Articles in PresS. J Neurophysiol (June 3, 2015). doi:10.1152/jn.00825.2014

Title

Activity in the human superior colliculus relating to endogenous saccade preparation and execution.

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Abstract

In recent years a small number of studies have applied functional imaging techniques to investigate visual responses in the human superior colliculus (SC) but few have investigated its oculomotor functions. Here, in two experiments, we examined activity associated with endogenous saccade preparation. We used 3T fMRI to record the hemodynamic activity in the SC while participants were either preparing or executing saccadic eye movements. Our results showed that not only executing a saccade (as previously shown) but also preparing a saccade produced an increase in the SC hemodynamic activity. The saccade-related activity was observed in the contralateral and to a lesser extent the ipsilateral SC. A second experiment further examined the contralateral mapping of saccade-related activity using a larger range of saccade amplitudes. Increased activity was again observed in both the contralateral and also ipsilateral SC that was evident for large as well as small saccades. This suggests that the ipsilateral component of the increase in BOLD is not due simply to small-amplitude saccades producing bilateral activity in the foveal fixation zone. These studies provide the first evidence of pre-saccadic preparatory activity in the human SC and reveal that fMRI can detect activity consistent with that of build-up neurons found in the deeper layers of the SC in studies of non-human primates.

Keywords:

Superior colliculus, fMRI, human, presaccade activity, saccade amplitude.

1. Introduction

The superior colliculus (SC) is a small midbrain structure that plays a crucial role in the control of eye movements (Sparks 1986; 1989; Munoz 2002). In non-human primates, the SC has a laminar organization. The superficial layers receive projections directly from the retina (Pollack and Hickey 1979) as well as from primary (Fries and Distel 1983) and extrastriate visual cortices (Abel et al. 1997). These layers are retinotopically organized (Cynader and Berman 1972) and contain visual neurons which are responsive to visual stimuli appearing at specific locations in the contralateral hemifield (Robinson and McClurkin 1989). The intermediate and deeper oculomotor layers receive inputs from other subcortical regions such as substantia nigra (SNr), as well as from cortical regions such as the frontal eye field (FEF) (Leichnetz et al. 1981) and lateral intraparietal visual area (LIP) (Lynch et al. 1985). Together, the superficial and the deep layers form a two-dimensional 'motor-map' in which saccadic movements are encoded as vectors for magnitude and direction (Robinson 1972). The magnitude of saccades is encoded along the rostrocaudal axis while saccadic direction is encoded along the mediolateral axis. This map is the product of neurons which are organized according to their movement field centres (Sparks et al. 1976). The cells located rostrally have been termed 'fixation' neurons (Munoz and Wurtz 1993; 1992) although they may more accurately encode very small amplitude saccades (Krauzlis et al. 1997), while cells located caudally encode larger amplitude saccades and gaze shifts (Krauzlis et al. 1997), with those located medially having an upward component and those located laterally having a downward component (Robinson 1972).

Neurophysiological studies of the response characteristics of neurons in the intermediate and deeper layer neurons have revealed subsets of cells based on their functional characteristics (for a review see: Wurtz 2000). During active fixation, neurons located in the rostral pole region that represents the fovea fire continuously and are thought to suppress the activity of more remote neurons involved in the processes of saccade target selection and initiation. Neurons in the deeper layers, but located more caudally, have been termed *visuo-motor prelude neurons* or simply 'build-up' neurons (Munoz and Wurtz 1995b) to reflect their involvement in the preparation to make a saccade. Build-up neurons fire continuously from target onset until a saccade is initiated, suggesting a role in the process of saccade preparation and target selection independent of saccade initiation (Basso and Wurtz 1998; Horwitz and Newsome 2001b). By contrast *burst neurons* located in the intermediate layers have low levels of activity after the stimulus presentation, but produce a vigorous burst of activity before and during saccade execution (Munoz and Wurtz 1995b). This suggests that visuo-motor burst neurons may be involved in saccade execution without being

involved in the target selection process (Basso and Wurtz 1998; McPeek and Keller 2002; Munoz and Wurtz 1995a).

