Article:
Burke, MRF and Coats, RO (2016) Dissociation of the rostral and dorsolateral prefrontal cortex during sequence learning in saccades: a TMS investigation. Experimental Brain Research, 234 (2). pp. 597-604. ISSN 0014-4819

https://doi.org/10.1007/s00221-015-4495-2

Dissociation of the rostral and dorsolateral prefrontal cortex during sequence learning in saccades: a TMS investigation.

Burke, M.R. & Coats, R.O.

School of Psychology, University of Leeds, Leeds. LS2 9JT. U.K.

KEYWORDS: dorsal stream, eye movements, learning, memory, prefrontal cortex

Abstract

This experiment sought to find if differences exist between the dorsolateral prefrontal cortex (DLPFC) and the medial rostral prefrontal cortex (MRPFC) for performing stimulus-independent and stimulus-oriented tasks respectively. To find a causal relationship in these areas we employed the use of trans-cranial magnetic stimulation (TMS). Prefrontal areas were stimulated whilst participants performed random or predictable sequence learning tasks at stimulus onset (1st presentation of the sequence only for both Random and Predictable), or during the inter-sequence interval. Overall, we found that during the predictable task a significant decrease in saccade latency, gain and duration was found when compared to the randomized conditions, as expected and observed previously. However, TMS stimulation in DLPFC during the delay in the predictive sequence learning task reduced this predictive ability by delaying the saccadic onset and generating abnormal reductions in saccadic gains during prediction. In contrast, we found that stimulation during a delay in MRPFC reversed the normal effects on peak velocity of the task with the predictive task revealing higher peak velocity than the randomized task. These findings provide causal evidence for independent functions of DLPFC and MRPFC in performing stimulus-independent processing during sequence learning in saccades.

Introduction

The prefrontal cortex (PFC) plays a unique role in a variety of different cognitive capacities. The localisation of function within this cortical area has proven to be an arduous task for psychologists due to its size and the multitude of different cognitive tasks it contributes to. This paper is concerned with finding evidence for a double dissociation between the dorsolateral prefrontal cortex (DLPFC, BA9) and the medial rostral prefrontal cortex (MRPFC, BA10) in performing stimulus-independent (SI) and stimulus-oriented (SO) eye-movement tasks respectively. An SO task requires attentional vigilance and perception for the recognition of an unexpected visual stimulus, whilst an SI task implements a maintenance or a mental representation of the stimuli (i.e. location) and can generate a response in the absence of the relevant stimuli if the same stimuli is expected (Burgess et al, 2007). It is currently unclear from previous research if SO and SI tasks share a common brain network within the prefrontal cortex (i.e. anatomically overlap), or utilize different sub-regions within this area.

Using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) a number of previous studies have provided evidence for a functional segregation of rostral prefrontal cortex into a medial and lateral area (for meta-review see Gilbert et al., 2006). Medial rostral prefrontal cortex (MRPFC) has been generalized to reveal more perceptual and attention related activation, whereas lateral rostral prefrontal cortex (LRPFC) is more involved in working memory. These results led to the formation of the 'gateway hypothesis' (Burgess et al, 2007), which rests upon the assumption that there is a clear distinction between SO (that is more reliant on MRPFC) and SI (that involves more lateral RPFC part of the DLPFC mentioned later) tasks. Burgess et al (2007) suggests that the function of MRPFC is in attending during SO tasks, while LRPFC is involved in switching between SO and SI tasks, and finally DLPFC is involved in the short-term storage of information for SI tasks.

There are various studies including fMRI imaging that have found evidence for DLPFC playing a role in spatial working memory (for reviews see: Wager and Smith 2003; Owen et al., 2005). The memory-guided saccade paradigm is commonly used to study the retention of spatial information.

Whilst fixating on a target, participants must memorise the location of a target stimulus as it is briefly flashed in their peripheral view and then after a delay they must perform a memory-guided saccade to the position of the target stimulus. Participants with a lesion of the DLPFC made significantly less accurate saccades than healthy controls (Pierrot-Diesilligny et al, 1991). In addition, TMS stimulation of the DLPFC during the delay period of this paradigm also produced significantly less accurate saccades, which again suggests that the DLPFC is indeed involved with the retention of the spatial information involved in this task (Müri et al, 1996). The DLPFC is also involved in predictive saccades, this occurs when the visual stimulus is moving to a predictable location and as such participants make the saccade to the location before the stimulus has appeared there (Pierrot-Diesilligny et al, 2004). Lesions to the DLPFC significantly reduced the amount of predictive saccades performed (Pierrot-Diesilligny et al, 2003). A previous study performed in this lab revealed activity in both MRPFC (BA10) and DLPFC (BA9) during a predictive eye movement task further indicating a role for these areas in memory and motor control (Burke and Barnes, 2008). Finally, causal evidence for DLPFC in memory and learning was observed when transcranial magnetic stimulation (TMS) was applied over the DLPFC during a serial reaction time task that significantly impaired the participants' implicit procedural learning of the sequence as evidenced by a lack of reduction in reaction time as the sequence was repeated (Pascual-Leone et al, 1996).

