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7 **Human dorsolateral prefrontal cortex is involved in visual**
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10 **search for conjunctions but not features: a theta TMS**
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13 **study**
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Abstract

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5 Functional neuroimaging studies have shown that the detection of a target defined
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7 by more than one feature (for example, a conjunction of colour and orientation)
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9 amongst distractors is associated with the activation of a network of brain areas.
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11 Dorsolateral prefrontal cortex (DLPFC), along with areas such as the frontal eye
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13 fields (FEF) and posterior parietal cortex (PPC), is a component of this network.
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15 While TMS had shown that both FEF and PPC are necessary for, and not just
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17 correlated with, successful conjunction search, this is not the case for DLPFC. To
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19 test the hypothesis that this area is also necessary for efficient conjunction search,
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21 TMS was applied over DLPFC and the effects on conjunction and feature (in this
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23 case colour) search performance compared with those when TMS was delivered
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25 over area MT/V5 and a vertex control stimulation condition. DLPFC TMS impaired
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27 performance on the conjunction search task but was without effect on feature
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29 search, similar to findings when TMS is delivered over PPC or FEF. Vertex TMS had
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31 no effects whereas MT/V5 TMS significantly improved performance with a time
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33 course that may indicate that this was due to modulation of V4 activity. These
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35 findings illustrate that, like FEF and PPC, DLPFC is necessary for fully effective
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37 conjunction visual search performance.
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Keywords

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53 TMS, visual search, DLPFC, V5. Theta stimulation
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Introduction

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2 Detecting and locating a target in the presence of distractors constitutes a basic
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4 function of the visual system. Despite its apparent straightforward nature, a number
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6 of brain areas have been implicated in performing the task, particularly when the
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8 object being searched for is identified by a combination of attributes, and activates
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10 regions in the visual, parietal and frontal cortices (Donner et al, 2000). The necessity
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12 of the involvement of some of the areas implicated by both lesion findings (e.g. Collin
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14 et al, 1982; Eglin et al, 1991) and imaging studies in humans (e.g. Donner et al,
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16 2002; Makino et al, 2004) has been tested using transcranial magnetic stimulation
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18 (TMS) (Ashbridge et al, 1997; Walsh et al., 1998a; Muggleton et al, 2003). This
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20 technique has shown that both frontal eye fields and posterior parietal cortex regions
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22 are necessary for detection of a search target defined by a conjunction of features,
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24 but not for visual search tasks where a single quality of the stimulus, such as colour,
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26 defines the target (Ashbridge et al, 1997; Walsh et al, 1998a; Ellison and Walsh
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28 1998). Furthermore, the timing of the contribution of these two areas has been
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30 dissociated, with an earlier involvement for FEF than PPC (O'Shea et al, 2004; Kalla
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32 et al 2008: see also Juan et al., 2008).

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43 The role of the dorsolateral prefrontal cortex (DLPFC) in visual search has yet to be
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45 probed with TMS. This area is frequently associated with working memory and this is
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47 consistent with a hypothesised role for memory in visual search (Wolfe, 1994;
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49 Triesman and Gelade, 1980) in the prevention of revisiting already searched
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51 locations. In line with this view, there is evidence of a bias away from recently
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53 examined locations e.g. Klein and MacInnes (1999). However, use of a paradigm in
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55 which the locations of the array elements was changed frequently during a trial did
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57 not reveal any deleterious effects on search performance (Horowitz and Wolfe,
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1998). The absence of a relationship between working memory capacity and search set-size/reaction time slopes (Kane et al, 2006) may be more consistent with memory being important in representing the target, rather than remembering the searched locations. Despite disagreements on the role played by memory in search, there is broad, but not complete, agreement that it does indeed play a role (Beck et al, 2006; Kristjansson, 2000). If this were the case then DLPFC would be a prime candidate for fulfilling this role. Common activations in DLPFC have been reported in the same subjects performing visual search and memory search (Makino et al, 2004). They proposed that the common process was the monitoring and manipulating of multiple elements and that target matching was another possible function of this area, a cognitive process previously associated with both visual and memory search (Hillstrom and Logan, 1998).

