Brain and Behavior: A Task-Dependent Eye Movement Study

Recent electrophysiological and behavioral studies have found similarities in the neurology of pursuit and saccadic eye movements. In a previous study on eye movements using closely matched paradigms for pursuit and saccades, we revealed that both exhibit bimodal distributions of latency to predictable (PRD) and randomized (RND) stimuli; however, the latency to each type of stimulus was different, and there was more segregation of latencies in saccades than pursuit (Burke MR, Barnes GR. 2006. Quantitative differences in smooth pursuit and saccadic eye movements in humans. Exp Brain Res. 175(4):596-608). To investigate the brain areas involved in these tasks, and to search for correlates of behavior, we used functional magnetic resonance imaging during equivalent PRD and RND target presentations. In the contrast pursuit > saccades, which reflects velocity-dependent versus position-dependent activities, respectively, we found higher activation in the dorsolateral prefrontal cortex (DLPFC) for pursuit and in the frontopolar region for saccades. The reverse contrast revealed higher activity for the frontal eye fields (FEF), supplementary eye fields (SEF), dorsal prefrontal cortex (DLPFC), superior colliculus, brainstem, and cerebellum (CBM) (Petit et al. 1997; Berman et al. 1999; Gaymard and Pierrot-Deseilligny 1999; Petit and Haxby 1999; O’Driscoll et al. 2000; Yan et al. 2001; Missal and Keller 2002; Rosano et al. 2002; Keller and Missal 2003; Krauzlis 2004). Several of these areas have been implicated in the maintenance of short-term memory, including the DLPFC (pursuit: Schmid et al. 2001; saccades: Pierrot-Deseilligny et al. 2005), FEF (pursuit: MacAvoy et al. 1991; saccades: Gaymard et al. 1999; Pierrot-Deseilligny et al. 2005) and MT (in monkeys) (Bisley et al. 2004). This extensive overlap in activation during the initiation and maintenance of these eye movements is not fully understood and has thus prompted the following study.

The main goals of the study are to 1) identify brain areas specific for motion processing (pursuit) and position processing (saccades). The study employs both pursuit that uses principally velocity information, and saccades/gaze-shifting that principally uses positional information, to study eye movements (Rashbass 1961). We have incorporated a blocked design using either pursuit or saccadic eye movements. We use a combination of eye velocity memory and visual feedback for maintenance (Becker and Fuchs 1985; Morris and Lisberger 1987; Bennett and Barnes 2005). In addition to the differences observed in the maintenance of these eye movements, a previous experiment comparing the latency of responses to PRD or RND targets revealed a greater distinction between the PRD and RND stimuli for saccades than for pursuit (Burke and Barnes 2006). In support of this finding, Liston and Krauzlis (2005) found that pursuit and saccades share the same decision signal but differ in the response thresholds to random target presentations. In contrast, other behavioral studies have found that pursuit and saccades share similar mean preparation times to PRD and RND stimuli (Joiner and Shellhamer 2006).

Electrophysiological recording and functional imaging have provided detailed information about the pathways involved in the generation of pursuit and saccades (for a review, see Pierrot-Deseilligny et al. 2004). For both pursuit and saccades, visual information about the target is conveyed to primary occipital regions in the brain (V1, V2, and V3) before information is relayed to other areas including the medial temporal areas (MT), medial superior temporal area (MST), parietal eye fields, frontal eye fields (FEF), supplementary eye fields (SEF), dorsolateral prefrontal cortex (DLPFC), superior colliculus, brainstem, and cerebellum (CBM) (Petit et al. 1997; Berman et al. 1999; Gaymard and Pierrot-Deseilligny 1999; Petit and Haxby 1999; O’Driscoll et al. 2000; Yan et al. 2001; Missal and Keller 2002; Rosano et al. 2002; Keller and Missal 2003; Krauzlis 2004). Several of these areas have been implicated in the maintenance of short-term memory, including the DLPFC (pursuit: Schmid et al. 2001; saccades: Pierrot-Deseilligny et al. 2005), FEF (pursuit: MacAvoy et al. 1991; saccades: Gaymard et al. 1999; Pierrot-Deseilligny et al. 2005) and MT (in monkeys) (Bisley et al. 2004). This extensive overlap in activation during the initiation and maintenance of these eye movements is not fully understood and has thus prompted the following study.

