Article:
Gonzalez, CC, Billington, J and Burke, MR (2016) The involvement of the fronto-parietal brain network in oculomotor sequence learning using fMRI. Neuropsychologia, 87. pp. 1-11. ISSN 0028-3932

https://doi.org/10.1016/j.neuropsychologia.2016.04.021

The involvement of the fronto-parietal brain network in oculomotor sequence learning using fMRI

Claudia C Gonzalez[1], Jac Billington[2] and Melanie R Burke[2]

[1] Sport, Health and Exercise Sciences, Brunel University, Uxbridge, UB8 3PH, UK.

Email: Claudia.Gonzalez@brunel.ac.uk

[2] School of Psychology, University of Leeds, Leeds, LS2 9JT, UK.

Jac Billington email: J.Billington@leeds.ac.uk

M. R. Burke email: m.r.burke@leeds.ac.uk

Corresponding Author: Dr Claudia Gonzalez, Sport, Health and Exercise Sciences, Brunel University, Uxbridge, UB8 3PH, UK.

Email: Claudia.Gonzalez@brunel.ac.uk

Tel:+44(0)1895267617

Abstract

The basis of motor learning involves decomposing complete actions into a series of predictive individual components that form the whole. The present fMRI study investigated the areas of the human brain important for oculomotor short-term learning, by using a novel sequence learning paradigm that is equivalent in visual and temporal properties for both saccades and pursuit, enabling more direct comparisons between the oculomotor subsystems. In contrast with previous studies that have implemented a series of discrete ramps to observe predictive behaviour as evidence for learning, we presented a continuous sequence of interlinked components that better represents sequences of actions. We implemented both a classic univariate fMRI analysis, followed by a further multivariate pattern analysis (MVPA) within a priori regions of interest, to investigate oculomotor sequence learning in the brain and to determine whether these mechanisms overlap in pursuit and saccades as part of a higher order learning network. This study has uniquely identified an equivalent frontal-parietal network (dorsolateral prefrontal cortex, frontal eye fields and posterior parietal cortex) in both saccades and pursuit sequence learning. In addition, this is the first study to investigate oculomotor sequence learning during fMRI brain imaging, and makes significant contributions to understanding the role of the dorsal networks in motor learning.

Key words: memory; prediction; pursuit; saccade; fMRI; MVPA.

Highlights

- Oculomotor sequence-learning was examined with an analogous saccade and pursuit task
- Prediction was observed from the second presentation and maintained throughout
- MVPA analysis allowed for the identification of novel and familiar activation
- Results indicated PPC, DLPFC and FEF activation within regions for known sequences
- This network may represent a higher order structure responsible for learning

1. Introduction

The ability to learn sequences of movements and use this information to interact with our environment is a basic function of the human brain, and often involves a transition from reactive to predictive motor control (Säfström, Johansson, & Flanagan, 2014). Predictive estimations are internally generated and utilized in skilled behaviour to minimise error and decrease processing delays in the sensorimotor system. Both saccadic and pursuit eye movements exhibit this predictive behaviour during repeated stimulus presentations involving the use of short-term memory storage (Barnes & Asselman, 1991) and much is now known about the mechanisms that guide these behaviours (for pursuit, see Barnes & Asselman, 1991; Missal & Heinen, 2004; Schmid, Rees, Frith, & Barnes, 2001; for saccades, see Lu, Matsuzawa, & Hikosaka, 2002). In addition, there is now substantial evidence of some commonalities in the neural networks between these two eye movement types (Krauzlis, 2005; Nyffeler, Rivaud-Pechoux, Wattiez, & Gaymard, 2008; Orban de Xivry & Lefèvre, 2007). Despite these advances in the understanding of predictive control, little is known about the neural networks involved in oculomotor sequence learning and how these support general motor learning. Indeed, there are inherent differences between the two eye movement types, in that pursuit eye movements normally rely on error correction obtained from stimulus feedback (Barnes & Asselman, 1991), whilst saccades are considered ballistic movements and can be initiated in the absence of a visual stimulus (Leigh & Zee, 1991). Furthermore, prediction in pursuit is observed after previously sampling the stimulus or cueing (Barnes & Asselman, 1991; Barnes & Donelan, 1999; Becker & Fuchs, 1985); whilst prediction in saccades can occur without this previous sampling, but wrong predictions are associated with certain costs (i.e., accuracy and timing). Thus, investigations into the learning mechanisms of these two systems will provide further insight into how the central nervous system combines different modes of motor control to achieve a common goal. Early investigations into prediction suggested that saccadic and pursuit movement preparations are influenced by similar brain regions, as the phase transition to predictive responses is similar for

both eye movement types (Burke & Barnes, 2006; Joiner & Shelhamer, 2006); however different temporal characteristics (i.e. saccades initiate predictive responses earlier than pursuit) may reflect distinct neural activation to release the motor command (Burke & Barnes, 2008).

Evidence from electrophysiological and fMRI studies show the involvement of the frontal eye fields (FEF) and supplementary eye fields (SEF) for both pursuit and saccades as part of a common predictive process (Carpenter, 2004; Drew & van Donkelaar, 2007; Gagnon, Paus, Grosbras, Pike, & O'Driscoll, 2006; Krauzlis, 2005; Nyffeler et al., 2008). In addition, the dorsolateral prefrontal cortex (DLPFC) has been shown to play an important role in working memory mechanisms (Pierrot-Deseilligny, Müri, Rivaud-Pechoux, Gaymard, & Ploner, 2002), and also plays an important role in volitional motor control. The DLPFC has direct connections to the FEF and SEF and is involved in the control of voluntary saccades (Heide et al., 2001), memory-guided saccades (Nyffeler et al., 2002), and in the planning of pursuit (Ding et al. 2009; Schmid et al. 2001). In addition, transcranial magnetic stimulation to this area impairs short term memory retention of spatial information in the serial reaction time task (SRTT) (Robertson, Tormos, Maeda, & Pascual-Leone, 2001). Thus, the DLPFC seems to be a higher-order structure for short-term retention and manipulation of spatial information that is needed to learn a motor sequence (Robertson et al., 2001). Furthermore, the posterior parietal cortex (PPC) has been implicated in this process and is thought to provide spatial storage of target locations (Pierrot-Deseilligny, Milea, & Müri, 2004). The fronto-parietal network described above is highly reminiscent of the recently identified "attentional network" (for review see Ptak, 2012), and the synchronization of these regions is important for working memory formation (Salazar, Dotson, Bressler, & Gray, 2012). Given this overlap in brain regions in the literature, we hypothesize that this same network may also be utilized in the storage of short-term motor memory when learning short sequences of saccadic or pursuit eye movements. Overlapping areas may suggest a general network for oculomotor sequence learning irrespective of eye movement type, whilst distinct activation would point to different coding (e.g., timing, velocity, etc.) for each subsystem.

Current theories on learning, indeed suggest that the brain does not learn in a "unitary" manner but that it integrates different types of information via "dissociable" neural systems (for review, see Gheysen & Fias, 2012). However, alternative explanations point to a motor learning 'core network' (see Hardwick, Rottschy, Miall, & Eickhoff, 2013). Thus, no consensus has been reached on how learning, as a common goal, occurs within the oculomotor system.

The current experiment implements a novel analogous saccadic and pursuit sequence learning task with comparable visual and temporal characteristics. Thus, we examined whether learning would take place at a similar rate and whether overlapping networks in pursuit and saccades would account for these reactive to predictive transitions, indicative of learning a motor sequence. In addition, unlike previous single or double-step/ramp experiments, our sequence learning task involved continuous interlinked component sequences that better represent sequentially-linked actions. Uniquely, a multivariate pattern analysis (MVPA) was implemented into our fMRI data to detect subtler differences in the reactive to predictive transitions that occur when learning a motor sequence. The MVPA uses response pattern identification techniques to discriminate between cognitive states and has been found to be more sensitive than conventional mass-univariate approaches (for review see Norman, Polyn, Detre, & Haxby, 2006).

The main aims of the study were: (i) identify (similar and distinct) brain areas used during oculomotor learning in saccades and pursuit and, (ii) to utilize MVPA to test whether the key brain areas important for oculomotor sequence learning (DLPFC, the FEF and the PPC) and show differences in patterns of activation to new versus familiar sequences.

2. Methods

2.1. Participants

Thirteen participants 22 to 34 years of age (9 females, mean age 26.1 years, SD 3.83) with normal or corrected eyesight and no known neurological conditions took part in the study. Testing comprised 2 experimental sessions, one in the visuomotor laboratory (IPS, Leeds, UK) and a second session in the fMRI scanner (Salford Hospitals, Manchester, UK). These sessions took place approximately 1 week apart. This study was approved by the local and regional NHS ethical committees and by The University of Manchester and Leeds ethical committees and conducted in accordance with the standards laid out in the 1964 Declaration of Helsinki. All participants gave informed consent prior to each experimental session.