We tested the hypothesis that DLPFC is, like FEF and PPC, necessary for efficient performance of conjunction visual search. In doing so, we employed methods similar to those used in our previous investigations of these other areas (Muggleton et al, 2003, 2008; O'Shea et al, 2004, 2007). The visual area MT/V5, typically involved in motion processing was selected as a control site for non-specific visual system effects as it is involved in visual processing, but was not expected to be involved in colour-form conjunction search. A signal detection theory (SDT) approach was used, with performance measured by means of the sensitivity measure d' , as well a bias measure which allowed the tendency to miss the target or make false alarms to be quantified. Due to the potential discomfort that might be expected to result from TMS delivered over DLPFC, a consequence of its relatively anterior location resulting in less tolerable effects on muscles/nerves in the vicinity, we employed theta TMS (Huang et al, 2005; Vallesi et al, 2007). Stimulation applied in this manner results in

1 prolonged disruption of the targeted area as a consequence of a relatively short
2 period of TMS delivery (seconds rather than the multiple minutes required for the
3 more typical offline stimulation used, in which TMS is delivered at 1 Hz). As testing
4 takes place in the post-TMS period, any interference with performance attributable to
5 the effects of discomfort or blinks and facial twitches is avoided.
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11 **Methods**

12 **Subjects**

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24 Twelve subjects (8 male, 4 female, mean age 28.3 years) were tested on each
25 experimental condition. The same subjects performed all three conjunction
26 conditions. Seven of them also performed the feature search task, along with five
27 new subjects (6 male, 6 female, mean age 27.5 years). For six subjects in the
28 conjunction task this experiment was their first experience of TMS and the same was
29 the case for five subjects for the feature search task. All subjects gave informed
30 consent prior to taking part in the experiment and standard exclusion criteria for TMS
31 were applied. The study was approved by the local ethics committee.
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46 **Task**

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51 The time course of a trial is illustrated in Figure 1. Following a fixation of a random
52 duration (300-700ms) the search array was presented for a duration determined by
53 means of a thresholding procedure as outlined below. A colour pattern mask
54 (composed of the same colours making up the stimuli, see below) was then
55 presented until subjects indicated via a keyboard response whether or not they
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thought a target had been present in the array. Stimuli were presented on a 15' CRT VDU at a distance of 57cm from a chin rest from which they were viewed. Presentation software ran on an IBM compatible Pentium III based PC. Search arrays subtended two degrees by two degrees of visual angle with twelve elements in the arrays each of width and height 0.25 degrees. Search elements were diagonals oriented to the left or right which were either red (CIE $x = 0.615$, $y = 0.346$, luminance 20 cd.m^{-2}) or green (CIE $x = 0.279$, $y = 0.577$, luminance 20 cd.m^{-2}). The background was uniform grey with a luminance of 63 cd.m^{-2} . For half of the subjects the target was a green diagonal oriented to the right (/). In this case half of the distractors were red and in the same orientation as the target and half were green in the opposite orientation. For the other subjects the stimuli were reversed, such that the target was red and oriented to the left (\) with green distractors having the same orientation and red distractors in the opposite orientation.

Prior to presentation of the experimental conditions, the duration for which the array was to be displayed was determined for each subject using an adaptive algorithm which fitted performance to a Weibull psychophysical function using the method described by Kontsevich and Tyler (1999). Briefly, this method presented the array for a given duration, the response to which would provide the maximum information in recalculating an estimation of the psychophysical function. This allowed estimation of the presentation time required for 75% accuracy on the task from a block of 40 trials. Such blocks were run until the estimate of the threshold varied by less than ten percent on two consecutive blocks. Typically this only required two or three blocks.

