initiation of the automatic pro-saccade must be handicapped in some way to allow time for the voluntary anti-saccade response to

VISUAL GRASP REFLEX
Flexive orienting response towards a novel visual stimulus.

FRONTAL EYE FIELD
An area in the frontal lobe that receives visual inputs and produces movements of the eye.

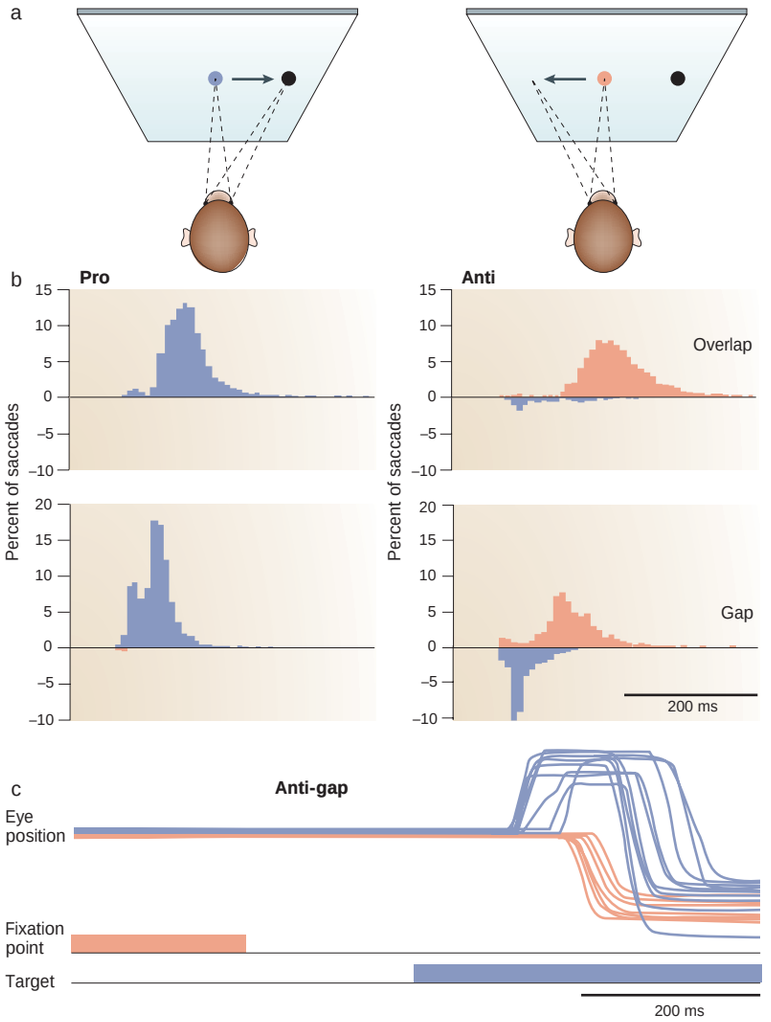


Figure 1 | **The anti-saccade task. a** | The colour of a central fixation marker can be used to instruct the subject to generate either a pro-saccade (left) or an anti-saccade (right). **b** | Distribution of reaction times from a monkey for correct (above abscissa) and error (below abscissa) responses in the pro-saccade task (left) and the anti-saccade task (right). If the fixation marker remains lit during target appearance (overlap condition — top panels), reaction times are increased and direction errors are uncommon, compared with when the fixation marker is absent at target appearance (gap condition — bottom panels). **c** | Representative eye position traces recorded from a monkey performing the anti-saccade task in the gap condition. Correct responses are in red and error responses are in blue. Modified, with permission, from REF. 27 © (1999) Society for Neuroscience.

accumulate towards threshold. How are these two processes of saccadic suppression and voluntary response generation represented in the brain and how are they handicapped in the anti-saccade task?

Neurophysiological findings in monkeys

Many cortical and subcortical structures are involved in the suppression and/or generation of saccadic eye movements (BOX 1). Single-neuron activity has been recorded in a number of these brain areas in monkeys performing the anti-saccade task, including the dorsolateral prefrontal cortex (DLPFC)[29,30], the lateral intraparietal area[31–34], the supplementary eye fields (SEF)[35–37], the FEF[28,38] and the SC[18,27].

The SC forms a vital node in the saccade network (BOX 1) because it receives convergent input from almost all of the cortical and subcortical structures that are involved in controlling saccades. Together with the FEF, the SC projects directly to the paramedian pontine reticular formation to provide the necessary input to the saccadic premotor circuit for saccade initiation[39]. Therefore, understanding how neurons in the SC and FEF participate in the suppression of automatic responses and the generation of goal-directed saccades is crucial for explaining behaviour in the anti-saccade task.

Suppression of the automatic pro-saccade. The SC and the FEF contain distinct populations of fixation and saccade neurons[40] whose discharges are modulated in a reciprocal manner in the anti-saccade task[27,28] (FIG. 2). Fixation neurons are tonically active during visual fixation and they cease to discharge during the execution of saccades. Saccade neurons have a reciprocal pattern of activity; they are silent during fixation and discharge a high-frequency burst of action potentials for saccades to a certain region of the contralateral visual field that defines their response field. It has been hypothesized that a network of inhibitory interneurons participates in shaping the reciprocal discharges of fixation and saccade neurons[41,56].

Let us consider the gap condition when the stimulus appears in the right visual field, so that a rightward saccade is required in the pro-saccade task (blue traces in FIG. 2), and a leftward saccade is required in the anti-saccade task (red traces). During fixation of the central fixation marker, which also serves as the instructional cue to perform either a pro- or an anti-saccade, fixation neurons in the FEF and SC are tonically active, and saccade neurons have little or no activity (timepoint a in FIG. 2). Compared with pro-saccade trials, activity of fixation neurons is enhanced on anti-saccade trials (red traces above blue traces), while the activity of saccade neurons is reduced (red traces below blue traces). This reciprocal pattern of activity is apparent before the target appears and explains the anti-effect: longer reaction times on anti-saccade trials than on pro-saccade trials[1,6].

Around 100 ms into the gap period (timepoint b in FIG. 2), there is a drop in fixation neuron discharge[7] and a slow buildup of low-frequency activity among a subset of saccade neurons in both the SC[15,42] and the FEF[28,43]. This drop in fixation activity and the buildup of activity in saccade neurons during the gap period can account for the gap effect — the reduction in saccadic reaction times that occurs when a gap period is introduced between fixation point disappearance and target appearance[44–47].

The appearance of the visual stimulus in the right visual field leads to phasic activation of the visually responsive saccade neurons in the FEF and SC on the contralateral (left) side of the brain, and to phasic inhibition of saccade neurons on the ipsilateral (right) side (timepoint c in FIG. 2). On pro-saccade trials, saccade neurons on the left side also discharge a saccadic burst command for the rightward pro-saccade that follows immediately from the phasic visual response. On anti-saccade trials, the saccade neurons in the left FEF and SC must be inhibited so that saccade neurons in the

