Inhibitory Control and the Frontal Eye Fields

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Abstract

Inhibitory control mechanisms are important in a range of behaviors to prevent execution of motor acts which, having been planned, are no longer necessary. Ready examples of this can be seen in a range of sports, such as cricket and baseball, where the choice between execution or inhibition of a bat swing must be made in a brief time interval. The role of the FEFs, an area typically described in relation to eye movement functions but also involved in visual processes, was investigated in an inhibitory control task using transcranial magnetic stimulation (TMS). A stop signal task with manual responses was used, providing measures of impulsivity and inhibitory control. TMS over FEF had no effect on response generation (impulsivity, indexed by go signal RT) but disrupted inhibitory control (indexed by stop signal RT). This is the first demonstration of a role for FEF in this type of task in normal subjects in a task which did not require eye movements and complements previous TMS findings of roles for pre-SMA and inferior frontal gyrus (IFG) in inhibitory control.

INTRODUCTION

Inhibitory control in the context of prepotent actions is important in a variety of scenarios. This is readily seen in many occasions, such as driving toward a crossroad, where the choice of whether to execute or to withhold an action (acceleration or braking) must be made in a brief time window. Inhibitory control is also socially important and is thought to function to regulate behavior and to prevent the enacting of behaviors with negative social consequences (Howard, 2002; Valzelli, 1984). Deficits in inhibitory control are seen in clinical populations (e.g., Armstrong & Munoz, 2003; Schachar, Tannock, & Logan, 1993; Schachar & Logan, 1990) and impulsive violence (e.g., Gray, 1987).

Stop signal tasks can be used to provide measures of both inhibitory control and impulsivity (e.g., Schall, Hanes, & Taylor, 2000; Logan & Cowan, 1984; for a review, see Chambers, Garavan, & Bellgrove, 2009; Boucher, Palmeri, Logan, & Schall, 2007). In these tasks, a target is presented to which a response has to be made unless a stop signal is presented. Stop signals occur relatively rarely and their timing relative to the target can be varied to allow derivation of indices of inhibitory control and impulsivity. Performance on this task is usually described in terms of a race between the go and the stop processes, with whichever reaches threshold first governing production or withholding of the response to the target (Logan & Cowan, 1984). It is possible to calculate the time required to inhibit planned responses (stop signal RT [SSRT]) and impulsivity is indexed by the derived go response time (go RT). This task has been found to be sensitive to deficits in a range of clinical conditions, drug dependency, and pharmacological manipulations (e.g., Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006; Li, Milivojevic, Kemp, Hong, & Sinha, 2006; Ramaekers & Kuypers, 2006), and elevated SSRTs, indicating altered inhibitory control, have been seen in impulsive violent offenders (Chen, Muggleton, Juan, Tzeng, & Hung, 2008).

A range of brain areas have been linked to inhibitory control and impulsivity mechanisms. For example, studies of instrumental aggression (e.g., Blair, 2004) have implicated areas such as OFC and the amygdala in inhibitory control mechanisms. However, it has been argued that impulsivity, abnormalities of which are seen in impulsive violent behavior, may be largely dissociable and have different neurological substrates (e.g., Chambers et al., 2007). Consistent with this, transcranial magnetic stimulation (TMS) delivered over the pre-SMA, an area connected to regions implicated in inhibitory control (right inferior frontal gyrus and subthalamic nuclei; Aron et al., 2007), altered the ability to respond to the stop signals, indicative of altered inhibitory control, but was without effect on an impulsivity measure (Chen, Muggleton, Tzeng, Hung, & Juan, 2009). As well as pre-SMA, the role of right inferior frontal gyrus has also been investigated using TMS (Chambers et al., 2006). Like pre-SMA stimulation, TMS over this area was without effects on impulsivity.