1 The test blocks each consisted of 40 trials. Two blocks were presented as a baseline,
2 two five minutes following TMS and two final blocks 30 minutes after TMS. These
3 times of testing following TMS were chosen as the first was expected to coincide
4 with a time period of suppressive disruption of the area stimulated and the second
5 with a point at which the activity of the area would have returned to baseline levels.
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7 The task was programmed using C++ 6.0 (Microsoft Corporation) and also
8 incorporated an Eyelink system (SMI) which monitored eye position throughout the
9 task and automatically terminated trials on which saccadic eye movements or blinks
10 occurred when the search array was present of the screen.
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24 Each condition was performed on a different day, with sessions involving the
25 conjunction search task and stimulation over DLPFC, V5 or vertex or feature search
26 and DLPFC stimulation. Feature search was presented in the same manner as the
27 conjunction search and differed only in that the array elements were circles which
28 were green with a red target circle present on 50% of trials or *vice versa*.
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39 TMS

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43 TMS was delivered using a Magstim Super Rapid (Magstim Company, UK) via a 50
44 mm figure of eight coil. An offline stimulation protocol similar to that used by Huang
45 et al (2005) and Vallesi et al (2007) was used. Stimulation consisted of chains of 3
46 pulses with an inter-pulse interval of 20 ms delivered every 200 ms for 20 seconds
47 (i.e. theta burst stimulation, 50 Hz stimulation at 5 Hz) at 40% of the stimulator
48 maximum output (a level below the motor threshold of all subjects, confirmed by an
49 inability of this stimulation level to elicit motor twitches when delivered over the hand
50 motor area in the right hemisphere). A fixed level of stimulation was used as it has
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been shown that effective stimulation levels do not correlate between brain areas (Stewart et al, 2001).

This stimulation of the target site took place after determination of the threshold duration for the visual search task, and after subjects had performed two blocks of forty trials (baseline). After TMS, subjects were then presented with a further two blocks of forty trials starting five minutes after the end of stimulation and then again thirty minutes after stimulation offset. These times were based on the observed time course of effects seen in the motor cortex (Huang et al, 2005). Each subject performed the sequence of blocks for the conjunction task on three occasions (which were on different days) with the order of the stimulation sites randomised. For subjects who also took part in the feature search condition, this session was also randomly intermixed in the session order.

TMS Localisation

DLPFC stimulation sites were localized using the Brainsight Frameless Stereotaxy system (Rogue Research, Montreal, Canada). A high resolution structural MRI scan was obtained for every subject. This was normalised against a standard template (MNI T1) using the FSL software package (FMRIB, Oxford, UK), resulting in both a normalised structural scan and a matrix describing the transformation applied. This matrix was then used to transform the location of the stimulation site from standard space to the structural space for each individual. Coordinates used for DLPFC were 43,20,20 (Makino et al, 2004) and were selected as this area is active in both memory and visual search. Area V5/MT was localised with the coordinates 44, -67, 0 (Dumoulin et al, 2000) and then verified functionally by ensuring that when single

1 TMS pluses were delivered over it moving phosphenes were perceived. Functional
2 localisation has been successfully employed in a number of studies previously (e.g.
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4 Campana et al, 2002, 2006; Silvanto et al, 2005; Pascual-Leone and Walsh, 2001)
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6 and correlates well with localisation of V5 in imaging studies (Dumoulin et al, 2000;
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8 see Campana et al, 2006). Consistent with this, in all cases in the current study TMS
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10 over V5 localised using fMRI coordinates resulted in moving phosphenes being
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12 perceived (no subjects reported phosphenes during theta TMS delivery). The
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14 stimulation sites for one individual are illustrated in Figure 2.
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22 **Figure 2 about here**
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26 **Results**

