THE CONTRIBUTION OF THE RIGHT SUPRA-MARGINAL GYRUS TO SEQUENCE

LEARNING IN EYE MOVEMENTS.

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Brief Running Title: **Sequence Learning and the rSMG**

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Abstract

We investigated the role of the human right Supra-Marginal Gyrus (SMG) in the generation of learned eye movement sequences. Using MRI-guided transcranial magnetic stimulation (TMS) we disrupted neural activity in the SMG whilst human observers performed saccadic eye movements to multiple presentations of either predictable or random target sequences. For the predictable sequences we observed shorter saccadic latencies from the second presentation of the sequence. However, these anticipatory improvements in performance were significantly reduced when TMS was delivered to the right SMG during the inter-trial retention periods. No deficits were induced when TMS was delivered concurrently with the onset of the target visual stimuli. For the random version of the task, neither delivery of TMS to the SMG during the inter-trial period nor during the presentation of the target visual stimuli produced any deficit in performance that was significantly different from the no-TMS or control conditions. These findings demonstrate that neural activity within the right SMG is causally linked to the ability to perform short latency predictive saccades resulting from sequence learning. We conclude that neural activity in rSMG constitutes an instruction set with spatial and temporal directives that are retained and subsequently released for predictive motor planning and responses.

1. Introduction

The human motor system is extra-ordinarily adept at acquiring new skills and has developed sophisticated systems for the encoding and storage of spatial and temporal information that facilitate the coordinated and rapid performance of complex motor tasks (Barnes & Asselman, 1991; Kao & Morrow, 1994; Kowler & Steiman, 1979). This acquisition is accompanied by increased efficiencies in visuo-spatial processing, motor planning and motor execution (Gobel, Parrish & Reber, 2011). These gains are often achieved following sequence learning where task performance improves following repetitions of the same motor sequence (Nissen & Bullemer, 1987; Hikosaka, Miyashita, Miyachi, Sakai & Lu, 1998). Sequence learning can occur with saccadic eye movements when observers are required to make a series of saccades to visual targets that change in spatial location over time. Saccadic latency decreases with sequence repetition and the eye movements can even occur in advance of the onset of a new fixation stimulus (Gaymard, Pierrot-Deseilligny & Rivaud, 1990; Petit, Clark & Ingeholm, 1996; Schmid, Rees, Frith & Barnes, 2001; Barnes & Schmid, 2002; Simo, Krisky & Sweeney, 2005; Burke & Barnes 2007). In making these eye movements, observers can in effect anticipate future target locations based upon the spatial and temporal information pertaining to that specific sequence retained by memory mechanisms (Carpenter, 1988; Barnes & Asselman 1991).

The functional anatomy of sequence learning is based upon a network comprising numerous cortical and sub-cortical areas (Pascual-Leone, Wassermann, Grafman & Hallett, 1993; 1996; Gerloff, Corwell, Chen, Hallett & Cohen, 1997; Haaland, Harrington & Knight, 2000; Hikosaka, Nakamura, Sakai & Nakahara, 2002; Penhune & Doyon, 2002). For eye movements, the supplementary motor area (SMA), the supplementary eye field (SEF), frontal eye fields (FEF) and the dorsolateral prefrontal cortex (DLPFC) all make contributions to sequence learning (Muri, Rosler & Hess, 1994; Muri, Rivaud, Vermersch, Leger & Pierrot-Desseilligny, 1995; Petit et al., 1997; Lu, Matsuzawa & Hikosaka, 2002; Pierrot-Deseilligny, Milea & Müri, 2004). Also forming part of this network are cortical areas within the posterior parietal cortex (PPC) (Petit et al., 1997; Alvarez, Alkan, Gohel, Ward & Biswal, 2010), a functionally complex region important for the encoding, retention and retrieval of instruction sets that specify how movements are to be performed (Goodale & Milner, 1992; Culham & Kanwisher, 2001; Kravitz, Kadharbatcha, Baker & Mishkin, 2011; Culham & Valyear,

2006; Rawley & Constandinidis, 2009). One sub-division of the PPC in particular, the right supramarginal gyrus (rSMG) in Brodmann area 40, has been shown to be active when predictive saccades are performed (Perry & Zeki, 2000; Simó et al., 2005; Burke & Barnes, 2008b; Alvarez et al., 2010). Yet despite these persistent reports, the role of the rSMG in predictive eye movements remains largely unexplored.

To address this deficiency we employed Transcranial Magnetic Stimulation (TMS) to selectively disrupt neural activity within the rSMG whilst human observers performed a predictable or random saccadic eye movement task. We wished to determine whether neural activity in the rSMG was causally involved in the encoding and/or retention of the information required for the performance of the sequence learning task. To this end we measured the effects on performance of TMS pulses that were either delivered concurrently with the fixation stimuli (encoding) or during the inter-trial interval (retrieval).

2. Materials and Methods

2.1. Subjects

Nine neurologically normal, right handed subjects aged 20-45 (25 ± 7.5 years, 5 female) with normal or corrected to normal vision were recruited for the study from the University of Leeds. All subjects gave informed consent and completed a relevant medical history questionnaire before the experiments, and were given a monetary reward upon its completion. The study was approved by the University of Leeds Ethical Committee.

2.2. Apparatus

Visual fixation target stimuli were presented on a high resolution 17'' CRT colour monitor (Vision Master, Ilyama, Japan) 1024x768 pixels spatial resolution and 75Hz refresh rate with a mean luminance of 50cd/m2. The stimuli were white annular targets which subtended 0.5 degree of visual angle on the screen (see figure 1a) and were generated using Experimental Builder Software (SR Research Ltd., Canada). Subjects were

seated 57cm from the monitor with their chin and forehead secured on an Eyelink 1000 eye tracking system (SR Research Ltd, Canada). Left eye position was monitored throughout the experiment at a sample frequency of 500Hz for subsequent offline analysis. All experiments took place in a quiet room free of external light sources. Before each experimental block a 5 point calibration and validation was taken to ensure correspondence of the eye with the target on the screen to within an accuracy of $0.25 - 0.5°$.