2.2. Stimuli and Procedure

2.2.1. Set-up for the eye movement session

Participants were tested in a dark room while seated, with their heads positioned on a forehead and chin rest of an eye tracker (EyeLink, 1000Hz, SR Research Ltd, Canada). Participants were positioned 57 cm in front of a computer monitor (43 cm CRT colour monitor, 1024 by 768 pixel resolution, 75Hz, mean luminance of 50 cd/m^2), where the visual stimulus was presented. The stimuli during the experimental sessions were created using custom-made programs (COGENT, Psychtoolbox, MatLab, Mathworks, USA), and were exactly equivalent in both lab and fMRI environments, but comprised different sequences to avoid learning between sessions. Nine point eye movement calibrations took place prior to each experimental block (4 blocks in total) and rest breaks were given between each block, in which the lights were turned back on in order to avoid dark adaptation and fatigue. The experimental eye movement session lasted for approximately 60 minutes.

2.2.2. Set-up for the fMRI session

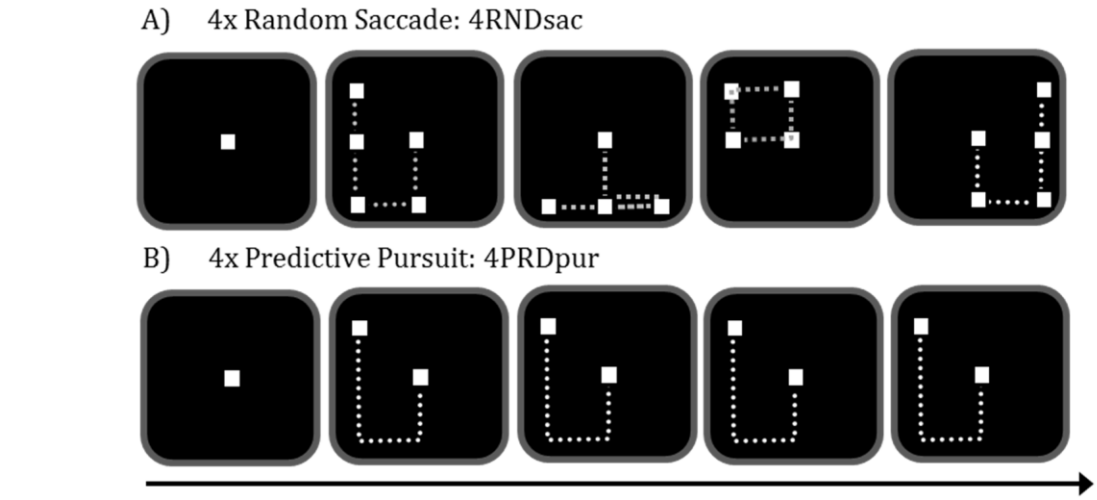
Eye movements were recorded inside the fMRI scanner using an ASL optical video eye tracker (Applied Science Laboratory, Bedford, MA) that sampled at a rate of 60 Hz. Eye movement data was inspected on-line to make sure that the participants were performing the task correctly. Participants were supine on the scanner bed. The head coil provided support for the participant's head and with the addition of cushions, helped to minimize head movements during scanning. An image of the eye was reflected via a mirror positioned on the head-coil to the ASL video camera positioned outside the scanner near the head of the participant. A second mirror on the head-coil was used to reflect an image of the stimulus to the participant via a projector screen (75 Hz, 180 x 110 mm screen size) at the participants' feet. The same stimulus from the laboratory experiments was used in the scanner and the 4 experimental blocks were counterbalanced between participants. New sequences were designed for the scanner sessions and all participants performed the same sequences in the same order within each block. Calibrations for the eye took place in the scanner prior to each experimental block. The room was kept as dark as possible and the lights were turned on in between blocks to maintain alertness. The fMRI experimental session also lasted approximately 60 minutes.

2.2.3. Stimulus

Experiments were designed to elicit saccadic and pursuit eye movements during predictable and random sequences. For all pursuit sequences, the visual stimulus consisted of a white squared target (15 x 15 pixels) that moved continuously in both horizontal and vertical directions over a black background. The target motion sequences started at the centre of the screen and comprised 4 constant speed (30°/s) ramps, each moving in one of four directions (left, right, up or down) along the x and y axis. The durations of each component (ramp) were fixed at 750ms to make the timings of responses predictable. This sequence of 4 components was repeated 4 times in a row comprising the motor sequence learning (predictable) condition (see Figure 1). The same target (white square) was used for saccade sequences, which consisted of 4 individual components (steps) along the four

possible directions; also starting from the centre of the screen (see Figure 1) and the duration of each component in the sequence was 750 ms as above. As in pursuit, the sequence of 4 target components was repeated 4 times in a row. Each component (step/ramp) within a sequence started at the end position of the previous target to generate a continuous motion target or pattern of jumps. We also included a control (random) condition in which the direction of the target and the durations of the target were pseudo-random (duration timings = 525, 750 or 1050 ms) within and between sequence presentations.

Each session consisted of 4 experimental blocks of equal duration: 1) 4 component predictable saccade (4PRDsac); 2) 4 component random saccade (4RNDsac); 3) 4 component predictable pursuit (4PRDpur); and 4) 4 component random pursuit (4RNDpur) sequences. The order of the experimental blocks was counterbalanced between participants. Participants' instructions were to follow the target with their eyes and were explicitly made aware that in predictable (PRD) blocks each sequence was repeated 4 times in a row, while in the randomized (RND) blocks all of the sequences were different from each other and from the PRD sequences. A fixation cue was presented at the beginning of 4 repeated sequences (in the 4PRDsac and 4PRDpur blocks) and at the start of 4 random sequences (in the 4RNDsac and 4RNDpur blocks) and lasted for 3000 ms, after which the cue flashed (250 ms) indicating the start of 4 repeated or random sequences. Participants were given 3000 ms rest immediately followed by the 3000 ms fixation between each sequence. This 6000 ms timing allowed for the haemodynamic response to drop closer to baseline in-between each sequence presentation. Participants performed a total of 20 unique sequences repeated 4 times each (80 sequences in total) in the learning PRDsac and PRDpur blocks, and 80 unique sequences in the control RNDsac and RNDpur blocks.



Task	Fixation	s1	s2	s3	s4
Timing	3000ms	3000ms	3000ms	3000ms	3000ms

Figure 1. Examples of 4RND saccade sequences (A) and 4PRD pursuit sequences (B). Figure A shows the 4 different sequences (s1, s2, s3 and s4) across the random saccade block (4RNDsac), whilst B shows the 4 identical sequence presentations in a predictive pursuit block (4PRDpur). Fixations and each individual sequence of 4 components were equal in duration (3000 ms). Each component in a PRD sequence had identical duration and amplitude, while components had different timings and amplitudes in the RND sequences. The target is illustrated at each saccadic component and at the beginning and end of each pursuit sequence for schematic purposes.

2.3. Eye Data Analysis

Eye movement data sampled at 1000 Hz were obtained from the Data Viewer software (SR research Ltd, Canada) and blinks were automatically eliminated from the raw data prior to analysis. Data Viewer bridged gaps within the missing data using linear interpolation. Eye displacements and velocities were analysed using a custom made programme in MATLAB (version 7.8, Mathworks Inc., USA) designed for each stimulus type and each eye movement type as described below. Eye movement data was also obtained from the scanning environment (60Hz), which revealed an

identical pattern of responses from the participants during all conditions, although the signal was significantly noisier. For the purpose of clarity we will present only the laboratory based data within this section.

Temporal and spatial eye movement measures were used to assess whether participants were learning the sequences (reactive to predictive behaviour) by comparing the PRD repeated sequences to the (control) RND sequences as well as comparing between the repeated sequences (s1, s2, s3 and s4) within the PRD condition (effects of repetition). Finally, comparisons between these repeated sequences in saccades and pursuit were performed to determine differences in learning between the oculomotor systems.

2.3.1. Smooth pursuit

Intrusive and catch-up saccades were eliminated from the smooth pursuit eye movement data using a previously described technique (Bennett & Barnes, 2003). Linear interpolation techniques were used to link the resulting gaps due to the removal of the saccades. The velocity traces were then filtered using a 10Hz low-pass, zero phase filter. Peak velocity (PV) was identified for each component in the PRD and RND sequences and plotted for visual inspection to ensure that the first peak was detected. After peak identification, time to peak velocity (TTPV) was calculated from the target onset of each component or ramp and averaged to compare between PRD and RND conditions. Position error was calculated as the averaged absolute error across each PRD and RND sequence with respect to the target location.

In contrast to single ramps, which can reliably measure pursuit latency when pursuit velocity crosses 0°/s, our continuous stimulus does not show consistent start velocity values across the multiple components; particularly, when the direction of the eye and the target is maintained from one component to the other (i.e., no zero crossing). Thus, pursuit onsets of a continuous eye movement to multiple components (ramps) can be problematic to identify, as eye velocity at the start of each

ramp is influenced by the decaying response to the prior ramp (see Barnes & Schmid, 2002). We therefore implemented a more global temporal assessment to investigate the effects across the repeated sequences and calculate the overall differences in timing between eye movements and the target stimulus for PRD sequence trials by performing a cross-correlation analysis of the velocity signals of the entire sequences (also see Barnes & Schmid, 2002). The cross-correlation between the target and each PRD sequence (i.e., s1, s2, s3 and s4) was performed. The time at which the maximum correlation was reached (t_{COR}) was calculated and used to describe the time delay between the eye velocity and the corresponding moving stimulus. Eye velocity X and Y traces were combined to create a single eye velocity trace, which was used to compare with the target velocity. This resulted in a t_{COR} value irrespective of direction.