In our experiment we used a double dissociation between MRPFC and DLPFC in performing SO and SI sequence learning tasks. Our design exploited the ability of individuals to predict a sequence of stimuli when it is repeated (SI), and compare it to performance of randomly appearing stimuli (SO). In this design, participants should maintain a mental representation of the sequence (in the SI condition) in order to facilitate following the targets when the sequence is repeated.

Hence our hypotheses follow that when using TMS to selectively disrupt neural activity in MRPFC at target onset during the random (SO) condition eye movements would be affected. Likewise, eye movements should also be affected when disrupting neurons in DLPFC during the delay in the predictive (SI) condition.

Method

Participants

12 undergraduates either from the University of Leeds or the Leeds Metropolitan University with either normal or corrected vision were recruited for the study. All participants gave informed consent and completed a medical history questionnaire that was relevant to the use of TMS. The study was approved by the University of Leeds Ethical Committee and adhered to BPS guidelines. All 12 participants were absent of any neurological or visual disorders (as identified by the questionnaires) and none of the subjects reported any visual, psychological or neurological disturbances during testing.

Materials

The visual stimuli were presented in a dark room on a 19" CRT colour monitor (Vision Master, Ilyama, Japan) with a 1024x768 resolution, 75Hz refresh rate and with a mean luminance of 50cd/m2. The sequences of visual targets and the onset of TMS stimulation were generated using Experimental Builder software (SR Research Ltd., Canada). The participant's left eye movements were recorded remotely using an Eyelink 1000 eye tracking system (SR Research Ltd., Canada), recording at 1000Hz, which was positioned centrally just below the monitor. Participants' heads were restrained using a chin and forehead rest attached to a table top. TMS was delivered using a 70mm diameter 'figure of eight' coil with a Magstim Rapid2 stimulator (Magstim Company Ltd., Wales). TMS pulses were fixed at 40% of the maximum output (2.6 T) for all participants, which is based on preliminary testing (ensuring the stimulation did not induce adverse effects e,g, eye twitching) and previous studies using single-pulse TMS in the prefrontal cortex of healthy young volunteers (Basso et al., 2010, 27-42% of max stimulator output). Furthermore, previous studies have shown little correlation between the threshold for stimulation in motor cortex and thresholds for non-motor areas (Stewart et al., 2001), and points to the suggestion that varying this threshold might not be optimal for the cognitive tasks and brain areas used in this study. Given both regions were within the prefrontal cortex, an adjustment for cortical thickness was not deemed necessary. We utilised the easily applied

and cost-efficient International 10-20 EEG system which uses electrode positions of an EEG cap in order to locate the cortical areas we needed to stimulate (Herwig, 2003). Since MRPFC and DLPFC are relatively large brain regions on each hemisphere using this approach proved very simplistic. One caution was that the orbitofrontal cortex is relatively close to various facial muscles, which if stimulated would generate facial twitches which could interfere with the eye-tracking equipment. We therefore implemented test stimulation to acclimatise participants and ensure interference with facial and eye muscles were not observed.

Procedure

After completing a medical history questionnaire, reading the TMS information sheet and giving their informed consent, participants were requested to wear an EEG electrode cap in order to locate the DLPFC and MRPFC on each hemisphere of the brain (which corresponded to electrodes F3/F4 and Fp1/Fp2 respectively) and these areas were subsequently stimulated and highlighted using a marker pen. These areas also approximately corresponded to the brain areas identified in a previous fMRI experiment looking at prediction in eye movements (Burke and Barnes, 2008). The participant's eyes were calibrated between each block of trials and heads were restrained using forehead padding and chin rests. Participants performed 16 blocks of 40 trials in 2 testing sessions (on two separate days) in a dark room absent of external light or noise sources. Whilst participants were carrying out the eye movement task an experimenter would hold the TMS coil perpendicular to the area with continuing checking of position throughout each block of trials (block duration ~ 3-4 mins).