Introduction

The 2 principal types of eye movement used for obtaining detailed information about the visual world are pursuit and saccades. The primary function of pursuit is to maintain an object of interest near to the fovea during motion of the object, which is achieved with a combination of smooth and saccadic movements. Conversely, goal-directed saccades rapidly redirect the fovea onto stationary objects of interest. In a previous paper, we have addressed the behavioral similarities between pursuit and saccadic eye movements to randomized (RND) and predictable (PRD) target motion that principally reflect the visually driven versus memory-driven responses of pursuit and saccades, respectively. The idea that working memory is used in predictive saccadic control to hold positional information is a familiar one (Droulez and Berthoz 1991). Less familiar, perhaps, is the evidence that a similar form of working memory is used to hold velocity information for predictive pursuit (Collins and Barnes 2005; Burke and Barnes 2007). The segregation of memory-based and feedback-driven components for pursuit is more demanding than for saccades because continued pursuit employs a combination of eye velocity memory and visual information about the target is conveyed to primary occipital regions in the brain (V1, V2, and V3) before information is relayed to other areas including the medial temporal areas (MT), medial superior temporal area (MST), parietal eye fields, frontal eye fields (FEF), supplementary eye fields (SEF), dorsolateral prefrontal cortex (DLPFC), superior colliculus, brainstem, and cerebellum (CBM) (Petit et al. 1997; Berman et al. 1999; Gaymard and Pierrot-Deseilligny 1999; Petit and Haxby 1999; O’Driscoll et al. 2000; Yan et al. 2001; Missal and Keller 2002; Rosano et al. 2002; Keller and Missal 2003; Krauzlis 2004). Several of these areas have been implicated in the maintenance of short-term memory, including the DLPFC (pursuit: Schmid et al. 2001; saccades: Pierrot-Deseilligny et al. 2005), FEF (pursuit: MacAvoy et al. 1991; saccades: Gaymard et al. 1999; Pierrot-Deseilligny et al. 2005) and MT (in monkeys) (Bisley et al. 2004). This extensive overlap in activation during the initiation and maintenance of these eye movements is not fully understood and has thus prompted the following study.

This study employs both pursuit that uses principally velocity information, and saccades/gaze-shifting that principally uses positional information, to study eye movements (Rashbass 1961). We have incorporated a blocked design using either pursuit or saccadic eye movement responses made to PRD or RND target motion in a 2 factorial block design (PRD pursuit, RND pursuit, PRD SAC, and RND saccades). The control has provided a baseline measurement of visual activation and fixation and thus allows us to establish activation in relation to the eye movement alone in the test paradigms. We used both a boxcar basis function and a linear time-dependent basis function in order to evaluate the sustained activation and time-dependent changes in activation, respectively, over a block of presentations.

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saccades, 2) establish differences in the predominantly memory-driven (PRD) and visually driven (RND) pathways in the brain, and 3) segregate the functional magnetic resonance imaging (fMRI) responses into sustained- and learning-related activations. We hypothesize that pursuit and saccades will reveal many brain regions in common during their eye movement responses, but differences will exist in the use of these areas during either the velocity-dependent or position-dependent tasks. In addition, we expect to observe activation in the DLPFC and SEF in response to the PRD paradigm based on previous studies (Pierrot-Deseilligny et al. 2005; Simo et al. 2005, Heinen and Liu 1997).

Methods

Subject Population
Twelve right-handed healthy adults (7 females) between the ages of 20 and 39 years (mean age 26.4 years) took part in the experiment. Full informed written consent was obtained in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964). The subjects had no known neurological, psychological, or oculomotor abnormalities, and no abnormalities were found on their structural magnetic resonance imaging scans. Subjects were free to wear contact lenses to correct for any visual impairment during the experiment.

Experimental Design
All scanning took place in the Welcome Trust Clinical Research Facility (Manchester, UK) using a 1.5-T Philips Intera scanner with a SENSE head coil. Subjects were supine in the scanner and viewed target motion on a large gray screen positioned ~1 m from the end of the scanner via a reflective mirror system positioned on the head coil. Eye movements were monitored throughout using an infrared limbus-tracking device (MR-eyetracker, CRS Ltd., Cambridge, UK) attached to the head coil by a custom-built holding device (CRS Ltd.). Foam pillows were used to minimize head motion during the scanning session. The visual stimulus was presented using custom-made software that back projected a moving target onto the screen in front of the subject. The visual fixation stimulus comprised a circular annulus positioned in the center of the screen (FIX), and the tracking target was a white (unfilled) square (T1) with similar dimensions to the fixation target (subtending 1.2° on the eye). All subjects also performed the experiment under laboratory conditions using a similar limbus tracker (IRIS, Skalar Medical BV, CRS Ltd.) prior to being scanned, to obtain behavioral performance data.

Paradigms
The paradigms were designed to equalize the timing aspects of the 2 types of stimuli, pursuit and saccades. Note that in order to reduce the number of corrective saccadic intrusions during pursuit eye movements, we incorporated a variation of the Rashbass paradigm (1961). This paradigm uses a step followed by smooth motion in the opposite direction and has been found to significantly reduce the number of corrective saccades (see Burke and Barnes 2006). We also used a gap for both pursuit and saccade trials to optimize the latency of the responses by releasing fixation prior to target appearance (saccade Reuter-Lorenz et al. 1991; pursuit: Krauzlis and Miles 1996). A return step-ramp movement back to the center of the screen was also included for pursuit, which served to remove any return saccade made by the subject at the end of the motion and place the eyes back to center of the screen ready for the next stimulus. Similarly, a step back to center was used in the saccadic task. As the target stimulus was presented for a maximum of 800 ms for the outward and also the return movement, the differences in movement time between saccades and pursuit were minimized.