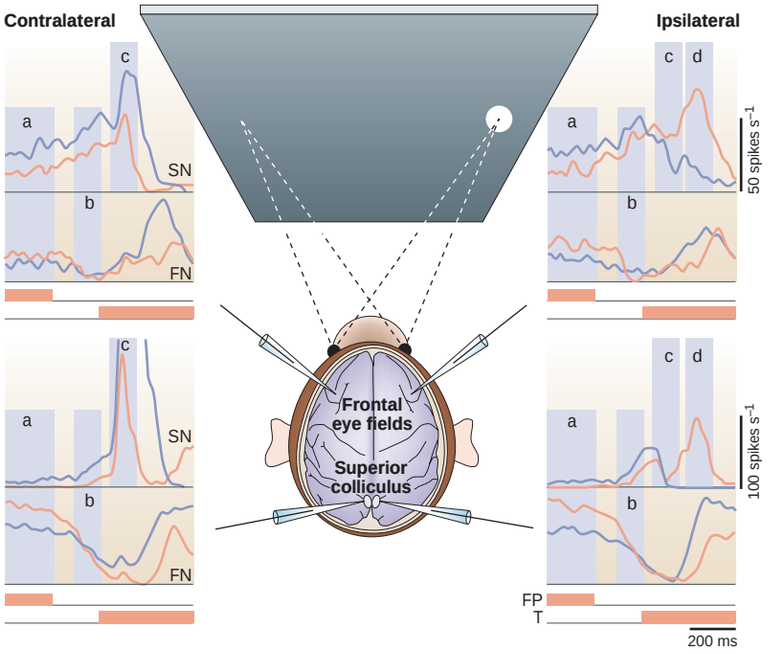


Figure 2 | **Discharges recorded from a fixation neuron (FN) and a saccade neuron (SN) in frontal eye field and superior colliculus when a monkey performs the pro-saccade and anti-saccade tasks in the gap condition.** Blue traces, pro-saccade trials; red traces, anti-saccade trials. Traces are aligned on target appearance. Presentation of the target on the right side leads to direct activation of saccade neurons that are visually responsive on the left side of the brain. These cells must be inhibited and saccade neurons on the right side activated to drive the leftward anti-saccade. Before target appearance, fixation neurons are more active on anti-saccade trials, while saccade neurons are more active on pro-saccade trials. The neurons were recorded individually. FP, fixation point; T, target.

right FEF and SC can be activated to drive the leftward anti-saccade (timepoint d in the right panel of FIG. 2). During the visual and motor responses, fixation neuron activity in both the SC and the FEF falls to a minimum.

What happens in the SC and FEF when a direction error is triggered? Recall from FIG. 1c that such errors occur only on anti-saccade trials and most frequently in the gap condition. These direction errors are the result of insufficient inhibition of saccade neurons in the FEF and SC before the target appears (FIG. 3). Without sufficient inhibition, the incoming visual transient response that is produced by the appearance of the target, sums with elevated pretarget activity and an express saccade is triggered, driving the eyes towards the stimulus instead of away from it. Most importantly, these direction errors can be predicted on the basis of the discharge of saccade neurons in the FEF and SC before the target appears[18,28]: excessive pre-target activity among saccade neurons is correlated with increased error rates.

So, correct performance in the anti-saccade task requires top-down inhibition of saccade neurons in the SC and FEF before the target appears. This can be represented in an accumulator model as a decrease in the pretarget level of neural activation, which moves the system further away from the saccadic threshold (FIG. 4b). This inhibition of the saccade neurons on anti-saccade trials ensures that the phasic visual response that is initiated by the appearance of the target will not exceed saccadic threshold. The target vector can then be inverted into the saccadic vector, and activity on the side of the brain ipsilateral to the target (coding the contraversive anti-saccade) can begin to build towards threshold as activity on the side contralateral to the target (coding the automatic pro-saccade) dies away.

It is unlikely that the activity of saccade neurons in the FEF and SC alone can account for the threshold crossing that is required for the generation of correct anti-saccades. For many saccade neurons, the magnitude of the saccadic burst that accompanies anti-saccades of the optimal vector is weaker than the magnitude of the visual response that accompanies the presentation of the target into their response fields[27,28]. If the visual response of FEF and SC saccade neurons does not trigger the saccade, then how does the saccade response do so, given that it is weaker in magnitude?

One possibility is that the threshold is not constant, but rather increases transiently after the sudden appearance of a visual stimulus. Omnipause neurons in the brainstem reticular formation tonically inhibit the saccade-generating circuit, and these neurons must be silenced before a saccade can be triggered[48,49]. Omnipause neurons discharge at a constant tonic rate during fixation and pause for saccades in all directions. Their constant tonic discharge rate, even during the gap condition[50], indicates that the threshold for saccade initiation might be stable. However, the discharge of these neurons transiently increases immediately after the sudden appearance of visual stimuli[50–52]. So, it is possible that the saccadic threshold increases immediately after target appearance so that, in the anti-saccade task, it is harder for the transient visual response to trigger the automatic pro-saccade, but the weaker saccade burst can trigger the correct anti-saccade.

Another possibility is that saccadic activity in other brain areas contributes to the accumulation of activity towards the threshold for saccade generation. One area that might provide such a signal to supplement the motor command for anti-saccades is the SEF[53,54]. Neurons in the SEF have both visual and motor responses, and these responses are increased on anti-saccade trials[36,37]. So, SEF motor commands sent to the brainstem premotor circuit can augment motor commands from the FEF and SC for the successful production of volitional anti-saccades. This means that action potentials from saccade neurons in the SC, FEF and SEF together could contribute to the accumulation of pre-saccadic activity that is required to cross the threshold and trigger the anti-saccade. However, projections from the SEF to the brainstem are believed to terminate predominantly on omnipause neurons[55]. It therefore remains to be determined how the SEF can influence brainstem burst neurons to augment the input from the FEF and the SC.

Inhibition of saccade neurons in the FEF and SC seems to be crucial for suppressing the automatic pro-saccade on anti-saccade trials. What are the possible sources of this signal in the brain? One possibility is that a

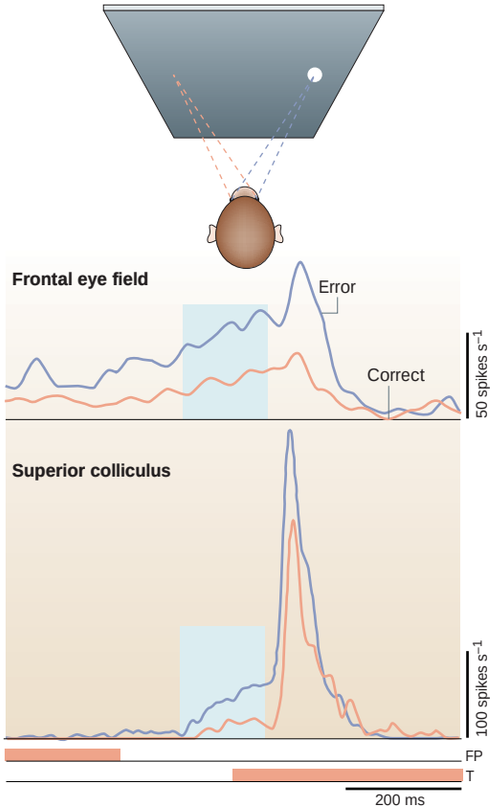


Figure 3 | **Activity of individual saccade neurons in the frontal eye field and superior colliculus.** Responses for correct anti-saccades (red traces) are compared with responses for erroneous pro-saccades (blue traces). The pre-target activity of saccade neurons (light blue box) can be used to predict behaviour[18,28]. FP, fixation point; T, target.

subset of fixation neurons in the FEF and SC themselves inhibits the saccade neurons[41,56,57]. Although fixation neurons have been identified as output neurons from the FEF and SC, it is possible that some instead are interneurons. Recall that fixation neurons have greater activity at the time of target appearance in the anti-saccade condition, and this signal could be used to inhibit the saccade neurons directly. Alternatively, fixation neurons in the FEF might project to inhibitory interneurons in the SC to inhibit saccade neurons. However, the question remains, where does the signal come from to enhance the activity of FEF and SC fixation neurons on anti-saccade trials? There are several possibilities.

One possible source of this signal is the SEF. As stated above, the visual and saccade-related responses of many neurons in the SEF are greater for anti-saccades than for pro-saccades. Many SEF neurons, especially fixation neurons, also show increased activation on anti-saccade trials during the instruction period that precedes target presentation, and the activity of these neurons is lower on trials in which the monkey generates a direction error[36,37]. The SEF projects directly to the FEF[58] and SC[59], so SEF efferents could excite local inhibitory interneurons to exert inhibition of saccade neurons in these structures.