This paradigm has been implemented previously in this lab, but with different TMS stimulation sites that included the right supramarginal gyrus (Burke et al., 2013). In addition this previous study incorporated two control conditions of: (i) stimulation at the vertex, and (ii) no TMS. In the present study two TMS protocols ('target' and 'delay') were delivered to two brain areas DLPFC and MRPFC on either the right or left hemisphere, whilst participants performed the 'predictable' (PRD) or 'random' (RND) fixation task resulting in 16 conditions. Both task conditions (PRD and RND) began with the presentation of a fixation target (a small white circle, 0.5 degrees in diameter) in the centre of

the screen for 1000ms (or between 1000 and 1500ms for random conditions). Following the presentation of the initial fixation target an identical target was presented 5° to the left, right, above or below this initial target. This was repeated for a total of 4 fixation targets presented sequentially per trial. In the predictable condition each target appeared for 750ms before moving to a new position and the same sequence of 4 targets was presented 4 times per block. In the random condition the duration of the fixation targets varied between 525ms and 1275ms and the positional shifts of the targets were varied for each sequence. There was a 2 second interval between each trial to allow for repositioning of the eye back to the centre of the screen. Each block consisted of 40 trials (40 unique sequences for the random condition and 10 unique sequences repeated 4 times each for the predictable condition), but blocks were counterbalanced across individuals. All sequences involved stimuli (and eye movements) crossing the midline to avoid lateralization effects. The target TMS protocol delivered one pulse to the cortical area at the same time as each target was presented after the initial fixation target. The delay TMS protocol delivered two pulses; one at target offset and another during the delay 525ms later between each sequence. Because the first trial in each 4 trial series of the predictable condition is unknown and thus is essentially random to the participant, these trials were removed from the analysis for the predictable condition.

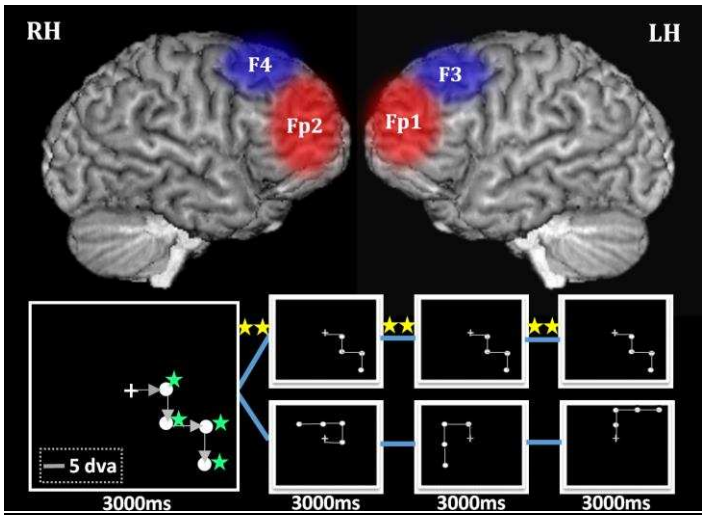

Figure 1: Image depicting stimulation sites of TMS on dorsolateral prefrontal cortex (DLPFC in blue) and rostral prefrontal cortex (MRPFC in red) on the right and left hemisphere. We aimed to stimulate within the centre of these regions with the coil positioned perpendicular to the skull. The lower

images show the stimulus sequences (3 seconds long) that are either presented predictably (same sequence repeated 4 times in a row) or randomly (each sequence was different). The green stars on the lower left screen image depicts the stimulation during target onset, whereas the yellow stars in-between each sequence presentation depicts the stimulation during the delay condition. Each target was always positioned 5 degrees of visual angle (up, down, left or right) from the preceding target.

Design and Analysis

In order to identify the effects of TMS on our participants' ability to perform accurate saccades we measured their reaction time to perform each saccade within the sequence, alongside some saccade metrics including saccadic gain, duration and peak velocity. These metrics were calculated with DataViewer (SR Research, Ontario, Canada) in the same way as previously described (Burke et al., 2013). Briefly, blinks were automatically removed and saccade onset was identified using velocity >50°/s, with latency taken from target onset to saccade onset. The saccadic reaction time was calculated as the time taken from target onset to the onset of the first saccade to the target that exceeded 2 degrees of visual angle. Saccadic amplitude was calculated as distance from the fixation point to the end-point of the first saccade (peak velocity was also obtained for this saccade via the software). Saccadic gain was obtained by dividing saccade amplitude by the target distance (5°).

A slower reaction time in predictable trials during TMS would indicate that the area being stimulated is important for the rapid processing of temporal information required to initiate the learned saccade, whereas early initiation in randomized trials could indicate disruption of the inhibition processes involved in visually-guided responses. A disruption of the saccade gain would indicate the area being stimulated is important for the processing of spatial information during the saccade whilst a disruption of the peak saccade velocity would indicate the area being stimulated is important for a more motor related function. A 2 (Right/Left) x 2 (Delay/Target) x 2 (MRPFC/DLPFC) x 2 (Random/Predictable) repeated measures ANOVA was used to calculate the significant main effects. A Bonferroni corrected post-hoc ANOVA analysis was performed on any significant interactions to control for multiple

comparisons. None of these ANOVA's revealed a significant effect of hemisphere, and so data was collapsed across left and right hemisphere in the analysis presented below.