Double Cue-Gap-Step Ramp (pursuit)
In this paradigm, subjects were initially given a visual fixation cue (FIX) (200–400 ms) positioned in the center of the screen. This cue was then extinguished during a GAP (200–600 ms) before a target appeared (T1) either to the left or to the right of the prior cue (3° or 6°: equivalent to 200 ms of target motion). The target proceeded to move through the center of the screen with velocities of 15° or 30° per second for 500–800 ms before being extinguished. This target (T12) then reappeared, displaced by a more eccentric step (step magnitude as defined above), and moved toward the center of the screen for 500–800 ms before being extinguished at the center. Subjects were required to fixate FIX and smoothly track T11 and T12 (see Fig. 1) (see Burke and Barnes 2006).

Double Cue-Gap-Step (SAC)
This paradigm was designed to mimic the above condition, but with steps rather than smoothly moving ramps. Subjects again were given a visual fixation cue (FIX) for 200–400 ms in the center of the screen, followed by a GAP (200–600 ms). A target then appeared (T11) either to the left or to the right of the prior cue at amplitudes of 5° or 15° and was visible for 500–800 ms. This same target (T12) then reappeared in the center of the screen. Subjects were required to fixate FIX and make a saccade to T11 and T12 (see Fig. 1) (Burke and Barnes 2006).

PRD Condition (PRD)
For the PRD conditions, the subjects were presented with the same stimulus “presentation,” either pursuit or SAC, 8 times in a row denoting a “block.” The stimuli presented had the same direction and speed/amplitude in all 8 presentations. The gap time remained the same for each stimulus presentation; however, the interstimulus interval (ISI: time between each stimulus presentation) was randomized from 500–1500 ms (see Fig. 2A).

Random Condition (RND)
For the random condition, the subjects were again presented with the stimulus presentation, pursuit or SAC, 8 times in a row. However, each of the 8 stimulus presentations differed in direction and/or speed/amplitude. The timing of the gap and ISI were also randomized within each presentation in the range 200–600 ms and between presentations by 500–1500 ms, respectively (see Fig. 2B).

Control/Baseline (CON)
In this condition, the visual fixation cue appeared and disappeared using the same timing as the PRD pursuit and SAC conditions mentioned above in order to mimic visual stimulation without any eye movements. This was used as the baseline to specifically isolate the eye movement component from the activity associated with the visual stimulus. Five blocks (2 × PRD, 2 × RND, and 1 × CON block) comprised a “template.” A template either contained the pursuit or SAC stimulus presentations using the sequence 1) PRD, RND, PRD, RND, and CON or 2) RND, PRD, RND, PRD, and CON. The experiments formed a design of alternating pursuit and SAC templates with a calibration (CAL) performed at the beginning of each of these sets (see Fig. 2). The CAL involved the subject continuously tracking a sinusoidally moving target centered on the screen with velocities of 15° or 30° per second for 500–800 ms before being extinguished. This target (T11) then reappeared, displaced by a more eccentric step (step magnitude as defined above), and moved toward the center of the screen for 500–800 ms before being extinguished at the center. Subjects were required to fixate FIX and smoothly track T11 and T12 (see Fig. 1) (Burke and Barnes 2006).
(amplitude ± 15°) in the horizontal plane of motion. Each of the 12 subjects performed the eye-movement paradigms in a single-recording session lasting ~45 min each. The subjects performed 6 pursuit and 6 SAC templates per session containing 5 blocks in each. This resulted in a total of 12 blocks for each condition; PRD pursuit, RND pursuit, PRD SAC, RND SAC, and CON for each subject.

BOLD fMRI Data Acquisition and Analysis
All recordings were obtained on a 1.5-T Philips Gyroscan Intera scanner using a SENSE head coil. All scans used appropriate angles (flip angle = 90°) to include whole-brain coverage (field of view = 256 mm, acquisition matrix = 64 × 64, repetition time = 3000 ms, echo time = 10 ms, voxel size = 3.5 mm³, slice thickness = 3.5 mm, gap thickness = 1.5 mm, number of axial slices = 38 slices/dynamic). Prior to each functional run, 2 dummy scans were performed to allow for stabilization of the longitudinal magnetization. In total, subjects performed 11 volumes per block and 55 volumes per template that resulted in 660 volumes during a single session. fMRI data were obtained in radiological convention in DICOM format and transformed into ANALYZE format using Statistical Parametric Mapping software (SPM2) (Wellcome Department of Imaging Neuroscience: http://www.fil.ion.ucl.ac.uk/spm/). Data were then preprocessed in SPM2 in the following way; slice timing was corrected, followed by spatial realignment of head motion (Friston et al. 1995), and normalization into Montreal Neurological Institute (MNI) coordinates (Mazziotta et al. 1995). Smoothing was performed using a 9-mm full-width half maximum Gaussian filter. The data were high-pass filtered (cutoff at 128 s), and global drifts were removed using proportional scaling. Prior to each session a T₁-weighted axial anatomical image was acquired from each subject.