Another possible source for the inhibition of saccade neurons in the FEF and SC is the DLPFC. Neurons in the DLPFC project directly to the SC[60,61] and the FEF[62], but the function of these projections remains unknown. Funahashi and colleagues[29] recorded from neurons in the DLPFC when monkeys performed a delay version of the pro- and anti-saccade tasks. They found that some neurons coded the stimulus location whereas other neurons coded the required response direction during the delay period. Such a role for the DLPFC in arbitrary stimulus–response mapping has been confirmed in other studies[63,64]. For example, a large proportion of DLPFC neurons showed differences in their baseline activity between a spatial, object and association task while monkeys were looking at a central fixation marker before a stimulus was presented[65]. These differences in activation probably reflect differences in preparatory set and could be involved in pre-setting the excitability of neurons in the SC and FEF. Alternatively, other populations of neurons in the DLPFC that have yet to be recorded in the anti-saccade task could provide inhibition to the saccade neurons in the FEF and SC.

A third source of inhibition of saccade neurons in the FEF and SC could be the substantia nigra pars reticulata (SNpr)[66]. A subset of neurons in the SNpr discharges tonically during fixation and pauses for saccades[67,68]. Some of these neurons project directly to the SC[69] and the thalamus, which in turn projects to the FEF. So, tonic neurons in the SNpr, which contain GABA (γ-aminobutyric acid), could exert tonic inhibition over saccade neurons in both the SC and FEF, and this inhibition could be enhanced on anti-saccade trials.

The neurophysiological recording studies described above have shown that a crucial step in the successful completion of the anti-saccade task is the inhibition of saccade neurons in the FEF and SC to ensure that the phasic visual response that is generated by the appearance of the target cannot trigger an automatic pro-saccade. This inhibition must be present before the target appears and is represented in the accumulator model as a reduction in baseline pre-target activity of saccade neurons before target appearance (solid line in FIG. 4b). If this inhibition is absent or weak (FIG. 4b, dashed line), then the incoming visual response will trigger a direction error. Further work is required to address the precise role of the DLPFC, SEF and SNpr as possible sources of the inhibition of saccade neurons in the FEF and SC that is required for the successful completion of the anti-saccade task.

Vector inversion. How is the location of the visual stimulus transformed into the appropriate motor command for the execution of saccades? This problem is relatively straightforward for pro-saccades because the visual response is mapped directly onto the saccade neurons in the FEF and SC. However, this is not a trivial problem in the anti-saccade task because the visual response is initially mapped to the wrong population of saccade neurons in the SC and FEF. This activity must be suppressed and instead a saccade response must be generated by saccade neurons on the opposite side of the

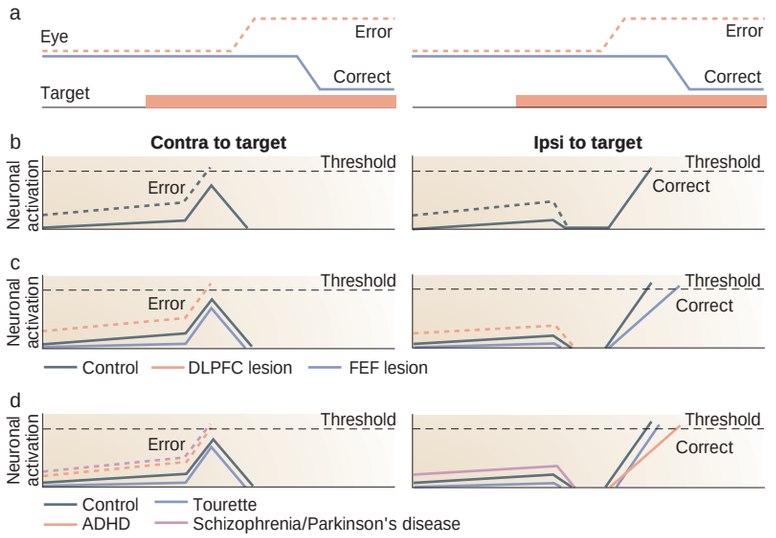


Figure 4 | **An accumulator model can be used to represent the accumulation of saccade activity in the brain on anti-saccade trials. a** | Schematized correct (solid traces) and error (dashed traces) responses. **b** | Hypothesized neural activation for correct and error responses. Activity contralateral to the target (left panel) must be suppressed and activity ipsilateral to the target (right panel) must grow to trigger the anti-saccade. **c** | Hypothesized activation for control subjects (grey traces) contrasted with patients with lesions of the frontal eye field (FEF; blue traces) and dorsolateral prefrontal cortex (DLPFC; red traces). **d** | Hypothesized activation for control subjects (grey traces) contrasted with patients diagnosed with attention-deficit hyperactivity disorder (ADHD; red traces), Tourette's syndrome (blue traces), Parkinson's disease and schizophrenia (pink traces). Dashed traces refer to error trials.

brain. Somewhere between the initial registration of target appearance and the generation of the saccadic burst in the FEF and SC, the target vector must be transformed (inverted) into the movement vector.

One area that might have a crucial role in vector inversion is the lateral intraparietal area (LIP). This area is located at the interface between sensory and motor processing[70–72]. Gottlieb and Goldberg[31] recorded from neurons in area LIP while monkeys performed pro- and anti-saccades. Most of the recorded neurons in LIP represented the target vector. Few neurons represented the direction of movement, and their activity occurred late. More recently, Zhang and Barash[32,33] employed a memory-delayed version of the anti-saccade task and identified a paradoxical type of response among visual neurons in LIP. On anti-saccade trials, when the saccade vector but not the target vector was aligned with the response field of the neuron, these neurons were activated about 50 ms after the visual neurons on the opposite side of the brain. Although the discharge was not visual, it seemed to be visual in that it was observed at a fixed latency after target appearance, well within the range of visual responses in LIP, and it declined to baseline during the memory period, long before movement initiation.

Zhang and Barash[32,33] concluded that the presence of the paradoxical activity in a subset of visual neurons in LIP might represent a remapped visual response. They argued that in the time immediately after target presentation, "some context-categorization process" switched on a non-standard input pathway. This inverted signal is appropriate to feed to frontocollicular regions to initiate the correct anti-saccade. Whether this paradoxical signal actually participates in vector inversion remains to be determined.

The FEF might also be important in vector inversion. Sato and Schall[38] used a singleton search task with a manipulation of pro- and anti-saccade responses to dissociate target selection from saccade selection. In most singleton search tasks, the subject must identify an odd-ball stimulus among several uniform distractors. Sato and Schall used colour to identify the singleton and the shape of the singleton to instruct the type of response. When the singleton was a vertical bar, the monkey was required to initiate a pro-saccade to the singleton. When the singleton was a horizontal bar, the monkey was required to initiate a saccade away from the singleton. Sato and Schall[38] identified two types of neuron in the FEF. Type I neurons selected the singleton and the endpoint of the saccade (saccade vector). The time of singleton selection among type I neurons did not vary with saccadic reaction time. Type II neurons, on the other hand, selected only the endpoint of the saccade, and their selection times varied with saccadic reaction times. Sato and Schall[38] concluded that visual selection and saccade selection are different processes.

Future experiments are required to elucidate the exact mechanisms for the implementation of vector inversion. Nonetheless, evidence has accumulated to indicate that neurons in both the LIP[32,33] and the FEF[38] participate in the process.

Imaging and ERP studies in humans

There is now experimental evidence showing that the setting of pre-target excitability of saccade neurons is also crucial if humans are to perform the anti-saccade task correctly. This evidence has come from event-related potential (ERP) and functional imaging studies. ERP studies have found that the pre-saccadic negativity that can be recorded over frontal and central cortical sites is larger for anti-saccades than for pro-saccades[73–75]. Furthermore, trials with direction errors are associated with reduced negativity immediately before target presentation, compared with correct anti-saccade trials[76]. Although the low spatial resolution of ERPs is insufficient to identify where these differences originate, these studies show important differences between pro- and anti-saccade trials that are present before target presentation. A role for parietal areas in vector inversion is supported by the analysis of post-stimulus ERPs[76]. These show that a negative potential shifts from the hemisphere contralateral to the stimulus to the hemisphere ipsilateral to the stimulus (contralateral to the movement), which is consistent with the time course of paradoxical visual responses in LIP neurons[32,33].

