Neural correlates of spatial orienting in the human superior colliculus

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Anderson EJ, Rees G. Neural correlates of spatial orienting in the human superior colliculus. J Neurophysiol 106: 2273–2284, 2011. First published July 13, 2011; doi:10.1152/jn.00286.2011.—A natural visual scene contains more information than the visual system has the capacity to simultaneously process, requiring specific items to be selected for detailed analysis at the expense of others. Such selection and inhibition are fundamental in guiding search behavior, but the neural basis of these mechanisms remains unclear. Abruptly appearing visual items can automatically capture attention, but once attention has been directed away from the salient event, return to that same location is slowed. In non-human primates, signals associated with attentional capture (AC) and subsequent inhibition of return (IOR) have been recorded from the superior colliculus (SC)—a structure known to play a pivotal role in reflexive spatial orienting. Here, we sought to establish whether similar signals could be recorded from the human SC, as well as early retinotopic cortical visual areas, where signals associated with AC and IOR have yet to be investigated with respect to oculomotor responses. Using an optimized oculomotor paradigm together with high-field, high-spatial resolution functional magnetic resonance imaging and high-speed eye tracking, we demonstrate that BOLD signal changes recorded from the human SC correlate strongly with our saccadic measures of AC and IOR. A qualitatively similar pattern of responses was found for V1, but only the inhibitory response associated with IOR persisted through V2 and V3. Although the SC plays a role in mediating these automatic attentional biasing signals, the source of these signals is likely to lie in higher cortical areas.

function orienting; retinotectal pathway

THE VISUAL ENVIRONMENT contains more information than our visual system has the capacity to simultaneously process, so specific items within a scene are selected for detailed analysis at the expense of others (Awh et al. 2006; Fecteau and Munoz 2006). Such selection and inhibition are fundamental in guiding our exploratory search behavior, but the neural basis of these mechanisms remains a long-standing topic of debate.

Visual selection occurs through a combination of automatic, stimulus-driven processes and goal-driven influences (Theeuwes 2010). For example, an abruptly appearing visual object, such as a brief flash of light, automatically captures attention and draws our eyes toward it for more detailed scrutiny. Subsequently, once attention has been directed away from the location of a salient event, return to that same location is slowed (or inhibited) compared with orienting toward a new event elsewhere (Klein 2000). Both attentional capture (AC) and subsequent inhibition of return (IOR) represent the automatic consequences of a salient visual event on orienting of attention. In everyday life, these influences are thought to act as “foraging facilitators”—biasing attention toward novel items in a visual scene and away from recently inspected items (Klein 1988, Klein and MacInnes 1999).

Typically, a cue-target task is used to probe the effects of AC and IOR on behavioral and neural responses. A brief flash of light is presented peripherally (the cue), followed by a second visual stimulus (the target) presented at the same or opposite location as the cue (Posner et al. 1982). The speed with which an eye movement is made to the target location indicates the degree of AC or IOR induced by the salient cue. Manipulating the time between the presentation of the cue and the target modulates these automatic attentional effects: a short cue-target interval induces strong AC, whereas a longer cue-target interval favors IOR.

Signals associated with AC and IOR have recently been recorded from the superior colliculus (SC) of macaque monkeys (Bell et al. 2004; Dorris et al. 2002; Fecteau et al. 2004; Fecteau and Munoz 2005). The SC is part of the retinotectal pathway and plays a pivotal role in the network for reflexive spatial orienting, receiving a rich input from many cortical and subcortical areas implicated in this function (Lund 1972; Munoz et al. 2000; Wilson and Toyne 1970). Further evidence for collicular mediation of IOR comes from brain-damaged patients (Posner et al. 1985; Sapir et al. 1999) and interactions with oculomotor mechanisms thought to arise in the SC (Abrams and Dobkin 1994).

To date, few studies have attempted to investigate the functional role of the SC in humans. This is largely because of its small size and deep midbrain location, making it difficult to record signals from with conventional neuroimaging techniques (Wall et al. 2009). The prominent blood vessels of the upper brain stem induce pulsatile movement artifact, which can contaminate the recorded signal if not circumvented. Despite these difficulties, it has been possible to retinotopically map the human SC (DuBois and Cohen 2000; Katyal et al. 2010; Schneider and Kastner 2005), record visual responses to static and moving stimuli (Schneider and Kastner 2005; Sylvester et al. 2007), and demonstrate attentional modulations (Gitelman et al. 2002; Himmelbach et al. 2007; Katyal et al. 2010; Schneider and Kastner 2009), all with functional magnetic resonance imaging (fMRI). However, despite the critical role the SC plays in oculomotor control, very few studies have attempted to record oculomotor signals from the human SC (Anderson et al. 2008; Krebs et al. 2010a, 2010b; Petit and Beauchamp 2003). This may in part be due to the further technical challenges faced when attempting to record eye movement responses within a high magnetic field.

Signals associated with spatial orienting also occur within the geniculostriate pathway, but there has been little inves-
tigation of whether automatic attentional biases within the oculomotor system are also represented in this pathway, such as early retinotopic visual cortex. We therefore took advantage of the spatial coverage of fMRI in order to also record and characterize signals from V1 to V3. Responses from early cortical visual areas have been shown to correlate with both AC and IOR for a manual version of the cue-target task in humans (Lepsien and Pollmann 2002; Muller and Kleinschmidt 2007) but have yet to be investigated with respect to oculomotor responses.