Results

Reaction Time

As previous studies have found, our predictive saccades were ~100ms faster than visually-guided saccades, but also tended to be more variable. Thus, as expected the repeated measures ANOVA revealed a significantly reduced reaction time in the predictive (mean = 109ms; std ± 41ms) compared to the random (mean = 211ms; std ± 21ms) task ($F_{(1,11)}$=226.3, $p < 0.0001$, η^2=0.958) indicating that subjects were able to predict during repeated presentations of the same stimulus in the 2nd, 3rd and 4th presentation of the sequence. We therefore ran post-hoc analyses on the predictable and random tasks independently to avoid this large effect interfering with the hypotheses of interest i.e. stimulation site and timing. In the random task we found a significant increase in normal reaction time to the stimuli when TMS stimulation was applied during the target onset (219ms; ±22ms) compared with during the delay (203ms; ± 21ms) ($F_{(1,11)}$=42.2; $p < 0.001$; $\eta^2 = 0.789$) (see Figure 2). In addition, we found a trend for these longer reaction times to be more prominent with the stimulation in the MRPFC (164ms; ±61ms) ($F_{(1,11)}$=4.47; $p = 0.058$; $\eta^2 = 0.289$) when compared to the DLPFC (158ms; ±61ms).

During the predictable sequence presentations we found a weak trend for interruption in predictive reactions times when stimulating during the delay (115ms, ±42ms), compared to stimulation during target onset (104ms; ±40ms) ($F_{(1,11)} = 3.64$; $p = 0.08$; $\eta = 0.249$), but no further interactions were observed.

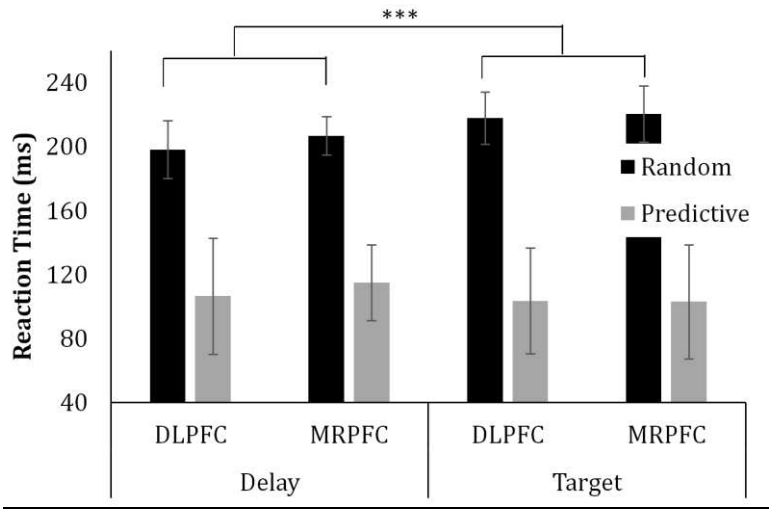

Figure 2: There was a clear difference in reaction times of ~100ms between predictable (black bars) and random (grey bars) sequence tasks in both TMS stimulation conditions (delay and target) explored. Error bars denote the standard deviation measured within the group for each task/condition. There was also a significantly longer reaction time during the random condition for the target compared to the delay condition. The convention used for all graphs is: *** is $p < 0.001$, ** is $p < 0.01$, * is $p < 0.05$).

Saccade Gain

Again a full ANOVA with all variables was initially performed and a significant main effect of task was found (predictable versus random) ($F_{(1,11)} = 79.256$; $p < 0.001$; $\eta^2 = 0.888$). Therefore we performed post-hoc analyses on PRD and RND tasks independently to investigate effects further within these tasks. During the predictable task, saccadic gains were more hypometric when TMS stimulation was applied at target onset (mean = 0.9; ±0.21), when compared with stimulation during the delay (mean = 0.86; ±0.25) ($F_{(1,11)} = 12.832$; $p = 0.004$, $\eta^2 = 0.903$). We also saw a significant decrease in saccadic gain in MRPFC when compared to DLPFC ($F_{(1,11)}=5.518$; $p = 0.039$; $\eta^2 = 0.572$). In contrast there were no effects of timing of stimulation or brain area during the random task. No interaction between TMS onset and brain area was observed. We also analysed saccade duration data and found no significant differences in this metric for any of our stimulation conditions.