2.3.2. Saccades

Saccades were computed from the eye velocity traces and identified as samples with velocity exceeding 100°/s. Saccadic PVs were plotted and visually inspected for accuracy. Saccade time to peak velocity (TTPV) was calculated for each component in each PRD and RND sequence and measured from target onset (at each component) to the time of saccade PV, using the first saccade made to the target's location. The TTPV and absolute eye end position error to target location were also measured (in degrees) for each component of the sequences in both PRD and RND conditions. Similar to pursuit, cross-correlations (t_{COR}) were also performed between the saccade velocities and the corresponding target across PRD sequences to identify timing shifts of the repeated sequences.

A repeated measures ANOVA (IBM SPSS statistics, version 20, NY, USA) was used to identify significant behavioural differences between the PRD and RND conditions in saccades and pursuit, and a second repeated measures ANOVA was implemented to investigate learning between the identical presentations (s1, s2, s3 and s4) within the PRD saccadic and pursuit sequences (effects of repetition). Finally, we determined whether there were any (learning) differences between saccade

and pursuit PRD sequences. These results were then used to model our contrasts from the fMRI data. Interactions between variables were evaluated using a Bonferroni corrected post-hoc test. A significance level of $P < 0.05$ was established for all statistical analyses. Results and graphs are expressed as means and standard deviations (*SD*).

2.4. fMRI acquisition and analysis

Data was collected using a 3T (Phillips 3.0 T Achieva) MRI scanner with an eight-channel SENSE head-coil (Achieva 3.0 T Neuro Coil) designed to reduce the signal-to-noise ratio. A T1-weighted image (256 x 256 x 176, voxel size = $1mm^3$) covering the whole brain was obtained prior to the experimental runs. The 4 experimental runs corresponded to the 4 experimental blocks described above (4PRDpur, 4RNDpur, 4PRDsac and 4RNDsac). Scans were collected using T2*-weighted gradient echo pulse sequence (TR of 2000 ms, TE of 35 ms; 90° flip angle, FOV of 250 mm, 1.8 x 1.8 x 4 mm^3 voxel size and a total of 30 slices) covering the whole brain. Data was pre-processed in the standard way using BrainVoyager QX version 2.8 (Brain Innovations B.V. Maastrict, the Netherlands), and included: slice time correction, motion correction, spatial realignment, co-registration with each individual's anatomical image and transformed into Talairach space (Talairach Daemon software, http://www.nitrc.org) (Lancaster et al., 2000). Finally data were filtered using a temporal high-pass filter at 128 Hz cut-off frequency to remove scanner drifts.

We used a general linear model to gain estimates of voxel activation to each experimental block. The regressors in the design matrix were boxcar functions designed to model the activity during each presentation of a sequence (3 seconds) resulting in the modelling of 80 PRD and RND sequences (240 second blocks), with the fixation also modelled independently (3 seconds) (i.e., Fixation, s1, s2, s3 and s4). These boxcar functions were then convolved with an individual estimate of the haemodynamic response function.

We performed overall contrasts between PRD pursuit and PRD saccadic sequences and also performed contrasts for the RND sequences between eye movement types. Second, based on behavioural results, we identified regions of interest (ROIs) associated with predictive behaviour (as evidence of learning a sequence) and performed an MVPA analysis in which we compared ROI activation in (reactive) s1 and (predictive) s4 within the PRD saccade and pursuit sequences (effects of repetition). We used this approach to assess if patterns of activity within our ROI contain information to decode whether the task was random (s1) or predictive (s4).

2.4.1. Univariate GLM Block design

We ran a fixed effects analysis for each participant (using Brain Voyager QX, Brain Innovations, Netherlands) and then did a 2nd level random effects analysis (RFX) group analysis using a GLM and applied a threshold of T > 3.5 and only accepted clusters >30 voxels. We ran a Bonferroni correction to avoid the issues associated with multi-comparisons (type 1 errors) using family-wise error in Brain Voyager with a threshold of P < 0.05. Furthermore, a cluster-size of 30 was employed to reduce false discovery and allowing us to focus on the larger regions of interest. We performed contrasts to identify PRD and RND activation in both saccades and pursuit (PRDsac > PRDpur; RNDsac > RNDpur), and also performed an overall contrast for PRD > RND across eye movement types (see Table 1). These contrasts provide a summary of the activation between each movement type during reactive sequence tracking when compared to sequence learning.

2.4.2. Regions of interest (ROI) and Multivariate Pattern Analysis (MVPA)

Given that the 1st presentation of each sequence (in the PRD condition) was behaviourally equivalent to the random condition (see Figure 2), participants did not predict during that first sequence presentation and thus were not using memory (responding reactively). Our multivariate analysis could then compare this first sequence (s1) to the last presentation of the sequence (s4) since, in both

sequences, the stimulus position/motion and timing was exactly the same. Thus, to generate the regions of interest for the MVPA, we performed a second univariate F-contrast analysis ($p < 0.001$, cluster size = 10 voxels) using the 2nd presentation of the sequence only, for the predictive and random pursuit and saccade sequences, for each participant independently. This resulted in each participant having ROIs for PFC, PPC and FEF for the random and predictive tasks for each eye movement type, which could subsequently be used for the MVPA analysis.

The multivariate pattern analysis was performed using a MATLAB (The Mathwork, Inc., USA) implemented Library for Support Vector Machines (LIBSVM) (Chang & Lin, 2001). Specificity of responses within neuronal populations was tested for s1 versus s4 for each ROI (mean size 26 voxels) and each participant. The data for each ROI were combined and normalised for all 13 participants and the number of features included all voxels (between 257 and 324). A leave-one-out procedure was used to train the support vector machine (SVM) on 75 randomly selected trials of each sequence position, and tested on the remaining 5.

In order to test whether the classifier was performing significantly above chance, the analysis was re-run with a random permutation of trials (as shown by the dotted lines on the graphs in figure 5). In this permutation the s1 (RND) and s4 (PRD) labels were randomly assigned during the training phase i.e. s4 could be labelled RND, and the s1 as PRD. Given these random assignments we would predict that the classifier should perform at chance levels under these conditions as no pattern exists. Indeed, this is what we found as the mean 95th and 99th percentile for pursuit (with the random permutation) for all ROI was 50.4 and 50.6 and s1 vs. s4 for saccades was 50.4 and 50.6 (see Figure 5).

Since the data used for ROI classification above (s2) was taken within the same experimental session as the data used for the test and training sets in MVPA (s1, s3 and s4), we wanted to check for possible "double-dipping" (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009) and/or colinearity. To do this we performed an additional MVPA analysis as described above using ROI's generated from an

independent experimental session (an 8 target sequence learning task) where again the second sequence within the task was used for generating ROI's. We obtained similar results in classification accuracy using this alternative data set, indicating that our results are not due to circularity or colinearity within the data sets. Finally, anatomical localization of our ROI's was achieved by obtaining the mean activation for each cluster (X, Y and Z) in Talairach coordinates and then using Talairach Daemon for the inquiry of brain region/area.

3. Behavioural Results

3.1. Predictive versus Random

Results revealed that TTPV and absolute errors values of the repeated sequences (s2, s3 and s4) were not statistically different ($P > 0.05$). Thus, these repeated responses were averaged and referred to as predictive (PRD) responses and compared with the first presentation of a sequence (s1) and RND responses. It was also determined whether s1 and RND responses were statistically different in any measure within each eye movement type.

Analysis of pursuit TTPV showed that overall, the PRD eye responses achieved PV sooner compared to RND and s1 ($F_{(2,24)}= 89.8$; $P < 0.001$) (Figure 2A). Similarly, saccadic PRD responses had shorter TTPVs compared to RND and s1 ($F_{(2,24)}= 83.105$; $P < 0.001$) (Figure 2B). The post-hoc comparing the TTPV for s1 and RND were not significantly different in either saccade or pursuit sequence learning tasks ($P = 0.58$ and $P = 1.00$ for saccade and pursuit respectively). In addition, TTPV shifts of the PRD sequences were larger for saccades (~ 224 ms) compared to pursuit (~ 84 ms).

Saccade absolute errors revealed that less accurate end-point location of the first saccade to the target during the averaged PRD responses were less accurate compared to s1 and RND ($F_{(2,24)}= 33.339$; $P < 0.001$) (Figure 4C). This is in accordance with saccades of a predictive nature, which display reduced amplitudes and peak velocities and are less accurate than visually-guided saccades

(Bronstein & Kennard, 1987; Smit, Van Gisbergen, & Cools, 1987). In contrast, absolute errors for pursuit were not different between s1, RND or PRD sequence presentations (P = 0.113) (Figure 2D).