Here, we set out to investigate whether signals associated with AC and IOR could be recorded from the human SC, as well as V1–V3, using fMRI. To overcome the known difficulties in recording reliable signals from the human SC, we used high-spatial resolution, high-field fMRI, using a sequence optimized for imaging subcortical structures, together with high-speed infrared video-based eye tracking (sampling at 240 Hz) for accurately recording saccadic eye movements within the MRI scanner. To prevent cardiac-induced physiological noise influencing the recorded BOLD signals, we adapted established algorithms to correct for cardiac-induced brain stem motion (Glover et al. 2000; Hutton et al. 2010). We then determined whether signals recorded from the SC, and early cortical visual areas, correlated with our behavioral measure of AC and IOR—saccade latencies.

MATERIALS AND METHODS

To maximize the strength of the recorded BOLD signal from the human SC we employed a block design fMRI paradigm (Friston et al. 1999). For this purpose, we weighted the proportion of trials in a block to favor either AC or IOR. In an initial behavioral experiment outside the scanner, we used an adapted version of the cue-target task and manipulated the cue-target timing and cue-target location to maximally emphasize these effects.

Participants

Nine right-handed healthy participants, aged 25–32 yr, with normal or corrected to normal visual acuity, gave written informed consent to take part in both the behavioral and fMRI experiments. All procedures were approved by the local ethics committee.

Behavioral Experiment

The purpose of the initial behavioral experiment, conducted outside the scanner, was to select stimulus parameters that maximized the effects of AC and IOR for use in the fMRI experiment.

Stimuli. Stimuli were presented on a uniform dark gray background with a central light gray fixation cross (Fig. 1A). Each trial began with participants maintaining central fixation for 0 to 500 ms (onset randomly jittered in 50-ms intervals). Two light gray ring placemarkers were then presented simultaneously 8.5° either side of fixation. After 500 ms, one of the rings brightened for 75 ms to cue either the cued (“SAME”) or the uncued (“OPPOSITE”) location. Participants made a rapid eye movement to fixate the target and returned to central fixation. A variable delay of 425–925 ms then followed (depending on cue-target ISI) to ensure that each trial lasted 2,000 ms (excluding initial jitter). The proportion of “SAME” trials varied across conditions: condition 1 50% SAME trials, condition 2 75% SAME trials, condition 3 25% SAME trials. For each condition, participants performed blocks of 64 trials, with the ISI fixed throughout the block. For the functional magnetic resonance imaging (fMRI) experiment trial timing differed slightly: initial fixation 500 ms, placemarkers 500 ms, cue 75 ms, ISI 0 or 400 ms, target 500 ms, final fixation 525 ms or 125 ms (for ISI 0 ms or 400 ms, respectively). Total trial time = 2,100 ms. Saccadic latencies were calculated for all cue-target combinations and are presented graphically as a function of ISI in Figs. 2 and 4. B and C. Example eye position traces for 2 representative trials, showing a rightward (upward) and a leftward (downward) saccade, recorded during the behavioral experiment outside the scanner (B, black trace) and during the fMRI experiment inside the scanner (C, black trace). A saccade velocity of >30°/s was used to detect the onset of a saccade (vertical black bar).

Fig. 1. Cue-target oculomotor task. A: participants maintained central fixation for 50–500 ms (jittered onset), then 2 peripheral ring placemarkers appeared either side of fixation for 500 ms, 1 of the rings briefly brightened for 75 ms, followed by an interstimulus interval (ISI) of 0, 50, 200, 300, 400, 500 ms before a target appeared (solid white circle) at either the cued (“SAME”) or the uncued (“OPPOSITE”) location. Participants made a rapid eye movement to fixate the target and returned to central fixation. A variable delay of 425–925 ms then followed (depending on cue-target ISI) to ensure that each trial lasted 2,000 ms (excluding initial jitter). The proportion of “SAME” trials varied across conditions: condition 1 50% SAME trials, condition 2 75% SAME trials, condition 3 25% SAME trials. For each condition, participants performed blocks of 64 trials, with the ISI fixed throughout the block. For the functional magnetic resonance imaging (fMRI) experiment trial timing differed slightly: initial fixation 500 ms, placemarkers 500 ms, cue 75 ms, ISI 0 ms or 400 ms, target 500 ms, final fixation 525 ms or 125 ms (for ISI 0 ms or 400 ms, respectively). Total trial time = 2,100 ms. Saccadic latencies were calculated for all cue-target combinations and are presented graphically as a function of ISI in Figs. 2 and 4. B and C. Example eye position traces for 2 representative trials, showing a rightward (upward) and a leftward (downward) saccade, recorded during the behavioral experiment outside the scanner (B, black trace) and during the fMRI experiment inside the scanner (C, black trace). A saccade velocity of >30°/s was used to detect the onset of a saccade (vertical black bar).
right or left location. After the cue had been extinguished, an interval [interstimulus interval (ISI)] of 0, 50, 200, 300, 400 or 500 ms followed before a target appeared (solid white circle) either at the cued location (cue-target location “SAME”) or at the opposite location (cue-target location “OPPOSITE”). Participants were instructed to make a rapid eye movement to fixate the target and then return to central fixation. A variable delay of 425–925 ms followed (depending on ISI) to ensure that each trial lasted 2,000 ms (excluding initial jitter).