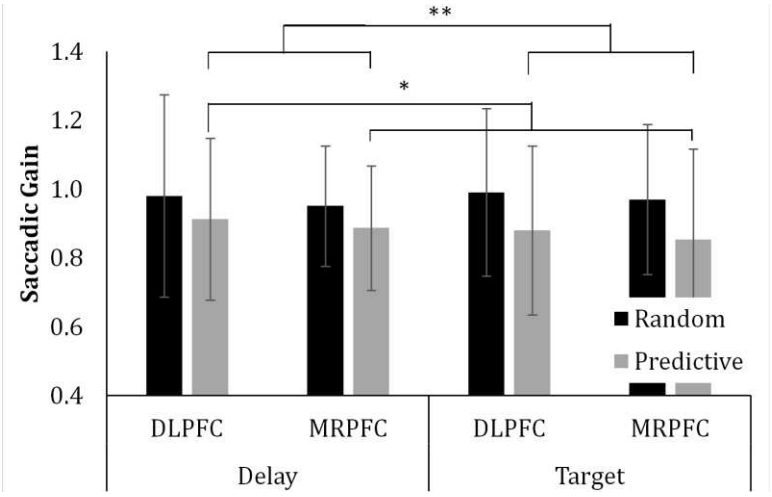

Figure 3: We found that gain of the saccade to the target was shorter (more hypometric) in the predictive conditions (shown in black) than random sequences (shown as grey bars). The error bars denote the between subject standard deviation. We found significant decreases in the gain for stimulation at target onset compared to delay stimulation only during the predictable tasks. In addition, the gain in medial rostal prefrontal cortex was lower than in dorsolateral prefrontal cortex.

Peak Velocity

Firstly, a significant effect between random and the predictive task was observed ($F_{(1,11)} = 25.586$, $p < 0.001$, $\eta^2 = 0.699$), with the random revealing higher peak velocity (270.2deg/s ±30.8) than predictive (252.3deg/s ±25.6), as found for gain and RT. Post-hoc analysis revealed significant effects in both random and predictable tasks when looking at differences in peak velocity between brain areas and TMS stimulation timing conditions. For the random tasks we found a significant decrease in peak velocity for MRPFC (254.2deg/s ±55.1) when compared to DLPFC (285.5 deg/s ±30.6) ($F_{(1,11)} = 5.971$; $p = 0.038$; $\eta^2 = 0.605$) but no effect of timing. In predictable tasks we found significantly higher peak velocity when TMS stimulation was applied during the delay when compared to target onset ($F_{(1,11)} = 13.856$; $p = 0.003$; $\eta^2 = 0.923$). We also found a significantly higher peak velocity in DLPFC than MRPFC ($F_{(1,11)} = 5.191$; $p = 0.044$; $\eta^2 = 0.547$). No interactions were observed.

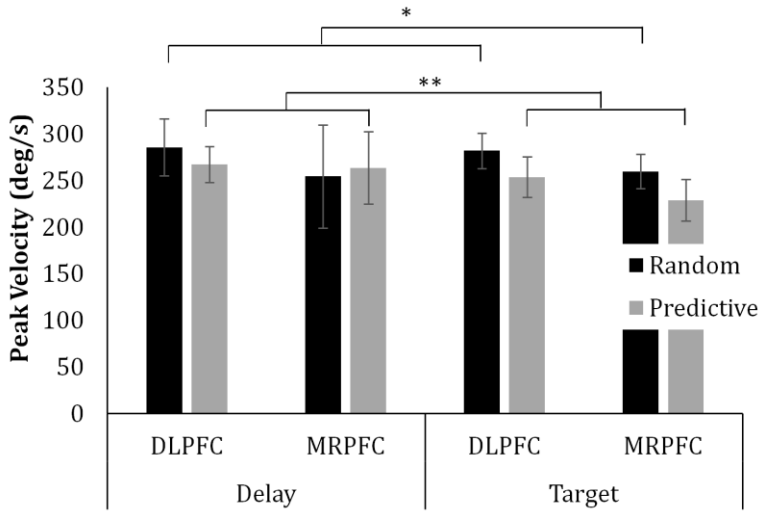

Figure 4: Peak velocity differences between the stimulation sites (medial rostal prefrontal cortex (MRPFC) and dorsolateral prefrontal cortex (DLPFC)) and timings (Delay versus Target) with predictable tasks shown as black bars and randomized responses as grey bars. Error bars denote the standard deviation from the mean. Peak velocity was slower for stimulation during target onset (in both DLPFC and MRPFC) when compared to stimulation during the delay in predictable sequences. For random sequences we observed higher peak velocity during DLPFC stimulation compared to MRPFC stimulation.

