Dissociating the contributions of human frontal eye fields and posterior parietal cortex to visual search

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Running head: Dissociation of FEF and PPC in visual search
Abstract

Imaging, lesion and transcranial magnetic stimulation (TMS) studies have implicated a number of regions of the brain in searching for a target defined by a combination of attributes. The necessity of both frontal eye fields and posterior parietal cortex in task performance has been shown by the application of TMS over these regions. The effects of stimulation over these two areas have, thus far, proved to be remarkably similar and the only dissociation reported being in the timing of their involvement. We tested the hypotheses that (1) FEF contributes to performance in terms of visual target detection (possibly by modulation of activity in extrastriate areas with respect to the target) and (2) that PPC is involved in translation of visual information for action. We used a task where the presence (and location) of the target was indicated by an eye movement. Task disruption was seen with FEF TMS (with reduced accuracy on the task) but not with PPC stimulation. When a search task requiring a manual response was presented, disruption with PPC TMS was seen. These results show dissociation of FEF and PPC contributions to visual search performance and that PPC involvement seems to be dependent on the response required by the task whereas this not the case for FEF. This supports the idea FEF involvement in visual processes in a manner which might not depend on the required response whereas PPC seems to be involved when a manual motor response to a stimulus is required.

Keywords: conjunction search, voluntary saccades, dissociation
Introduction

The apparently straightforward task of detection of the presence or absence a target amongst distractors is associated with a number of regions in the brain in circumstances where the target is defined by a combination of features, such as shape and colour, which can be shared with distractors. Involvement of the posterior parietal cortex has been implicated by imaging studies (Donner et al. 2002; Corbetta et al. 1995) and the necessity of the area shown by both patient studies (Friedman-Hill et al. 1995) and the application of transcranial magnetic stimulation (TMS) (Ashbridge et al. 1997; Walsh et al. 1998; Kalla et al. 2008). Similar involvement of frontal eye fields has been illustrated (Donner et al. 2002; Muggleton et al. 2003; O'Shea et al. 2004). The pattern of disruption seen as a consequence of TMS application for these areas has, to date, been broadly similar. Elevated response times are found when large search arrays (which allow eye movements) are presented (Ashbridge et al. 1997; Walsh et al. 1998) and reduced sensitivity is seen when small, short duration displays (without eye movements) are used (Muggleton et al. 2003; O'Shea et al. 2004; Kalla et al. 2008). The most notable differences seen have been in the timing of the involvement of the two areas. O'Shea et al (2004) showed that the time window of disruption of performance with FEF TMS was early (40-80 ms) following search array presentation, broadly in line with the timing of target selection in this region seen in electrophysiology studies (Schmolesky et al. 1998; Nowak et al. 1997; Sato and Schall 2003). This is earlier than the disruption previously seen with PPC stimulation for large search arrays (100-160 ms, Ashbridge et al. 1997) and a recent comparison of the involvement of the two areas using the same task and subjects obtained a similar temporal dissociation (0-40 ms for FEF, 120-160 ms for PPC, Kalla et al. 2008).
Other than this temporal dissociation, differences in the relative contribution of these two areas to search performance remain to be clarified. Both have been suggested to be part of a distributed network involved in visual processing (Corbetta and Shulman 1998). FEF contains neurons that respond to behaviourally relevant stimuli rather than to visual attributes (Goldberg and Segraves 1989; Mohler et al. 1973) and has been described in terms of a saliency map for saccades (Schall and Bichot 1998). Target discrimination in FEF occurs independently of saccade programming (Juan et al. 2004; Juan et al. 2008) and it has been suggested that FEF plays a role in modulating extrastriate cortex activity with respect to the target (Moore et al. 2003; Taylor et al. 2007). If is were the case then altered performance following FEF TMS might be a consequence of disruption of FEF modulation of extrastriate cortex with respect to the search target (Grosbras and Paus 2003; Silvanto et al. 2006; Ruff et al. 2006). Similarly, PPC has also been shown to respond to behaviourally relevant stimuli, frequently being argued to play a role in the binding of features to a single object representation (Friedman-Hill et al 1995, Triesman 1996). PPC has also been proposed to have a role in spatial localisation of the target, consistent with a role in coordinate transformation and spatial updating across saccades (van Donkelaar & Muri 2002) as well as having saccade related functions (e.g. Elkington et al 1992, Muri et al 2000, Priori et al 1993). Deficits following TMS might represent spatial uncertainty in localising the target if it is present (Ellison et al. 2003). The later role of the PPC may also be consistent with modulatory effects on visual cortex activity. However, the later timing and the fact that PPC, unlike FEF, is important in trials in a visual search task when no target is presented (target absent trials, Ashbridge et al 1997), may be more consistent with the visuomotor transformation required for manual responses (Ellison et al. 2003).
Work to date using TMS and visual search tasks has typically required the indication of the presence or absence of a target in a search array and target localisation is not usually explicitly required. Additionally, few studies have directly compared the effects of FEF and PPC TMS within the same study, using the same task and response requirements. We used a visual search task where the presence or absence of the target was indicated by generating or withholding an eye movement to the target location to test the hypotheses that (1) FEF contributes to performance in terms of visual target detection and (2) that PPC is involved in translation of visual information for action. Thus, we predicted differing patterns of disruption for the two areas with FEF TMS expected to disrupt task accuracy in terms of identifying the presence or absence of the target and PPC TMS to result in spatial uncertainty, reflected in variability of the endpoints of generated saccades.
Materials and Methods