Experimental conditions. In three experimental conditions we varied the proportion of trials on which the target appeared at the cued location. The proportion of “SAME” trials was 50% (condition 1), 75% (condition 2), or 25% (condition 3). For each of these conditions, participants performed blocks of 64 trials, with the ISI fixed throughout the block. Within a block, the right and left locations were cued with equal probability (presented in a random order), and hence the target also appeared at the right or left location equally often. Each participant performed 18 blocks in total (3 conditions × 6 ISIs). Participants were not informed that the proportion of trials differed between blocks, and block presentation order was randomized for each participant.

Eye movement recording. Eye movements were recorded with a high-speed video eye tracker (Cambridge Research Systems, [www.crsltd.com](http://www.crsltd.com)) sampling at 250 Hz. To determine the speed at which an eye movement was initiated (saccade latency), data were analyzed off-line with custom programs written in MATLAB ([http://www.mathworks.com](http://www.mathworks.com)). A saccade velocity criterion of >30°/s was used to determine the onset of a saccade, and eye position traces were inspected for all trials to ensure that the onset of a saccade had been correctly identified (Fig. 1, B and C). Trials were discarded if steady fixation was not maintained prior to presentation of the cue, and trials counted as errors if a saccade was made to the wrong location, e.g., to the opposite placemarker.

fMRI Experiment

Stimuli and experimental conditions. In separate experimental blocks we weighted the proportion of trials to emphasize either signals at the cued location (greater proportion of SAME trials) or signals at the uncued location (greater proportion of OPPOSITE trials). As in the behavioral experiment, within each block the right and left locations were cued with equal probability (presented in a random order), and hence the target also appeared at the right and left locations equally often. This allowed us to compare signal biases at either the cued or the uncued location for different ISIs, providing us with a measure of “same-location advantage” (AC) for a short ISI and “same-location disadvantage” (IOR) for a long ISI. We did not present blocks with 100% SAME or 100% OPPOSITE trials, as this would have made the task completely predictable, and thereby abolish any reflexive component to the orienting signals. Similarly, it was not desirable to present equal proportions of SAME and OPPOSITE trials within a single block, because although this would have maintained maximum unpredictability, it would also have diluted the effects of interest. Note that although the proportion of trials within a block was weighted to have 75% SAME or OPPOSITE trials, overall across any single scan run the numbers of same and opposite trials were equal.

Our initial behavioral experiment (see Results) demonstrated that AC was maximal at an ISI of 0 ms and that IOR was maximal at an ISI of 400 ms (Fig. 2). These two ISIs were therefore chosen for use in a block design fMRI experiment, making a total of four experimental block conditions: proportion 1 (75% SAME trials) at ISI 0 ms

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Fig. 2. Saccadic latencies from behavioral experiment outside scanner. A: group mean saccadic latencies were calculated for targets appearing at the same location as the cue (SAME, ◦) or at the opposite location to the cue (OPPOSITE, □). For each of the 3 conditions saccade latencies are plotted as a function of cue-target ISI. Saccadic latencies were shorter for targets appearing at the cued location compared with the opposite location if the ISI was short (<200 ms). This “same-location advantage” quantifies the reflexive attentional capture (AC) by the salient cue. At longer ISIs (>200 ms) saccadic latencies were shorter for targets appearing at the opposite location to the cue compared with the same location as the cue. This “same-location disadvantage” quantifies inhibition of return (IOR). B: effects of AC and IOR are best revealed by calculating the relative difference in saccadic latency for targets appearing at the opposite location compared with the same location as the cue. Positive values signify a “same-location advantage” (AC), and negative values signify a “same-location disadvantage” (IOR). Increasing the proportion of SAME location trials enhanced the “same-location advantage” of AC, whereas increasing the proportion of OPPOSITE trials enhanced the “same-location disadvantage” associated with IOR. Error bars indicate SE.
Spatial orienting in human superior colliculus

A baseline) lasting 18.4 s. Each participant performed five scan runs of

In the main experiment, eye movements were recorded with an MRI-compatible ASL504 LRO infrared video-based eye tracker (http://www.asleyetracking.com) sampling at 240 Hz, with a spatial resolution of 0.5°. Saccadic latencies were analyzed off-line with adapted versions of the same dedicated routines described for the behavioral experiment, using the same criteria for saccade detection and errors.

Eye tracking. During the main experiment, eye movements were recorded with an MRI-compatible ASL504 LRO infrared video-based eye tracker (http://www.asleyetracking.com) sampling at 240 Hz, with a spatial resolution of 0.5°. Saccadic latencies were analyzed off-line with adapted versions of the same dedicated routines described for the behavioral experiment, using the same criteria for saccade detection and errors.

Scanning details. All participants performed five experimental scan runs, a functional localizer for the SC, and meridional mapping to localize the borders between V1, V2, and V3. All images were acquired with a Siemens 3T Allegra MRI scanner with standard head coil.

Main experimental scans. In each scan run the four experimental block conditions (A–D) were presented twice. Block condition order was randomized for each scan run and each participant. Each experimental block consisted of 16 trials and lasted 33.6 s. Trial timing differed slightly from the behavioral experiment to ensure that all trials had the same total length (2,100 ms): initial fixation 500 ms, placemarkers 500 ms, cue 75 ms, ISI 0 ms or 400 ms, target 500 ms, final fixation 525 ms or 125 ms (depending on ISI 0 ms or 400 ms). Experimental blocks were interleaved with blocks of fixation (used as a baseline) lasting 18.4 s. Each participant performed five scan runs of the experimental task.