Inhibitory control has also been widely investigated with eye movement tasks. Lying in proximity to the pre-SMA and the supplemental eye fields, FEFs are also typically investigated in the context of their role in eye movements.
The functional roles of fixation neurons, movement neurons, and visually responsive neurons make this region an ideal for the investigation of inhibitory process (Lo, Boucher, Pare, Schall, & Wang, 2009; for a review, see, Schall, Stuphorn, & Brown, 2002). Although classically FEF is mainly associated with eye movement-related functions, many monkey neurophysiological studies have demonstrated a role for FEF in visual selection without eye movements (e.g., Thompson, Bichot, & Schall, 1997; for a review, see Schall, 2009). This has also been the subject of much recent investigation and in humans where FEF has been shown to be involved in visual tasks in the absence of eye movements (Kalla, Muggleton, Juan, Cowey, & Walsh, 2008; O’Shea, Muggleton, Cowey, & Walsh, 2004; Muggleton, Juan, Cowey, & Walsh, 2003). This visual involvement has been shown to be dissociable from saccade generation in both monkeys and humans (Juan et al., 2008; Juan, Shorter-Jacobi, & Schall, 2004). In tasks involving eye movements, when generating saccades away from a target, FEF shows differential coherence with pre-SMA compared with when generating a saccade to a target (Miller, Sun, Curtis, & D’Esposito, 2005) and has also been shown to be active in a saccade countermanding task on stop signal trials (Curtis, Cole, Rao, & D’Esposito, 2005).

Evidence from studies investigating saccades, in tasks such as the countermmanding paradigm, suggests that FEF is involved in inhibitory control, at least in the context of eye movements. Hanes and Carpenter (1999), using such a task in monkeys, found evidence for a race between FEF saccade neurons responding to the target and FEF fixation neurons on stop trials. In agreement with this, Curtis et al. (2005), using a countermmanding task in an fMRI study, found that FEF responded when a saccade had to be generated but had a greater response when the signal to inhibit such a saccade was presented during a trial. Similarly, using single unit recordings in monkeys, Thompson, Biscoe, and Sato (2005) found that manual responses are associated with inhibition of FEF movement neurons when the task does not require a saccade to be made. These findings suggested that the FEF might serve a general function related to inhibitory control in the absence of the involvement of eye movements. Here we used TMS and a stop signal response task to investigate the involvement of human FEF in inhibitory control and impulsivity when saccades were neither the relevant response nor required for successful performance, requiring instead manual responses to be made to the stimuli presented. In Experiment 1, a conventional stop signal task in which targets were presented in the periphery was used to investigate the causal role of FEF on the task. In Experiment 2, the targets were presented in the center of the screen to exclude potential covert processes related to eye movements that were possible in Experiment 1. Several studies have shown a role for FEF in visual selection independent of eye movements (e.g., Juan et al., 2008; Muggleton et al., 2003; Ro, Farnè, & Chang, 2003) and its role on the stop signal task (e.g., Curtis et al., 2005). We therefore predicted that TMS delivered over this area would affect inhibitory control while being without effect on impulsivity.

EXPERIMENT 1

Methods

Participants

Nine volunteer college students (aged 21–35 years, mean = 25.7, 7 men, 2 women, all right-handed) took part in the experiment. All gave informed consent before participation. The experiment was approved by institutional review board of the Chang-Gung Memorial Hospital, Taoyuan.

Apparatus

Testing took place in a sound attenuated room. Stimuli were presented on a 19-in. CRT screen using video resolution of 800 × 600 pixels and a vertical refresh rate of 100 Hz. The subjects sat 75 cm in front of the screen, the center of which was at eye level. The task was programmed using E-prime running on a Pentium IV PC, which controlled the presentation of the stimuli as well as recording response information.

Procedure

Task. At the beginning of each trial, a central fixation dot appeared for 500 msec. Following offset of the central fixation dot, a white dot was presented to the left or right of the fixation at 9° of eccentricity on the horizontal meridian (see Figure 1). On 75% of trials (go trials), subjects were required to make a keypress response on a response box with the left index finger when the dot was presented on the left or with the right index finger when the dot was presented on the right. On 25% of these trials, the central fixation dot reappeared and acted as an instruction to withhold responses to the peripheral target. Eye movements were not monitored in the task.