Early imaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) identified cortical areas that are activated differentially during anti- and pro-saccade tasks[77–81]. Specifically, parietal and frontal areas have an increased blood-oxygen-level-dependent (BOLD) signal and cerebral blood flow on anti-saccade trials. However,

these early studies used block designs in which subjects typically performed alternating blocks of pro- and anti-saccades. With this block design it is not possible to determine when these areas are activated during the task. Event-related imaging provides a means to dissociate preparatory from saccade-related BOLD activity. Recent studies[82–84] have used event-related designs and found that, during the instruction period before target appearance and movement initiation, the BOLD signal in frontal areas (SEF, FEF and DLPFC) is greater on anti-saccade trials than on pro-saccade trials. It will be interesting to test whether the BOLD signal differs in these areas between correct anti-saccade trials and trials with direction errors.

There is now converging evidence from primate electrophysiology, human ERP and event-related fMRI studies that top-down inhibition of saccade neurons is crucial to ensure the suppression of the automatic pro-saccade on anti-saccade trials. Several areas of the frontal cortex and basal ganglia might be involved in this top-down control of the saccade-generating circuit.

Clinical studies

Because of the dependency on frontal and basal ganglia structures, the anti-saccade task has emerged as an important clinical tool for investigating development and dysfunction in various neurological and psychiatric disorders[85,86]. A quick test of anti-saccade function is often included in a bedside neurological exam. Patients can be instructed to look either towards or away from the wiggling fingers of the physician to assess saccadic suppression ability. Many patient groups have now been studied with the anti-saccade task and some of the key findings can be interpreted in the context of the neurophysiological findings that are described above to make specific predictions about how pathophysiology can influence top-down inhibitory control of saccade neurons and accumulation of activity toward saccadic threshold. We now review only a small part of this literature to illustrate how the accumulator model can be used to interpret the clinical findings.

Important developmental changes have been identified in the ability of normal children and adults to perform the anti-saccade task[5,87–90]. Young children (<8 years of age) have difficulty in suppressing the automatic pro-saccade in the anti-saccade task. Many of the direction errors that are triggered by children are corrected quickly, revealing that these young subjects have no difficulty in understanding the task. Rather, their difficulty is in suppressing the automatic pro-saccade to the target. This suppression ability develops gradually in school-age children, and adult levels of performance are achieved only at about 18 years of age. These developmental changes have been attributed to protracted maturation of the frontal lobes well into the second decade[91]. This gradual improvement in the ability to suppress the automatic pro-saccade is presumably the result of improved inhibitory control over the saccade-generating circuitry. Because young children have reduced inhibitory control, they will have difficulty in pre-setting the excitability of saccade neurons in the FEF and SC before the target appears (FIG. 4b; dashed traces). On the other hand, normal adults can selectively inhibit pretarget activity in saccade neurons (FIG. 4b; solid traces) so that it is easier to suppress automatic pro-saccades in the anti-saccade task.

Analysis of patients with discrete cortical lesions has provided important insight into how the brain solves the anti-saccade task. Patients with discrete lesions of the DLPFC have difficulty in suppressing the automatic pro-saccade in the anti-saccade task[92–95]. It is believed that the DLPFC provides important top-down signals to the FEF and perhaps the SC to inhibit the automatic pro-saccade[96,97]. Removal of the DLPFC presumably reduces the ability of subjects to inhibit saccade neurons in the FEF and SC selectively on anti-saccade trials, resulting in too much pretarget activity that will sum with the incoming visual response to trigger direction errors (FIG. 4c; red dashed traces). Lesions of the FEF, on the other hand, do not reduce the ability to suppress the automatic pro-saccade, but instead impair the ability to generate the voluntary anti-saccade[98,99]. The loss of saccade neurons in the FEF will reduce input to the SC and the saccade premotor circuitry, thereby increasing the time that is required to accumulate activity to threshold so as to trigger the voluntary anti-saccade (FIG. 4c; blue solid traces).

A number of studies have shown that patients with schizophrenia perform poorly on anti-saccade tasks[100]. Two common findings are increased error rates and prolonged reaction times for correct anti-saccades. This behaviour shows a striking similarity to that of patients with prefrontal lesions, and many studies have confirmed a correlation between the frequency of direction errors and performance on the Wisconsin Card Sorting Test[101–103], an established test of prefrontal function. Consistent with the behavioural similarities between patients with schizophrenia and patients with frontal lobe lesions is a recent fMRI study that compared the BOLD signal associated with anti-saccades between patients with schizophrenia and control subjects and found differences in the right DLPFC[104]. Similar to patients with DLPFC lesions, patients with schizophrenia might have a reduced ability to suppress the activity of saccade neurons in the FEF and SC on anti-saccade trials (FIG. 4d; dashed pink trace) and a reduction in the rate of accumulation of activity for the correct anti-saccade (FIG. 4d; solid pink trace).

Attention-deficit hyperactivity disorder (ADHD) is characterized as a deficit in response inhibition[105]. Children and adults diagnosed with ADHD have marked difficulties in suppressing the automatic pro-saccade on anti-saccade trials[106]. Despite the increase in direction errors, there is no change in the mean reaction time of correct anti-saccades, implying no deficit in the ability to initiate a voluntary response. We have hypothesized that the increased occurrence of direction errors in ADHD is the result of compromised top-down control of saccade neurons in the FEF and SC. This results in excessive pretarget activity in the FEF and SC so that direction errors are easily triggered after appearance of the visual stimulus (FIG. 4d; red dashed trace).

A hallmark of Parkinson's disease (PD) is that patients have difficulty in generating voluntary responses[107]. Reaction times for correct anti-saccades are significantly increased in patients with PD[108–110], indicating that the activity required to trigger correct anti-saccades might accumulate more slowly in these patients (FIG. 4d; compare solid pink and black traces). Paradoxically, patients with PD are faster than control subjects at generating the automatic responses in the pro-saccade task, making more express saccades than age-matched control subjects[108]. As a consequence, significantly more direction errors are triggered on anti-saccade trials[110] (but see REFS 111,112). As a result of this reduced inhibitory control in PD, inappropriate top-down saccadic suppression might be present at stimulus onset, resulting in excessive activity in saccade neurons. This reduced inhibitory control is illustrated in the accumulator model as elevation of the pre-target baseline (FIG. 4d; dashed pink line).

Patients diagnosed with Tourette's syndrome produce a different pattern of results in the anti-saccade task[113]. Rather than generating more direction errors, these patients instead have increased reaction times in both pro- and anti-saccade tasks and, like control subjects, they generate few direction errors. At first this seems counterintuitive, because a hallmark of patients with Tourette's is their inability to suppress inappropriate actions. Perhaps as a consequence of adapting to the symptoms of the disorder, the patients have increased top-down inhibition acting on the saccade-generating system, thereby making it harder for activity to accumulate to trigger saccades in either pro- or anti-saccade conditions (FIG. 4d; solid blue traces).

The above review of clinical studies is by no means exhaustive (see REF. 86 for a more thorough review). Nonetheless, it shows how recent neurophysiological findings can be used to interpret the behaviour of clinical groups in the context of the accumulator model. Most importantly, there are specific predictions of how control signals might be impaired in these clinical groups. Specifically, the anti-saccade task is a good test of inhibitory control and the ability to generate voluntary actions. Top-down inhibitory control is required to reduce pre-target baseline activity among saccade neurons before target appearance, and insufficient inhibition will lead to increased direction errors. In addition, the anti-saccade task is also sensitive to deficits in initiation of movement that can alter the rate of accumulation of activity toward threshold. These predictions can now be tested by combining fMRI, ERP and behavioural investigations in the same patient groups.