For the main fMRI experiment a high-resolution EPI sequence, with 1.5 × 1.5 × 1.5-mm resolution (128 × 128 matrix, field of view 192 mm, TE 30 ms, acquisition time per slice 102 ms, TR 3.468), was used to acquire 34 near-axial interleaved slices positioned to optimize coverage of the upper brain stem and the occipital lobe. A total of 123 volumes were collected per scan run (lasting 7 min 7 s); 3 initial dummy volumes were discarded before the data were analyzed. A high-resolution T1-weighted structural scan was also acquired for every participant.

Physiological monitoring. The SCs reside close to the prominent blood vessels of the upper brain stem and hence are susceptible to cardiac-induced brain stem motion, resulting in signal modulations that increase noise and degrade the signal-to-noise ratio (SNR) of activation signals of interest. Therefore, a physiological noise model was constructed to account for artifacts related to cardiac and respiration phase, as well as changes in respiratory volume, with dedicated MATLAB code (Hutton et al. 2010).

Throughout the main fMRI experiment we recorded participants’ pulse and breathing, together with scanner slice synchronization pulses, using the Spike2 data acquisition system (Cambridge Electronic Design, http://www.ced.co.uk). The cardiac pulse signal was measured with an MRI-compatible pulse oximeter (model 8600 F0, Nonin Medical, Plymouth, MN) attached to the participant’s finger. Thoracic movement was monitored with a pneumatic belt positioned around the abdomen close to the diaphragm.

The models for cardiac and respiratory phase and their aliased harmonics used here were based on RETROICOR (Glover et al. 2000) and a similar, earlier method (Josephs et al. 1997). However, we acknowledge that alternative methods have also been proposed to optimize BOLD signal recordings from the upper brain stem region (Harvey et al. 2008; Pattinson et al. 2009; Wall et al. 2009). Basis sets of sine and cosine Fourier series components, extending to the 5th harmonic (i.e., 5 terms) for the cardiac phase and the 3rd harmonic for the respiratory phase, were used to model the physiological fluctuations. The model for changes in respiratory volume was based on Birn et al. (2006). This resulted in a total of 17 regressors that were estimated at a reference slice—the slice that most closely bisected the SC midline—in each image volume to give a set of values for each time point. The resulting regressors were included as confounds in the first-level analysis for each participant. This approach proved to be effective in accounting for (and thereby eliminating) variance related to the cardiac cycle, particularly in the region of the upper brain stem (Fig. 3, A–C).

For two participants physiological noise data failed to record on one scan run each, so these scan runs were omitted from the analysis.

Functionally localizing the superior colliculus. In the same scanning session as the main experiment, we functionally localized the SC in all participants, using the same high-resolution EPI sequence and identical slice positioning. The SC receives dominant input from the nasal retina of the contralateral eye, and hence the left SC is preferentially activated by stimuli in the right hemifield and the right SC by stimuli in the left hemifield. In a block design paradigm, participants fixated centrally while passively viewing black and white checkerboard stimuli (reversing at 8 Hz) that stimulated the right or left hemifield, extending from 0.5° to 13.5° eccentricity, interleaved with a fixation baseline. Two runs of 123 volumes were acquired per subject: 3 dummy volumes, 6 volumes per stimulus block (20.8 s), 6 volumes per rest block (20.8 s), and 5 repetitions of each hemifield stimulation.

Functionally localizing primary visual areas. To retinotopically map areas V1–V3, each participant underwent an additional scan session. With a standard EPI sequence (in-plane resolution 3 × 3, slice thickness 2 mm, 1-mm gap, 64 × 64 matrix, TR 1.56 s), 24 interleaved slices were acquired, oriented parallel to the calcarine sulcus, and positioned to optimize coverage of the occipital cortex. Participants fixated centrally while passively viewing blocks of reversing black and white checkerboards (8 Hz) that stimulated either the vertical or the horizontal meridian, interleaved with a fixation baseline. Two runs of 205 volumes were acquired per participant: 5 dummy volumes, 10 volumes per stimulus block, 10 volumes per rest block, and 5 repetitions of stimulating each meridian.

fMRI analysis. Imaging data for the main experiment and the SC localizer were analyzed using SPM5 (http://www.fil.ion.ucl.ac.uk). The first three images from each scan run were discarded and the remaining images realigned and coregistered to the individual’s T1 structural image. All high-resolution data were smoothed with a 3-mm isotropic Gaussian smoothing kernel.

For the main experiment, activated voxels for each experimental condition were identified with a statistical model containing a linear combination of regressors representing the time series of each of the four experimental conditions and the fixation baseline. Each regressor was convolved with a synthetic hemodynamic response function. Additional regressors representing the physiological noise data were added to this model as 17 separate regressors of no interest. Correction for the effects of serial autocorrelations was applied with the AR(1) method (as recommended for single-subject analyses by Smith et al. 2007). The general linear model, as employed by SPM5, was used to generate parameter estimates for each regressor at every voxel. Data were scaled to the global mean of the time series and high-pass filtered to remove low-frequency signal drifts.