2.3. Experimental Protocol

The experiment employed a within-subjects design. Two TMS protocols were used (2-pulse (2P) and 4-pulse (4P)) which were delivered to the rSMG of each subject as well as to a control site at the vertex. In addition, there was also a no-TMS condition to establish baseline performance, giving a total of five conditions. For each condition subjects performed two experimental blocks consisting of either predictable or random eye movement sequences (see figure 1a). Both sequences began with the presentation of fixation target, a small white annulus ($0.5°$ diameter), that appeared in the centre of the screen for ~1000ms (actual duration 1013ms given the restrictions of the screen resolution). Following the offset of this initial fixation target a similar target was then presented at another location on the screen $5°$ either to the left, right, up or down. This $5°$ positional change was repeated for a total of four targets that were presented sequentially (see figure 1a). The subjects were instructed to make the necessary eye movements to allow re-fixation of the target following each change in stimulus position. In the predictable condition each target appeared for 750ms before moving to a new position and the same sequence of 4 targets was repeated 4 times (see figure 1a). This repetition of the sequence allows subjects to predict each component of the sequence from the second sequence presentation (Barnes & Schmid, 2002). In the random sequence the duration of the target stimuli varied between 525ms and 1275ms, and the pattern of positional shifts of the target stimulus also varied for every sequence (see figure 1a). The random sequences were therefore temporally and spatially unpredictable. There was a 1 second interval between each trial to allow for repositioning of the eye back onto the centre of the screen ready for the next sequence of eye movements.

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Each block consisted of 40 trials (i.e. 40 unique sequences for random trials and 10 unique sequences repeated 4 times (also 40 trials) for predictable trials – see figure 1b) that lasted around 3.5 minutes. Subjects performed 10 blocks of 40 trials in two sessions that were pseudo-randomized within and between subjects. These 10 blocks comprised a predictable and random block for each of the TMS stimulus conditions: (i) 2 pulse TMS on SMG (SMG2P), (ii) 2 pulse TMS on the vertex (V2P), (iii) 4 pulse TMS on SMG (SMG4P), (iv) 4 pulse TMS on the vertex (V4P), and (v) no TMS. In between blocks and conditions the lights were restored and there was a short break to reduce fatigue.
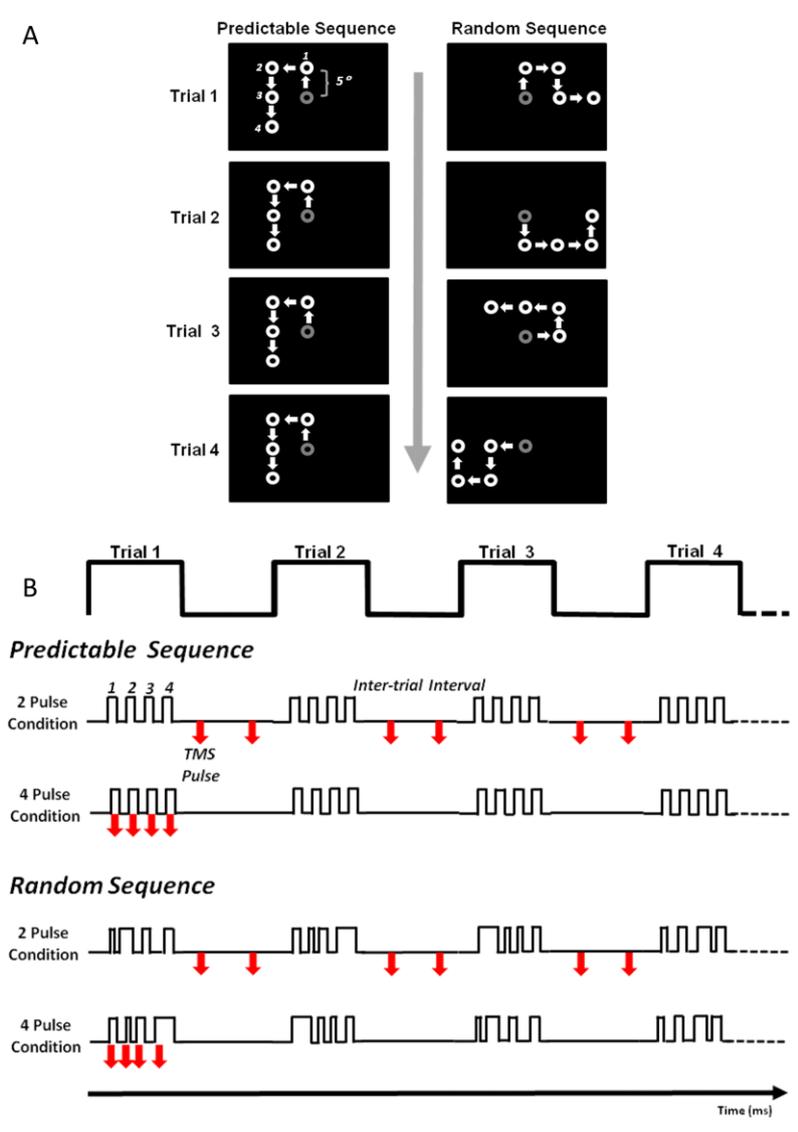
Figure 1. A) *Eye Movement Stimuli*: The visual fixation stimuli used for the study comprised annular targets (0.5° diameter) which were presented in a temporal sequence. Each trial began with the first fixation

stimulus (grey annulus in the diagram) appearing in the centre of screen and following its offset another target appeared in a different location 5° to the left, right, up or down from its original location. This was repeated four times in each trial. The changes in position occurred in either a predicitable (left hand side) or a random (right hand side) manner. In the predictable sequence the same positional changes were presented for every four trials whilst in the randon sequence a different series of positional changes were presented in every trial. In addition the onset duration of the fixation stimuli in the randon sequence varied (between 525 and 1275ms), whereas in the predictable sequence the visual stimuli were always presented for 750ms. B) *TMS Protocols:* A schematic illustrating the delivery of the TMS pulses relative to the onset of the fixation stimuli in each trial for the predictable and random sequences. Two TMS protocols were used: 1) a 2 pulse condition where two TMS pulses were delivered to either the SMG or the control site during the inter-trial interval. 2) a four pulse condition were 4 pulses were delivered at the onset of each new fixation stimulus.