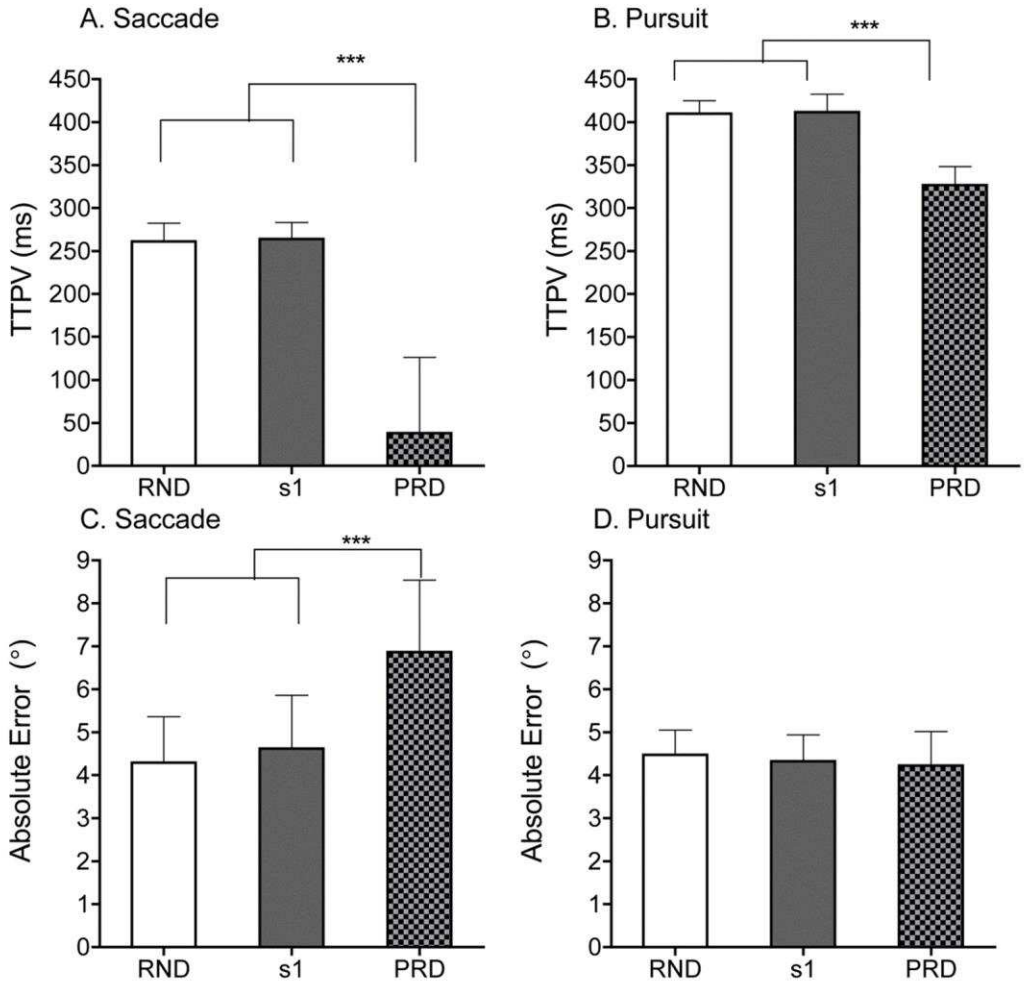


Figure 2. Mean and standard deviations of TTPV values for RND, s1 and PRD saccade (A) and pursuit (B) responses; and saccade (C) and pursuit (D) mean absolute values across sequence types. The graphs show that the repeated PRD sequences (s2.4) were different from s1 and RND sequences, but that the (reactive) s1 and RND sequences were not statistically different. Absolute error differences were only seen in saccade responses (C), with PRD responses exhibiting larger errors compared to s1 and RND.

3.2. Effects of repetition (within PRD)

Cross-correlations of the whole sequences were computed between the first and the repeated sequences (in PRD conditions) and the target to assess timing shifts within identical presentations. In PRDpur, the time of maximum cross-correlation (t_{COR}) between the repeated responses and the target revealed a sequence main effect ($F_{(3,36)}$= 33.98; P < 0.001). The pursuit repeated sequences (s2, s3 and s4) showed reduced t_{COR} values compared to s1 responses (all P < 0.001), but no differences were observed between these repetitions (P > 0.05) (Figure 3A). Similarly, PRDsac t_{COR} values also revealed a significant sequence effect ($F_{(3,36)}$= 33.98; P < 0.001) with shorter temporal shifts in the repeated responses with respect to the target compared to s1 (all P < 0.001) and no differences between the repeated sequences (P > 0.05) (Figure 3B).

To determine whether temporal shifts differed between saccades and pursuit, we calculated the absolute differences from s1 to each repeated sequence (s2-s1, s3-s1 and s4-s1). Analysis of these relative differences showed significant differences across the repetitions ($F_{(2,24)}$= 4.26; P = 0.026) and a main affect between saccades and pursuit ($F_{(1,12)}$= 28.46; P < 0.001) (Figure 4), but no significant interaction (P = 0.12). Thus, the random (s1) to predictive temporal shifts are considerably larger in saccades than pursuit even after a single presentation.

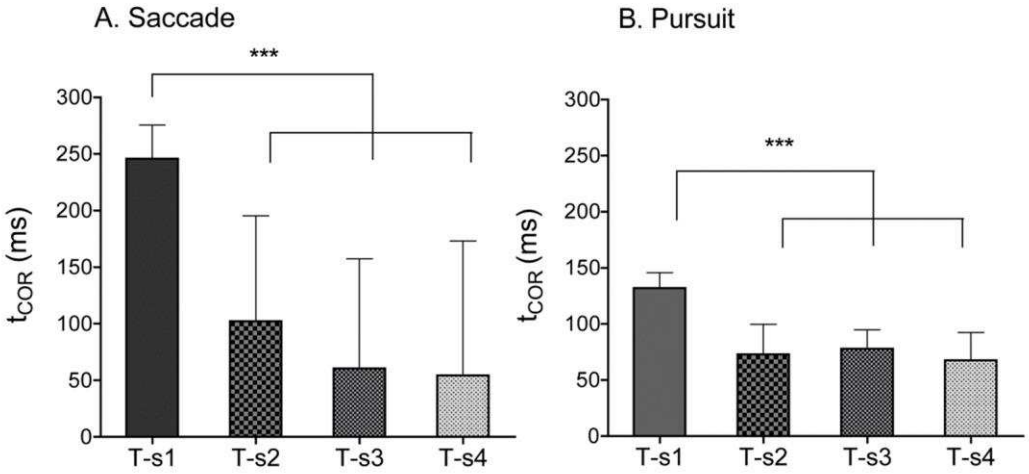


Figure 3. Mean t_{COR} (and SD) values for 4PRDpur (A) and 4PRDsac (B). The cross-correlations between the target (T) and the identical sequences (s1, s2, s3 and s4) showed shorter temporal shifts

from the target during the repeated sequences compared to s1. These temporal shifts were evident following one presentation of the stimulus and maintained throughout the repetitions.

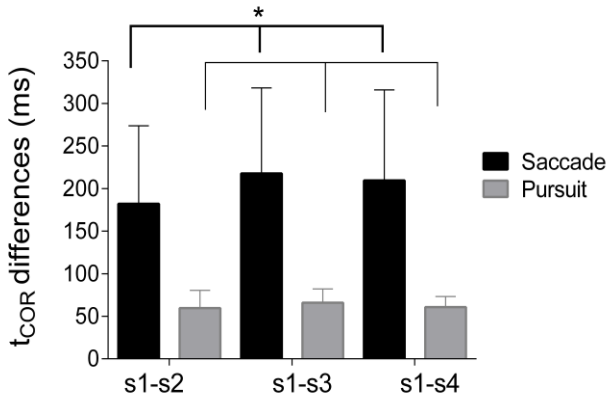


Figure 4. Absolute t_{COR} differences between repeated sequences and s1 for saccades (in black) and pursuit (in grey). The graph shows clear differences between oculomotor systems when making direct comparisons of the reactive (s1) to predictive (s2-4) temporal shifts. Saccades show larger differences compared to pursuit across all repetitions.

4. fMRI Results

4.1. Predictive versus Random

We ran two main univariate analyses of the data to identify BOLD differences between the learning of sequences for saccades and pursuit. The comparison between eye movements (saccades and pursuit) revealed higher activity in a region of the middle temporal lobe (BA22), supplementary motor area (BA8) for saccades and the anterior cingulate and the Insula for pursuit. The random sequence condition yielded higher activity in the premotor cortex (BA6) and pons for saccades with the caudate and inferior frontal lobe (BA47) more active in pursuit.

Contrasts		TAL		Z value	P value	Brain Area
PRDsac > PRDpur	46	-35	-3	3.33	< 0.001	MTG, BA22
	-16	33	46	3.19	< 0001	SFG, FEF, BA8
PRDpur > PRDsac	14	-10	36	-3.78	< 0.001	Anterior Cingulate, BA24
	42	-22	21	-3.48	< 0.001	Insula, BA13
RNDsac > RNDpur	12	-18	64	4.12	< 0.001	SMA, BA6
	12	-21	-28	3.61	< 0.001	Brainstem, Pons
RNDpur > RNDsac	-36	-39	2	-4.96	< 0.001	Caudate
	38	30	-13	-4.22	< 0.001	Inferior Frontal Lobe, BA47
RND > PRD (all)	32	19	-1	4.74	<0.0001	Insula
	36	-89	10	4.38	<0.0001	MOG, BA19
	-18	-63	57	4.06	<0.0001	SPL, BA7
	-18	-23	42	3.96	<0.0001	Post. Cingulate, BA31

Table 1. Random effects analysis of the contrasts from the predictive and random sequences between eye movement types, and across eye movements for the identification of the overall random and predictable sequence activation. The grey rows indicate activity for pursuit and the white rows for saccades. The abbreviations used are as follows: PRDpur = the repeated pursuit sequences; RNDpur = the randomized pursuit sequences; PRDsac = the repeated saccadic sequences; RNDsac = the randomized saccade sequences. BA refers to Brodmann Area. SMA = supplementary motor area; MOG = middle occipital gyrus; SPL = superior parietal lobe.