To identify the right and left SCs, voxels in the upper brain stem that showed greater activity to contralateral hemifield stimulation compared with fixation baseline were identified with a threshold for significance of \( P = 0.05 \) uncorrected. A 4-mm-radius sphere centered over the participant’s SC (using anatomic markers for guidance) was used to restrict activated voxels to within the SC (Fig. 3D). Both
Cluster and spherical region of interest (ROI) mask volume images were then created for the right and left SC on a per-participant basis. Parameter estimates were averaged across all voxels within the masks, for each condition of interest. The patterns of responses for the right and left SC were indistinguishable, so data have been averaged bilaterally for presentation.

V1, V2, and V3 were identified according to standard procedures (Sereno et al. 1995). The fMRI data were preprocessed and modeled with SPM5: the first five images from each scan run were discarded and the remaining images realigned and coregistered to the individual’s T1 structural image. Time series representing stimulation of the vertical meridian, horizontal meridian, and rest were modeled. Mr-Gray software (http://white.stanford.edu/~brian/mri) was used to segment the white and gray matter for cortical flattening of the occipital pole. The fMRI activation map was superimposed on the flatmap of visual cortex and the boundaries between V1, V2, and V3.
defined by the transitions between voxels representing the horizontal and vertical meridians. Mask volume images were created for V1, V2, and V3 for each participant, and the fMRI signal associated with each of our experimental conditions was extracted. A threshold of \( P = 0.001 \) uncorrected was used to extract voxels activated by our conditions of interest; activity was then averaged across these voxels for each condition.

RESULTS

Behavioral Experiment

Using a cue-target task, as illustrated in Fig. 1, we measured the latency of saccades made toward a target that followed a salient cue, at either the same or the opposite location, for a range of ISIs. In three separate experimental conditions we tested the effect of changing the proportion of trials on which the target appeared at the same location as the cue: 50% SAME trials (condition 1), 75% SAME trials (condition 2), and 25% SAME trials (condition 3).

Saccadic latencies. Group mean saccadic latencies were calculated across participants for each of the three conditions tested and plotted as a function of cue-target ISI (see Fig. 2). For all conditions, the influence of the cue significantly changed depending on the ISI, as evidenced by a significant interaction between cue-target location (same, opposite) and ISI (0, 50, 200, 300, 400, 500 ms)—condition 1: \( F(5,40) = 14.591, P < 0.001; \) condition 2: \( F(5,40) = 47.315, P < 0.001; \) condition 3: \( F(5,40) = 11.683, P < 0.001.\)

For condition 1, in which the target appeared at the cued location on 50% of trials, saccadic responses were faster for targets appearing at the cued location compared with the opposite location if the ISI was short (<200 ms). This “same-location advantage” quantifies the capture of attention by the salient cue (Fecteau and Munoz 2006; Jonides and Irwin 1981). At longer cue-target ISIs (>200 ms) saccadic responses were slower for targets appearing at the cued location compared with the opposite location. This “same-location disadvantage” quantifies IOR. The effects of AC and IOR are best revealed by calculating the relative difference in saccadic latency for targets appearing at the opposite location compared with the same location as the cue. Plotting this difference (opposite-same) as a function of cue-target ISI directly shows these spatial orienting biases, with positive values signifying a “same-location advantage” (AC) and negative values signifying a “same-location disadvantage” (IOR) (Fig. 2).

In condition 2, the target appeared at the same location as the cue on a greater proportion of trials (75% SAME trials), which enhanced the effects of AC and reduced the effects of IOR compared with condition 1 (Fig. 2). This is best illustrated at an ISI of 0 ms, where the “same-location advantage” increased from 44 ms (condition 1) to 76 ms (condition 2); however, this increase in AC only trended toward significance \([t(8) = -2.201, P = 0.059]\). The corresponding reduction in IOR, best illustrated at an ISI of 400 ms, where the “same-location disadvantage” decreased from 19 ms (condition 1) to 3 ms (condition 2), also did not reach significance \([t(8) = -1.897, P = 0.094]\), and there was no significant interaction between condition (1, 2), cue-target location (same, opposite), and ISI (0, 50, 200, 300, 400, 500 ms) \(F(5,40) = 0.376, P = 0.862\).

In condition 3, the target appeared at the opposite location to the cue on a greater proportion of trials (75% OPPOSITE trials), and in this case the effects of IOR were enhanced but there was minimal effect on AC compared with condition 1 (Fig. 2). Again, this is best illustrated at an ISI of 400 and 0 ms, respectively, where the “same-location disadvantage” of 19 ms (condition 1) increased to 42 ms (condition 3) \([t(8) = 3.511, P = 0.008]\) and the “same-location advantage” decreased from 44 ms (condition 1) to 35 ms (condition 3), but this change was not significant \([t(8) = 0.669, P = 0.522]\). Once again, the interaction between condition (1, 3), cue-target location, and ISI did not reach significance \(F(5,40) = 0.441, P = 0.817\).

Thus, although changing the proportion of SAME/OPPOSITE trials exaggerated the effects of AC and IOR, the three-way interaction between condition (1, 2, 3), cue-target location, and ISI was not significant \(F(10,80) = 0.582, P = 0.824\).