Although much is known about the SC from neurophysiological studies of non-human primates, much less is known about the functions of the human SC. To date only a small number of studies have used functional magnetic resonance imaging (fMRI) to investigate the visual and oculomotor functions of the human SC. The scarcity of fMRI studies of the SC reflects several methodological factors: firstly, it is a difficult structure to study in detail because of its small size and deep location and secondly, it is located close to main vascular structures which introduce physiological noise in the midbrain and brain stem area (Guimaraes et al. 1998). A few studies have applied fMRI to investigate the human SC and have confirmed the presence of a retinotopic organisation for visual stimuli (DuBois and Cohen 2000; Schneider and Kastner 2005; Sylvester et al. 2007; Wall et al. 2009). Saccade-related activity has also been investigated in the human SC using fMRI (Gitelman et al. 1996; Himmelbach et al. 2007; Krebs et al. 2010a; Krebs et al. 2010b; Petit and Beauchamp 2003). Gitelman et al. (1996) and Himmelbach et al. (2007) reported saccade-related activity in the colliculus in a visual search task, but did not show significant activity associated with the execution of voluntary cued saccades. The presence of activity for the search task was attributed to the greater cognitive and attentional task-demands required. Krebs et al. (2010b) used a voluntary cued saccade task and revealed activity in the SC that showed a small contralateral bias consistent with the contralateral oculomotor map revealed by single cell recording and stimulation of deeper layer neurons (Schiller, & Stryker, 1972). Krebs et al. (2010a) have shown that activity associated with centrifugal saccades (made away from the centre), is greater than for the centripetal return saccades made back to centre, although the reasons for this are not clear. Petit et al. (Petit and Beauchamp 2003) compared SC responses for saccades, head and eye-plus-head (or gaze) movements using peripheral targets that are more similar to the stimuli used in most neurophysiological studies of the SC. Activity was found in the SC along with other sub-cortical structures in the basal ganglia and thalamus for eye, head and gaze movements. Functional imaging has therefore revealed saccade-related activity in the human SC but the studies performed to date have not been able to dissociate activity associated with saccade preparation from that associated with saccade execution.

These findings suggest that human SC is likely to be organized similarly in humans and in other primates. Thus, if SC organization is the same across all primates, then the neural activity associated with the preparation of a saccade should be measurable with fMRI. This approach has

been successful in revealing activity relating to saccade preparation in oculomotor regions of the human frontal and parietal corticies (Curtis and Connolly 2008).

However, to the best of our knowledge, the presaccadic activity in human SC has never been measured. The first goal of this study is to investigate the neural response of human SC associated with the preparatory phase prior to saccadic movements and to compare it to that associated with saccade execution, using a go/no-go voluntary saccade paradigm. Activity in the SC was significantly increased during saccade preparation, and was further increased during saccade execution, consistent with the sustained activity of build-up neurons and the transient response of burst neurons in the intermediate layers of the SC. Activity for return saccades made back to fixation was much reduced, consistent with other reports Krebs et al. (2010a). The BOLD response associated with saccade preparation and execution were not strongly lateralised, as would be expected on the basis of the contralateral mapping of saccades demonstrated by neurophysiological studies (Robinson 1972). The bilateral BOLD response could plausibly reflect activity in the rostral pole region that is thought to encode small saccades and microsaccades (Hafed and Krauzlis 2012) rather than more caudal activity associated with larger saccades. A second study was therefore performed, in which participants executed saccades of different amplitudes and minimal fixation delays, with the aim of maximising activity contralateral to the movement. A bilateral increase in BOLD response was again observed that was not modulated by saccade amplitude. We discuss the possible origins of ipsilateral activity in terms of the different neural signals that might contribute to the overall BOLD response.

2. Experiment 1: presaccadic activity in SC

In order to examine activity specifically associated with saccade preparation a go/no-go task was implemented in an event-related fMRI design (see figure 1). A symbolic arrow-cue was presented at central fixation to indicate saccade direction during a variable delay period. On 'go' trials this was followed by the offset of the arrow that indicated a horizontal saccade should be executed towards a saccade goal specified by a continuously presented peripheral landmark. Gaze was held at this peripheral location for a variable delay period so activity associated with the outward saccade could be distinguished from that of the return saccade made back to central fixation. On no-go trials the offset of the arrow was immediately followed by the onset of the fixation cross, indicating that gaze should be held at the central location. The aim was to examine activity associated with saccade preparation and to dissociate this from activity relating to saccade execution and the return back to fixation.

2.1. Materials and Methods

2.1.1. Participants

Fifteen healthy participants (9 females) took part in this experiment. All had normal or corrected to normal vision. They were screened for MRI contraindications according to standard procedures and written consent was obtained. The experimental procedure was in accord with the Declaration of Helsinki and was approved by the appropriate local ethics committee.

2.1.2. Stimuli and task

Computer generated visual stimuli were projected by a LCD projector onto a rear-projector screen at the end of the scanner bore and were viewed via a mirror mounted on the headcoil, giving an image of 25° x 20° visual angle. The stimuli were created using a combination of MATLAB (The Mathwork, Inc.), ASF (Schwarzbach 2011) and Psychtoolbox-3 (Brainard 1997; Pelli 1997).

The stimuli are shown schematically in Figure 1. A white central fixation cross (0.5°) was presented on a black background, flanked by two saccade targets placed at a distance of 3° on each side of the cross. Each target comprised a white dot (diameter of 0.05°) representing the exact location of the saccade target and a surrounding white circle (diameter of 0.5°) to give the target greater visibility during central fixation. There were two conditions:

1. In the ‘go’ condition, an arrow was presented that overlapped the central fixation cross and pointed to either the left or the right target. During the *saccade preparation* stage the participant had to prepare a saccade to the cued target while keeping their gaze on the central fixation cross. Following a one second delay, the arrow disappeared along with the vertical bar of the original fixation cross, leaving only the horizontal bar. For the *saccade execution* phase the participants had to perform a saccade toward the cued saccade goal (continuously presented peripheral landmark). Following the outward (centrifugal) saccade, gaze was held at the saccade goal for a variable Inter Stimulus Interval (ISI). At the end of this time, a white arrow (0.2°) pointing to the central fixation cross was briefly presented (200ms) in the centre of the target. At this point, the participants had to perform a centripetal saccade toward the central fixation point. At the offset of the 200ms arrow, the vertical member of the fixation cross re-appeared. Gaze was then held on the central cross until the next trial commenced.