4.2. Multivariate Pattern Analysis: effects of repetition

The response of the first sequence of each PRD set of 4 repeated sequences was determined as reactive based on behavioural results and since participants did not know the sequence on its first presentation. In this way, we have an ideal comparison in that the same motor response to identical visual stimuli (within PRD conditions or sequence learning task) can be directly compared by using the 1st sequence presentation versus the final (or 4th) sequence presentation. We found significant

activation to the second presentation of the repeated sequence (in which prediction was evident and remained during the repeated sequences) in frontal eye fields (BA8), posterior parietal cortex (BA7), the dorsolateral prefrontal cortex (BA9) in pursuit (Figure 5, left) and saccades (Figure 5, right). These identified ROI's from s2 were additionally verified from a previous study investigating prediction to a single repeated saccadic and pursuit target (Burke & Barnes, 2008). A Multivariate Pattern Analysis (MVPA) was performed within these ROIs (identified for pursuit and saccades) to see if the classifier could correctly ascertain differences between the (reactive) 1st and (predictive) 4th sequence. Using the 99th confidence percentile we found classifier could identify sequence 1 (reactive) from sequence 4 (PRD) in BA8 with an accuracy of 84%, BA7 of 86%, and BA9 of 85% for pursuit eye movements (Figure 5, left bar graphs). The results from the MVPA analysis during saccades for the 1st versus the 4th sequence revealed classification accuracies for BA8 of 72%, BA7 as 73%, and BA9 as 72% (see Figure 5, right bar graphs).

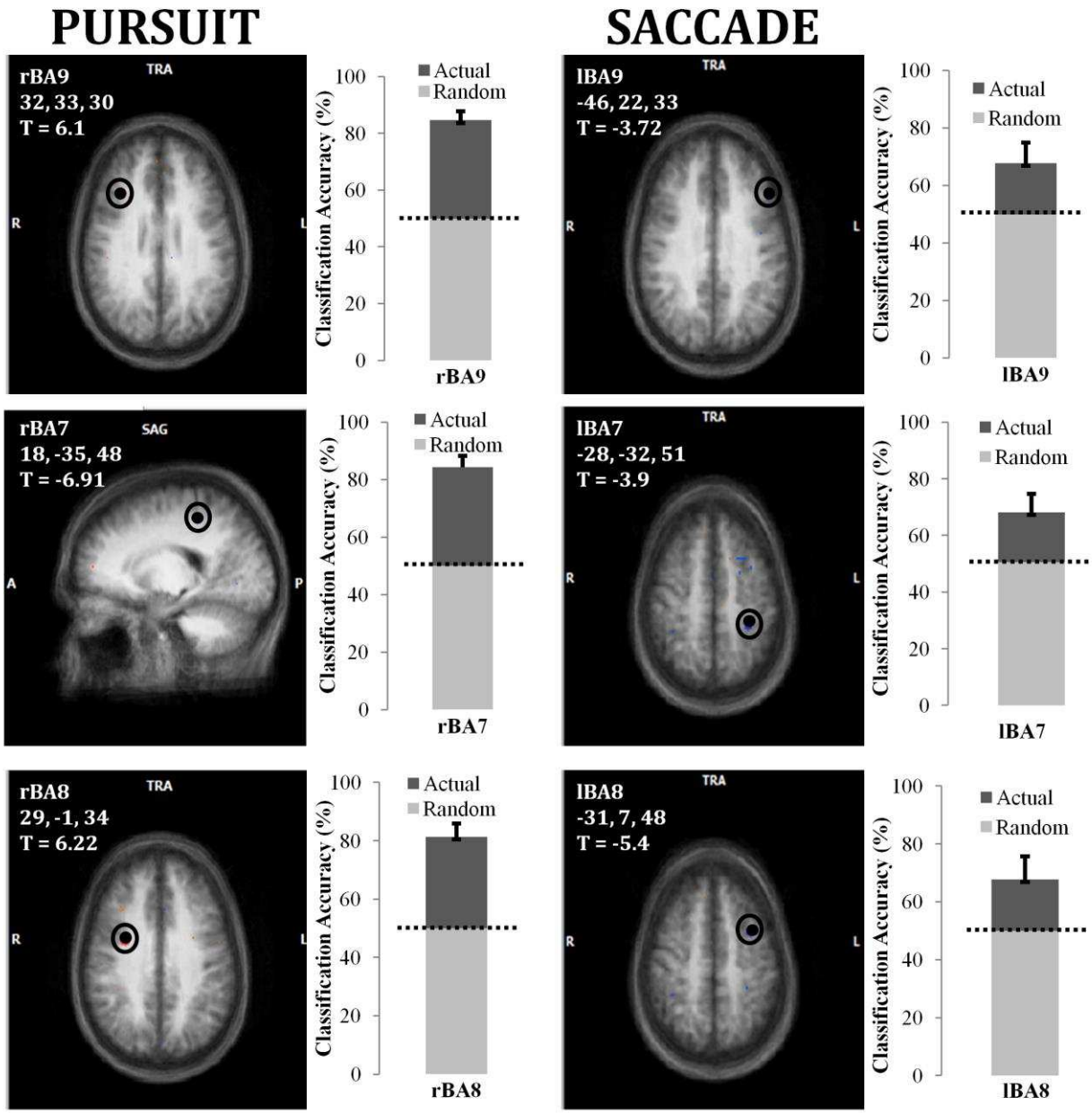


Figure 5: Regions of Interest (ROIs, black dots) are presented on an averaged brain created from all 13 participants in the study and hence are not direct representations of brain regions. The details for these ROIs are displayed in the top left-hand corner of each brain image denoting: brain region, peak X, Y, Z coordinates (Talairach), and T-value across all participants. ROIs were identified from s2 in which prediction as evidence of learning occurred. We then compared activation of these in (reactive) s1 versus (predictive) s4. The graph on the right of each image shows the classification accuracy for

the 1st sequence data and the 4th sequence data using an MVPA analysis. The bar depicts classification accuracy when labelling each sequence (s1-s4) correctly, the dotted line indicates chance levels (i.e. ~50% with 2 conditions)) The error bars on the graphs denote classification accuracy for the 99th percentile.

5. Discussion

In this current study we aimed to identify similarities and differences in the processing streams utilized in learning sequences of saccadic and pursuit eye movements. More specifically, we intended to identify if the neural activity within the dorsal processing network (and also found in a priori studies on prediction: DLPFC, FEF and PPC; for review see: Lencer & Trillenberg, 2008) can dissociate between repeated and randomized sequences. To address these aims we firstly qualified that our participants show anticipatory eye movement responses to repeated sequences in both pursuit and saccades (as shown by the t_{COR} data, Figure 3). Both eye movements revealed learning of the sequence from the second presentation in both oculomotor subsystems. This effect has been observed previously to (single-ramp) stimuli in which all targets start from the central fixation point (Burke & Barnes, 2006), but not to continuously moving stimuli.

5.1. Univariate analysis

To establish the differences between the networks involved in learning for pursuit and saccades when using directly comparable stimuli, we firstly employed a univariate random effects analysis. This approach revealed significant differences in the learning of saccadic versus pursuit sequences in MTG (BA22) and FEF (BA8) for saccades, and anterior cingulate and insula for pursuit. These areas map well with research on prediction and anticipation in eye movements, suggesting that learning and prediction may be processes that occur in series (Burke & Barnes, 2008). A previous study by Burke and Barnes (2008) in which single targets were presented, also found BA22 increased in

activity with increasing repetitions or learning. In contrast to some previous studies on prediction, we found higher activity in FEF for learning sequences of saccades, whereas others have found a stronger role in FEF for visually-guided stimuli (Gaymard, Pierrot-Deseilligny, & Rivaud, 1990; Gaymard, Ploner, Rivaud-Péchoux, & Pierrot-Deseilligny, 1999; Burke & Barnes, 2008). However, Grosbras et al (2001) found a dissociation of function within FEF for the learning of familiar saccadic sequences when compared to new sequences mainly in dorsomedial FEF, whereas lateral FEF was activated irrespective of sequence familiarity. Given that the area of activation in our study more closely resembled the dorsomedial FEF, our data supports this theory.

The anterior cingulate has shown activation in fMRI studies in relation to complex motor control, error detection/monitoring and anticipation (Luu, Flaisch, & Tucker, 2000), hence activity in this area is more associated with pursuit. This area also has links with the DLPFC and BA7 and may form part of the attentional network described in the introduction (Devinsky, Morrell, & Vogt, 1995). Our study also suggests an important role in the learning of sequences for pursuit eye movements. The insula was also found to be more active for learning sequences of pursuit and has been found previously in association with pursuit during periods of target blanking (Lencer & Trillenberg, 2008), however others have found this area to be more prominent in saccades (O'Driscoll et al., 1998). Our data provides a role of the insula cortex in the learning of sequences of movements during tracking possibly important for motor skill development.