2.4. TMS Protocol

TMS was delivered to pre-specified cortical locations (rSMG or vertex) using 70 mm diameter 'figure of eight' coils which were secured in a tripod and placed over the scalp tangentially with the handle pointing backward and orientated parallel with the floor (sagittal orientation for SMG and transverse orientation for vertex). The coils were connected to a Magstim Rapid2 stimulator (Magstim Company Ltd., Wales) which was triggered using TTL pulses derived from the Experimental Builder stimulus software. This allowed us to accurately control the delivery of the TMS pulses relative to the onset of the visual stimuli (see figure 1b).

TMS pulses were fixed at 40% of the maximum output of the stimulator coils (2.6 T) which has previously been found to be an effective approach to TMS stimulation in the adjacent angular gyrus region (Cattaneo, Silvanto, Pascual-Leone & Battelli, 2009; Cappelletti, Fregni, Spelke & Pascual-Leone, 2007; Muggleton, Postma, Moutsopoulou, Nimmo-Smith, Marcel & Walsh, 2006). Other studies have noted that the traditional motor threshold approach to TMS intensities may not be an appropriate estimate of neurocognitive processing (Stewart, Walsh & Rothwell, 2001). These pulses were delivered as part of two

protocols: 1) a Four-pulse Condition (4P), where a single TMS pulse was delivered coincident with each of the four changes in target position during each trial (see figure 1b) for the first sequence only in a trial, and 2) a Two-pulse Condition (2P) where paired TMS pulses (2 pulses separated by 525ms) were delivered during the inter-trial period (the first at target offset the second 525ms later) (see figure 1b). This design was employed to disrupt brain activity at two main processing time-points: 1) during target appearance and 2) during the inter-trial delay between sequence presentations. Delivery of TMS at time point 1 was used to disrupt the encoding or acquisition of the stimuli using a temporal configuration similar to that used in previous studies where disruption to the encoding of different categories of visual stimuli has been shown to be maximised when TMS pulses are delivered coincidently with stimulus onset (McKeefry, Burton, Vakrou, Barrett & Morland, 2008; Pitcher, Charles, Devlin, Walsh & Duchaine, 2009; Silson, McKeefry, Rodgers, Gouws, Hymers & Morland, 2013). Concurrent stimulation of this nature also minimizes interference with the normal saccadic response to each target, as TMS delivered after 100ms from target onset tends to cause disruption of the motor response (Schluter, Rushworth, Passingham & Mills, 1998), which can confound any earlier encoding effects. In contrast delivery of TMS at time point 2 allowed us to focus on the retention of information relating to learned sequences during the inter-trial interval. Behavioural data show that retention of information occurs after only one repetition of a predictable sequence (Barnes & Schmid, 2002) and previous studies have demonstrated that disruption of the neural mechanisms that are responsible for the retention of information in spatial working memory tasks can be achieved when TMS is limited to the delay phase of the task (Oliveri, Turriziani, Carlesimo, Koch, Tomaiuolo & Panella, 2001).

2.5. Selection and Identification of areas for TMS

All nine subjects who participated in this study, took part in previous fMRI experiment for which anatomical and functional neuroimaging data was obtained. The fMRI experiment was a block design where the subjects (n = 12) performed the same predictable and random saccadic sequence learning tasks as used in the current experiment in an fMRI scanner (Philips 3T Achieva scanner, Philips Electronics, N.V.). Functional scans were acquired using T2* weighted spin echo pulse with a TR of 2000ms, TE of 35ms, a 90° flip angle, a

250mm FOV, 1.8mm x 1.8mm x 4mm^3 voxel size, and a total of 30 slices per volume. The scans were pre-processed using SPM8 (The FIL Methods group, FIL, U.K.) which involved spatial realignment, coregistration, normalization, spatial smoothing (8mm FWHM gaussian filter) and a temporal high-pass filter with a 128Hz cut-off frequency to remove scanner drifts. Contrasts between the predictable and randomized sequences were performed for each subject (1st level), prior to a group level random effects analysis (RFX) of this contrast. The results of the group analysis (n=12) are shown in Figure 2 which highlights the significant activations (Z > 3.5) generated by the predictable versus random contrast. Type 1 errors were controlled for by using a cluster level FWE and FDR correction (p < 0.05). Regions were identified and displayed using SPM Anatomy toolbox (Simon Eickhoff, SPM8, FI). The SPM8 software was used to co-register the functional data with individual structural MRI scans and peak activation in right supra-marginal gyrus (Brodmann area 40) for each of the 9 subjects was identified (see Figure 3). These data were subsequently used for TMS localization (see below).