In order to observe both mean-level sustained activation and learning-related activation (i.e., linear increases or decreases in activation over time), we performed both a boxcar analysis and a first-order parametric time-dependent analysis, respectively. For this, 2 design matrices were generated using A) all 11 volumes in each block for the "time-dependent parametric design" and B) the last 9 volumes in a block for the "boxcar design." The latter design was devised in order to remove the initial transient responses observed in behavioral studies to the PRD stimulus (Barnes and Asselman 1991). We used a general linear model with a boxcar basis function to generate contrasts for each participant (Worsley and Friston 1995). The contrasts for each subject were then placed into a secondary random effects analysis (one sample t-test) in order to obtain a mean activation for all subjects to each resultant contrast. Design A was used to convolve a linear basis function with the hemodynamic response function in order to observe any task × time-dependent interactions, that is, linear increases or decreases of brain activity over time ( Büchel et al. 1996). Again, the results from each subject were placed into a random effects analysis (one sample t-test) in order to obtain a group-level response. All reported activation is shown at a level of t > 3.5 and with small volume corrections (region of interest [ROI] = 10 mm) on the maximum activated cluster in the brain regions mentioned (Figs 4 and 5) using a family wise error (P < 0.05) to correct for multiple comparisons. This is with the exception of the DLPC in Figure 5D and MT in Figure 4 (upper graph) that did not reach this significance (ROI = 8 mm, P < 0.09). All data are plotted using the MNI convention. All figures display group activations on a T₁-weighted anatomical template with the anatomical identification of areas being processed in the anatomy toolbox provided by SPM2 or the WFU_pickatlas (Maldjian et al. 2003).

Eye-Movement Analysis
Eye movements were sampled at 200 Hz in both the scanning and laboratory environment. We applied a low-pass filter (80 Hz) to all eye-movement data including target data in order to reduce noise, before being stored for further off-line analysis. Pursuit eye-movement data were preprocessed in order to remove the saccadic component in velocity profiles based on previously defined and established acceleration (750/s²) and velocity (400/s) criteria; a linear interpolation was then used to join the gap in the data (for details of this analysis, see Bennett and Barnes 2005). The saccades captured using this technique were stored for later analysis. Data were filtered at 30 Hz using a zero-phase digital filter. The eye-movement data obtained in the scanner were useful for ensuring qualitative similarity between the scanning and laboratory environments. However, we found the signal during scanning could be lost due to its fixture to the head coil and therefore the data from the scanner could not be used to generate quantitative results of magnitude or latency. Preprocessed data from the laboratory were then analyzed in MatLab (The Mathworks, Inc, Natick, MA). Latency from target onset was found using a method similar to Lekwuwa and Barnes (1996b), by calculating 10% of the peak eye-velocity and forming a linear regression from this point back to the abscissa. The point at which the eye velocity and abscissa crossed was defined as eye-movement onset. Target onset was subtracted from eye-movement onset in order to obtain latency. Latency to the last 5 targets in each block was used to generate the mean responses for both PRD and RND responses. This resulted in 1140 latency values for each subject (720 pursuit and 720 SAC responses). We calculated the percentage correct of appropriate responses by using a latency of 80 ms as a border between PRD and RND responses, that is, <80 ms correct for PRD trials and a latency >80 ms was correct for RND trials. We used 80 ms as it has been established that approximately 80–100 ms is the approximate time needed for the brain to process visual information and prepare an appropriate response (Carl and Gellman 1987; Gellman et al. 1990), and for gap paradigms, this reaction time is reduced (Reuter-Lorenz et al. 1991; Knox 1996). For details of analysis and behavioral results, please refer to Burke and Barnes (2006).

Results
Eye-Movement Results
Inspection of the scanning data revealed that subjects were performing in a qualitatively similar manner in both the laboratory and scanning environments. By the second or third
presentation of the PRD stimulus, subjects were making anticipatory eye movements where the eyes were starting to move prior to the target onset (resulting in a negative latency) in both the pursuit and SAC tasks. Conversely, in the RND tasks, eye movements were initiated after target onset.

Mean Latency
Presented below are mean latencies for all subjects from the laboratory-based environment (Fig. 3). All subjects revealed a significant difference between RND and PRD conditions in both pursuit and SAC trials although the pursuit trial latencies were less distinctly segregated. We observed no significant difference in the latency between differing target velocity (pursuit) or displacement (SAC) levels. The overall mean latency for RND pursuit was 156 ms (±27 ms) and for PRD pursuit was 0 ms (±57 ms), that is, at target onset. Mean latency for RND SAC trials was 212 ms (±86 ms) and for PRD SAC was –213 ms (±39 ms), that is, 213 ms prior to target onset. The standard deviation for PRD trials was significantly higher than RND trials (P > 0.01) in both pursuit and SAC. Note that the range of latencies in the RND condition did not show any evidence of a second population of "express saccades" (Fischer and Ramsperger 1986; Burke and Barnes 2006).

fMRI Results
Eye-Movement Activation (pursuit Alone and SAC Alone)
Analysis of the subject data revealed many areas in common during the production of pursuit and saccadic eye movements and displayed both overlapping and segregated activation within these areas. In relation to the pursuit eye-movement conditions, we found significant activation in the right FEF (BA6), right inferior temporal gyrus, BA21, the right prefrontal cortex (PFC, BA9/46), visual area 5 (V5), the left CBM, and brainstem (see Fig. 4, upper graph). Negatively activated regions for pursuit revealed higher bilateral activation in the early visual areas V1 and V2 and bilaterally in the supramarginal gyrus (SMG, BA40).