Subjects

Eight subjects (5 male, 3 female, mean age 23 years. all right handed) took part in the study. All were normal healthy volunteers and gave informed consent prior to participating. The local ethics committee approved the study.

Task

The task was programmed in C++ (Visual Studio 6) and presented using an IBM compatible PC on a 17 inch CRT monitor with a refresh rate of 100 Hz. Eye position was monitored using a SMI Eyelink I system, modified for use with TMS, with a sampling rate of 250 Hz. The time course of a typical trial is illustrated in Figure 1. The Eyelink system was calibrated at the start of each block, and each trial began with a correction of any eye drift. This was followed by the presentation of a fixation cross for a random duration between 300 and 700 ms, after which the trial array was presented. This consisted of a circular array of 8 stimuli, presented equally spaced and equidistant from the fixation cross at 10 degrees of visual angle. Distractors were red or blue diagonals with each colour associated with a different orientation (e.g. red / and blue \). A target, present in 50% of the trials, was either a red diagonal in the same orientation as the blue diagonals or vice versa. Each subject was assigned a target that remained the same for all blocks for that individual. Half of the subjects had a red target and half a blue target. When the array was presented subjects were required to either make a saccade to the target (if there was one present) or remain looking at the fixation cross (if no target was present). The array remained on the screen for 1s. This duration was selected to
allow sufficient time for performance of the task, meaning any effects on saccade latency due to TMS would not affect accuracy, while being a reasonable time to maintain fixation. Each block consisted of 40 trials. Subjects were tested on two occasions, one for each stimulation site (see below) with two blocks for the relevant site and two no TMS blocks on each occasion. The order of blocks was randomised for each subject.

**TMS**

TMS at 10 Hz for 500 ms starting concurrent with the onset of the search array was delivered by means of a Magstim 200 Super Rapid Stimulator. A 70 mm coil was used for PPC stimulation whereas a 50 mm coil was used for FEF as use of the larger coil over this area can result in twitches and blinks. A fixed stimulation level of 60% of maximum stimulator output was used because it has proven successful and replicable in many studies and over a wide range of tasks (Ashbridge et al. 1997; Rushworth et al. 2002; Muggleton et al. 2003; Ellison and Cowey 2007; Hung et al. 2005; Juan et al. 2008) and because motor cortex excitability does not provide a good guide to TMS thresholds in other cortical areas (Stewart et al. 2001).