Cluster size	Z score	MNI (x)	MNI (y)	MNI (z)	Hemisphere	Area
Brain Areas for Sequence Learning						
2711	4.17	-20	-106	2	L	V1/V2
3049	3.94	60	-41	28	R	IPL/SMG
1692	3.58	-18	-8	73	L	BA6
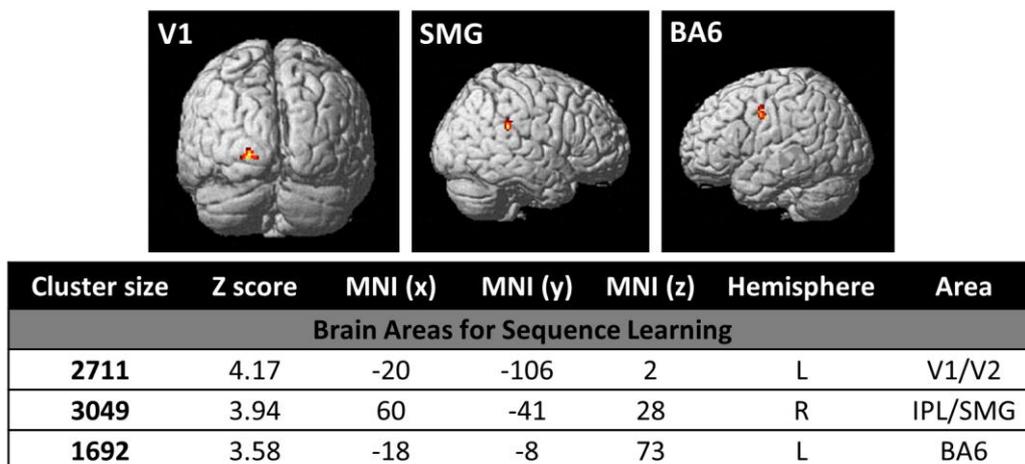
Figure 2. The details of the significant brain areas activated during the learning of a saccadic sequence are shown in the table and are represented as a mean activation on a template brain image (SPM Anatomy toolbox, FIL, UK). The group RFX analysis for the contrast between the predictable and randomized saccadic sequence presentations from the 12 subjects participating in the fMRI study are shown. The anatomical locations found to be significantly more active for the sequence learning task are shown above the table,

and include: (i) the primary visual cortex (V1), (ii) the superior marginal gyrus (SMG), and (iii) BA6 which is possibly part of the frontal eye fields (FEF). The table provides the key anatomical details of the brain areas involved in the tasks (Z score > 3.5) in order of significance.

Subject	MNI (x)	MNI (y)	MNI (z)
1	50	-30	24
2	58	-46	50
3	62	-32	50
4	44	-38	38
5	68	-36	32
6	68	-34	22
7	68	-34	26
8	66	-20	16
9	32	-48	54
Mean	57	-35	34
STD	12.8	8.4	14.0
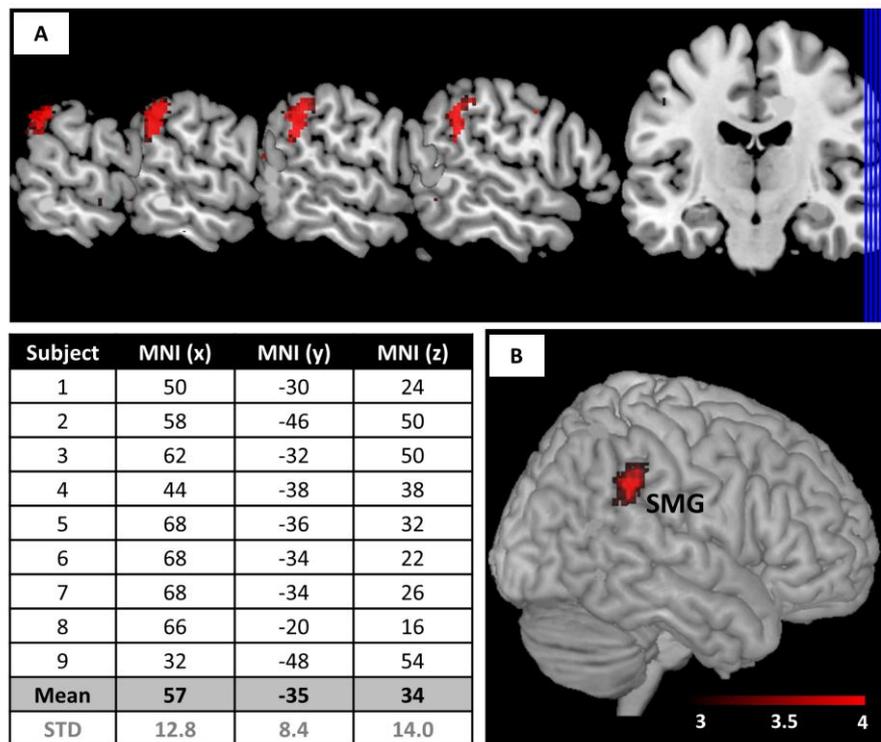
Figure 3. Figures A and B shows group level supramarginal gyrus (BA40, SMG) activity on the right hemisphere of a template brain (Ch2, MRICroN, NITRIC) for the contrast between predictable and random sequences of saccades (Z > 3, shown by legend). Individual MNI coordinates for each subject are displayed in the table with reported means (± std) for the 9 subjects who participated in the TMS experiment.

In addition to the SMG stimulation site we also selected the vertex as a control site for TMS stimulation. The vertex site was determined using anatomical landmarks on the surface of the skull and was defined and marked on the subjects' scalps as the point of intersection between the inion-nasion line and a line joining the inter-trachial notches of the ears (Schenk et al., 2005). This control stimulation site corresponds to the Cz position of the 10-20 EEG electrode placement system (Jasper, 1957).

The PPC is commonly divided into the superior parietal lobe (SPL) which lies dorsal to the intra-parietal sulcus (IPS), and the more ventral inferior parietal lobe (IPL), which comprises the angular gyrus (AG), the supramarginal gyrus (SMG) and the temporo-parietal junction (TPJ) (Cabeza et al., 2008; Olson & Berryhill, 2009; Hutchinson et al., 2009). Accurate targeting of each subject's right SMG for TMS was achieved using procedures previously described by this and other laboratories (Sack et al., 2009; McKeefry et al., 2008) using a 3-D ultrasound digitizer CMS30P (Zebris, Tübingen, Germany) in conjunction with the BrainVoyager QX software (version 2.0 Brain Innovation, Netherlands). Briefly, structural MRI scans were co-registered with the subjects head by linking the position of ultrasound transmitters placed on the subject's head with pre-specified anatomical landmarks - the nasion and the two incisurae intertragicae. These points were then co-registered with the same pre-defined anatomical points on the head representation (mesh) of the subject. Similarly, a local co-ordinate system was set up for the TMS coil by linking pre-specified points on the coil with the ultrasound transmitters. Once this co-registration had taken place, the coil could then be navigated and placed over specific cortical areas with accuracy. Once the correct coil position for rSMG stimulation was located and marked on the subject's scalp with a marker pen, he/she was then positioned on the Eyelink headrest for recording eye movements. Regular checks of coil position were made throughout testing.