Baseline parameters. Before experimental blocks as outlined above, each subject took part in a session with no stop signal trials. The purpose of this was to obtain each subject’s mean go RT in the absence of stop signals. Next, each individual subject’s stop signal delay (SSD) was obtained. SSD is a measure of the probability of responding for a given SSD (the inhibition function) in accordance with the race model of Logan and Cowan (1984). The latency of the stop process can be estimated from the start time, which is under experimental control in the form of SSDs, to the end of the stop process, which is inferred from the observed go RT distribution. SSD can be determined by adjusting the time between the onset of the go stimulus and that of the stop signal. To obtain the measure for each individual, stop signals were presented on 25% of trials and subjects were required to press a button within
the range of the mean RT plus two standard deviations (obtained from the trials presented with no stop signal). Fast responses were encouraged. This was expected to limit any strategies involving slowing of responses to reduce error rates (see Chen et al., 2008). The default SSD was initially set at 170 msec and was adjusted until the subject’s accuracy on stop trials reached 50%. If the subject performed better than this, then the SSD was increased by 40 msec. Conversely, failure resulted in SSD being decreased by 40 msec. A critical SSD was computed that represented the time delay required for the subject to succeed in withholding a response in the stop trials half of the time (Chen et al., 2009).

**TMS blocks.** The main body of the experiment consisted of two conditions; one of these involved FEF TMS (over the right FEF, the site of interest) and the other one involved vertex TMS (a control for auditory/tactile TMS sensations). In each condition, subjects received 20 blocks, 10 blocks for TMS stimulation and the other 10 blocks without TMS, which served as another control condition. Each experimental block included 48 trials and lasted approximately 4 min. The order of TMS and no TMS blocks was randomized within each condition for every subject. Three SSDs were presented to each subject on the basis of their individual baseline SSDs; baseline SSD, 40 msec less than baseline SSD and 40 msec more than baseline SSD. Thus, if a subject’s SSD was 210 msec, the other two conditions were 170 and 250 msec. The occurrence and the order of the three SSDs were randomized within each block. During blocks with TMS, two pulses with an interpulse interval of 100 msec were delivered over the relevant stimulation site concurrent with the onset of the go signal. A Magstim Super Rapid machine was used (Magstim Company, Wales, UK) to deliver TMS at 65% of maximum output (approximately 1.3 T, duration of one pulse = less than 1 msec) over the FEF and the vertex. A fixed stimulation level was used because it has proven successful and replicable in many studies and over a wide range of tasks (e.g., Juan et al., 2008; Ellison & Cowey, 2007; Hung, Driver, & Walsh, 2005; Muggleton et al., 2003; Rushworth, Passingham, & Nobre, 2002; Ashbridge, Walsh, & Cowey, 1997) and because motor cortex excitability does not provide a good guide to TMS thresholds in other cortical areas (Stewart, Walsh, & Rothwell, 2001). Stimulation was delivered via a 70-mm figure of eight coil held clamped in position. In the FEF TMS condition, the coil was placed tangentially over the FEF. In the vertex TMS condition, it was placed parallel to the sagittal midline (with the direction of the current over the stimulation site travelling in the same lateral to medial direction).

**FEF stimulation sites were localized in each subject by transformation of the MRI coordinates (33, 5, 65; Muggleton et al., 2003, see Figure 2) from standard space to that of individual MRIs from each participant. These coordinates are the average location of FEF stimulation, which resulted in disruption of conjunction visual search performance and are close to the MNI equivalent location of the Talairach...**
coordinates identified as the average FEF location by Paus (1996; 30, 6, 60). Briefly, this procedure consisted of normalizing subjects’ individual scans against the MRI template image (using the FSL software package, FMRIB, Oxford, UK). This produced a file containing the mathematical description of the transform that was then used to convert the stimulation site coordinates from standard space to that of the individual being tested. These were then labeled on the brain image in the Brainsight software and the locations to be stimulated marked on the head of the subject following coregistration of the subject with their structural scan. This method has proved successful and reliable in identifying FEF in previous studies involving both eye movements and cognitive processes (Juan, Muggleton, Cowey, & Walsh, 2008; Nuding et al., 2008).