Overall, across both eye movement types we found that PRD responses revealed no above threshold activation when contrasted to the RND condition, and the RND trials revealed higher activation in the insula, the middle occipital gyrus (BA19), superior parietal lobe (BA7) and the posterior cingulate (BA31). Interestingly, Lindner et al (2006) suggested the insula is part of a parieto-insular network that provides the interaction between predicted and experienced sensory events during retinal motion which could be why this region is also significantly active for both predictive and random responses. Our data support these findings and again argue for an overlapping network of control for

novel and familiar sequences. In addition, we have found BA19 part of the occipital cortex to be more active for randomized sequences, which is in-line with a previous study (Burke and Barnes, 2008), suggesting that visually-driven responses cause greater activation of early visual areas. A more un-expected finding was the activation of the superior parietal lobe (BA7) for randomized sequences when compared to predictive. A number of studies have found the superior parietal lobe to be more active during extra-retinal memory-driven pursuit (Lencer et al., 2004), and parietal eye field areas important for visually-guided saccades and pursuit (Petit & Haxby, 1999; Burke and Barnes, 2008). Our data has revealed activation in the parietal cortex for both randomized and familiar sequences, but that there may be differences in the area for each. Activation for randomized sequences was more superior (SPL) than activation for the repeated sequences (IPL), but both appear to be within BA7. Our results suggest a distinction within BA7 for more novel and familiar stimuli.

5.2. Multivariate analysis

One major problem with the univariate approach used above is the need to use contrasts to reveal activation. Our data shows clear overlap in the network between saccades and pursuit, and also to novel and familiar sequences and fixation. To investigate this network further we employed a multivariate approach that allows interrogation of a common "dorsal" network for learning in order to identify if the pattern of activation within regions are key to this oculomotor learning.

We found significant activation in parietal areas for sequence learning in both saccades and pursuit that included Brodmann areas 7, 8 and 9, relating to the Posterior Parietal Cortex (PPC), the Frontal and Supplementary Eye Fields (FEF/SEF), and the Dorsolateral Prefrontal Cortex (DLPFC) regions respectively. The BA8 activation for both pursuit and saccades is within the FEF region, but also borders with the SEF brain area. It is likely that both areas are important for the sequence learning task explored (Shichinohe et al., 2009). The supplementary eye fields (SEF) have a well-established role in oculomotor learning in saccadic eye movements that comes from a plethora of single-unit recording studies that show how these neurons are modulated during predictive tasks (for review

see Pierrot-Deseilligny et al., 2002) and other oculomotor learning tasks (Chen & Wise, 1995; Lu et al., 2002). There have been a number of imaging studies that have investigated the role of SEF in pursuit eye movements and have come to similar conclusions, with clear evidence for a role in prediction/anticipation during internally driven oculomotor movements (Burke & Barnes, 2008; Gagnon, O'Driscoll, Petrides, & Pike, 2002; Schmid et al., 2001). Furthermore, recent single-cell recordings during predictive pursuit have dissociated SEF activation to the planning of pursuit, whereas activation of FEF is suggested to be primarily involved in generating the motor command for pursuit execution (Fukushima, Fukushima, Warabi, & Barnes, 2013; also see Drew & van Donkelaar, 2007). This supports the role of SEF as a higher order structure for planning and learning, irrespective of eye movement type (Nyffeler et al., 2008). Previous studies have compared saccades and pursuit activation during fMRI in prediction, and generally agree that both systems share a common network with some sub-regional differences (Burke & Barnes, 2008; Krauzlis, 2005; Nyffeler et al., 2008). However, most previous studies use single target presentations, with very few studies using fMRI to investigate more complex short-term motor learning in the form of a series of oculomotor movements as described here.

The ***Frontal Eye Fields (FEF)*** contain sub-regions for pursuit and saccades (Petit, Clark, Ingeholm, & Haxby, 1997; Petit & Haxby, 1999; Rosano et al., 2002) and previous evidence supports the role of the FEF in memory and more specifically, spatial priming (Offen, Gardner, Schluppeck, & Heeger, 2010; O'Shea, Muggleton, Cowey, & Walsh, 2007) as neuronal firing often reveals pre-target build-up (Dorris & Munoz, 1998) that is modulated by a previously known target location (Connolly, Goodale, Goltz, & Munoz, 2005). Our MVPA analysis also revealed a significant ability to classify whether the data was from sequence 1 or sequence 4 within this area, indicating that this area is important for the accumulation of information during learning. Due to the clear connections between FEF and PPC, much work has focused around the role of FEF in spatial attention and its involvement in the 'dorsal attention network' (Tseng et al., 2013). It is clear that this network is essential for spatial attention

during unpredictable saccade generation (Campana, Cowey, Casco, Oudsen, & Walsh, 2007) and mediating search strategies (Lane, Smith, Schenk, & Ellison, 2012), however the role of PPC - FEF network in predictable tasks in pursuit is less clear. Further evidence shows modulation of activity during single predictable saccades in FEF during single-unit recordings in monkeys (Sommer & Wurtz, 2000). The present study has shown that an area related to medial FEF or lateral SEF is important in oculomotor learning (both pursuit and saccades) of sequences of movements, and importantly, we have found the pattern of activity within these regions hold the key to this learning mechanism.

Activation in the ***Dorsolateral Prefrontal Cortex (DLPFC)*** was found during our repeated sequence learning paradigm in both saccades and pursuit. We have found activation in this area previously for both types of eye movement when making predictive eye movements to a single target (Burke & Barnes, 2008). Other studies have found this area has been mainly associated with very short-term memory acquisition for single target locations (Heinen & Liu, 1997), and one previous study with prediction (Schmid et al., 2001). Our MVPA results demonstrate that this area is important in both saccades and pursuit during early motor learning for a series of movements. The BOLD level signal also revealed DLPFC activation in the pursuit sequence versus random contrast, but not in saccades possibly indicating different modes of action for each eye movement type. Previous studies have demonstrated a role of the dorsal part of the prefrontal cortex in location memory, as part of the 'where' pathway (Munk et al., 2002), supporting the findings reported here.

An area of the right hemisphere labelled BA7 that forms part of the ***Posterior Parietal Cortex*** (**PPC)** has previously been associated with the selection of movements (Deiber, Honda, Ibañez, Sadato, & Hallett, 1999). More recently however, significant activation during spatial tasks has been reported suggesting a role in spatial attentional processes (Corbetta, Patel, & Shulman, 2008). Others have found that this area may also provide information about predictive shifts of attention during implicit learning tasks and acts in a probabilistic manner as part of the dorsal network mediating expectation

of a cue/target (Manginelli, Baumgartner, & Pollmann, 2013) and is modulated by predictability. Our study shows that this area is indeed associated with the learning of a series of simple oculomotor movements in the brain for both pursuit and saccades.

Evidence from single cell recordings and from brain stimulation in humans suggest that the DLPFC is involved in the control of spatial memory in saccades (memory-guided saccades with short delays and predictive saccades) (Pierrot-Deseilligny et al., 2004). Furthermore, lesion studies also identify the PPC as an important structure for visuospatial integration and spatial updating for double-step saccades and show that the triggering of intentional saccades is modulated by the FEF (Pierrot-Deseilligny et al., 2002; Pierrot-Deseilligny et al., 2004). Our data further contributes to this understanding by suggesting that learning is encoded within the pattern of activation within these areas (especially for saccades) rather than using alternative brain regions for the storage of this information, hence patterns within this network change depending of if the sequence is novel or remembered.

Interestingly, we found peak activation to reveal some hemispheric asymmetries between the eye movement types with pursuit being more right hemisphere dominant, and saccades more left. Given that we controlled for spatial and temporal shifts within our sequences for equal right and left shifts, then this asymmetry in the frontal lobe is unlikely to be a consequence of any low level stimulus related effects (i.e. direction bias), but is more likely to reflect a true difference between activation for learning for each eye movement type. However, further investigation is needed to verify this as a true laterality effect. Early neuroimaging studies in saccades have often revealed a bias to the left hemisphere during internally driven saccades (Dejardin et al., 1998; Gaymard, Rivaud, & Pierrot-Deseilligny, 1993; Grosbras, Lobel, Van de Moortele, LeBihan, & Berthoz, 1999; Petit et al., 1993), but no such bias is apparent in visually-guided saccades (Luna et al., 1998), indicating a left hemisphere dominance for memory in saccadic eye movements. We also report that this hemisphere bias is

apparent in FEF for saccades, suggesting a stronger role of the left hemisphere in oculomotor learning during saccades. In contrast, studies in pursuit eye movements have shown that right FEF lesions in humans cause the most significant deficits in predictable pursuit when compared to left FEF or parietal lesions (Heide, Kurzidim, & Kömpf, 1996). Further support for lateralization of learning in pursuit to the right hemisphere comes from imaging studies. Ding et al (2009) revealed a clear right-sided effect in DLPFC when pursuing occluded moving target using an internal memory mechanism, also supporting the effects reported here for more memory driven approaches to be right lateralized in pursuit.