For saccades only, we found significant activation bilaterally in the SEF (BA6), the right middle temporal gyrus (MTG, BA37/39) the right frontopolar regions (FP, BA10), the left PFC (BA9), and the left CBM (see Fig. 4). We found negative activation for saccades bilaterally in the inferior frontal gyrus (IFG, BA45/44), in the right PFC (BA9), and at a lower level of significance in early visual areas V1 and V2 (not shown in Fig. 4). It should be noted that much of this activation was bilateral at lower levels of significance.

Pursuit versus Saccades (Combined PRD and RND)
Boxcar Block Design. We found that pursuit had higher activation than SAC in the contrast pursuit > saccades in the right PFC (BA9), with additional activation also observed in the right MTG (BA21) (see Fig. 5A). Saccade trials revealed higher activation in the right SEF (BA6) and bilaterally in the IFG (BA45/44), the left FP (BA10), and the left visual area BA18.

Time-Dependent Block Design. We observed time-dependent linear increases in activation in the contrasts pursuit > SAC in bilateral SMG, BA40, V5, and the dorsal posterior cingulate, BA31 (see Fig. 5B). The linear increases for the SAC stimulus were found bilaterally in the superior temporal gyrus (STG, BA22/42/41), bilaterally in visual area 2 (V2, BA18), bilaterally in the superior parietal lobe (SPL, BA7), and the right IFG (BA44/45) (see Fig. 5B).

Predictive versus Random (Combined pursuit and SAC)
Boxcar Block Design. The contrast between PRD > RND trials for both pursuit and saccadic eye movements (see Fig. 5C) revealed high activation levels bilaterally in SEF (BA6), in the left angular gyrus (BA39), the left SPL (BA7), and the left IFG (BA44/...
The specific objective of this experiment was to compare brain activity in 2 very different oculomotor tasks, one related to shifting gaze from one position to another and the other related to continuous pursuit of a moving object. Moreover, we aimed to compare 2 different forms of these tasks, predictive and nonpredictive, that resulted in anticipatory or reactive behavior, respectively, as evidenced by the major differences in timing of response initiation (Fig. 3). The tasks were carefully designed to ensure that the stimulus paradigms were equivalent in both their temporal and spatial characteristics, thus avoiding some of the problems associated with previous fMRI studies on smooth pursuit and saccades. The experiment was also specifically designed to remove brain activation related to the visual stimulus itself by incorporation of the baseline condition, thus isolating the observed activation to the eye-movement plan, retrieval, and execution only. We have identified isolated areas that are specific to the comparison between PRD and RND conditions; we hypothesize that these areas reflect differences in activation between the predominantly visually generated (RND) and the predominantly memory-generated (PRD) components of the eye-movement response, respectively. We acknowledge that during PRD pursuit eye movements, the picture is more complex than for saccades, in that pursuit is maintained via a combination of memory-driven feed-forward and visual information. We assume that our RND pursuit responses are predominately visually driven because the predictive network is unlikely to become fully enabled within the period of each ramp (maximum duration 800 ms) (Morris and Lisberger 1987). On this basis, we expect that the contrast of PRD with RND conditions will reveal greater activity in areas related to predictive processing, particularly the use of short-term memory.

Another key aspect of our findings in this respect is the implementation of a linear time-dependent parametric model over a block of trials, which has allowed the changes over time, associated with learning in the PRD paradigm, to be assessed. We have identified other areas specific to the comparison of ocular pursuit and saccadic gaze shifts, which we suggest are related to motion processing versus the processing of positional information, respectively. An important factor in this comparison has been the implementation of a novel design matrix (partial block analysis). The rationale for this is based on previous behavioral findings (Barnes and Asselman 1991; Burke and Barnes 2006), showing that learning in the PRD paradigm takes place over the first 2–3 presentations of the stimulus, after which a steady state is attained. The partial block analysis allows the transient part of the response (which is basically equivalent to the RND response) to be ignored, so that the observed blood oxygen level-dependent (BOLD) activation over the remainder of the block more clearly identifies the difference between the steady state PRD and RND conditions. This approach has not previously been used in comparative pursuit and saccadic fMRI studies and has provided us with the ability to contrast these eye-movement types more appropriately.

It should be noted that our objective in this study has not been to discriminate between the forms of eye movement, smooth and saccadic, but between pursuit and gaze shifting. Ocular pursuit in natural situations involves a combination of smooth and occasional saccadic components; our pursuit task was designed to minimize the saccadic component and obtain reasonable equivalence in the PRD and RND paradigms. As expected, the findings for the pursuit and gaze-shifting tasks presented here not only show clear similarities with many previous studies (Berman et al. 1999; Gaymard and Pierrot-Deseilligny 1999; O’Driscoll et al. 2000; Tanabe et al. 2002; Pierrot-Deseilligny et al. 2005) but also show distinct activation related to the specific paradigms and contrasts we have used. We have thus provided a novel approach to looking at predictive eye movements inside the fMRI scanner. In order to interpret our findings, we will consider them in the context of the specific areas of interest previously associated with oculomotor control, notably those identified by Krauzlis (2005). For this purpose, we will refer to Figure 6, where we have attempted to relate the organization in general terms to functional models of pursuit and saccadic control. The basis of such models is that they contain 2 parts, a direct visual feedback