Analysis. Go RTs were filtered by removing error trials and trials with latencies below 200 msec. In addition, individual mean RTs for the correct trials were analyzed after removal of outliers from the RT distribution (defined as responses more than two standard deviations from the mean) on a subject-by-subject basis. The estimation of the internal response time to the stop signal (SSRT) was calculated using the distribution of go signal RTs and the probability of responding given an SSD (the inhibition function) in accordance with the race model of Logan and Cowan (1984). The latency of the stop process can be estimated from the start time, which is under experimental control in the form of SSDs, to the end of the stop process, which is inferred from the observed go RT distribution. In this study, SSRTs for each stop signal time were estimated using the integration method (Hanes & Carpenter, 1999; Hanes, Patterson, & Schall, 1998) then averaged to produce an overall estimate of SSRT. Although this method assumes that the SSRTs are constant across trials, violation of this assumption does not significantly alter the outcome of the analysis (Hanes et al., 1998; Logan & Cowan, 1984). Notwithstanding this, Band, van der Molen, and Logan (2003) found observed SSRTs are affected by SSDs. Consequently, we calculated the average SSRT for SSDs where the proportion of trials in which subjects failed to inhibit responding lay between 0.15 and 0.85 (Band et al., 2003). SSRT was calculated on the basis of the relationship between the SSD, the SSRT, and the distribution of go RTs. The distribution of go RTs was integrated from the time of onset of the go signal. For each SSD, a probability of responding was obtained. If
the SSD of 50 msec resulted in an error rate = 0.20, then the end of the stop process should be at a point equal to 20% of the go RT distribution. Therefore, if the point corresponding to 20% of the go RT distribution was 252 msec, the observed SSRT would be 252 − 50 = 202 msec. The rest of the SSRTs were calculated using the same procedure. A summary SSRT was acquired by averaging the observed three SSRTs that corresponded to .15 < p (respond) < .85 (Band et al., 2003).

Results

Repeated measures ANOVA was carried out for go RT (for correct and failed trials), SSRT and accuracy with factors of TMS site (FEF, vertex, and no TMS), and response hand. As there was no significant effect of response hand, F(1, 8) = 2.993, p = .122, and neither was there a significant interaction between the mean RTs of response hands across the different stimulation site conditions, F(2, 16) = 1.371, p = .282, the data were collapsed for this factor and the analysis repeated with it omitted. Post hoc comparisons were made using the least significant difference test.

Go RTs (Correct Responses) (Impulsivity)

Figure 3A shows the mean go RTs. There were no significant effects of TMS condition on go RTs, F(2, 16) = 0.2, p = .82.

Go RTs (Incorrect Responses)

Figure 3B shows the mean go RTs when responses were not inhibited appropriately. Again there was no significant effect of TMS on go RTs for these responses, F(2, 16) = 0.051, p = .951.

Mean Error Rates

Figure 3C shows the mean error rates. Significant differences were observed among the error rates for the three TMS conditions, F(2, 16) = 4.73, p = .024. The mean error rate when TMS was applied to FEF was significantly higher than when applied to vertex (p = .03) and also higher than in the no TMS condition (p = .019). There was also a significant interaction between SSD and stimulation site, F(4, 32) = 4.105, p = .009 (see Figure 4). This was due to elevated errors (failures to cancel responses) for the shortest SSD, F(2, 16) = 6.028, p = .011, FEF versus vertex p = .032, FEF versus no TMS p = .014, vertex versus no TMS p = .809.

SSRT (Inhibitory Control)

Figure 3D shows the mean SSRTs for the different TMS conditions. There were significant differences across the different conditions, F(2, 16) = 9.55, p = .002. The SSRT for FEF TMS was significantly longer than for vertex TMS, t_{0.5}(8) = 3.325, p = .01, and the no TMS condition, t_{0.5}(8) = 3.331, p = .01.

In the study of the role of inferior frontal gyrus (IFG) in inhibitory control by Chambers et al. (2006), they found a significant effect of session on the modulation of performance by TMS. For this reason, we analyzed the data described above with an additional factor of block order. This was without significant effect on any of the measures: go RT × block, F(2, 16) = 0.239, p = .79; uncanceled go RT × block, F(2, 16) = 0.983, p = .396; uncanceled rate × block, F(2, 16) = 0.367; and SSRT × block, F(2, 16) = 3.281, p = .064. The performance of individual subjects is shown in Supplementary Table 1.