2.6. Data Analysis

Eye movement data was analyzed using the Data Viewer (SR research, Ontario, Canada) software. Blinks were automatically detected when the pupil image was lost and eliminated from the raw data files. Saccades were identified using a velocity and acceleration based parser algorithm with a velocity threshold of 50°/s. Saccade onsets to the target were obtained for each target in each sequence and latency was calculated from target onset to saccade onset. All saccades outside of 500ms before target presentation and 300ms after target presentation were discounted since predictive saccades could happen very early and are highly variable but reactive saccades are characteristically more uniform and are faster than 300ms (Carpenter, 1988). Saccade amplitude was obtained by calculating the distance from the saccade onset to

saccade offset for each target in each sequence. We did not include corrective saccades in the amplitude measures and took the first saccade to the target as a measure of spatial memory in the predictive conditions. Only saccades with amplitudes between 2 and 12 degrees were analysed in order to remove blinks (which can be interpreted by the camera as saccades) and small corrective saccades. Furthermore saccades with a peak velocity of greater than 1000m/s were rejected to also aid in the removal of blinks. The closest qualifying saccade to the stimulus presentation was taken as the response to the target and the end point of this saccade was used for amplitude measures. There were very few errors (<1%) made by subjects since the task involved viewing visible targets.

We used a 5 (TMS condition) x 2 (Predictive or Random block) x 4 (trial number) repeated measure ANOVA to calculate significant main effects. This was followed by a post-hoc anova analysis (Bonferroni corrected) on any significant interactions between conditions to control for effects of multiple comparisons.

3. Results

In order to establish the effect of TMS disruption on rSMG function we measured three key saccadic eye movement parameters: latency, amplitude and peak velocity. Delays in saccadic latency onset following the delivery of TMS to rSMG would indicate that neural activity in this area is essential for the temporal processing of information that permits the usually short latency predictive saccades. A disruption to the amplitude of the saccade during TMS, may alternatively imply a greater spatial memory role for rSMG, whereas a change in peak velocity induced by TMS would suggest a more motor related function of SMG.

3.1. Saccade Latency

The latency to each target in the sequence was calculated, by averaging over all 4 targets in that sequence since no sigificant differences in latency were observed between targets within a sequence. We performed this on each of the 4 repetitions of the sequence for the predictable task and across the 10 unique sequences which resulted in an overall mean for the 1st repetition (trial 1), the 2nd (trial 2), the 3rd (trial 3) and 4th (trial 4) for each subject. The same was done for the random condition although the averaging over

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the sequences for trials 1 – 4 was over unique sequences and not repetitions. This was performed for all of the 5 conditions (No TMS, V2P, V4P, SMG2P, SMG4P) in the experiment. A repeated-measures ANOVA (5 x 2 x 4) found that mean latency was significantly lower in predictable than random blocks of trials ($F_{(1,8)}$ = 366.9, p<0.001, d = 1.00), and a significant interaction between predictability and trial ($F_{(3,6)}$ = 132.1, p <0.001, d = 1.0) indicated that there was a highly significant difference between the 1st trial in a predictable block and the subsequent trials 2, 3 and 4 (p < 0.001), but not for the random block (see figure 3). This clearly indicates that subjects show substantial and maintained learning of the sequence from the 2nd presentation of the sequence onwards during the predictable trials.

We also found a significant interaction between predictability and condition ($F_{(4,5)}$ = 5.185, p = 0.05, d = 0.64). A post-hoc analysis of this interaction revealed that there was a significant difference in the predictable block between the SMG2P condition and the control conditions (p<0.05) (see figure 4). These data show a clear effect of TMS on the latency of the response when applied over the SMG during the inter-trial interval of a predictable trial, but no effect when the sequences are randomized.
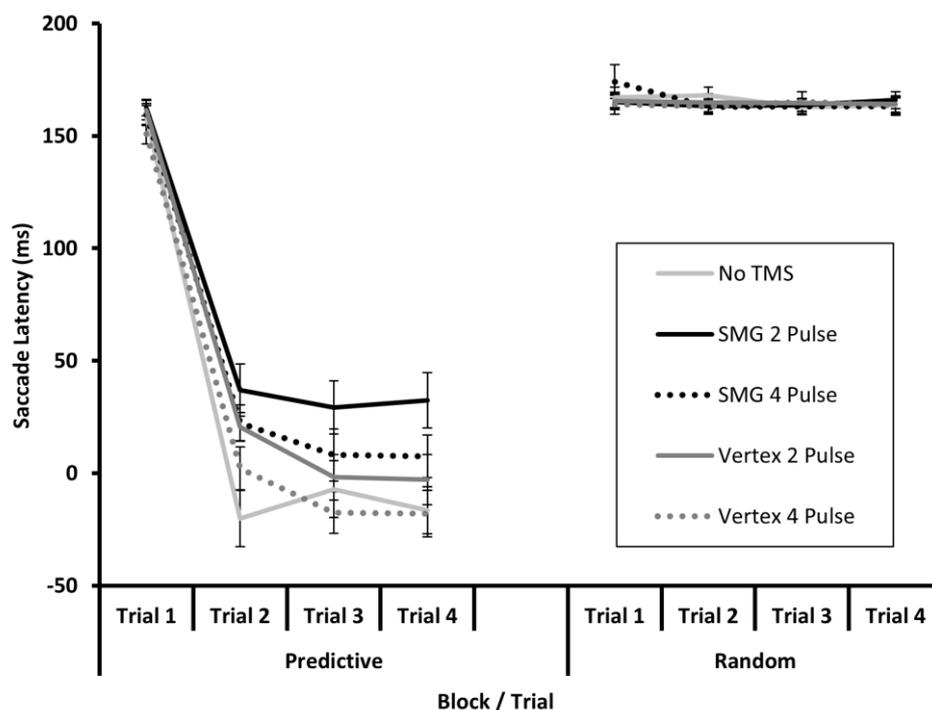
Figure 4: Mean saccade latency for all subjects to each of the 5 conditions. The results from the delivery of TMS pulses to the SMG are shown in black and those where pulses wheres delivered to the vertex control