6. Conclusions

This is the first study (to the authors knowledge) to look at oculomotor sequence learning in both pursuit and saccades using directly comparable stimuli (same temporal and spatial properties) during fMRI. The behavioural results show that both pursuit and saccades demonstrate clear learning of the sequence by the 2nd presentation of the short sequences in repeated presentations. In addition the univariate GLM analysis revealed clear overlap of activation when both eye movement types relied solely on the learning of directional information rather than velocity (as often in the case for pursuit). A further multivariate analysis within a priori regions of interest (dorsal network) indicated PPC, DLPFC and FEF all show differences of activation patterns within regions for novel versus known sequences. Given the differences between the two types of eye movements (e.g., feedback versus feed-forward motor responses) this network may represent a higher order structure responsible for learning. These findings may be further utilised to compare with other motor systems (e.g., hand) to investigate brain regions important for signal sharing with the oculomotor system and motor system specific networks during the learning of visuomotor tasks. This provides the first fMRI evidence for the involvement of the "dorsal network" in short-term oculomotor learning in the brain.

References

Barnes, G. R., & Asselman, P. T. (1991). The mechanism of prediction in human smooth pursuit eye movements. *The Journal of Physiology*, *439*, 439–61.

Barnes, G. R., Barnes, D. M., & Chakraborti, S. R. (2000). Ocular pursuit responses to repeated, single-cycle sinusoids reveal behavior compatible with predictive pursuit. *Journal of Neurophysiology*, *84*(5), 2340–55.

Barnes, G. R., & Donelan, S. F. (1999). The remembered pursuit task: evidence for segregation of timing and velocity storage in predictive oculomotor control. *Experimental Brain Research*, *129*(1), 57–67.

Barnes, G. R., & Schmid, A. M. (2002). Sequence learning in human ocular smooth pursuit. *Experimental Brain Research*, *144*(3), 322–35. http://doi.org/10.1007/s00221-002-1050-8

Becker, W., & Fuchs, A. F. (1985). Prediction in the oculomotor system: smooth pursuit during transient disappearance of a visual target. *Experimental Brain Research*, *57*(3), 562–75.

Bennett, S. J., & Barnes, G. R. (2003). Human ocular pursuit during the transient disappearance of a visual target. *Journal of Neurophysiology*, *90*(4), 2504–20. http://doi.org/10.1152/jn.01145.2002

Bronstein, a M., & Kennard, C. (1987). Predictive eye saccades are different from visually triggered saccades. *Vision Research*, *27*(4), 517–20.

Burke, M. R., & Barnes, G. R. (2006). Quantitative differences in smooth pursuit and saccadic eye movements. *Experimental Brain Research*, *175*(4), 596–608. http://doi.org/10.1007/s00221-006-0576-6

Burke, M. R., & Barnes, G. R. (2008). Brain and behavior: a task-dependent eye movement study. *Cerebral Cortex*, *18*(1), 126–35. http://doi.org/10.1093/cercor/bhm038

Campana, G., Cowey, A., Casco, C., Oudsen, I., & Walsh, V. (2007). Left frontal eye field remembers "where" but not "what." *Neuropsychologia*, *45*(10), 2340–2345. http://doi.org/10.1016/j.neuropsychologia.2007.02.009

Carpenter, R. H. S. (2004). Supplementary eye field: keeping an eye on eye movement. *Current Biology: CB*, *14*(11), R416–418. http://doi.org/10.1016/j.cub.2004.05.032

Chen, L. L., & Wise, S. P. (1995). Neuronal activity in the supplementary eye field during acquisition of conditional oculomotor associations. *Journal of Neurophysiology*, *73*(3), 1101–1121.

Connolly, J. D., Goodale, M. A., Goltz, H. C., & Munoz, D. P. (2005). fMRI activation in the human frontal eye field is correlated with saccadic reaction time. *Journal of Neurophysiology*, *94*(1), 605–611. http://doi.org/10.1152/jn.00830.2004

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron*, *58*(3), 306–324. http://doi.org/10.1016/j.neuron.2008.04.017

Deiber, M. P., Honda, M., Ibañez, V., Sadato, N., & Hallett, M. (1999). Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: effect of movement type and rate. *Journal of Neurophysiology*, *81*(6), 3065–3077.

Dejardin, S., Dubois, S., Bodart, J. M., Schiltz, C., Delinte, A., Michel, C., … Crommelinck, M. (1998). PET study of human voluntary saccadic eye movements in darkness: effect of task repetition on the activation pattern. *The European Journal of Neuroscience*, *10*(7), 2328–2336.

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain: A Journal of Neurology*, *118 (Pt 1)*, 279–306.

Ding, J., Powell, D., & Jiang, Y. (2009). Dissociable frontal controls during visible and memory-guided eye-tracking of moving targets. *Human Brain Mapping*, *30*(11), 3541–52. http://doi.org/10.1002/hbm.20777

Dorris, M. C., & Munoz, D. P. (1998). Saccadic probability influences motor preparation signals and time to saccadic initiation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *18*(17), 7015–7026.

Drew, A. S., & van Donkelaar, P. (2007). The contribution of the human FEF and SEF to smooth pursuit initiation. *Cerebral Cortex*, *17*(11), 2618–24. http://doi.org/10.1093/cercor/bhl169

Fukushima, K., Fukushima, J., Warabi, T., & Barnes, G. R. (2013). Cognitive processes involved in smooth pursuit eye movements: behavioral evidence, neural substrate and clinical correlation. *Frontiers in Systems Neuroscience*, *7*, 4. http://doi.org/10.3389/fnsys.2013.00004

Gagnon, D., O'Driscoll, G. A., Petrides, M., & Pike, G. B. (2002). The effect of spatial and temporal information on saccades and neural activity in oculomotor structures. *Brain: A Journal of Neurology*, *125*(Pt 1), 123–139.

Gagnon, D., Paus, T., Grosbras, M.-H., Pike, G. B., & O'Driscoll, G. A. (2006). Transcranial magnetic stimulation of frontal oculomotor regions during smooth pursuit. *The Journal of Neuroscience*, *26*(2), 458–66. http://doi.org/10.1523/JNEUROSCI.2789-05.2006

Gaymard, B., Pierrot-Deseilligny, C., & Rivaud, S. (1990). Impairment of sequences of memory-guided saccades after supplementary motor area lesions. *Annals of Neurology*, *28*(5), 622–626. http://doi.org/10.1002/ana.410280504

Gaymard, B., Ploner, C. J., Rivaud-Péchoux, S., & Pierrot-Deseilligny, C. (1999). The frontal eye field is involved in spatial short-term memory but not in reflexive saccade inhibition. *Experimental Brain Research*, *129*(2), 288–301.

Gaymard, B., Rivaud, S., & Pierrot-Deseilligny, C. (1993). Role of the left and right supplementary motor areas in memory-guided saccade sequences. *Annals of Neurology*, *34*(3), 404–406. http://doi.org/10.1002/ana.410340317

Gheysen, F., & Fias, W. (2012). Dissociable neural systems of sequence learning. *Advances in Cognitive Psychology / University of Finance and Management in Warsaw*, *8*(2), 73–82. http://doi.org/10.2478/v10053-008-0105-1

Grosbras, M.H. (2001). Human Cortical Networks for New and Familiar Sequences of Saccades. *Cerebral Cortex*, *11*(10), 936–945. http://doi.org/10.1093/cercor/11.10.936

Grosbras, M. H., Lobel, E., Van de Moortele, P. F., LeBihan, D., & Berthoz, A. (1999). An anatomical landmark for the supplementary eye fields in human revealed with functional magnetic resonance imaging. *Cerebral Cortex (New York, N.Y.: 1991)*, *9*(7), 705–711.

Hardwick, R. M., Rottschy, C., Miall, R. C., & Eickhoff, S. B. (2013). A quantitative meta-analysis and review of motor learning in the human brain. *NeuroImage*, *67*, 283–297. http://doi.org/10.1016/j.neuroimage.2012.11.020

Heide, W., Binkofski, F., Seitz, R. J., Posse, S., Nitschke, M. F., Freund, H. J., & Kömpf, D. (2001). Activation of frontoparietal cortices during memorized triple-step sequences of saccadic eye movements: an fMRI study. *The European Journal of Neuroscience*, *13*(6), 1177–89.

Heide, W., Kurzidim, K., & Kömpf, D. (1996). Deficits of smooth pursuit eye movements after frontal and parietal lesions. *Brain: A Journal of Neurology*, *119 (Pt 6)*, 1951–1969.

Heinen, S. J., & Liu, M. (1997). Single-neuron activity in the dorsomedial frontal cortex during smooth-pursuit eye movements to predictable target motion. *Visual Neuroscience*, *14*(5), 853–865.

Joiner, W. M., & Shelhamer, M. (2006). Pursuit and saccadic tracking exhibit a similar dependence on movement preparation time. *Experimental Brain Research*, *173*(4), 572–86. http://doi.org/10.1007/s00221-006-0400-3

Krauzlis, R. J. (2005). The control of voluntary eye movements: new perspectives. *The Neuroscientist*, *11*(2), 124–37. http://doi.org/10.1177/1073858404271196

Kriegeskorte, N., Simmons, W. K., Bellgowan, P. S. F., & Baker, C. I. (2009). Circular analysis in systems neuroscience: the dangers of double dipping. *Nature Neuroscience*, *12*(5), 535–540. http://doi.org/10.1038/nn.2303

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., … Fox, P. T. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping*, *10*(3), 120–31.