**Discussion**

The specific objective of this experiment was to compare brain activity in 2 very different oculomotor tasks, one related to shifting gaze from one position to another and the other related to continuous pursuit of a moving object. Moreover, we aimed to compare 2 different forms of these tasks, predictive and nonpredictive, that resulted in anticipatory or reactive behavior, respectively, as evidenced by the major differences in timing of response initiation (Fig. 3). The tasks were carefully designed to ensure that the stimulus paradigms were equivalent in both their temporal and spatial characteristics, thus avoiding some of the problems associated with previous fMRI studies on smooth pursuit and saccades. The experiment was also specifically designed to remove brain activation related to the visual

**Figure 4.** Results from all subjects for the contrasts PUR only (upper graph) and SAC only (lower graph) when the baseline activation has been removed for the partial volume analysis. Red to yellow colors display positive activation to that contrast and blue to cyan colors show negative activation. A lighter color reflects a higher t value. View of the brain is shown by the white letters: L = left side, R = right side, ANT = anterior, and POS = posterior. BS = brainstem, ITG = inferior temporal gyrus, and V1/V2/V5 = visual areas 1, 2, and 5.
pathway associated with reactive control, supplemented by a secondary (indirect) efference copy pathway, that is associated with predictive control (Barnes and Asselman 1991; Droulez and Berthoz 1991). The latter includes short-term memory processes for either positional or velocity information that are likely to be located in PFC and/or the parietal cortex and activated via SEF (Fig. 6). Our assumption is that predictive activity induced in our behavioral paradigms specifically requires the use of short-term memory because responses are based on prior experience; there are no other motion or direction cues.

**Occipital Lobe**

In our model, processing starts appropriately with visual input to the occipital areas (left side of Fig. 6). We found higher activation bilaterally in the primary visual areas (V1 and V2) in association with the reactive (RND) condition in contrast PRD < RND. This finding has not been reported previously for PRD versus RND trials, which may be due to the differences in our design when compared with previous studies. This increased activation in early visual areas is possibly due to the need for increased attention to the visual stimulus during RND trials (Büchel et al. 1998). Floyer-Lea and Matthews (2004) recently found that activity in early motor areas (M1), during the tracking of a visual stimulus with the hand, is also decreased with learning. Another plausible explanation could relate to the extent of activation, as the RND trials would generate a larger surface area of retinal activation when compared with the PRD trials over a block.
Parietal Lobe and Extrastriate Cortex

The next stage of processing our model highlights are 3 closely related parietal areas (V5, SMG, and SPL) that are known to be involved in spatiotemporal integration (see Fig. 6).

Visual Area 5
V5 is classically associated with the processing of visual motion information (Newsome et al. 1985). In this study, V5 was only minimally activated in the left hemisphere by the contrast of pursuit with baseline (Fig. 4), but this is probably because our baseline specifically invoked visual fixation, which is known to excite multiple visual association areas including V5 (Richter et al. 2004), and the primary visual cortex. By contrast, left V5 was highly activated in the time-dependent contrast for both pursuit > SAC and PRD > RND, implying a particularly prominent role in the PRD pursuit condition. This study and others show that V5 clearly contributes to PRD eye movements in both pursuit and saccades. However, it is still unclear how this area contributes to generating predictive eye movements and if it is part of the feed-forward network also involved in maintained pursuit when vision of the target is provided.

Supramarginal Gyrus
The contrast pursuit > SAC also revealed a significant bilateral time-dependent increase in activation in SMG (BA40) within each block of presentations for the pursuit task. In contrast, time-dependent increases in activity were found in the SPL for the SAC condition in the contrast pursuit < SAC. SMG has previously been associated with both saccades and smooth pursuit, with lesions in this area causing an increase in latency for visually guided saccades and affecting latency, initial velocity, and acceleration in pursuit (Thurston et al. 1988; Heide et al. 1996). Lencer et al. (2004) found the SMG to be more active during the blanking of a smooth pursuit target when compared with continuous target presentations, revealing a functional role for the maintenance of velocity information when no visual feedback is available. This implies that the SMG may be associated with velocity memory, perhaps as part of the indirect efference copy feedback system shown in Figure 6, and our findings are consistent with this conclusion.

Superior Parietal Lobe
In the time-dependent contrast of pursuit with SAC (Fig. 5B), it is evident that there is more activity associated with SMG during pursuit but more activity in SPL during gaze shifting. That SPL is more associated with gaze shifting is supported by the evidence of Duhamel et al. (1992), who showed that SPL plays a role in updating the representation of visual space during a remembered saccadic eye movement and anticipating the retinal consequence of an intended eye movement (Duhamel et al. 1992). The findings in the current study add to previous findings by providing evidence of a graduation of activity from SPL, providing more positional control, via IPL, to SMG that integrates time and position/velocity information. In support of this, others have found that the IPL (lying between SPL and SMG) plays a critical role in the integration of spatial and temporal information (Assmus et al. 2003).