Saccadic errors. Saccades made to the wrong location were considered errors, even if a corrective saccade was subsequently made to the correct target location. Errors were rare for saccades made toward a target appearing at the cued location, for all conditions and all ISIs (Table 1). More direction errors were made when the target appeared at the location opposite the cue [significant main effect of cue-target location \(F(1,8) = 16.442, P = 0.004\)] and were more frequent at shorter ISIs [significant main effect of ISI \(F(5,40) = 3.258, P = 0.015\), which resulted in a significant interaction between cue-target location and ISI \(F(5,40) = 3.548, P = 0.010\), but this did not differ across conditions (no main effect of condition \(F(2,16) = 3.150, P = 0.070\) and no interaction between condition, cue-target location, and ISI \(F(10,80) = 1.425, P = 0.185\)].

fMRI Experiment

The behavioral experiment showed that increasing the proportion of trials on which the target appears at the same location as the cue enhances the effects of AC at an ISI of 0 ms, whereas increasing the proportion of trials on which the target appeared at the opposite location to the cue enhances the effects of IOR at an ISI of 400 ms (Fig. 2). We used these optimized parameters in a block design fMRI experiment and simultaneously recorded eye movements to determine whether BOLD signals recorded from the human SC and early visual areas modulated with these orienting biases.

Saccadic latencies. Similar to the behavioral experiment, group mean saccadic latencies were calculated for all trial types and plotted as a function of cue-target ISI (Fig. 4). The pattern of responses recorded in the behavioral experiment was replicated for saccades made during the fMRI experiment. That is, the influence of the cue-target location significantly changed depending on the cue-target ISI, for both proportions 1 and 2, as evidenced by a significant interaction between cue-target location (same, opposite) and ISI (0, 400 ms)—propotion 1: \(F(1,8) = 13.029, P = 0.007; \) proportion 2: \(F(1,8) = 12.351, P = 0.008\).

Analysis of variance across the two conditions confirmed the expected main effect of cue-target location \(F(1,8) = 13.368, P = 0.006\) as well as the interaction between cue-target location and ISI \(F(1,8) = 15.053, P = 0.005\), but there was no main effect of trial proportion \((1, 2) \ F(1,8) = 0.533, P = 0.824\) and no three-way interaction between proportion \((1, 2),\)
Saccadic errors. Similar to the behavioral experiment, direction errors were rare for saccades made toward a target appearing at the cued location, for both conditions and both ISIs (Table 1). More direction errors were made when the target appeared at the location opposite the cue [significant main effect of cue-target location $F(1,8) = 10.349$, $P = 0.012$]. However, there were no other significant main effects and no interactions.

**fMRI Data**

**BOLD signal responses from the superior colliculus.** We first functionally defined the SC ROIs in all nine participants and then measured BOLD signal responses evoked by each of our four experimental conditions (A–D), compared with fixation baseline. Consistent with our predictions, BOLD signals recorded from the SC showed a strong correlation with our behavioral measure (saccadic latency) of AC and IOR (Fig. 5). This was evident as significantly greater activity associated with condition A than with condition B [$t(8) = 2.919$, $P = 0.019$], indicating a significant “same-location advantage” for a short ISI. Similarly, there was a significant decrease in activity associated with condition C compared with condition D [$t(8) = -2.817$, $P = 0.023$], indicating a significant “same-location disadvantage” for a long ISI. Analysis of variance confirmed a significant interaction between proportion ($1$, $2$) and ISI (0, 400 ms) [$F(1,8) = 11.071$, $P = 0.010$]. Furthermore, by contrasting condition A with condition C we could more directly compare facilitatory and inhibitory responses at the cued location, as

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**Table 1. % Saccade direction errors**

<table>
<thead>
<tr>
<th>Cue-Target ISI</th>
<th>0</th>
<th>50 ms</th>
<th>200 ms</th>
<th>300 ms</th>
<th>400 ms</th>
<th>500 ms</th>
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<tr>
<td>Behavioral experiment</td>
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<tr>
<td>Condition 1 (50% same) Same</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.6</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Opposite</td>
<td>14.1</td>
<td>11.5</td>
<td>7.8</td>
<td>10.9</td>
<td>2.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Condition 2 (75% same) Same</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Opposite</td>
<td>19.8</td>
<td>9.4</td>
<td>19.8</td>
<td>10.4</td>
<td>4.2</td>
<td>7.3</td>
</tr>
<tr>
<td>Condition 3 (25% same) Same</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3.1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Opposite</td>
<td>9.7</td>
<td>11.1</td>
<td>5.2</td>
<td>3.1</td>
<td>4.5</td>
<td>1.7</td>
</tr>
</tbody>
</table>

| fMRI experiment | | | | | | |
| Proportion 1 (75% same) Same | 0.2 | 0.0 |
| Opposite | 12.8 | 7.7 |
| Proportion 2 (25% same) Same | 0 | 0.2 |
| Opposite | 10.1 | 4.9 |

Values are given as percentages. Saccades made to the wrong location were considered errors. Errors were rare for saccades made toward a target appearing at the cued location, for all conditions and all interstimulus intervals (ISIs). For both the behavioral and functional magnetic resonance imaging (fMRI) experiments, more direction errors were made when the target appeared in the opposite location to the cue. In the behavioral experiment, more errors were made at shorter ISIs, but this did not differ across conditions. For the fMRI experiment, there was no significant effect of ISI or condition.
interaction between proportion (1, 2) and ISI (0, 400 ms) remained significant for all—V1: $F(1,8) = 9.479, P = 0.015$; V2: $F(1,8) = 7.551, P = 0.025$; V3: $F(1,8) = 10.097, P = 0.013$.