27 Data were analysed by means of d-prime scores calculated for each time period and
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29 condition in the experiment. D' scores were calculated as the difference between the
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31 z-scores of the proportion of correct responses on the target present trials (hit rate,
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33 h) and the proportion of incorrect responses on target-absent trials (false alarm rate,
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35 f) according to the equation: $d' = z(h) - z(f)$ (where the z scores represent the area
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37 under a normally distributed curve with a mean of 0 and a standard deviation of 1 for
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39 the h and f ratios).
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48 Response times were not analysed as only accuracy had been emphasised in
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50 performing the task. Performance on the conjunction task was subjected to a
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52 repeated measures ANOVA with factors of TMS site (DLPFC, V5, vertex) and time
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54 (baseline, 5 minutes post, 30 minutes post TMS). Data are illustrated in Figure 3.
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1 This revealed a main effect of site ($F(2,22) = 3.48, p = 0.049$) and a site by time
2 interaction ($F(4,44) = 5.283, p = 0.001$). None of the individual comparisons for the
3 main effect of site were significant. Individual ANOVAs with a factor of time were
4 used for each site to investigate the interaction. This revealed significant effects
5 following DLPFC stimulation ($F(2,22) = 4.134, p = 0.013$) with post-hoc t-tests
6 showing that this was due to worse performance for the period after TMS (baseline
7 vs 5 min post TMS, mean 1.415, S.E.M. 0.093 vs mean 1.112, S.E.M. 0.151, $p =$
8 0.025). Additionally there was a significant effect for V5 ($F(2,22) = 5.331, p = 0.013$).
9 But in this case post-hoc tests showed that performance in both periods after TMS
10 were significantly better than baseline (baseline mean 1.294, S.E.M. 0.096, 5
11 minutes post-TMS mean 1.751, S.E.M. 0.145, $p = 0.024$; 30 minutes post-TMS mean
12 1.678, S.E.M. 0.128, $p = 0.002$).

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Feature search was analysed using repeated measures ANOVA with time as a
factor. No effects of TMS were seen ($F(2,22) = 0.0603, p = 0.556$).

Figure 3 about here

Conclusions

These findings confirm the prediction that dorsolateral prefrontal cortex is necessary for successful visual search for a target defined by a conjunction of features but not one defined by a single attribute. Theta burst TMS delivered over this area caused a significant reduction in d prime only for the former task and was without effect on the latter. As expected, vertex TMS was without effect on the conjunction task. In