Conclusions

Neural circuits have evolved to give us voluntary, flexible control over behaviour. Many lively and colourful debates between partners can be avoided when glances to attractive individuals are suppressed and gaze is instead diverted in the opposite direction. This flexible control over voluntary behaviour is a hallmark of executive control. In the case of the anti-saccade task, it requires the top-down inhibition of automatic pro-saccade responses and the generation of voluntary anti-saccades. Future work should be directed at identifying the precise neural substrate required for saccadic suppression and vector inversion.

Here, we have reviewed recent neurophysiological, imaging and behavioural performance data collected from the anti-saccade task. Monkey neurophysiological data can be combined with human neuroimaging data to identify the neural substrates that are required for saccadic suppression and vector inversion in humans. These results, when combined with behavioural performance data, can be used to make specific predictions of signal abnormalities in various patient groups that can be tested directly in the laboratory. So, the anti-saccade task is emerging as an important tool to investigate not only normal brain function, but also dysfunction in various neurological and psychiatric disease conditions. In the future, this task might be important to evaluate future treatment protocols that are designed to ameliorate deficits in response inhibition and movement initiation.

1. Hallett, P. E. Primary and secondary saccades to goals defined by instructions. *Vision Res.* **18**, 1279–1296 (1978). **This study introduced the anti-saccade task.**
2. Amador, N., Schlag-Rey, M. & Schlag, J. Primate antisaccades. I. Behavioral characteristics. *J. Neurophysiol.* **80**, 1775–1786 (1998).
3. Bell, A. H., Everling, S. & Munoz, D. P. Influence of stimulus eccentricity and direction on characteristics of pro- and antisaccades in non-human primates. *J. Neurophysiol.* **84**, 2595–2604 (2000).
4. Fischer, B. & Weber, H. Effects of stimulus conditions on the performance of antisaccades in man. *Exp. Brain Res.* **116**, 191–200 (1997).
5. Munoz, D. P., Broughton, J. R., Goldring, J. E. & Armstrong, I. T. Age-related performance of human subjects on saccadic eye movement tasks. *Exp. Brain Res.* **121**, 391–400 (1998).
6. Hallett, P. E. & Adams, B. D. The predictability of saccadic latency in a novel voluntary oculomotor task. *Vision Res.* **20**, 329–339 (1980).
7. Dorris, M. C. & Munoz, D. P. A neural correlate for the gap effect on saccadic reaction times in monkey. *J. Neurophysiol.* **73**, 2558–2562 (1995).
8. Forbes, K. & Klein, R. M. The magnitude of the fixation offset effect with endogenously and exogenously controlled saccades. *J. Cogn. Neurosci.* **8**, 344–352 (1996).
9. Fischer, B. & Weber, H. Express saccades and visual attention. *Behav. Brain Sci.* **16**, 553–610 (1993).
10. Fischer, B. & Boch, R. Saccadic eye movements after extremely short reaction times in the monkey. *Brain Res.* **260**, 21–26 (1983).
11. Pare, M. & Munoz, D. P. Saccadic reaction time in the monkey: advanced preparation of oculomotor programs is primarily responsible for express saccade occurrence. *J. Neurophysiol.* **76**, 3666–3681 (1996).
12. Hess, W. R., Burgi, S. & Bucher, V. Motor function of tectal and tegmental area. *Monatsschr. Psychiatr. Neurol.* **112**, 1–52 (1946).
13. Carpenter, R. H. S. in *Eye Movements: Cognition and Visual Perception* (eds Fischer, D. F. & Monty, R. A.) 237–246 (Erlbaum, Hillsdale, New Jersey, 1981).
14. Edelman, J. A. & Keller, E. L. Activity of visuomotor burst neurons in the superior colliculus accompanying express saccades. *J. Neurophysiol.* **76**, 908–926 (1996).
15. Dorris, M. C., Pare, M. & Munoz, D. P. Neuronal activity in monkey superior colliculus related to the initiation of saccadic eye movements. *J. Neurosci.* **17**, 8566–8579 (1997). **This paper shows that the level of pretarget activation of saccade neurons in the superior colliculus is negatively correlated with saccadic reaction times.**
16. Sparks, D., Rohrer, W. H. & Zhang, Y. The role of the superior colliculus in saccade initiation: a study of express saccades and the gap effect. *Vision Res.* **40**, 2763–2777 (2000).
17. Fischer, B., Gezeck, S. & Hartnegg, K. On the production and correction of involuntary prosaccades in a gap antisaccade task. *Vision Res.* **40**, 2211–2217 (2000).
18. Everling, S., Dorris, M. C. & Munoz, D. P. Reflex suppression in the anti-saccade task is dependent on prestimulus neural processes. *J. Neurophysiol.* **80**, 1584–1589 (1998). **This study demonstrates that errors in the anti-saccade task are associated with a high level of pretarget excitation of saccade neurons in the primate superior colliculus.**
19. Luce, R. D. *Response Times: Their Role in Inferring Elementary Mental Organization* (Oxford Univ. Press, Oxford, 1986).
20. Carpenter, R. H. & Williams, M. L. Neural computation of log likelihood in control of saccadic eye movements. *Nature* **377**, 59–62 (1995). **An experimental study that supports the accumulator model of saccade initiation.**
21. Ratcliff, R. A diffusion model account of response time and accuracy in a brightness discrimination task: fitting real data and failing to fit fake but plausible data. *Psychon. Bull. Rev.* **9**, 278–291 (2002).