site in dark grey. Data from the 2 pulse conditions are shown as solid lines and those from the the 4 pulse TMS conditions as dotted lines. The no-TMS condition is shown as a light grey solid line. The predictable and random responses are separated to the left and right of the graph, respectively. The mean latency for each of the repetitions of the sequences (1st, 2nd, 3rd and 4th) are shown along the Y axis. Error bars represent +/- 1 standard error from the mean.

3.2. Saccade Accuracy

The mean saccadic amplitude was calculated for each repetition of the trials in the predictable and random sequences (Figure 5). We found significantly larger amplitudes for the random saccades and shorter amplitudes for repetitions of the predictable task ($F_{(1,8)}$ = 46.68, p < 0.001, d = 0.85). An interaction between the trial number and the predictablity of the task ($F_{(3,6)}$ = 36.82, p < 0.001, d = 0.95) was found and post-hoc analysis of this interaction revealed that the trial difference was entirely driven by the difference between the 1st trial and subsequent trials in the predictive task only (p<0.005) (see Figure 5). TMS stimulation over the SMG revealed no significant effects on the amplitude (accuracy) of the saccadic eye movement.
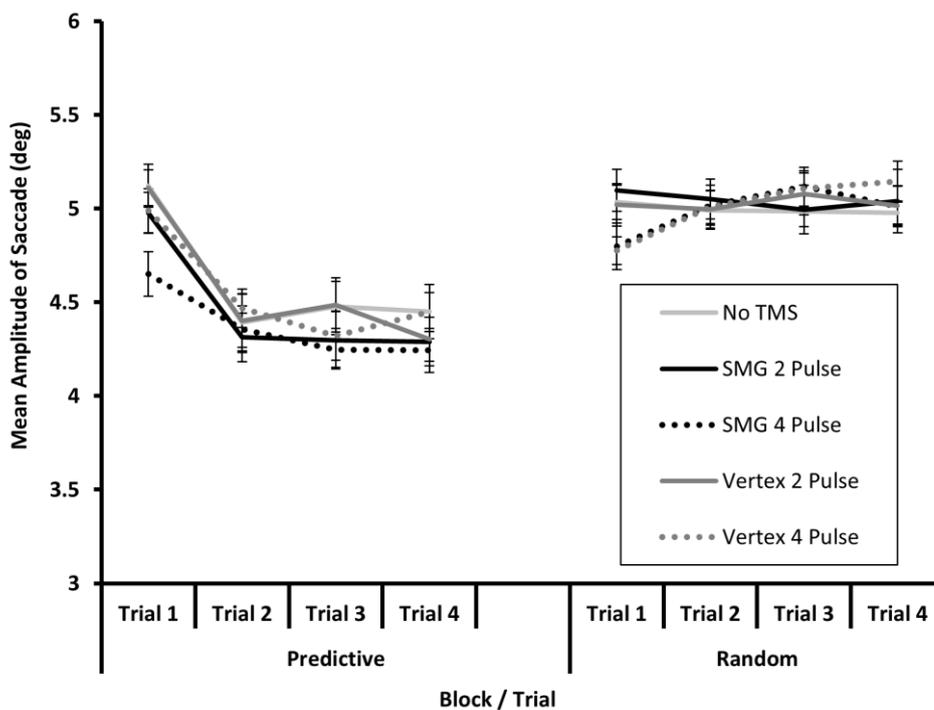
Figure 5. Mean saccade amplitude in degrees for each of the TMS stimulation conditions. Conventions used in this figure are the same as in figure 3.

3.3. Saccade Peak Velocity

In order to observe effects of the TMS stimulation on the velocity of the saccade, we investigated peak velocity to each of the five conditions (see figure 6). Statistical analysis of these data revealed no signfiicant difference between the conditions in peak velocity, indicating that TMS had no affect the metrics of the saccade once it had been initiated. In-line with the saccadic amplitude findings outlined above, we did observe a significant reduction in peak velocity to the predictable sequences ($F_{(1,8)}$ = 24.07, p<0.005, d = 0.75). The 2nd, 3rd and 4th sequence has a reduced peak velocity when compared to the 1st sequence (p < 0.01). The results indicating that predictablity of the targets has a important effect on the metrics of a saccade but not SMG stimulation.
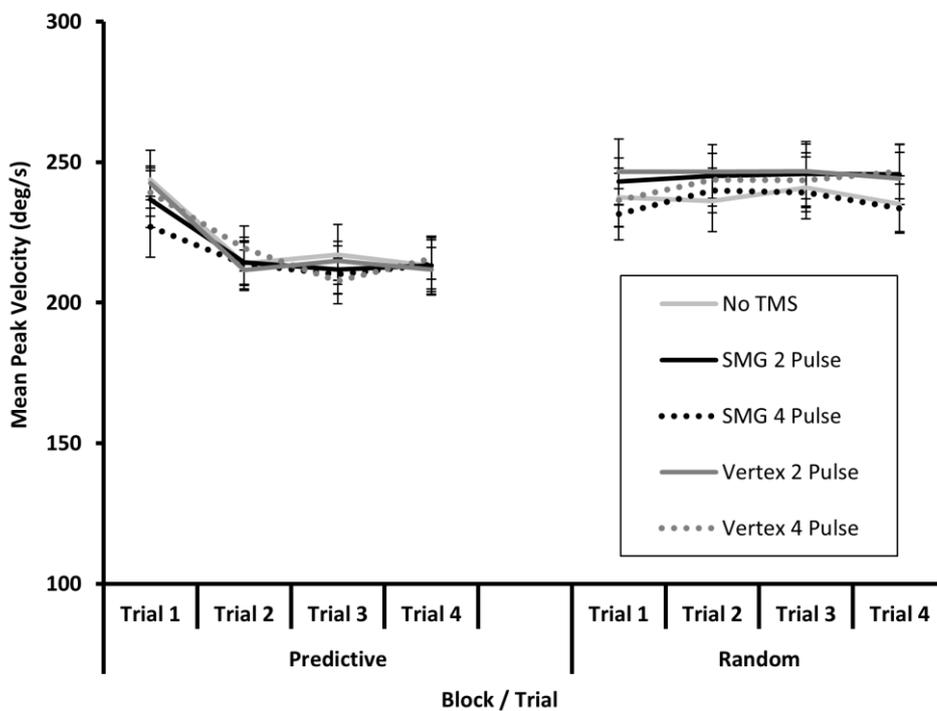
Figure 6. Mean peak velocity in degrees per second for each of the conditions shown, as a function of the sequence repetitions (or trials). Conventions used in this graph are the same as for figures 3 and 4.