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2 contrast, TMS delivered over MT/V5 (the control site) resulted in improved
3 conjunction search performance.
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7 There are several points to address in considering these findings, not least whether
8 the DLPFC effect can be considered specific to the site of stimulation (rather than
9 merely reflecting spread of effects to other areas), and why MT/V5 TMS actually
10 improved performance. It might be argued that the second of these points, the
11 MT/V5 facilitation, goes some way to supporting the specificity of the DLPFC effect.
12 Facilitation of visual search as a consequence of V5 TMS has been reported
13 previously (Walsh et al, 1998b) using stimulation parameters more commonly
14 employed in cognitive tasks (i.e. TMS delivered at 10 Hz for 500 ms during stimulus
15 presentation). In the latter case it was argued that TMS of V5 had a facilitatory effect
16 because the disruption V5 processes may have led to a decrease in inhibition of V4
17 (i.e. if V4 and V5 were in competition with one another for resources, the
18 disorganisation of V5 would have benefitted V4 – this logic is the basis of other
19 enhancement effects e.g. Seyel et al, 1995; Hilgetag et al, 2001; Rushworth et al,
20 2001). This explanation is also in keeping with the nature of the connections
21 between these two areas (Walsh et al, 1998b; Walsh and Pascual-Leone, 2003). It is
22 worth noting that V5 TMS has been used in tasks of this type before without an
23 associated improvement in visual search performance (e.g. Muggleton et al, 2003).
24 This discrepancy may be because the offline stimulation paradigm used here may
25 result in a persistent modulation of V4, rather than a more transient one in the case
26 of on-line stimulation. It might also be the case that such a time course difference
27 accounts for why no V5 effect was seen by Muggleton et al (2003), in which briefly
28 presented stimuli were employed, but was seen in the study of Walsh et al where the
29 stimuli were presented for 700 ms. This, however, remains conjecture in the absence
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1 of information regarding the time course of the V5 effect and the relative paucity of
2 information regarding the effects of V4 TMS on cognitive tasks. It does, however,
3 place some limits on the degree to which any spread of effect following DLPFC
4 stimulation may have contributed to the deficits in performance seen as a
5 consequence of TMS delivered over this site. The effects seen following V5 TMS
6 would be highly unlikely to result in facilitation if connected areas were also disrupted
7 because of their connections to the targeted area. There are strong reciprocal
8 connections from V1 to V5 (Felleman and Van Essen, 1991) and given the
9 fundamental role of V1 in vision, and the previously reported disruptive effects of
10 TMS over V1 on conjunction search performance (Juan and Walsh, 2003), it seems
11 unlikely that the effects of theta burst TMS delivered in the manner used in the
12 present experiment are due to a spread of disruption to distally connected areas.
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31 Disruption of conjunction (but not feature) search using TMS has now been shown
32 for TMS delivered over FEF, PPC and DLPFC. Although FEF and PPC involvement
33 in the task have been dissociated at a temporal level it remains to be shown how
34 they differ at a mechanistic level. It has been shown that working memory capacity, a
35 function ascribed to DLPFC, does not correlate with visual search performance in
36 terms the set-size/response time slope seen in such tasks (Kane et al, 2006). The
37 role of this area may be more consistent with guidance of performance with respect
38 to the target. This seems to bear similarities with the role suggested for FEF in the
39 modulation of extra-striate responses to a visual stimulus (e.g. Moore and Fallah,
40 2001; Silvanto et al, 2007). It may be the case that DLPFC 'holds' a representation of
41 the target of the search and this information is used by FEF to modulate areas to
42 which it is connected in a spatially specific manner. This suggests that DLPFC
43 induces biases in the responses of areas such as FEF. As TMS studies have shown
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1 that disruption with FEF TMS occurs very early after stimulus onset it may be,
2 however, that DLPFC provides more of an ongoing influence than a specifically
3 stimulus-locked one. Additionally, it would be predicted that, while spatially specific
4 effects would be associated with FEF, this would not be the case for DLPFC.
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11 It has been proposed that DLPFC is involved when a task requires manipulation of
12 several pieces of information (Petrides, 1995), and it was this process that was
13 argued to be the factor in memory and visual search responsible for the common
14 DLPFC activation seen by Makino et al (2004). This explanation would be consistent
15 with the results here, where DLPFC TMS disrupted conjunction, but not feature
16 search. In the case of feature search, the target is identifiable by a single attribute,
17 whereas the conjunction target always shares an attribute with the distractors, which
18 may mean that there are more candidate targets to be considered before making a
19 response.
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35 In summary, DLPFC is necessary for conjunction visual search but not feature visual
36 search. How its contribution to performance of this type of task differs from areas
37 such as FEF and PPC remains to be clarified and appropriate task manipulations will
38 be necessary to further address this.
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Figures

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5 Figure 1: Experimental procedure. The time line for a typical trial. The duration of
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7 the array presentation was individually determined for each subject prior to
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9 experimental blocks to set baseline performance at 75% correct. Stimuli were green
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11 or red diagonal lines (shown as white or black here). In the example shown the
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13 target is the black diagonal /. In the feature search task the stimuli were circles and
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15 the target was an odd coloured singleton.
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22 Figure 2: Site localisation. The sites over which TMS was delivered are illustrated for
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24 one individual. These were derived from transformation of fMRI coordinates for each
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26 site, carried out for each subject individually using their own structural MRI scan.
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32 Figure 3: Task performance. a) Performance on the conjunction search task for
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34 baseline, 5 minutes post TMS and 30 minutes post TMS. b) Performance on feature
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36 search with DLPFC TMS. All error bars represent the standard error of the mean
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Figure 1