Discussion

Our study aimed to find evidence for MRPFC being involved in performing random stimulus-orientated saccades and for DLPFC being involved in performing predictive stimulus-independent saccades during our sequence learning task. We chose a double dissociation approach to avoid any issues associated with inappropriate control conditions often encountered during TMS experiments. Firstly our results revealed no effects of lateralization in any of the saccade metric measured as expected (Müri et al., 2000) and hence we collapsed data across the hemispheres.

Reaction Time Effects: From our results we can see that the timing of the stimulation (delay versus target onset) had opposite effects depending on if the subjects performed reactive responses (SO) or

predictive responses (SI). In the random condition, stimulation during the target presentation resulted in longer RT when compared to stimulation during the delay and this was true for both brain areas. This suggests that disruption was caused to the normal processing during the target presentation in random tasks. We found this effect to be more prominent in MRPFC than DLPFC. During the predictive responses we found more disruption to the "normal" predictive mechanisms (when compared to the same task with no stimulation observed in Burke et al., 2013) in the delay compared to target onset stimulation condition in DLPFC. It should be noted that this previous study (Burke et al., 2013) used a different group of 9 healthy young subjects to the current study and took place a year prior to the current experiment. However, both studies support the hypothesis presented in the introduction in that MRPFC is more affected by stimulation during target onset than DLPFC, given its SO role.

The prefrontal cortex is thought to be involved in inhibition of unwanted saccades and our results are in support of previous studies demonstrating this effect (Coubard et al., 2003). However, further to a number of previous studies which have found stimulation of TMS at the time of target onset causes this reduction in inhibiting reflexive saccades (Coubard and Kapoula, 2005), we have also found that stimulation during a delay between sequences of reflexive saccades can also cause this effect. This is highly possible in our task given the tasks were blocked according to task i.e. predictable or random. The increase in latency observed in this study to more "planned" or predictive responses has also been found by stimulating DLPFC. A study by Nagel et al (2008) demonstrated that stimulation in DLPFC (and also FEF and SEF) during a gap between fixation and the target, resulted in an increase of the saccadic latency. Their interpretation is consistent with the findings reported here that stimulation in DLPFC during the delay is disrupting a "preparatory set" or a pre-programmed saccade (or in our case a sequence of saccades) resulting in longer latencies for these predictable trials. Our findings also support Kovel et al (2011) who investigated Superior Colliculus (SC) activity while simultaneously deactivating DLPFC (by cooling) in macaques. They attribute the disruption in performance to reduced inhibitory control within SC resulting in poor preparatory activity within SC as shown here.

However, we also find a similar disruption to the temporal release of information when stimulating MRPFC during the delay, indicating a similar role in releasing the signal to generate a saccade.

No evidence in this study was found for MRPFC being involved in the timing of a saccadic eye movement in this task. A plethora of neuroimaging studies have implicated the involvement of DLPFC in ocular-movement tasks, but not MRPFC, so this finding is not unexpected (Alvarez et al, 2010). In-line with the data presented here Koechlin and Summerfield (2007) have provided an excellent model of prefrontal cortex function. This model suggests polar lateral prefrontal cortex (equivalent to BA10, MRPFC) provides a "branching control" mechanism that holds a number of possible responses, and is responsible for switching between these options based on the current situation. Thus MRPFC requires external input for monitoring purposes and switching between these tasks. The model additionally states that the anterior lateral prefrontal cortex (equivalent to BA9/46, DLPFC) is more involved in "episodic control", where previous information is stored and subsequently accessed at the right time. These findings are directly in-line with this Koechlin and Summerfield (2007) model; however this study provides new causal evidence of this function within the PFC.

Saccade Gain Effects: We found no effects of saccadic duration between the timing of the TMS stimulation and/or the brain areas stimulated, but we did find some interesting effects in the gain of the saccades that were generated by our participants. In theory, errors in gain generally denote a distortion of the spatial memory for that target and indeed the significant effects we observed were only found in the predictable condition (where learning took place) and not in the randomized trials. To interpret these results it is important to recognise that predictive and memory-related responses tend to reveal an undershoot or hypometric saccade (Becker and Fuchs, 1969; Henson, 1979) to the remembered target location, and indeed this same task revealed an average reduction in saccadic gain between random and predictive targets of 0.1 (with no TMS or vertex stimulation) in a previous, directly comparable, study (Burke et al, 2013). In this study, we found a reduction in gain from the random to the predictable task of 0.06 when stimulation was applied to DLPFC, and 0.1 with stimulation in MRPFC (see figure 3). This suggests that stimulation of MRPFC is not changing the

saccade accuracy, as the difference between random and predictive gain was in-line with our previous study of 0.1 (Burke et al., 2013). However, stimulation of DLPFC resulted in a reduction in this hypometric effect in predictive responses and hence a distortion of the "normal" predictive effect. This indicates that again DLPFC is also involved in the storage of spatial information during the delay of a sequence learning task and that disrupting activity of the neurons within this area results in a change in the "memory-related undershoot" normally observed in prediction/memory. Furthermore, this is the first study to demonstrate a causal relationship between this hypometric response in prediction/learning and the DLPFC.