Frontal Lobe
Central to our model are regions in the frontal lobe, which include DLPFC, SEF, and FEF (see Fig. 6).

Dorsolateral Prefrontal Cortex
In line with original expectations, we found major differences in activity in PFC when comparing PRD and RND conditions. Most notably, we found a bilateral time-dependent increase in DLPFC within each block (Fig. 5D). The time-dependent changes mirror the changes in the predictive component of eye movement that principally occur over the first 2–3 presentations of each block (Barnes and Asselman 1991). One previous study on PRD pursuit eye movements (Schmid et al. 2001) demonstrated a time-dependent decrease in activation in DLPFC during the PRD conditions, but the area involved lay approximately midway between, and anterior to, the 2 areas identified above; it was actually closer to the area of PFC that we identified as having more sustained activity in the RND response (Fig. 5C). The rationalization for decreasing activity associated with learning is that it represents transition to a more automated response with less decision making and use of working memory than required in early stages of learning. This greater activity in random conditions has been found in other studies showing the DLPFC’s involvement in response selection but not maintenance (Rowe et al. 2000; Koch et al. 2006). However, a major difference in our study is that learning occurs much more rapidly than in other experiments (e.g., Koch et al. 2006), the time-dependent changes occurring within blocks lasting 33 s and containing only 8 repetitions. The increase in DLPFC activity in the PRD condition is expected in the first stages of the learning process, when the positional or velocity information is rapidly being laid down in working memory. Given that almost exactly the same area of DLPFC was activated in our study and the more prolonged learning study of Koch et al. (2006), it is possible that the initial increase in working memory load is followed by a subsequent decrease as the shift occurs from controlled to automatic processing. This is also in line with a recent connectivity study in PFC (Baeg et al. 2007).

We also found higher sustained activations in the right DLPFC (BA9) for pursuit when contrasted with saccades, in approximately the same area as that exhibiting the time-dependent predictive activity. The DLPFC has been associated with pursuit eye movements in other previous studies (Schmid et al. 2001; Lencer et al. 2004; Pierrot-Deseilligny et al. 2005; Nagel et al. 2006), although Heide et al. (1996) reported that lesions in this area do not cause deficits in pursuit eye movements. However, in a comparison of patients with similar left- and right-sided PFC lesions, Lekwuwa and Barnes (1996a) did find that right-sided lesions caused a greater deficit in sinusoidal pursuit at frequencies where prediction is required (>0.4 Hz), suggesting that the right side is more important for pursuit that requires the use of short-term memory. Our observation that right-sided DLPFC activation is greater for the velocity-dependent pursuit task than for the position-dependent saccade task may therefore indicate that this area is specifically associated with velocity storage and/or processing. This is supported by the finding (Fig. 4) that the same area is active in the pursuit task alone but is deactivated for the saccade task alone. Interestingly, the reverse appears to be true for the left DLPFC (Fig. 4), suggesting that it may be more specialized for short-term storage of positional information.

DLPFC has long been associated with working memory (Fuster 1973; Passingham 1985; Goldman-Rakic 1990), as well as being involved in executive functions such as decision making and selection (Milner 1963, Rowe et al. 2000). In addition, recent papers by Hagler and Sereno (2006) have shown that the
DLPFC is probably multifunctional, suggesting roles in target selection, working memory, and attention to salient objects. We have concentrated here on the area of DLPFC normally associated with working memory, but it is evident that other areas of PFC are also involved, probably reflecting other executive functions associated with our tasks.

Supplementary Eye Fields
The demonstration of higher sustained activation in the SEF in the predictive condition was one of the principal predicted outcomes of this experiment. SEF involvement in pursuit has previously been demonstrated in monkeys (Heinen and Liu 1997; Missal and Heinen 2004) and is thought to be involved in timing and initiation of internally generated responses. During the sequential performance of saccadic eye movements in monkeys, SEF plays an important role in memorizing the saccade location and order (Isoda and Tanji 2003). In humans, Gaymard et al. (1990) found a deficit in memory-guided saccades in subjects with lesions in SEF. Our results are in agreement with these previous studies and demonstrate a clear involvement of the SEF in the PRD control of both saccades and pursuit eye movements, establishing its role in memory-guided eye movements in humans. Note that our analysis implies that this role is sustained throughout a block of presentations because SEF does not feature in the time-dependent analysis discussed below. This is to be expected because internal response initiation is required for each individual presentation within a block. The higher activation observed in SEF during saccades when contrasted against the pursuit condition may be associated with the differences in actual motor response. Saccadic activity requires a stronger burst of activity than the more sustained activity of pursuit. In addition, the behavioral results associated with this experiment (Fig. 2) indicate that timing of response initiation for saccades is much more tightly clustered than for pursuit. Both of these factors are likely to result in a higher level of BOLD activity for saccades than pursuit. Clearly SEF is important in the generation of both pursuit and saccades (Fig. 6), but interestingly, we show it is more prominent in the position-dependent saccadic tasks when a direct contrast can be performed against pursuit.