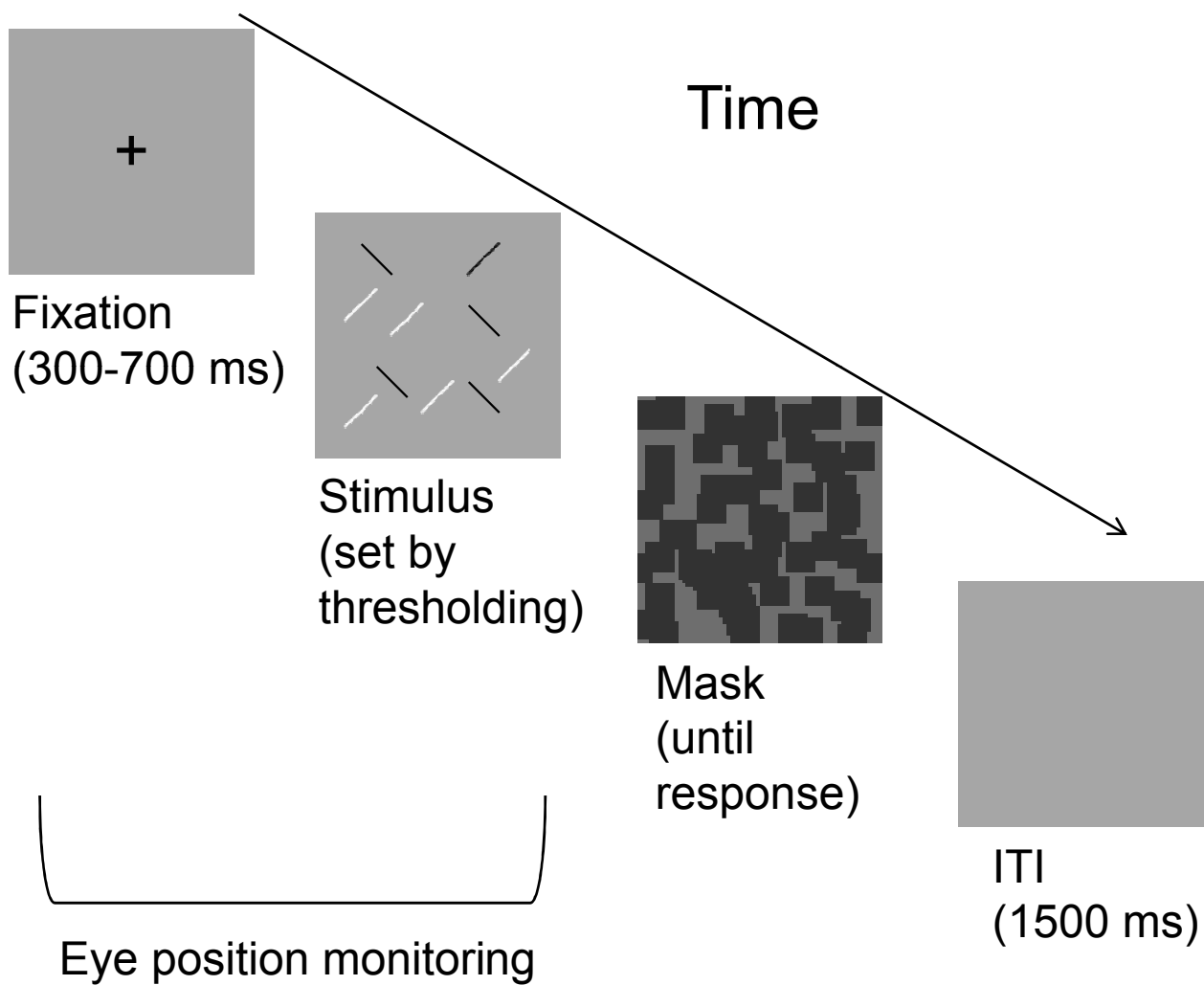
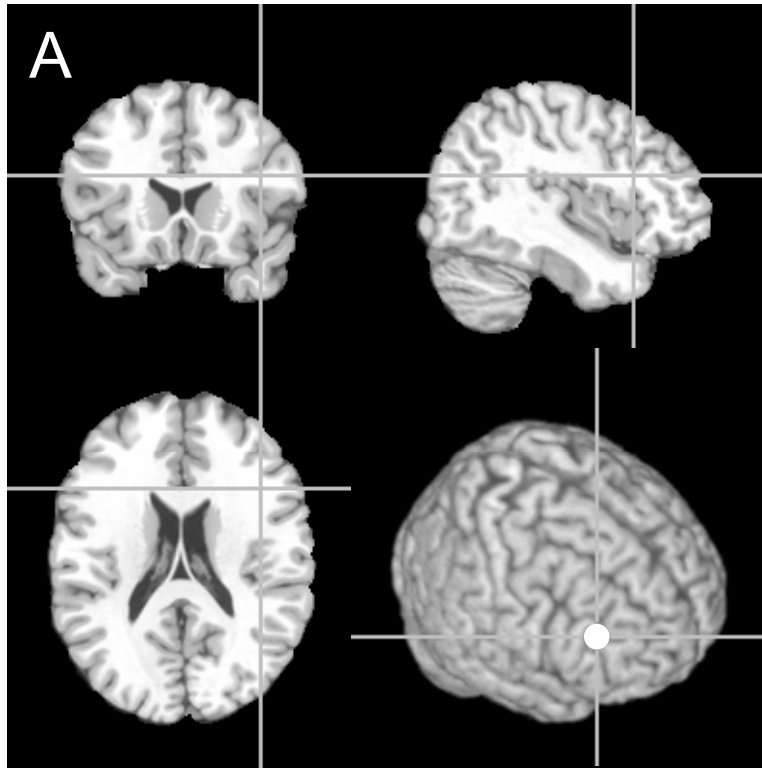