Peak Velocity Effects: We found that there was an overall reduction in peak velocity in the predictive task when compared to the randomized tasks. We also observed this effect in a previous study using the same paradigm when no TMS was applied (reduction of ~20 deg/s in PRD task compared to RND task) (Burke et al., 2013). There is a linear relationship between duration of the saccades and their amplitude that is known as the main sequence, and this also applies to saccadic velocity with higher velocity resulting in larger saccadic amplitudes (Bahill et al., 1975). Our data revealed a clear decrease in peak velocity during the predictive tasks (in-line with the decrease in saccadic gain above) in all but one of our conditions. Interestingly, stimulation in MRPFC during the delay resulted in the opposite effect with higher peak velocity for predictive versus the random (of 9 deg/s). From this data we can suggest that MRPFC is an area that is important for establishing saccadic metrics such as peak velocity, and possible storage of these metrics for future use.

There is very little evidence of the role of the rostral prefrontal cortex (ba10) in eye movements and more research has focused on its role in prospective memory. Burgess et al (2003) suggested a dissociation of the medial and lateral portions of rostral prefrontal cortex with internally-generated thought and maintaining thought respectively; however we find a role for the MRPFC for the storage of saccade metrics with disruption resulting in a change in peak velocity during internally generated saccades. Our results support a number of neuroimaging studies that suggest a role for the rostral medial prefrontal cortex in "internal" or self-referential signals (Gilbert et al., 2006; Burgess et al., 2007; Hassabis et al., 2007; Mason et al., 2007; Raichle and Synder, 2007; Boorman et al., 2009), but

further contributes to the literature by demonstrating a causal relationship between MRPFC and generating internally-driven (predictive) saccades during a sequence learning task.

One possible limitation to this study is the timing of the pulse at target onset. Some may argue that this pulse should be delivered later (~100ms post-target onset) in order to optimally disrupt the processing signal. However it is worth noting we wanted to disrupt very early attentional processing in this brain region and a number of studies that have found stimulation at target onset to be optimal in paradigms similar to ours in brain areas that include FEF (Martin and van Donkelaar, 2012) and SMG (McKeefry et al., 2008). A good comparison study is by Bosch et al., (2012) who stimulated the frontal lobe during an oculomotor task at several time points including: 25ms, 50ms and 75ms post target. Bosch et al (2012) found that all time points of stimulation resulted in equivalent disruption of saccadic latency. Furthermore, Schluter et al (1998) found stimulation in frontal areas 100ms post-target onset causes disruption to the actual motor programming and hence eye movement response rather than and any underlying cognitive function (which was the aim of the present study).

To conclude, we have revealed a dicotomy of function between DLPFC and MRPFC in terms of reaction time. The results support the original hypothesis that DLPFC is more involved in SI tasks and MRPFC in SO tasks. Stimulating DLPFC during the delay caused disruption to the temporal release of a premotor plan and, in predictable tasks, to the saccadic gain and peak velocity. Hence, DLPFC is important for remembering the location of the target for the upcoming saccade. However, contrary to our original hypothesis, we additionally found that both areas (MRPFC and DLPFC) contribute in different ways to internally-driven actions. DLPFC is primarily concerned with saccadic timing (premotor release of the action) and accuracy of the motor plan, whereas MRPFC is more involved in updating and storage of saccade metrics such as peak velocity.

References

Bahill AT, Clark MR, Stark L (1975) The main sequence a tool for studying human eye movements. Mathematical Biosciences 24(3-4):191-204.

Basso D, Ferrari M, Palladino P (2010) Prospective memory and working memory: Assymetrical effects during frontal lobe TMS stimulation. Neuropsychologia 48:3282 - 3290.

Becker W, Fuchs AF (1969) Further properties of the human saccadic system: eye movements and correction saccades with and without visual fixation points. Vision Research 9:1247-1258.

Boorman ED, Behrens TE, Woolrich MW, Rushworth MF. (2009) How green is the grass on the other side? Frontopolar cortex and the evidence in favour of alternative courses of action. Neuron 62:733–743.

Burgess PW, Scott SK, Frith CD (2003) The role of the rostral frontal cortex area (area 10) in prospective memory: a lateral versus medial dissociation. Neuropsychologia 41: 906-918.