22. Trappenberg, T. P., Dorris, M. C., Munoz, D. P. & Klein, R. M. A model of saccade initiation based on the competitive integration of exogenous and endogenous signals in the superior colliculus. *J. Cogn. Neurosci.* **13**, 256–271 (2001).
23. Hanes, D. P. & Schall, J. D. Neural control of voluntary movement initiation. *Science* **274**, 427–430 (1996).
24. Gold, J. I. & Shadlen, M. N. Representation of a perceptual decision in developing oculomotor commands. *Nature* **404**, 390–394 (2000).
25. Ratcliff, R., Cherian, A. & Segraves, M. A comparison of macaque behavior and superior colliculus neuronal activity to predictions from models of two-choice decisions. *J. Neurophysiol.* **90**, 1392–1407 (2003).
26. Pare, M. & Hanes, D. P. Controlled movement processing: superior colliculus activity associated with countermanded saccades. *J. Neurosci.* **23**, 6480–6489 (2003).
27. Everling, S., Dorris, M. C., Klein, R. M. & Munoz, D. P. Role of primate superior colliculus in preparation and execution of anti-saccades and pro-saccades. *J. Neurosci.* **19**, 2740–2754 (1999).
28. Everling, S. & Munoz, D. P. Neuronal correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. *J. Neurosci.* **20**, 387–400 (2000).
References 27 and 28 show differences in the activity of neurons in the superior colliculus and FEF between pro-saccades and anti-saccades.
29. Funahashi, S., Chafee, M. V. & Goldman-Rakic, P. S. Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature* **365**, 753–756 (1993).
30. Desouza, J. F., Iversen, S. D. & Everling, S. Preparatory set activity associated with pro-saccades and anti-saccades within the primate prefrontal cortex. *Soc. Neurosci. Abstr.* **33**, 661.10 (2003).
31. Gottlieb, J. & Goldberg, M. E. Activity of neurons in the lateral intraparietal area of the monkey during an antisaccade task. *Nature Neurosci.* **2**, 906–912 (1999).
32. Zhang, M. & Barash, S. Neuronal switching of sensorimotor transformations for antisaccades. *Nature* **408**, 971–975 (2000).
33. Zhang, M. & Barash, S. Persistent LIP activity in memory-antisaccades: working memory for a sensorimotor transformation. *J. Neurophysiol.* **91**, 1424–1441, (2004).
References 32 and 33 describe paradoxical visual responses in LIP neurons in an anti-saccade task.
34. Toth, L. J. & Assad, J. A. Dynamic coding of behaviourally relevant stimuli in parietal cortex. *Nature* **415**, 165–168 (2002).
35. Olson, C. R. & Gettner, S. N. Neuronal activity related to rule and conflict in macaque supplementary eye field. *Physiol. Behav.* **77**, 663–670 (2002).
36. Schlag-Rey, M., Amador, N., Sanchez, H. & Schlag, J. Antisaccade performance predicted by neuronal activity in the supplementary eye field. *Nature* **390**, 398–401 (1997).
The first study to contrast the activity of SEF neurons between pro-saccade and anti-saccade trials.
37. Amador, N., Schlag-Rey, M. & Schlag, J. Primate antisaccade II. Supplementary eye field neuronal activity predicts correct performance. *J. Neurophysiol.* 26 Nov 2003 [epub ahead of print].
38. Sato, T. R. & Schall, J. D. Effects of stimulus-response compatibility on neural selection in frontal eye field. *Neuron* **38**, 637–648 (2003).
This study demonstrates that visual selection and saccade selection are different processes in the FEF.
39. Schiller, P. H., True, S. D. & Conway, J. L. Deficits in eye movements following frontal eye-field and superior colliculus ablations. *J. Neurophysiol.* **44**, 1175–1189 (1980).
40. Munoz, D. P. & Schall, J. D. in *The Superior Colliculus: New Approaches for Studying Sensorimotor Integration* (eds Hall, W. C. & Moschovakis, A.) 55–82 (CRC, Boca Raton, Florida, 2003)
41. Munoz, D. P. & Istvan, P. J. Lateral inhibitory interactions in the intermediate layers of the monkey superior colliculus. *J. Neurophysiol.* **79**, 1193–1209 (1998).
42. Munoz, D. P. & Wurtz, R. H. Saccade-related activity in monkey superior colliculus. I. Characteristics of burst and buildup cells. *J. Neurophysiol.* **73**, 2313–2333 (1995).
43. Dias, E. C. & Bruce, C. J. Physiological correlate of fixation disengagement in the primate's frontal eye field. *J. Neurophysiol.* **72**, 2532–2537 (1994).
44. Saslow, M. G. Effects of components of displacement-step stimuli upon latency of saccadic eye movements. *J. Opt. Soc. Am.* **57**, 1024–1029 (1967).
45. Mayfrank, L., Mobashery, M., Kimmig, H. & Fischer, B. The role of fixation and visual attention in the occurrence of express saccades in man. *Eur. Arch. Psychiatry Neurol. Sci.* **235**, 269–275 (1986).
46. Munoz, D. P. & Corneil, B. D. Evidence for interactions between target selection and visual fixation for saccade generation in humans. *Exp. Brain Res.* **103**, 168–173 (1995).
47. Weber, H. & Fischer, B. Gap duration and location of attention focus modulate the occurrence of left/right asymmetries in the saccadic reaction times of human subjects. *Vision Res.* **35**, 987–998 (1995).
48. Scudder, C. A., Kaneko, C. S. & Fuchs, A. F. The brainstem burst generator for saccadic eye movements: a modern synthesis. *Exp. Brain Res.* **142**, 439–462 (2002).
49. Moschovakis, A. K., Scudder, C. A. & Highstein, S. M. The microscopic anatomy and physiology of the mammalian saccadic system. *Prog. Neurobiol.* **50**, 133–254 (1996).
An authorative review of the neurophysiology and anatomy of the saccadic eye movement system.
50. Everling, S., Pare, M., Dorris, M. C. & Munoz, D. P. Comparison of the discharge characteristics of brain stem omnipause neurons and superior colliculus fixation neurons in monkey: implications for control of fixation and saccade behavior. *J. Neurophysiol.* **79**, 511–528 (1998).
51. Evinger, C., Kaneko, C. R. & Fuchs, A. F. Activity of omnipause neurons in alert cats during saccadic eye movements and visual stimuli. *J. Neurophysiol.* **47**, 827–844 (1982).
52. King, W. M., Precht, W. & Dieringer, N. Afferent and efferent connections of cat omnipause neurons. *Exp. Brain Res.* **38**, 395–403 (1980).
53. Schlag, J. & Schlag-Rey, M. Unit activity related to spontaneous saccades in frontal dorsomedial cortex of monkey. *Exp. Brain Res.* **58**, 208–211 (1985).
54. Schlag, J. & Schlag-Rey, M. Evidence for a supplementary eye field. *J. Neurophysiol.* **57**, 179–200 (1987).
55. Shook, B. L., Schlag-Rey, M. & Schlag, J. Direct projection from the supplementary eye field to the nucleus raphe interpositus. *Exp. Brain Res.* **73**, 215–218 (1988).
56. Munoz, D. P. & Fecteau, J. H. Vying for dominance: dynamic interactions control visual fixation and saccadic initiation in the superior colliculus. *Prog. Brain Res.* **140**, 3–19 (2002).
57. Meredith, M. A. & Ramoa, A. S. Intrinsic circuitry of the superior colliculus: pharmacophysiological identification of horizontally oriented inhibitory interneurons. *J. Neurophysiol.* **79**, 1597–1602 (1998).