EXPERIMENT 2

Methods

Because the go target was presented in the periphery and the stop signal was presented in the center in Experiment 1, it could be argued that any FEF TMS effects were a consequence of inhibition and shifting of attentional resources related to stop signal processing. In Experiment 2, to specifically exclude the involvement of covert attention in the task, we used a variation of the stop signal task in which the go target and the stop signal were both presented centrally. This ensured that any TMS effects observed in this experiment could not be a consequence of any FEF functions related to the spatial allocation of attention or effects on saccadic eye movements.

Procedure

The general methods and the TMS parameters in Experiment 2 were similar to those in Experiment 1. Because we had established that vertex TMS had no effects on stop signal task, we used no TMS as our control comparison to decrease unnecessary TMS pulses delivered to our participants. Therefore, we had one condition composed of 10 blocks of FEF TMS trials and another 10 blocks of No TMS trials in this experiment.

Task

At the beginning of each trial, a central fixation cross was presented for 500 msec. Following offset of the central fixation cross, a white go signal was presented in the center of the screen against a black background. Arrowheads were constructed as equilateral triangles with an edge length of 18 mm. On 75% of trials (go trials), subjects were required to make a keypress response on a response box with the left index finger when a left arrowhead was presented or with the right index finger when a right
On 25% of the trials (stop trials), the central go signal changed from triangles to rhombuses and acted as an instruction to withhold responses to the go signal. Subjects received 20 blocks of trials, 10 blocks for FEF TMS and the other 10 blocks of no TMS trials. The order of TMS and no TMS blocks was randomized within each condition. Each experimental block included 48 trials and lasted approximately 4 min, identical to the previous experiment; the occurrence and the order of the three SSDs were randomized within each block.
Participants

Nine volunteer college students (aged 20 to 27 years, mean 22.9, 5 men, 4 women, all right-handed) took part in the experiment. Two of the subjects participated in the Experiment 1. All gave informed consent before participation. The experiment was approved by institutional review board of the Chang-Gung Memorial Hospital, Taoyuan.

Results

The $t$ tests were carried out for go RTs (for correct and failed trials), SSRTs, and accuracy with factors of TMS site (FEF and no TMS).

Go RTs (Correct Responses) (Impulsivity)

Figure 5A shows the mean go RTs. There were no significant effects of TMS condition on go RTs, $t_{0.5}(8) = 0.779$, $p = .458$.

Go RTs (Incorrect Responses)

Figure 5B shows the mean go RTs when responses were not inhibited appropriately. Again there was no significant effect of TMS on go RTs for these responses, $t_{0.5}(8) = 0.402$, $p = .699$.

Mean Error Rates

Figure 5C shows the mean error rates (noncanceled rates). Significant differences were observed between the error rates for the two TMS conditions, $t_{0.5}(8) = 3.298$, $p = .011$. The FEF TMS impaired subjects’ performance by 10.3% (FEF TMS, 65.6% vs. No TMS, 55.3%). There was no significant interaction between SSD and stimulation site, $F(2, 16) = 1.768$, $p = .202$ (see Figure 6). There was a main effect for the different TMS conditions, $F(1, 8) = 10.458$, $p = .012$, and also a significant effect for the different SSDs, $F(2, 16) = 30.878$, $p < .001$.

SSRT (Inhibitory Control)

Figure 5D shows the mean SSRTs for the different TMS conditions. There was a significant difference between the two conditions, $t_{0.5}(8) = 3.836$, $p = .005$. The FEF

![Figure 4](image-url) The inhibition function, that is, the rate of failure to cancel responses on trials where a stop signal was presented as a function of the SSD used. A significant elevation in error rates was seen for short SSDs with FEF TMS (*$p = .032$ FEF vs. vertex TMS, $p = .014$ FEF vs. no TMS).
TMS significantly impaired subjects’ performance by 10 msec (FEF TMS, 185.6 msec vs. No TMS, 175.1 msec). To examine whether the length of critical SSD in modified the observed TMS effects, we categorized subjects into either a shorter SSD subgroup or a longer SSD subgroup and performed a two-way ANOVA analysis. The results showed significant interaction between groups and TMS condition, $F(1, 7) = 0.111, p = .749$. There was a main effect for TMS condition, $F(1, 7) = 9.323, p = .018$. There was no significant main effect for group, $F(1, 7) = 0.009, p = .927$. The performance of individual subjects in Experiment 2 is shown in Supplementary Table 2.