To summarize, we see a significant increase in saccadic latency for the predictable tasks only in the SMG 2 pulse paradigm that delivered TMS pulses between trials. This shows that SMG is causally linked with reducing processing time and generating an earlier response to a predictable sequence of targets. The results also show no significant effect of TMS stimulation on the actual metrics of the saccade (such as peak velocity and saccadic amplitude) once the saccade has been initiated. These results indicate that SMG is not causally linked to the remembered spatial location or motor plan of the action per se, but is responsible for the early temporal execution of the predictive response i.e. early release of the motor plan.

4. **Discussion**

In this study we have demonstrated a causal link between neural activity in the right SMG and the ability of human observers to perform short latency predictive saccades that occur as a result of sequence learning. We have found that when TMS was delivered to the SMG during inter-trial intervals, the ability to make anticipatory eye movements was impaired, as evidenced by increases in saccadic latency. In random eye movement sequences, where neither the spatial nor the temporal pattern of fixation shifts could be learned, delivery of TMS to the right SMG had no significant effect on performance. These findings suggest that neural activity within the right SMG during the inter-trial intervals holds vital information which must be retained or retreived in order that the anticipatory improvements, normally observed for saccades following sequence learning, can be realised.

Previous work on sequence learning has suggested that the anticipatory advantage of predictive eye movements is based upon the short-term storage of a pre-motor instruction set required for that eye movement (pursuit: Barnes & Asselman, 1991; Barnes & Donelan, 1999. saccades: Walker & McSorley, 2006; Burke & Barnes, 2008a; Collins & Wallman, 2012). This view has strong resonance with results from recent neuroimaging experiments where Silk et al (2010) have suggested that neural activity in the right SMG reflects the generation of spatial map or co-ordinate system via which information about target/object location can be retained. However, the results presented here indicate that neural activity in the rSMG is not causally linked to the remebered location of the eye movement, as saccadic accuracy

remains unaffected by the delivery of TMS. Instead, the significant increases in saccadic latency induced by TMS following sequence learning indicate a causal link between rSMG activity and the temporal control of the predicitive responses, possibly via the early release of the motor plan. What is evident from these results is that the rSMG should be regarded as an integral part of a wider cortical network, which is likely to include the SMA, SEF, FEF, DLPFC, cerebellum and basal ganglia, all of which contribute to oculomotor sequence learning (Muri et al., 1994; 1995 ; Petit et al., 1997 ; Lu et al. 2002 ; Hikosaka et al., 2002; Penhune & Doyon, 2002 Pierrot-Deseilligny et al., 2005).

Neural activity in the SMG has previously been shown to be important for the preparation of limb movements, even when they are not actually executed (Deiber, Ibanez, Sadato & Hallet, 1996; Deiber, Ibanez, Honda, Sadato, Raman & Hallett 1998; Krams, Rushworth, Deiber, Frackowiak & Passingham, 1998). However, this motor planning activity is strongly lateralised in the left hemisphere, a finding consistent with neuropsychological literature where the left parietal cortex has also been shown to be important for the acquisition of motor skills (Kimura, 1977). Similar left lateralisation has also been demonstrated for mechanisms involved in the temporal allocation of attention which have also been linked with motor planning (Hammond, 1982; Coull & Nobre, 1998; Coull, Frith, Buchel & Nobre, 2000). Human subjects with lesions to this area of the brain often have difficulties in the generation and the temporal control of motor sequences – known as *ideomotor apraxia* (DeRenzi Motti & Nichelli, 1980; DeRenzi, 1982; Harrington & Haaland, 1992; Rushworth, Nixon, Renowden, Wade & Passingham, 1997; Haaland et al., 2000). Thus whilst the left SMG is appears to be strongly implicated in the performance of skilled limb movement sequences (Cabeza, Ciaramelli & Moscovitch, 2012), our findings suggest that the SMG in the right hemisphere may play a similar role during the learning of eye movement sequences. In certain respects, this proposed function is reminiscent of what has been termed 'motor attention' (Rushworth et al., 1997; Rushworth, Ellison & Walsh, 2001a, Rushworth, Krams & Passingham, 2001b).