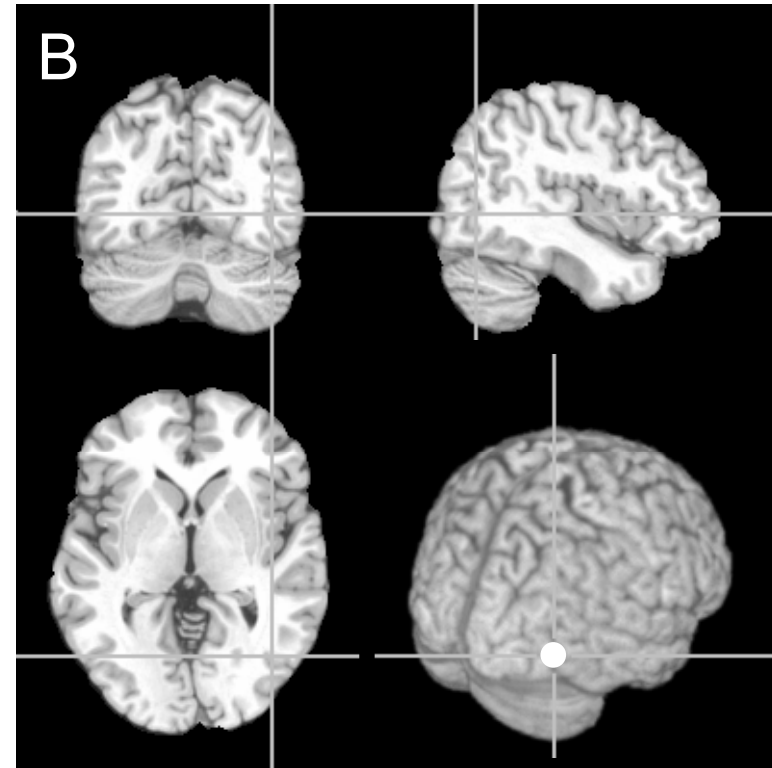