Lane, A. R., Smith, D. T., Schenk, T., & Ellison, A. (2012). The involvement of posterior parietal cortex and frontal eye fields in spatially primed visual search. *Brain Stimulation*, *5*(1), 11–17. http://doi.org/10.1016/j.brs.2011.01.005

Leigh, R. J., & Zee, D. S. (1991). *The Neurology of Eye Movements* (2nd ed.). Philadelphia: F. A. Davis Co.

Lencer, R., Nagel, M., Sprenger, A., Zapf, S., Erdmann, C., Heide, W., & Binkofski, F. (2004). Cortical mechanisms of smooth pursuit eye movements with target blanking. An fMRI study. *The European Journal of Neuroscience*, *19*(5), 1430–6. http://doi.org/10.1111/j.1460-9568.2004.03229.x

Lencer, R., & Trillenberg, P. (2008). Neurophysiology and neuroanatomy of smooth pursuit in humans. *Brain and Cognition*, *68*(3), 219–28. http://doi.org/10.1016/j.bandc.2008.08.013

Lindner, A., Haarmeier, T., Erb, M., Grodd, W., & Thier, P. (2006). Cerebrocerebellar circuits for the perceptual cancellation of eye-movement-induced retinal image motion. *Journal of Cognitive Neuroscience*, *18*(11), 1899–1912. http://doi.org/10.1162/jocn.2006.18.11.1899

Luna, B., Thulborn, K. R., Strojwas, M. H., McCurtain, B. J., Berman, R. A., Genovese, C. R., & Sweeney, J. A. (1998). Dorsal cortical regions subserving visually guided saccades in humans: an fMRI study. *Cerebral Cortex (New York, N.Y.: 1991)*, *8*(1), 40–47.

Luu, P., Flaisch, T., & Tucker, D. M. (2000). Medial frontal cortex in action monitoring. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *20*(1), 464–469.

Lu, X., Matsuzawa, M., & Hikosaka, O. (2002). A neural correlate of oculomotor sequences in supplementary eye field. *Neuron*, *34*(2), 317–325.

Manginelli, A. A., Baumgartner, F., & Pollmann, S. (2013). Dorsal and ventral working memory-related brain areas support distinct processes in contextual cueing. *NeuroImage*, *67*, 363–374. http://doi.org/10.1016/j.neuroimage.2012.11.025

Missal, M., & Heinen, S. J. (2004). Supplementary eye fields stimulation facilitates anticipatory pursuit. *Journal of Neurophysiology*, *92*(2), 1257–62. http://doi.org/10.1152/jn.01255.2003

Munk, M. H. J., Linden, D. E. J., Muckli, L., Lanfermann, H., Zanella, F. E., Singer, W., & Goebel, R. (2002). Distributed cortical systems in visual short-term memory revealed by event-related functional magnetic resonance imaging. *Cerebral Cortex (New York, N.Y.: 1991)*, *12*(8), 866–876.

Norman, K. A., Polyn, S. M., Detre, G. J., & Haxby, J. V. (2006). Beyond mind-reading: multi-voxel pattern analysis of fMRI data. *Trends in Cognitive Sciences*, *10*(9), 424–430. http://doi.org/10.1016/j.tics.2006.07.005

Nyffeler, T., Pierrot-Deseilligny, C., Felblinger, J., Mosimann, U. P., Hess, C. W., & Müri, R. M. (2002). Time-dependent hierarchical organization of spatial working memory: a transcranial magnetic stimulation study. *The European Journal of Neuroscience*, *16*(9), 1823–1827.

Nyffeler, T., Rivaud-Pechoux, S., Wattiez, N., & Gaymard, B. (2008). Involvement of the supplementary eye field in oculomotor predictive behavior. *Journal of Cognitive Neuroscience*, *20*(9), 1583–94. http://doi.org/10.1162/jocn.2008.20073

O'Driscoll, G. A., Strakowski, S. M., Alpert, N. M., Matthysse, S. W., Rauch, S. L., Levy, D. L., & Holzman, P. S. (1998). Differences in cerebral activation during smooth pursuit and saccadic eye movements using positron-emission tomography. *Biological Psychiatry*, *44*(8), 685–689.

Offen, S., Gardner, J. L., Schluppeck, D., & Heeger, D. J. (2010). Differential roles for frontal eye fields (FEFs) and intraparietal sulcus (IPS) in visual working memory and visual attention. *Journal of Vision*, *10*(11), 28. http://doi.org/10.1167/10.11.28

Orban de Xivry, J.-J., & Lefèvre, P. (2007). Saccades and pursuit: two outcomes of a single sensorimotor process. *The Journal of Physiology*, *584*(Pt 1), 11–23. http://doi.org/10.1113/jphysiol.2007.139881

O'Shea, J., Muggleton, N. G., Cowey, A., & Walsh, V. (2007). Human frontal eye fields and spatial priming of pop-out. *Journal of Cognitive Neuroscience*, *19*(7), 1140–1151. http://doi.org/10.1162/jocn.2007.19.7.1140

Petit, L., Clark, V. P., Ingeholm, J., & Haxby, J. V. (1997). Dissociation of saccade-related and pursuit-related activation in human frontal eye fields as revealed by fMRI. *Journal of Neurophysiology*, *77*(6), 3386–90.

Petit, L., & Haxby, J. V. (1999). Functional anatomy of pursuit eye movements in humans as revealed by fMRI. *Journal of Neurophysiology*, *82*(1), 463–71.

Petit, L., Orssaud, C., Tzourio, N., Salamon, G., Mazoyer, B., & Berthoz, A. (1993). PET study of voluntary saccadic eye movements in humans: basal ganglia-thalamocortical system and cingulate cortex involvement. *Journal of Neurophysiology*, *69*(4), 1009–1017.

Pierrot-Deseilligny, C., Milea, D., & Müri, R. M. (2004). Eye movement control by the cerebral cortex. *Current Opinion in Neurobiology*, *17*(1), 17–25. http://doi.org/10.1097/01.wco.0000113942.12823.e0

Pierrot-Deseilligny, C., Müri, R. M., Rivaud-Pechoux, S., Gaymard, B., & Ploner, C. J. (2002). Cortical control of spatial memory in humans: the visuooculomotor model. *Annals of Neurology*, *52*(1), 10–9. http://doi.org/10.1002/ana.10273

Poliakoff, E., Collins, C. J. S., & Barnes, G. R. (2005). Attention and selection for predictive smooth pursuit eye movements. *Cognitive Brain Research*, *25*(3), 688–700. http://doi.org/10.1016/j.cogbrainres.2005.08.016

Ptak, R. (2012). The frontoparietal attention network of the human brain: action, saliency, and a priority map of the environment. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *18*(5), 502–515. http://doi.org/10.1177/1073858411409051

Robertson, E. M., Tormos, J. M., Maeda, F., & Pascual-Leone, A. (2001). The role of the dorsolateral prefrontal cortex during sequence learning is specific for spatial information. *Cerebral Cortex*, *11*(7), 628–35.

Rosano, C., Krisky, C. M., Welling, J. S., Eddy, W. F., Luna, B., Thulborn, K. R., & Sweeney, J. a. (2002). Pursuit and saccadic eye movement subregions in human frontal eye field: a high-resolution fMRI investigation. *Cerebral Cortex*, *12*(2), 107–15.

Säfström, D., Johansson, R. S., & Flanagan, J. R. (2014). Gaze behavior when learning to link sequential action phases in a manual task. *Journal of Vision*, *14*(4). http://doi.org/10.1167/14.4.3

Salazar, R. F., Dotson, N. M., Bressler, S. L., & Gray, C. M. (2012). Content-specific fronto-parietal synchronization during visual working memory. *Science (New York, N.Y.)*, *338*(6110), 1097–1100. http://doi.org/10.1126/science.1224000

Schmid, a, Rees, G., Frith, C., & Barnes, G. (2001). An fMRI study of anticipation and learning of smooth pursuit eye movements in humans. *Neuroreport*, *12*(7), 1409–14.

Shichinohe, N., Akao, T., Kurkin, S., Fukushima, J., Kaneko, C. R. S., & Fukushima, K. (2009). Memory and decision making in the frontal cortex during visual motion processing for smooth pursuit eye movements. *Neuron*, *62*(5), 717–732. http://doi.org/10.1016/j.neuron.2009.05.010

Smit, A. C., Van Gisbergen, J. A., & Cools, A. R. (1987). A parametric analysis of human saccades in different experimental paradigms. *Vision Research*, *27*(10), 1745–62.

Sommer, M. A., & Wurtz, R. H. (2000). Composition and topographic organization of signals sent from the frontal eye field to the superior colliculus. *Journal of Neurophysiology*, *83*(4), 1979–2001.

Tseng, P., Chang, C.-F., Chiau, H.-Y., Liang, W.-K., Liu, C.-L., Hsu, T.-Y., … Juan, C.-H. (2013). The dorsal attentional system in oculomotor learning of predictive information. *Frontiers in Human Neuroscience*, *7*, 404. http://doi.org/10.3389/fnhum.2013.00404

Acknowledgements: We would like to acknowledge the MRC and the staff at the Magnetic Resonance Imaging Facility at Salford Royal for their support in running the fMRI experiments. We would also

like to thank Prof Graham Barnes, Dr Donna Lloyd and anonymous reviewers for comments on earlier versions of the manuscript.