**Site Localisation**

Sites for TMS stimulation were localised using the Brainsight system (Rogue Research). This was used to co-register each subject with their structural MRI scans on which the right FEF and right PPC had been marked. Only sites in the right hemisphere were used as stimulation of these produces effects in visual search tasks, irrespective of target location, whereas left hemisphere stimulation typically produces less consistent effects (Ashbridge et al. 1997,
Muggleton et al 2003). As we were interested in differences in the type of effect seen, rather than any specific investigation of laterality we chose to only stimulate the right hemisphere in the present experiment. The site marks were obtained by means of transformation of the FEF coordinates from Paus et al. (1997) and the coordinates for the PPC location associated with disruption of visual search performance (e.g. Göbel et al. 2001) using the FSL software package (FMRIB, Oxford). Briefly, this procedure consisted of normalizing subjects’ individual scans against the MRI template image. This produced a file containing a mathematical description of the normalization that was then used to convert the stimulation site coordinates from standard space to that of the individual being tested. This method has proved successful and reliable in identifying both FEF (e.g. Juan et al. 2008; Nuding et al. 2009) and PPC (e.g. Kalla et al. 2008; Muggleton et al. 2008) in previous studies. Stimulation sites are illustrated in Figure 1(b).

Data collection and analysis

Eye position information on each trial was sampled at 250 Hz by the Eyelink system throughout each trial. Saccades and blinks were also automatically detected and recorded and trials with blinks were excluded from further analysis. Saccades were automatically identified according to acceleration and amplitude criteria (minimum speed 30 degrees/s, minimum acceleration 8000 degrees/s²). The information used in analysis was presence (or absence) of a saccade on any given trial and saccade endpoint (with respect to the target). Performance (sensitivity) was scored in terms of d prime with hits (saccades made) and misses (saccades withheld) for target present trials, and false alarms (saccades made) and correct rejections (saccades withheld) for target absent trials. Bias (c) was also calculated from these measures and analysed. Additionally, for trials where saccades were made, the accuracy of the endpoint
was analysed. Accurate saccades were scored as those made towards the target such that the
endpoint was closer to the target element than any other element in the display and of
minimum amplitude of 1 degree (a level chosen as the minimum from which it was assumed
a direction had been reasonably selected for the saccade). All other saccades were scored as
inaccurate.
Results

Performance, in terms of sensitivity (d prime) is illustrated in Figure 2(a) and was analysed using repeated measures analysis of variance with factors of SITE (FEF or PPC) and stimulation (YES or NO). This showed a significant effect of stimulation ($F(1,7) = 13.686, p < 0.01$) and a significant site x stimulation interaction ($F(1,7) = 15.857, p < 0.01$). *Post-hoc* t-test showed that this was due to reduced sensitivity following FEF TMS relative to the FEF control condition ($t = 4.775, p < 0.005$) whereas there was no difference for the PPC TMS condition versus control ($t = 0.653, p > 0.5$). Bias scores ($c$) were also analysed in a similar manner, with the same factors, but no significant effects were seen (all $F$ values $< 2, p > 0.2$).

First saccade accuracy, i.e. whether the direction of saccades made were towards the location of the target element or not, was analysed in a similar manner, again employing an ANOVA with factors of SITE and STIMULATION. The data is illustrated in Figure 2 (b). No significant effects of site ($F(1,7) = 0.693, p > 0.4$) or TMS ($F(1,7) = .005, p > 0.9$) were seen. Thus task performance, in terms of ability to correctly judge whether a target was present or not, was reduced when TMS was delivered over FEF but not when delivered over PPC and neither stimulation site produced any effect in terms of saccade endpoint.

We also analysed the latencies of saccades with an ANOVA with factors of SITE and STIMULATION (as above). This data is illustrated in Figure 2 (c). No significant effects were seen (all $F < 1.7, p$ values $> 0.2$).