Figure 2



Right DLPFC: [43, 20, 20]



Right V5: [44, -67, 0]

Figure 3 a)

Conjunction search

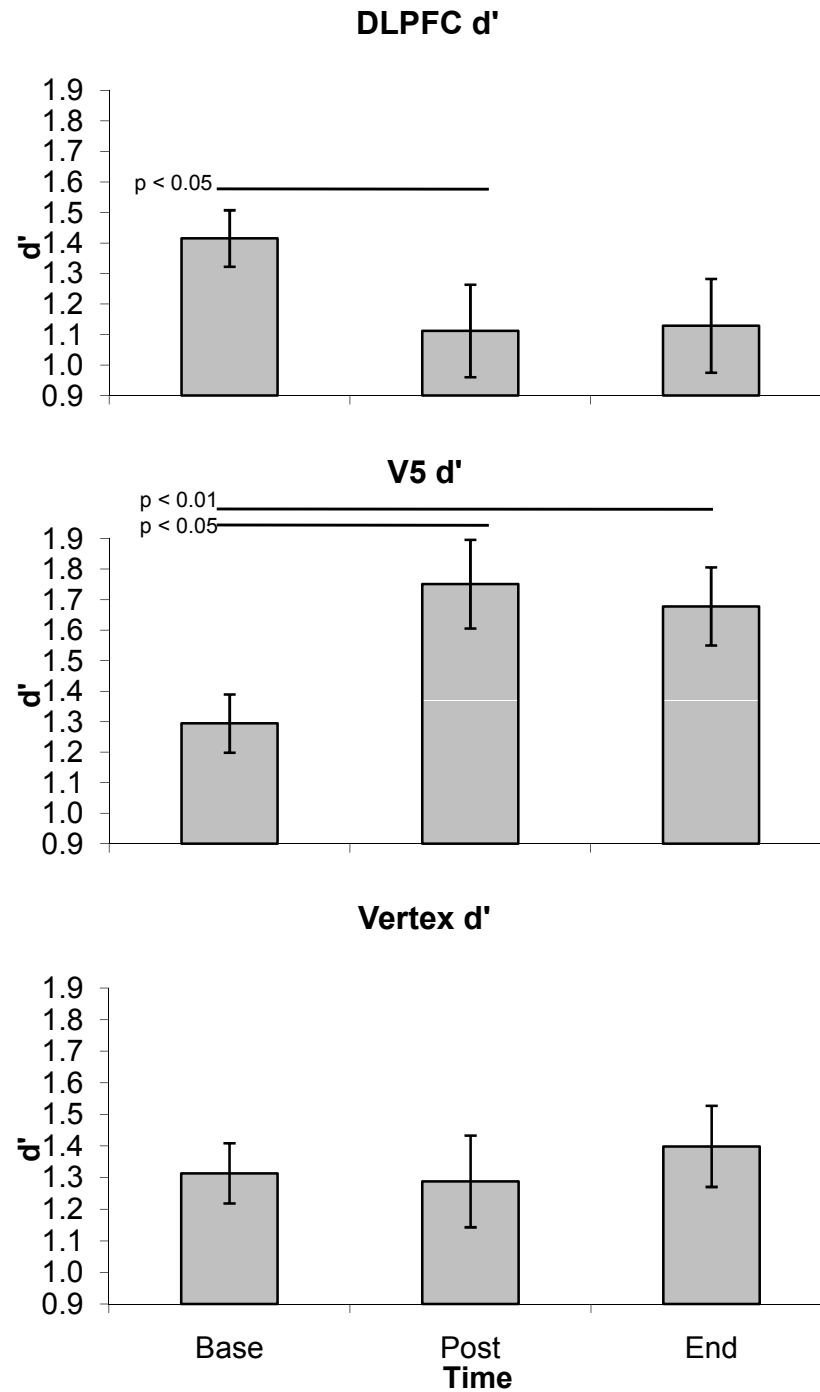


Figure 3 b)

Feature search