Alongside the networks involved in learning and attention, the right SMG has also been found to be important for memory guided eye movements (Simó et al, 2005; Burke & Barnes, 2008b). There is still debate as to whether the SMG is involved in memory-driven (volitional) (Simó et al., 2005; Burke & Barnes,

2008b) or visually-driven (reflexive) (Mort et al., 2003) eye movements, and neuroimaging studies have been unable to resolve this issue to date. The results presented here however, provide clear evidence of a causal involvement of the right SMG in the generation of volitional saccadic eye movements. In addition, they are consistent with the idea that segregated processing pathways exist for reflexive saccades, driven by externally presented visual stimuli and for voluntary saccades, driven by instructions derived from memory (Simó et al. 2005; Walker & McSorley, 2006).

4.1. Dorso-parietal versus Ventro-Parietal Processing Pathways

The retrieval of information from stored representations in order to mediate behavioral goals is a central aspect of memory function in the PPC (Vilberg & Rugg, 2008; Cabeza & Nyberg, 2000). In this respect it is distinct from encoding which is concerned with the actual acquisition of information that is subsequently retained in memory (Moscovitch, 1992; Ciaramelli et al., 2008). Consistent with this idea of retrieval, Silk et al. (2010) have suggested that the motor planning map retained by neural activity in the right SMG is used as a basis for the control of attentional shifts. This highlights the close association that has been found to exist between the mechanisms of memory and attention in the PPC proposed by many studies (Jonides, Smith, Koeppe, Awh, Minoshima & Mintun, 1993; Smith & Jonides, 1997; 1998; Courtney, Ungerleider, Keil & Haxby, 1997; Vandenburgh et al., 1996; Nobre et al., 1997; Ungerleider, Courtney & Haxby, 1998; Kessels, d'Alfonso, Postma & de Haan, 2000; Corbetta et al., 2000; Hussain et al., 2001; Rizzolatti & Matelli, 2003: Koch, Oliveri, Torriero, Carlesimo, Turriziani & Caltagirone, 2005; Curtis, 2006; Van Asselen, Kesseks, Neggers, Kapelle, Frijns & Postma, 2006; Berryhill & Olson, 2008a,b; Olson & Berryhill, 2009; Cabeza, Ciaramelli & Moscovitch, 2012; Corbetta & Shulman, 2002; Singh-Curry & Husain, 2009). One view is that attention and memory rely upon overlapping cortical networks sharing common neural resources within the PPC (Awh, Jonides & Reuter-Lorenz, 1998; Awh, Vogel & Oh, 2006; Postle Awh, Jonides, Smith & D'Esposito, 2004; Theeuwes, Belopolsky & Olivers, 2009). Neuroimaging studies point to cortical areas within the IPL as being important for integrating these attention and memory networks (Hu, Bu, Song, Zhen & Liu, 2009). Furthermore, the right SMG constitutes a key area where mechanisms of spatial attention and

spatial working memory overlap (Le Bar, Gitelman, Parrish & Mesulam, 1999; Silk, Bellgrove, Wrafter, Mattingley & Cunnington, 2010).

This close link between attention and memory is central to many current models of retrieval (e.g. Cabeza, 2008; Cabeza et al., 2012; Ciaramelli, Grady & Moscovitch, 2008). A common feature of such models is that attention and memory operate concurrently within functionally segregated systems located within dorsal and ventral anatomical sub-divisions of the PPC. The dorsal network is crucial for the retrieval of goal relevant information and for the top-down control of attention (endogenous attention). The ventral network supports attention/memory in the encoding of behaviorally relevant or unexpected stimuli (exogenous attention) (Vandenberghe et al., 1996; Nobre et al., 1997; Corbetta, Kincade, Ollinger, McAvoy & Shulman, 2000; Cabeza, Ciaramelli, Olson & Moscovitch, 2008; Cabeza et al., 2012; Corbetta & Shulman, 2002; 2011; Chambers, Stokes & Mattingley, 2004a; Chambers, Payne, Stokes & Mattingley, 2004b; Morris, Chambers & Mattingley, 2007; Singh-Curry & Husain, 2009; Hu et al., 2009). A number of findings suggest that the rSMG does not fall comfortably within either of these functional streams. For example, our TMS results failed to demonstrate that right SMG activity was required for stimulus encoding. This runs counter to the view that SMG is strongly engaged by target detection (Corbetta et al. 2000; Perry & Zeki, 2000) and is in marked contrast to other areas within the IPL, namely the temporal-parietal Junction (TPJ), which is activated by exogenous cues (Corbetta et al., 2000; Kincade, Abrams, Astafiev, Shulman & Corbetta, 2005). In addtion, the SMG does not appear to be implicated in the top-down control of attention as neuroimaging studies tend to reveal activations associated with these mechanisms localised within the SPL and IPS (Vandenburgh et al., 2012). Furthermore, TMS studies, whilst clearly demonstrating involvement of the AG in orienting/switching attention, fail to show any causal involvement of the SMG in attentional control mechanisms (Rushworth et al., 2001; Chambers et al., 2004b). However, the rSMG (Brodmann Area 40) does appear form part of a cortical network that is involved in orienting attention across *both* space and time (Coull & Nobre, 1998). So whilst certain aspects of SMG function conform neither to the classic views of dorso-parietal nor ventro-parietal cortical function, the right SMG may nonethelss constitute a link between these two processing pathways, forming a cortical site where there is interaction between

attentional attentional and stimulus encoding mechanisms. This idea of rSMG as an important node in the PPC is consistent with clinical findings which show that damage to this cortical area is frequently implicated in neglect (Coull & Nobre, 1998; Perry & Zeki, 2000; Corbetta & Shulman, 2011) and is interpreted as resulting from the disengagement of the ventral from the dorsal pathways following right SMG damage.

5. Conclusion

To conclude, we have used MRI-guided TMS to selectively disrupt function in the rSMG whilst human observers performed learned and random sequences of eye movements. We have demonstrated that the generation of short latency saccades, acquired following sequence learning, are casually dependent upon neural activity in the right SMG. We propose that neural processing in the rSMG constitutes an instruction set with spatial and temporal directives that are retained and subsequently released for predictive motor planning and responses.

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