Burgess PW, Dumontheil I, Gilbert SJ (2007) The gateway hypothesis of rostral prefrontal cortex (area 10) function. Trends in Cognitive Neuroscience 11(7): 290-298.

Burke MR, Barnes GR (2008) Brain and Behaviour: A task dependent eye movement study. Cerebral Cortex 18(1):126-135.

Burke MR, Bramley P, Gonzalez CC, McKeefry D (2013) The contribution of the human right supra-marginal gyrus to sequence learning in saccadic eye movements. Neuropsychologia 51(14):3048-3056.

Coubard O, Kapoula Z, Müri R, Rivaud-Péchoux S (2003) Effects of TMS over the right prefrontal cortex on latency of saccades and convergence. IOVS 44(2): 600-609.

Coubard O, Kapoula Z (2005) Dorsolateral prefrontal cortex prevents short-latency saccade and vergence: a TMS study. Cerebral Cortex 16(3): 425-436.

Gilbert SJ, Spengler S, Simons JS, Steele JD, Lawrie SM, Frith CD, Burgess PW (2006) Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. Journal Cognitive Neuroscience 18:932–948.

Hassabis D, Kumaran D, Maguire EA (2007) Using imagination to understand the neural basis of episodic memory. Journal of Neuroscience 27:14365–14374.

Henson DB (1979) Investigation into corrective saccadic eye movements for refixation amplitudes of 10 degrees and below. Vision Research 19: 57-61.

Herwig U, Satrapi P, Schonfeldt-Lecuona C (2003) Using the international 10-20 EEG system for positioning of trans-cranial magnetic stimulation. Brain Topography 16: 95-99.

Koechlin E, Summerfield C (2007) An information theoretical approach to prefrontal executive function. Trends in Cognitive Neuroscience 11(6):229-235.

Koval M, Lomber SG, Everling (2011) Prefrontal cortex deactivation in macaques alters activity in the superior colliculus and impairs voluntary control of saccades. Journal of Neuroscience, 31(23): 8659-8668.

Martin K, van Donkelaar P (2012) Expectations can modulate the frequency and timing of multiple saccades: a TMS study. Experimental Brain Research 221:3146.

McKeefry DJ, Burton, MP, Vakrou C, Barrett BT, Morland A. 2008. Induced deficits in speed perception by transcranial magnetic stimulation of human cortical areas V5/MT+ and V3A. J Neurosci 28:6848-6857.

Müri RM, Rivaud S, Vermersch AI, Leger JM, Pierrot-Diesilligny C (1996) Effects of transcranial magnetic stimulation over the region of the supplementary motor area during sequences of memory guided-saccades. Experimental Brain Research 104: 163-166.

Müri RM, Gaymard B, Rivaud S, Vermersch A, Hess CW, Pierrot-Deseilligny C (2000) Hemispheric asymmetry in cortical control of memory-guided saccades. A transcranial magnetic stimulation study. Neuropsychologia 38(8): 1105-1111.

Nagel M, Sprenger A, Lencer R, Kömpf D, Siebner H, Heide W (2008) Distributed representations of the “preparatory set” in the frontal oculomtor system: A TMS study. BMC Neurosci 9:89.

Owen AM, McMillan KM, Laird AR, Bullmore E (2005) N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. Human Brain Mapping 25(1):46e59.

Pascual-Leone A, Wassermann EM, Grafman J, Hallet M (1996) The role of the dorsolateral prefrontal cortex in implicit procedural learning. Experimental Brain Research 107: 479-485.

Pierrot-Diesilligny C, Rivaud S, Gaymard B, Agid Y (1991) Cortical control of reflexive visually guided saccades. Brain 114: 1473-1485.

Pierrot-Diesilligny C, Müri RM, Ploner CJ (2003) Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. Brain 126: 1460-1473.

Pierrot-Diesilligny C, Milea D, Müri RM (2004) Eye movement control by the cerebral cortex. Current Opinion in Neurology 17: 17-25.

Raichle ME, Snyder AZ (2007) A default mode of brain function: a brief history of an evolving idea. Neuroimage 37:1083–1090.

Schluter ND, Rushworth MF, Passingham RE, Mills KR (1998) Temporry interference in human lateral premotor cortex suggests dominance for the selection of movements.A stdy using transcranial magnetic stimulation. Brain 121: 785 – 799.

Stewart LM, Walsh V, Rothwell JC (2001) Motor and phosphene thresholds: a transcranial magnetic stimulation correlation study. Neuropsychologia 39(4):415-419.

Wager TD., Smith EE (2003) Neuroimaging studies of working memory: A meta-analysis. Cognitive, Affective & Behavioral Neuroscience 3(4): 255-274.