We further investigated any laterality effects of the FEF TMS effects on target present trials in terms of target detection accuracy, whether the saccade made on a present trial was in the appropriate direction, saccade latency and mean deviation of the saccade endpoint (all saccades) from the target. The data were analysed for the left and right hemisphere targets.
(the targets located above and below fixation were not included). The data from FEF TMS trials was compared with that from trials with no stimulation using paired t-tests. No significant effects were seen for any of the measures (all p > 0.19), (Accuracy: left targets, FEF: 94.7%, no TMS: 94.8%, right targets, FEF: 95.3%, no TMS: 96.4%, Saccade direction accuracy: left targets, FEF: 77.5%, no TMS: 81.2%, right targets, FEF: 84.0%, no TMS: 83.9%, Saccade latency: left targets, FEF: 605.6 ms, no TMS: 600.9 ms, right targets, FEF: 575.3 ms, no TMS: 589.8 ms, Saccade endpoint error: left targets, FEF: 1.49°, no TMS: 1.41°, right targets, FEF: 1.48°, no TMS: 1.30°).

PPC TMS control task

In light of the results from the main experiment we conducted a control task to ensure that our stimulation of PPC had been effective and that the absence of an effect of TMS for this condition on the task was not due to, for example, missing the target area. All but one of the same subjects was tested on a conjunction search task where the presence or absence of the target was indicated by a manual response rather than a saccade. Search arrays consisted of the same targets and distractors as in the saccade task, again with the target present on 50% of trials, but they were randomly distributed within a square (not shown to the subjects) of approximately 14 x 14 degrees of visual angle on the PC monitor. Additionally, arrays consisted of ten elements rather than eight. Arrays were presented until either a present or absent key press response (on a PC keyboard) was made and subjects were instructed to perform as fast as possible while minimizing errors. Stimulation was delivered over PPC, localized in the same manner as for the saccade task, or vertex. Additionally, trials with no stimulation were presented. TMS was delivered at 10 Hz for 500 ms at 60% of the machine maximum output and eighty trials per stimulation condition were presented in two blocks of forty trials. Median response times from correct trials are shown in Figure 3 and were analysed using repeated measures ANOVA with factors of SITE (PPC, vertex or none) and of...
trial TYPE (present or absent). This showed a significant effect of site ($F(1,6) = 13.093, p = 0.001$) and of type ($F(1,6) = 9.998, p = 0.02$). The type effect was due to slower responses for absent than present trials whereas the site effect was due to slower responses for PPC stimulation this was due to slower responses when TMS was delivered over PPC compared to both vertex and no TMS conditions ($p < 0.01$).
In humans, the involvement and necessity of both PPC and FEF in visual search for a target defined by a conjunction of attributes has been illustrated previously (Donner et al. 2002; Ashbridge et al. 1997; Muggleton et al. 2003). Dissociation of the contribution of these two areas has so far been limited to the timing of their involvement using TMS (Ashbridge et al. 1997; O'Shea et al. 2004; Kalla et al. 2008), with FEF involvement preceding that of PPC. Using a visual search task where the required response was a saccade to the target (if it was present) we investigated whether FEF and PPC would result in dissociable patterns of disruption.

Task disruption was seen for FEF TMS, which reduced sensitivity on the task (measured with d prime), but no effects were seen for PPC stimulation. These results show that it is possible to dissociate FEF and PPC contributions to visual search performance, although the absence of an effect of PPC stimulation differed from expectations. This was unlikely to have been a consequence of failure to stimulate PPC effectively. Numerous previous studies have shown visual search effects following PPC stimulation (Walsh et al. 1998; Ashbridge et al. 1997; Ellison et al. 2003), including those localising the site in the same manner (Kalla et al. 2008). Furthermore, we successfully found disruption on a search task requiring manual indication of the target presence in the same subjects (with the exception of one who was not available). The saccade search task used here offers the first instance of a visual search task in which disruption is not seen for both FEF and PPC TMS. One possibility for the difference in the effects of stimulating these two areas could be related to effects on the required motor response. It could be that the FEF disruption was a consequence of effects on saccade
latencies given that TMS over this area is known to delay voluntary saccades, whereas the angular gyrus in PPC has been implicated in reflexive saccades (Mort et al. 2003). Such a delay could result in some saccades not being generated before trials were terminated which, in turn, would produce a reduced accuracy score. However, the data do not support such a basis for the effect. First, mean saccade latencies were considerably lower than the cut off time, meaning it would be unlikely that a delay in saccades would push any responses so late as to render them misses rather than hits. Second, and more importantly, there was no indication that there was a significant effect of FEF TMS on saccade latencies, possibly due to the emphasis on accurate performance or the fact that saccade delays cause by TMS are sensitive to the exact timing of the TMS.