58. Huerta, M. F., Krubitzer, L. A. & Kaas, J. H. Frontal eye field as defined by intracortical microstimulation in squirrel monkeys, owl monkeys, and macaque monkeys. II. Cortical connections. *J. Comp. Neurol.* **265**, 332–361 (1987).
59. Shook, B. L., Schlag-Rey, M. & Schlag, J. Primate supplementary eye field: I. Comparative aspects of mesencephalic and pontine connections. *J. Comp. Neurol.* **301**, 618–642 (1990).
60. Goldman, P. S. & Nauta, W. J. Autoradiographic demonstration of a projection from prefrontal association cortex to the superior colliculus in the rhesus monkey. *Brain Res.* **116**, 145–149 (1976).
61. Leichnetz, G. R., Spencer, R. F., Hardy, S. G. & Astruc, J. The prefrontal corticotectal projection in the monkey; an anterograde and retrograde horseradish peroxidase study. *Neuroscience* **6**, 1023–1041 (1981).
62. Selemon, L. D. & Goldman-Rakic, P. S. Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. *J. Neurosci.* **8**, 4049–4068 (1988).
63. Asaad, W. F., Rainer, G. & Miller, E. K. Neural activity in the primate prefrontal cortex during associative learning. *Neuron* **21**, 1399–1407 (1998).
64. White, I. M. & Wise, S. P. Rule-dependent neuronal activity in the prefrontal cortex. *Exp. Brain Res.* **126**, 315–335 (1999).
65. Asaad, W. F., Rainer, G. & Miller, E. K. Task-specific neural activity in the primate prefrontal cortex. *J. Neurophysiol.* **84**, 451–459 (2000).
66. Hikosaka, O., Takikawa, Y. & Kawagoe, R. Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiol. Rev.* **80**, 953–978 (2000).
67. Hikosaka, O. & Wurtz, R. H. Visual and oculomotor functions of monkey substantia nigra pars reticulata. II. Visual responses related to fixation of gaze. *J. Neurophysiol.* **49**, 1254–1267 (1983).
68. Handel, A. & Glimcher, P. W. Quantitative analysis of substantia nigra pars reticulata activity during a visually guided saccade task. *J. Neurophysiol.* **82**, 3458–3475 (1999).
69. Hikosaka, O. & Wurtz, R. H. Visual and oculomotor functions of monkey substantia nigra pars reticulata. IV. Relation of substantia nigra to superior colliculus. *J. Neurophysiol.* **49**, 1285–1301 (1983).
70. Lynch, J. C., Graybiel, A. M. & Lobeck, L. J. The differential projection of two cytoarchitectonic subregions of the inferior parietal lobule of macaque upon the deep layers of the superior colliculus. *J. Comp. Neurol.* **235**, 241–254 (1985).
71. Colby, C. L., Duhamel, J. R. & Goldberg, M. E. Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. *J. Neurophysiol.* **76**, 2841–2852 (1996).
72. Gnadt, J. W. & Andersen, R. A. Memory related motor planning activity in posterior parietal cortex of macaque. *Exp. Brain Res.* **70**, 216–220 (1988).
73. Everling, S., Krappmann, P. & Flohr, H. Cortical potentials preceding pro- and antisaccades in man. *Electroencephalogr. Clin. Neurophysiol.* **102**, 356–362 (1997).
74. Evdokimidis, I., Liakopoulos, D., Constantinidis, T. S. & Papageorgiou, C. Cortical potentials with antisaccades. *Electroencephalogr. Clin. Neurophysiol.* **98**, 377–384 (1996).
75. Klein, C., Heinks, T., Andresen, B., Berg, P. & Moritz, S. Impaired modulation of the saccadic contingent negative variation preceding antisaccades in schizophrenia. *Biol. Psychiatry* **47**, 978–990 (2000).
76. Everling, S., Spantekow, A., Krappmann, P. & Flohr, H. Event-related potentials associated with correct and incorrect responses in a cued antisaccade task. *Exp. Brain Res.* **118**, 27–34 (1998).
77. O'Driscoll, G. A. *et al*. Functional neuroanatomy of antisaccade eye movements investigated with positron emission tomography. *Proc. Natl Acad. Sci. USA* **92**, 925–929 (1995).
78. Paus, T., Petrides, M., Evans, A. C. & Meyer, E. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. *J. Neurophysiol.* **70**, 453–469 (1993).
79. Sweeney, J. A. *et al*. Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *J. Neurophysiol.* **75**, 454–468 (1996).
80. Doricchi, F. *et al*. Neural control of fast-regular saccades and antisaccades: an investigation using positron emission tomography. *Exp. Brain Res.* **116**, 50–62 (1997).
81. Connolly, J. D., Goodale, M. A., Desouza, J. F., Menon, R. S. & Vilis, T. A comparison of frontoparietal fMRI activation during anti-saccades and anti-pointing. *J. Neurophysiol.* **84**, 1645–1655 (2000).
82. Connolly, J. D., Goodale, M. A., Menon, R. S. & Munoz, D. P. Human fMRI evidence for the neural correlates of preparatory set. *Nature Neurosci.* **5**, 1345–1352 (2002).
An important demonstration that frontal areas and not parietal areas carry preparatory signals for anti-saccades.
83. Desouza, J. F., Menon, R. S. & Everling, S. Preparatory set associated with pro-saccades and anti-saccades in humans investigated with event-related FMRI. *J. Neurophysiol.* **89**, 1016–1023 (2003).
Strong fMRI evidence that differences between pro-saccades and anti-saccades originate from differences in preparatory activity and not motor activity.
84. Curtis, C. E. & D'Esposito, M. Success and failure suppressing reflexive behavior. *J. Cogn. Neurosci.* **15**, 409–418 (2003).
85. Leigh, R. J. & Kennard, C. Using saccades as a research tool in the clinical neurosciences. *Brain* 7 Nov 2003 (doi 10.1093/brain/awh035).
A recent review covering the usefulness of saccadic motor tasks in clinical studies.
86. Everling, S. & Fischer, B. The antisaccade: a review of basic research and clinical studies. *Neuropsychologia* **36**, 885–899 (1998).
87. Fischer, B., Biscaldi, M. & Gezeck, S. On the development of voluntary and reflexive components in human saccade generation. *Brain Res.* **754**, 285–297 (1997).
88. Luna, B. *et al*. Maturation of widely distributed brain function subserves cognitive development. *Neuroimage* **13**, 786–793 (2001).
89. Klein, C. & Foerster, F. Development of prosaccade and antisaccade task performance in participants aged 6 to 26 years. *Psychophysiology* **38**, 179–189 (2001).
90. Fukushima, J., Hatta, T. & Fukushima, K. Development of voluntary control of saccadic eye movements. I. Age-related changes in normal children. *Brain Dev.* **22**, 173–180 (2000).
91. Fuster, J. M. *The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe* (Raven, New York, 1997).
92. Guitton, D., Buchtel, H. A. & Douglas, R. M. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp. Brain Res.* **58**, 455–472 (1985).
A seminal study showing that patients with frontal lobe lesions have high error rates in an anti-saccade task.
93. Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B. & Agid, Y. Cortical control of reflexive visually-guided saccades. *Brain* **114**, 1473–1485 (1991).
94. Pierrot-Deseilligny, C. *et al*. Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. *Brain* **126**, 1460–1473 (2003).
95. Walker, R., Husain, M., Hodgson, T. L., Harrison, J. & Kennard, C. Saccadic eye movement and working memory deficits following damage to human prefrontal cortex. *Neuropsychologia* **36**, 1141–1159 (1998).