Frontal Eye Fields
It has been found previously by Keating (1991) that FEF plays an important role in both PRD and RND pursuit. Interestingly, in this study FEF was found to be more active during the RND target motion for both pursuit and saccades. This greater activation of the FEF for RND target motion and SEF for PRD target motion has been found previously in saccades. Gaymard et al. (1990) found a severe deficit in memory-guided sequences of saccades in patients with lesions in SEF. In addition Simó et al. (2005) found higher activity for sensory-driven (RND) saccades. It is therefore believed that FEF is more involved in the preparation and triggering of purposeful saccades (Gaymard et al. 1999). Isoda and Tanji (2003) performed a comparative study looking at the neuronal responses in both SEF and FEF in monkeys to peripheral saccadic targets in a memorized order. They found SEF was more involved in planning, decoding, and updating sequences of eye movements and FEF more involved in determining the direction of the upcoming saccade. These findings support our results in demonstrating that FEF has a more prominent role in visually guided responses, whereas SEF is more involved in memory-guided responses for both saccades and pursuit.

Inferior Frontal Gyrus
We also found higher sustained activation in the IFG (ventral PFC) for saccades, as well as a time-dependent decrease combined with an overall reduction in sustained level in the predictive condition (Fig. 5C). This area has also been identified in recent studies revealing activation for both memory and visually driven responses, with a particular emphasis on spatial working memory (D’Esposito et al. 2000; Özyurt et al. 2006). Our findings support these previous studies but, in particular, suggest that the IFG is more involved in position-dependent tasks (SAC) than motion-dependent tasks (pursuit).

Frontopolar Regions
The frontopolar area (BA10) revealed sustained activation for saccades when contrasted with pursuit. This area has previously been associated with saccadic eye movements and is thought to play a role in subgoal monitoring during both working memory and episodic memory tasks (Braver and Bongiolatti 2002). Our results suggest that this area may be more involved in manipulating or monitoring position-dependent responses than motion-dependent responses and is more concerned with the spatial locations of targets.

The results presented in this study show time-dependent increases in activity in DLPFC for PRD eye movements in both pursuit and saccades. In addition, we find specialized pathways in the frontal lobe via DLPFC and/or IFG and FP that subserve either pursuit and/or saccades, respectively. Finally, we have found that a direct comparison between the PRD and RND conditions reveal a stronger role of SEF in memory-guided behavior and FEF in visually guided responses.

Cerebellum
The CBM represents the final output stage in our model (see Fig. 6). Interestingly, a linear increase in activation was observed in the right cerebellar hemisphere, possibly providing some evidence that the mechanism or region of reactive responses differs from that of PRD at this motor preparation stage. It may also suggest that the differences in timing between the PRD and RND conditions (Fig. 3) are associated with different areas of activation in the CBM. Previous studies have found the CBM to be essential in the timing and learning of motor skills and thus this linear increase could reflect the associated learning during the PRD condition (for reviews, see Ivry 1997; Robinson and Fuchs 2001; Bloedel 2004). This study provides new evidence that the signal in some areas linearly increase over time, possibly reflecting the buildup of the stored information; however, further event-related studies are needed to substantiate this claim.

Temporal Lobe
The temporal lobe does not feature in our model as its role in eye movements is not clearly understood, possibly due to a lack of investigation or inclusion. However, the role of the right MTG (BA21) in this study appears to be associated with the processing of velocity information (for pursuit) when compared with the saccadic eye-movement condition. Interestingly, we found increasing BOLD activity over a block of presentations in a more superior region of the temporal lobe (STG, BA22) during saccades and sustained BOLD signals in MTG for pursuit (see Fig. 5A,B, respectively). This suggests a dissociation of activity for saccades and pursuit in the temporal lobe for either
learning-related positional information (STG) or maintained velocity (MTG) information, respectively. This is the first fMRI study to show specific temporal responses of both pursuit and saccades and their associated velocity- and position-dependent attributes, respectively. The results presented here support recent findings that pursuit and saccades indeed share common brain regions for control; however this study provides novel evidence indicating that these regions are utilized to varying degrees depending on the task demands. For example, we found differing regions of activation in the frontal cortex, with position-dependent responses in the ventral PFC and left DLPFC and motion dependence in the right DLPFC. We also found a linear increase during pursuit in the SMG and linear increases for saccades in the superior temporal cortex, again revealing dissociation between areas related to spatiotemporal integration and spatial location information, respectively.

The results presented also show brain activity specific for either the visually driven (RND) or memory-driven (PRD) stimuli. Based on our original hypothesis, the SEP are important for the control and release of timing information for both pursuit and saccades in the PRD task, but in addition to this, we found the FEF were more important in the RND task for visually guided responses. The SPL was shown to be important for the maintenance of visual information over a block of PRD trials; whereas left V5, bilateral DLPFC, and the right CBM all revealed time-dependent linear increases in activation during PRD responses. The observed linear increase in activation reveals a more specific mechanism for these areas in motor learning.

Notes

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Address correspondence to Dr M.R. Burke, Faculty of Life Sciences, Moffat Building, The University of Manchester, PO Box 88, Sackville Street, Manchester M60 1QD, UK. Email: m.r.burke@manchester.ac.uk.

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