PPC TMS neither disrupted target detection performance nor saccade measures on the task while a control task confirmed that PPC TMS did disrupt search performance when the response was a manual one. This suggests that PPC involvement in visual search is dependent on the nature of the response required whereas this not the case for FEF. Further, it is known that this is not just a motor effect alone, as stimulation of PPC during search for a target defined by a single attribute, such as colour, does not result in disrupted performance. Recent findings with microstimulation (Juan et al. 2004) and TMS (Juan et al. 2008) support dissociation of visual and motor processes in human FEF. Such a dissociation has not been reported for PPC, which, while not meaning that no such dissociation exists, may be consistent with this is area performing functions related to the interpretation of extrastriate signals and visuo-motor transformation (Ellison et al. 2003). If this is the case then a single time point of disruption, possibly relative to the response time rather than visual onset, might be expected. Data obtained here suggest that the function performed by this area is necessary when a manual response is required during conjunction visual search but not when the motor
response is an eye movement. This means that, rather than being involved generally in the
translation of visual information for action in a response independent manner as we had
initially hypothesised, PPC seems to be involved in such a transformation when the response
is manual but not when it is a saccade. This is consistent with FEF involvement in the
detection of a conjunction search target involving visual processes that may be linked to a
saccade response or to a manual response, whereas PPC may be only involved when a
manual response has to be generated. The findings for PPC stimulation therefore differ from
our original hypothesis of a target localization function for this area, being instead indicative
of a response dependant visuo-motor transformation.

In summary, FEF is involved in visual search for a target defined by a combination of
features when the presence of a target has to be indicated by an eye movement but PPC is
not. When taken alongside previous findings that both of these areas are involved in search
conjunction search performance when a manual response is required, these results support a
visual processing role for FEF, which is therefore necessary irrespective of the response
required. In contrast, PPC involvement appears to be response dependant, possibly reflecting
a role in interpretation of signals for action when that action is a manual response.
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References


Figure legends

Figure 1: (a) Time line of a typical trial (black and white are used for target and distractors for illustrative purposes). Trials were initiated by subjects by means of the keyboard spacebar. Following a random duration fixation (300-700ms) the array was presented. This remained on screen until either a saccade was made or 1s had passed. An example correct response is shown by the arrow and the dashed circle highlights the target in the display (neither shown during the task).

(b) Stimulation sites. (i) PPC (coordinates equivalent to 42, -58, 52) and (ii) FEF (coordinates 31, -2, 47). These were localized in each subject by transforming the coordinates for each subject individually for their structural MRI scans using FSL (FMRIB, Oxford, UK) and then identifying the overlying scalp location using the Brainsight system (Rogue Research).

Figure 2: (a) D prime scores for each stimulation condition. Error bars indicate the standard error of the mean. A significant reduction in d prime was seen following TMS delivered over FEF.

(b) Accuracy of saccades directions for stimulation condition. Error bars indicate the standard error of the mean. No significant effects of TMS were seen.

(c) Saccade latencies for each stimulation condition. Error bars indicate the standard error of the mean. No significant effects of TMS were seen.

(d) Effects of TMS on response latency for the conjunction search task requiring manual responses to indicate the presence or absence of the target. Error bars indicate the standard error of the mean. A significant increase in response times was seen with TMS delivered over PPC.
Figure 1 (a)
Figure 2(a)

**FEF TMS**

* p < 0.01

**PPC TMS**

n.s.
Figure 2(b)

Comparison of accuracy between Sham TMS and No TMS treatments at FEF and ANG sites.
Figure 2(c)

The bar chart shows the saccade latency (ms) for different sites with and without TMS (Transcranial Magnetic Stimulation). The sites are labeled as No TMS and TMS. The chart indicates that the latency varies across different sites, with TMS generally increasing the latency compared to No TMS conditions.
Figure 2(d)

* $p < 0.01$