For V1 the pattern of BOLD signal responses evoked by each of our four experimental conditions (compared to baseline) was qualitatively similar to that found in the SC. There was a significant increase in activity associated with condition A compared with condition B [t(8) = 2.472, $P = 0.039$] and a relative decrease in activity associated with condition C compared with condition D, but this inhibitory effect only trended toward significance [t(8) = −2.026, $P = 0.077$], as did the direct comparison of condition A and condition C [t(8) = 2.112, $P = 0.068$]. For V2 and V3, the inhibitory effects of IOR were significant [condition C compared with condition D; V2: $t(8) = −3.232, P = 0.012$, V3: $t(8) = −2.700, P = 0.027$]; however, unlike the SC and V1, there was no evidence of increased activity associated with AC for either V2 or V3 [condition A compared with condition B; V2: $t(8) = 0.289, P = 0.780$, V3: $t(8) = 1.017, P = 0.339$], and the direct comparison of condition A and condition C did not reach significance [V2: $t(8) = 1.088, P = 0.308$, V3: $t(8) = 0.045, P = 0.965$].

We note that our functional data were modeled using the standard synthetic hemodynamic response function (HRF), as employed by SPM, which peaks at ~6 s. Although this HRF is thought optimal for the detection of visual responses in the retino-striatal pathway, an HRF that peaks earlier may be more sensitive at detecting visual responses in the SC (Wall et al. 2009). Despite this, the SC showed the closest correlation with our behavioral measure of AC and IOR and replicated the pattern of activity recorded from the SC of macaque monkey (Fecteau and Munoz 2005).

**DISCUSSION**

Using high-field, high-spatial resolution fMRI in combination with high-speed infrared eye tracking, we demonstrate that BOLD signals recorded from the human SC correlate with our behavioral measure of AC and IOR. Consistent with our predictions, a target presented at the same location as a salient cue, with minimal intervening time delay (<200 ms), elicited AC and an increase in BOLD signal, whereas a target presented at the same location as a salient cue, but with a greater intervening time delay (>200 ms), elicited IOR and a decrease in BOLD signal.

Our findings in humans are consistent with the pattern of responses recorded from visuomotor neurons in the intermediate layers of the macaque SC, where there is a clear relationship between target-related activity and saccadic reaction times (Bell et al. 2004; Fecteau et al. 2004; Fecteau and Munoz 2005). In these studies, a strong target-related response was associated with the initial capture of attention and a reduced target-related response associated with IOR at the cued location. In the case of IOR, in addition to the same-location disadvantage, there was a simultaneous opposite-location advantage, as evidenced by enhanced target responses at the opposite location to the cue. This pattern of response was not observed for visual neurons in the superficial layers of the SC, where decreased target-related activity was associated with IOR at the cued location but there was no evidence for...
enhanced responses associated with AC and no opposite side advantage associated with IOR. In light of the above findings, our fMRI results for the SC most likely reflect a dominant population response from visuomotor neurons in the intermediate layers of the SC.

We note that by weighting our experimental blocks in favor of responses at the cued location (75% SAME trials) or uncued location (75% OPPOSITE trials), we introduced an element of predictability to the task. In monkeys, explicitly informing the observer (by way of a stimulus color change) that the cue will predict the location of the upcoming target 75% of the time enhances the effects of AC (Fecteau et al. 2004). Although we did not explicitly inform our participants that the proportion of trial types differed between blocks, we did observe a small enhancement in both AC and IOR, and therefore it is possible that this information subconsciously biased their behavior. However, the effects we observed here are much weaker than those found previously by Fecteau and colleagues, who acknowledge that “this influence of relevance is subtle when compared with the large changes in neural activity that originate from the salient event alone (nonpredictive cue)” (Fecteau et al. 2004, p. 1735). So although our task may have introduced a top-down component, evidence suggests that the automatic component has a dominant influence on behavior, and on the correlated neural response. Hence, for simplicity, we shall continue to use the terminology AC to indicate a “same-location advantage” and IOR to indicate a “same-location disadvantage.”

Opinion remains mixed on where the biases in orienting signals originate in the visual system, and whether they act at the perceptual, motor, or attentional stages of processing. There are several lines of evidence for and against each possibility. Initial studies provided evidence against a purely sensory origin to the inhibitory effect by demonstrating that it is coded in spatiotopic rather than retinotopic coordinates (Posner et al. 1985), and temporal order judgments also showed no deficit in perception of the target at the cued location (Gibson and Egeth 1994; Maylor and Hockey 1985).

Fig. 6. BOLD responses from V1–V3. BOLD signal responses evoked by each of our 4 experimental conditions, compared with fixation baseline, for V1–V3, thresholded at $P = 0.001$ uncorrected, are shown. BOLD signal responses in V1 showed the pattern of activity most similar to that in the SC, although the interaction between condition and ISI remained significant for all areas. The increase in activity associated with AC was only evident in V1, whereas the decrease in activity associated with IOR persisted for V1–V3. Error bars indicate SE.
However, there is a temporo-nasal asymmetry for IOR (Muckhuyse and Theeuwes 2010; Rafał et al. 1989), consistent with the asymmetry in sensory input from the retina to the SC (Sylvestre et al. 2007), and IOR is seen in newborn infants, in whom the collicular pathway is far more developed than the cortical pathways (Harman et al. 1994). These latter findings have been interpreted as evidence in favor of a sensory mechanism within the retinotectal pathway generating IOR. Furthermore, as previously discussed, in macaque the initial sensory response to the target correlates with changes in behavior, and reductions in target-related response associated with IOR are observed in the superficial layers of the SC (as well as the intermediate layers), which is open-looped and therefore cannot receive feedback from upstream areas (Clower et al. 2001).