96. Pierrot-Deseilligny, C., Ploner, C. J., Muri, R. M., Gaymard, B. & Rivaud-Pechoux, S. Effects of cortical lesions on saccadic eye movements in humans. *Ann. NY Acad. Sci.* **956**, 216–229 (2002).
97. Gaymard, B., Ploner, C. J., Rivaud, S., Vermersch, A. I. & Pierrot-Deseilligny, C. Cortical control of saccades. *Exp. Brain Res.* **123**, 159–163 (1998).
98. Gaymard, B., Ploner, C. J., Rivaud-Pechoux, S. & Pierrot-Deseilligny, C. The frontal eye field is involved in spatial short-term memory but not in reflexive saccade inhibition. *Exp. Brain Res.* **129**, 288–301 (1999).
99. Davidson, M. C., Everling, S. L. A. & Munoz, D. P. Comparison of pro- and anti-saccades in primates. III. Reversible activation/inactivation of frontal eye field and superior colliculus. *Soc. Neurosci. Abstr.* **25**, 147.9 (1999).
100. Broerse, A., Crawford, T. J. & den Boer, J. A. Parsing cognition in schizophrenia using saccadic eye movements: a selective overview. *Neuropsychologia* **39**, 742–756 (2001).
101. Crawford, T. J., Haeger, B., Kennard, C., Reveley, M. A. & Henderson, L. Saccadic abnormalities in psychotic patients. I. Neuroleptic-free psychotic patients. *Psychol. Med.* **25**, 461–471 (1995).
102. Crawford, T. J. *et al*. Abnormal saccadic distractibility in patients with schizophrenia: a 99mTc-HMPAO SPET study. *Psychol. Med.* **26**, 265–277 (1996).
103. Rosse, R. B., Schwartz, B. L., Kim, S. Y. & Deutsch, S. I. Correlation between antisaccade and Wisconsin Card Sorting Test performance in schizophrenia. *Am. J. Psychiatry* **150**, 333–335 (1993).
104. McDowell, J. E. *et al*. Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. *Biol. Psychiatry* **51**, 216–223 (2002).
105. Barkley, R. A. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol. Bull.* **121**, 65–94 (1997).
106. Munoz, D. P., Armstrong, I. T., Hampton, K. A. & Moore, K. D. Altered control of visual fixation and saccadic eye movements in attention-deficit hyperactivity disorder. *J. Neurophysiol.* **90**, 503–514 (2003).
107. Lezak, M. D. *Neuropsychological Assessment* (Oxford Univ. Press, Oxford, 1995).
108. Chan, F., Armstrong, I. T., Pari, G., Riopelle, R. J. & Munoz, D. P. Saccadic eye movement tasks reveal deficits in automatic response inhibition in Parkinson's disease. *Neuropsychologia* (in the press).
109. Chen, Y. F., Chen, T. & Tsai, T. T. Analysis of volition latency on antisaccadic eye movements. *Med. Eng. Phys.* **21**, 555–562 (1999).
110. Briand, K. A., Strallow, D., Hening, W., Poizner, H. & Sereno, A. B. Control of voluntary and reflexive saccades in Parkinson's disease. *Exp. Brain Res.* **129**, 38–48 (1999).
111. Fukushima, J., Fukushima, K., Miyasaka, K. & Yamashita, I. Voluntary control of saccadic eye movement in patients with frontal cortical lesions and parkinsonian patients in comparison with that in schizophrenics. *Biol. Psychiatry* **36**, 21–30 (1994).
112. Vidailhet, M. *et al*. Eye movements in parkinsonian syndromes. *Ann. Neurol.* **35**, 420–426 (1994).
113. LeVasseur, A. L., Flanagan, J. R., Riopelle, R. J. & Munoz, D. P. Control of volitional and reflexive saccades in Tourette's syndrome. *Brain* **124**, 2045–2058 (2001).
114. Leigh, R. & Zee, D. *The Neurology of Eye Movements* (Oxford Univ. Press, Oxford, 1999).
115. Sparks, D. L. The brainstem control of saccadic eye movements. *Nature Rev. Neurosci.* **3**, 952–964 (2002).
116. Wurtz, R. H. & Goldberg, M. E. *The Neurobiology of Saccadic Eye Movements* (Elsevier, Amsterdam, 1989).
117. Maunsell, J. H. & Newsome, W. T. Visual processing in monkey extrastriate cortex. *Annu. Rev. Neurosci.* **10**, 363–401 (1987).
118. Andersen, R. A. Multimodal integration for the representation of space in the posterior parietal cortex. *Philos. Trans. R. Soc. Lond. B* **352**, 1421–1428 (1997).
119. Colby, C. L. & Goldberg, M. E. Space and attention in parietal cortex. *Annu. Rev. Neurosci.* **22**, 319–349 (1999).
120. Pare, M. & Wurtz, R. H. Progression in neuronal processing for saccadic eye movements from parietal cortex area LIP to superior colliculus. *J. Neurophysiol.* **85**, 2545–2562 (2001).
121. Ferraina, S., Pare, M. & Wurtz, R. H. Comparison of cortico-cortical and cortico-collicular signals for the generation of saccadic eye movements. *J. Neurophysiol.* **87**, 845–858 (2002).
122. Schall, J. D. Visuomotor areas of the frontal lobe. *Cereb. Cortex* **12**, 527–638 (1997).
A comprehensive review of the possible roles of different areas in the frontal lobe in visually guided movements.
123. Dias, E. C. & Segraves, M. A. Muscimol-induced inactivation of monkey frontal eye field: effects on visually and memory-guided saccades. *J. Neurophysiol.* **81**, 2191–2214 (1999).
124. Rivaud, S., Muri, R. M., Gaymard, B., Vermersch, A. I. & Pierrot-Deseilligny, C. Eye movement disorders after frontal eye field lesions in humans. *Exp. Brain Res.* **102**, 110–120 (1994).
125. Sommer, M. A. & Tehovnik, E. J. Reversible inactivation of macaque frontal eye field. *Exp. Brain Res.* **116**, 229–249 (1997).
126. Coe, B., Tomihara, K., Matsuzawa, M. & Hikosaka, O. Visual and anticipatory bias in three cortical eye fields of the monkey during an adaptive decision-making task. *J. Neurosci.* **22**, 5081–5090 (2002).
127. Stuphorn, V., Taylor, T. L. & Schall, J. D. Performance monitoring by the supplementary eye field. *Nature* **408**, 857–860 (2000).
128. Segraves, M. A. & Goldberg, M. E. Functional properties of corticotectal neurons in the monkey's frontal eye field. *J. Neurophysiol.* **58**, 1387–1419 (1987).
129. Sommer, M. A. & Wurtz, R. H. Composition and topographic organization of signals sent from the frontal eye field to the superior colliculus. *J. Neurophysiol.* **83**, 1979–2001 (2000).
130. Stanton, G. B., Goldberg, M. E. & Bruce, C. J. Frontal eye field efferents in the macaque monkey: II. Topography of terminal fields in midbrain and pons. *J. Comp Neurol.* **271**, 493–506 (1988).
131. Munoz, D. P., Dorris, M. C., Pare, M. & Everling, S. On your mark, get set: brainstem circuitry underlying saccadic initiation. *Can. J. Physiol. Pharmacol.* **78**, 934–944 (2000).
132. Gandhi, N. J. & Keller, E. L. Spatial distribution and discharge characteristics of superior colliculus neurons antidromically activated from the omnipause region in monkey. *J. Neurophysiol.* **78**, 2221–2225 (1997).
133. Segraves, M. A. Activity of monkey frontal eye field neurons projecting to oculomotor regions of the pons. *J. Neurophysiol.* **68**, 1967–1985 (1992).
134. Alexander, G. E., DeLong, M. R. & Strick, P. L. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* **9**, 357–381 (1986).
135. Nakahara, H., Doya, K. & Hikosaka, O. Parallel cortico-basal ganglia mechanisms for acquisition and execution of visuomotor sequences — a computational approach. *J. Cogn. Neurosci.* **13**, 626–647 (2001).
136. Hallett, M. Physiology of basal ganglia disorders: an overview. *Can. J. Neurol. Sci.* **20**, 177–183 (1993).
137. Kornblum, S., Hasbroucq, T. & Osman, A. Dimensional overlap: cognitive basis for stimulus-response compatibility — a model and taxonomy. *Psychol. Rev.* **97**, 253–270 (1990).
138. Wise, S. P. & Murray, E. A. Arbitrary associations between antecedents and actions. *Trends Neurosci.* **23**, 271–276 (2000).
139. Duncan, J. in *Attention and Performance VI* (ed. Dornic, S.) 49–61 (Erlbaum, Hillsdale, New Jersey, 1977).
140. Hommel, B. & Prinz, W. *Theoretical Issues in Stimulus-Response Compatibility* (Elsevier, Amsterdam, Holland, 1997).
141. Proctor, R. W. & Reeve, T. G. *Stimulus-Response Compatibility: An Integrated Perspective* (Elsevier, Amsterdam, Holland, 1990).
142. Simon, J. R. Reactions toward the source of stimulation. *J. Exp. Psychol.* **81**, 174–176 (1969).
143. Simon, J. R. & Berbaum, K. Effect of conflicting cues on information processing: the 'Stroop effect' vs. the 'Simon effect'. *Acta Psychol. (Amst.)* **73**, 159–170 (1990).
144. Riehle, A., Kornblum, S. & Requin, J. Neuronal coding of stimulus-response association rules in the motor cortex. *Neuroreport* **5**, 2462–2464 (1994).
145. Zhang, J., Riehle, A., Requin, J. & Kornblum, S. Dynamics of single neuron activity in monkey primary motor cortex related to sensorimotor transformation. *J. Neurosci.* **17**, 2227–2246 (1997).
146. Crammond, D. J. & Kalaska, J. F. Modulation of preparatory neuronal activity in dorsal premotor cortex due to stimulus-response compatibility. *J. Neurophysiol.* **71**, 1281–1284 (1994).
147. Stroop, J. R. Studies of interference in serial verbal reactions. *J. Exp. Psychol.* **18**, 643–662 (1935).
148. Glaser, M. O. & Glaser, W. R. Time course analysis of the Stroop phenomenon. *J. Exp. Psychol. Hum. Percept. Perform.* **8**, 875–894 (1982).
149. MacLeod, C. M. Half a century of research on the Stroop effect: an integrative review. *Psychol. Bull.* **109**, 163–203 (1991).
150. Eriksen, B. A. & Eriksen, C. W. Effects of noise letters upon the identification of a target letter in a nonsearch task. *Percept. Psychophys.* **16**, 143–149 (1974).

Acknowledgements

D.P.M. is supported by the Canadian Institutes of Health Research and the Canada Research Chair Program. S.E. is supported by the National Alliance for Research on Schizophrenia and Depression, CIHR and the EJLB Foundation. J. Fecteau and J. Connolly commented on an earlier version of the manuscript.

Competing interests statement

The authors declare that they have no competing financial interests.

Online links

DATABASES

The following terms in this article are linked online to:
OMIM: http://www.ncbi.nlm.nih.gov/Omim/
attention-deficit hyperactivity disorder | Parkinson disease | schizophrenia | Tourette's syndrome

Access to this interactive links box is free online.