**DISCUSSION**

TMS delivered over right FEF disrupted performance on a stop signal response task where a target position had to be indicated by a manual keypress unless a signal to withhold the response was presented. Specifically, SSRTs were elevated, as was the rate of failing to cancel a response when required to do so when the SSD was short. This pattern of change for these measures is indicative of disruption of inhibitory control as a consequence of FEF TMS. No effects on impulsivity as indexed by go RTs were seen.

Previously, TMS over FEF has been shown to disrupt saccades (Thickbroom, Stell, & Mastaglia, 1996) as well as performance on a range of visual tasks, even when saccades were unnecessary or prevented (Kalla et al., 2008; O’Shea et al., 2004; Muggleton et al., 2003). Effects on visual tasks as a consequence of FEF TMS include impairment of conjunction visual search performance (Muggleton et al., 2003), modulated priming (Muggleton, Juan, Cowey, Walsh, & O’Breathnach, in press; Campana, Cowey, Casco, Oudsen, & Walsh, 2007), and altered target detection (Grosbras & Paus, 2003) among others. The effects seen here are unlikely to be a consequence of disruption of either target detection or priming. Modulation of target detection is inconsistent with the absence of any effect on go RTs. Were subjects having greater difficulty in detecting the target to which they were to respond, elevation of this measure might reasonably be predicted if this were disrupted or reduced if target detection were facilitated, as has been sometimes seen with FEF TMS and single target detection (Grosbras & Paus, 2003), albeit with different stimulation parameters from those used in the present study. The results of Experiments 1 and 2 clearly suggest that effects on saccades also seem an unlikely source for the specific pattern of disruption seen, particularly given that saccades were not a performance measure and manual indication of the location of the target was required. Although it has been argued that saccade preparation and visual processing may be linked, particularly in the premotor theory of attention (Rizzolatti, 1983), a disruptive effect as a consequence of modulation of saccade-related processes would seem an unlikely candidate for an effect on SSRT/successful cancellation rate, particularly given the absence of an effect on go RT.

The pattern of disruption seen here shares a pattern with that previously reported on the same task with TMS delivered over pre-SMA (Chen, Muggleton, Juan, Tzeng, & Hung, 2009), which caused an alteration of inhibitory control. However, the effects with pre-SMA TMS differed from the FEF disruption seen here in that pre-SMA TMS modulated performance early in the experiment, a modulation that was greatly attenuated later. This change might suggest greater importance for pre-SMA in the formation of new inhibitory associations. There was no indication of a similar pattern for FEF TMS effects, with no effects of early/late experimental block on any measures.

Evidence from studies investigating a number of areas involved in saccade generation (Schall et al., 2000; Hanes et al., 1998) shows that it is the competition between gaze-shifting and gaze-holding mechanisms that determine if a saccade is produced, with FEF being one such area. One possibility is that rather than this FEF involvement being specific to saccades, it is more generally involved in inhibitory control. TMS delivered over FEF in the present study may therefore result in disruption by altering the ability of FEF to exert inhibitory control effectively, consequently elevating SSRTs. Although there is evidence from both monkey (Hanes et al., 1998) and imaging (Curtis et al., 2005) of competition between saccade and fixation neurons in FEF in determining whether a response is made in a countermanding task, the present data suggest that this competition is important independent of the response modality (e.g., Thompson et al., 2005). As there were no effects suggestive of modulation of any visual processes (which would be one possible explanation if go RTs had been elevated), further investigation may allow assessment of whether this, as appears to be the case, provides further evidence of that saccade and visual processes can be dissociated (c.f., Juan et al., 2004, 2008) with FEF important not only in the control of eye movement execution but also in the control of prepotent manual responses.

In summary, FEF, like IFG and pre-SMA, is involved in successful performance of the countermanding task with TMS delivered over this area resulting in elevated SSRTs and indicative of altered inhibitory control. Apart from...
the control of eye movement execution and inhibition, FEF may have a more general role when inhibitory control is necessary. Direct comparison between these areas, particularly with respect to maintenance of inhibition over time and how this relates to their functions (e.g., IFG and pre-SMA may be involved in forming new inhibitory associations, FEF may have a more general role when inhibitory control is necessary), remains an area for future investigation.

UNCITED REFERENCE
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