However, several lines of evidence also support the existence of an inhibitory feedback signal, either acting directly on SC neurons to suppress the incoming target-related response, or acting indirectly through reduced input (Dorris et al. 2002), or a combination of both (Awh et al. 2006). It should be noted at this point that, although our results reflect the consequences of AC and IOR on SC activity, we cannot make any conclusions about the origin of these effects. Any brain area acting as the source of the inhibitory signal would be expected to show the opposite pattern of results to that found within the SC. That is, for condition C, where we observed reduced activity in the SC (reflecting the inhibited response associated with IOR at the cued location), we would instead expect to see increased activity. This was not the pattern of activity we observed here in V1–V3 (Fig. 6), where a significant decrease in BOLD activity associated with inhibition persisted. A similar pattern of results for V1–V3 is also seen for IOR induced with a nonsaccadic version of the cue-target task (Muller and Kleinschmidt 2007). Thus, although early cortical visual areas appear to play a role in the expression of IOR, primary visual cortex, at least, does not appear to be a crucial component, as patients with V1 lesions still demonstrate IOR in their blind hemifield (Danziger et al. 1997).

One popular theory proposes that the inhibitory aftereffect is generated, at least in part, within the oculomotor system (Godijn and Theeuwes 2002; Rafał et al. 1989), the basis of this theory being that IOR does not occur when central fixation is maintained and attention is endogenously directed to a peripheral location by way of a central arrow cue. Under these conditions an attentional shift occurs independent of an eye movement, and this is thought to explain the lack of induced IOR. Neurons in the intermediate layers of the SC receive feedback from oculomotor areas (Dorris et al. 2002; Fries 1984; Lui et al. 1995; Lynch et al. 1985; Pare and Wurtz 1997) that show increased activity for inhibition (IOR), compared with facilitation (AC) (Lepsien and Pollmann 2002; Mayer et al. 2004; Muller and Kleinschmidt 2007). In particular, the FEF appears to play a role in biasing attention and eye movements away from previously attended locations and facilitating detection at new locations (Bichot and Schall 2002; Lepsien and Pollmann 2002; Ro and Rafał 1999), while the posterior parietal cortex, known to play an important role in exogenous orienting, has been implicated as the site for converting the inhibitory tag, generated in the midbrain, into spatiotopic coordinates (Sapir et al. 2004). Interestingly, lesions to the parietal cortex have been found to disrupt this environmentally mapped IOR, but retinotopic IOR remains intact (Sapir et al. 2004). Thus although cortical areas may be involved in modulating the expression of IOR, most likely via the pulvinar (Danziger et al. 2004), they may not be crucial for its generation.

Indeed, there is now growing evidence to suggest that IOR cannot be accounted for by any single mechanism, and in addition to an oculomotor component there is also considerable support for an attentional component (Chica et al. 2010; Kingstone and Pratt 1999; Lupianez et al. 1997, 2007). Furthermore, IOR exists for tasks that require a manual response instead of an oculomotor response, suggesting that the attentional and oculomotor components can be dissociated and potentially recruit separate neural mechanisms (Briand et al. 2000; Sumner et al. 2004). Using S-cone stimuli, which are invisible to the SC, Sumner and colleagues (2004) have shown that saccadic IOR critically relies on signals carried in the retinotectal pathway, whereas manual IOR does not. Thus it is possible that the pattern of responses recorded from the SC for our oculomotor version of the cue-target task would not be replicated for a manual version of the task (but see Muller and Kleinschmidt 2007).

The enhanced BOLD response associated with AC (observed for targets appearing at the cued location in condition A) was significant in SC but diminished in magnitude through early cortical visual areas V1–V3. A similar pattern of activity was found by Muller and Kleinschmidt (2007), who also noted that the magnitude of the facilitatory effect decreased from V1/V2 to V3/V4. Hence the attentional effects observed in the SC do not appear to have been inherited from early cortical visual areas. Greater attentional effects have been observed in V1–V3 in tasks requiring target discrimination at recently cued locations (Liu et al. 2005), and it is possible that task difficulty and response requirements modulate the expression of this attentional effect.

In this study we employed a block design fMRI paradigm to maximize the strength of the recorded BOLD signal, as block designs have repeatedly been shown to have superior power over event-related designs of equivalent length (Friston et al. 1999). However, now that robust signals associated with spatial orienting have been confirmed in the SC, event-related designs could be used in future to further characterize the role of the SC in mediating these facilitatory and inhibitory effects.

Conclusions

By simultaneously recording saccadic latencies and brain activity with high-speed infrared eye tracking and advanced fMRI imaging techniques, we showed a direct relationship between BOLD signal changes in the human SC and a saccadic latency-based measure of spatial orienting. A similar pattern of activity was also evident in V1, but to a lesser extent. The inhibitory effects associated with IOR persisted through V2 and V3. Hence, while it is clear that the SC plays an important role in mediating AC and IOR, the source of these biasing signals does not appear to originate in early cortical visual areas. Converging evidence suggests that both attentional and motoric factors contribute to IOR, and that these mechanisms rely on an interaction between the SC and higher cortical areas associated with exogenous spatial orienting.
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DISCLOSURES

There are no known potential conflicts of interest, financial or otherwise.

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