2. In the ‘no-go’ condition, the ‘preparation’ phase was the same as in the ‘go’ condition. However, when the arrow disappeared after 1s, the fixation cross remained as a cue for participants to hold their gaze at the central location. The no-go condition, which was the main condition of interest as it involves preparation without execution, was intended to lead participants to initialize the motor program needed to execute a saccade without actually executing it. Go trials were included primarily so that participants would know on every trial that execution might be required; without them they would be unlikely to prepare saccades in the no-go condition.

PLEASE INSERT FIGURE 1

It is important to note that arrow cues were used to specify the saccadic response to avoid potential exogenous shifts of attention that might arise if peripheral onsets were used as saccade targets and also to minimise the visual drive to the SC, so any activity observed should reflect oculomotor rather than visual responses. The difference between the 'go' and 'no-go' cues was made as small as possible, also to minimize any difference in visual drive between the conditions. In the saccade return-to-fixation phase of 'go' trials, the vertical member of the fixation cross appeared only when the peripheral arrow disappeared, timed when the eyes were likely to be moving, so that its onset did not provide either an exogenous cue or significant visual drive.

Both the ISI within trials and the ITI between trials had a duration drawn from a Poisson probability distribution (Hagberg et al. 2001) with an average of 4 seconds, a minimum of 2 seconds and a maximum of 12 seconds. Each scan run contained 40 trials (20 go and 20 no-go). Of the 20 trials in each condition, 10 involved a saccade (or suppressed saccade) to the left and 10 to the right. The 40 trials were presented in random order within each run. 8 runs were conducted, using different random orders.

2.1.3. Data acquisition

Data were acquired using a 3T Siemens TIM Trio MR scanner with a 32 channel array head coil. Functional images were acquired with a T_2*-weighted gradient-recalled echo-planar imaging (EPI) sequence (16 axial slices, TR 1500, TE 41 ms, flip angle 75°, resolution 2.0 mm isotropic, 96 x 96 matrix, FoV 192mm, bandwidth 752 Hz/Pixel, GRAPPA factor 2). The slices were positioned to include the midbrain and were tilted off-axial to avoid the eyes. The duration varied between scan runs according to the ISI and ITI values selected from the probability distribution. The mean was 5 min 26s (217 volumes). Structural data were acquired using a T_1-weighted 3D anatomical scan (MPRAGE, Siemens, TR 1830 ms, TE 5.56 ms, flip angle 11°, resolution 1x1x1 mm).

2.1.4. Data analysis

Data were analysed using BrainVoyager QX 2.3 (Brain Innovation, The Netherlands). The first 2 volumes of each run were discarded to avoid T1 saturation changes. Three-dimensional motion correction with trilinear interpolation was performed using the first volume as a reference, followed by slice time correction. The data were then temporally high-pass filtered using a cut-off frequency of 3cycle/run (~0.01 Hz). The preprocessed EPI scans were then coregistered with the anatomy. No spatial smoothing was performed on the functional data. The preprocessed data were analysed by running a general linear model (GLM) analysis with separate predictors for execution (go trials), return (go trials) and preparation (no-go trials). Rightward and leftward cued saccades (whether or not executed) were modelled separately. Each of the three events was modelled by convolving the predictor time course with a dual-gamma hemodynamic impulse response function (HRF) (Friston et al. 1998) and then scaling to unity. It is important to note that we optimized the signal estimation within the SC by using a HRF with an early peak (4.5 seconds), which has been demonstrated to be better suited to modelling hemodynamic activity in that particular region (Wall et al. 2009).

Activity in the SC was examined separately in each participant by defining a region of interest (ROI) corresponding to each SC (left and right) and averaging the blood-oxygen level dependent (BOLD) activity (beta values from the GLM) across all voxels within each ROI. The ROI was defined based on a *t*-map derived from the 'go' trials only (left and right sides pooled). A patch of activity at the known anatomical location of each SC was identified after suitable thresholding of the *t*-map and taken as the ROI. Activity related to saccade preparation was taken as the mean activity in 'no-go' trials within this ROI. Because different trials were used for defining the ROI and estimating preparation-related activity, these two measures are independent. To quantify the effect of preparing a saccade, the beta estimates were averaged across left and right SC but separately for ipsiversive and contraversive saccade directions, e.g. the beta values extracted from the left colliculus which corresponded to saccades toward the right visual field were averaged with those from the right colliculus which corresponded to saccades toward left visual field (contraversive). The resulting parameter estimates were tested for significant activity across participants by *t*-tests.

The contralateral mapping of saccade-related activity was further explored using a Contralaterality Index (CI) for both the left and the right SC. For each colliculus the CI was calculated using a modified version of the equation used by DeBois and Cohen (2000):

$$CI = \frac{Rightward\ Saccades - Leftward\ Saccades}{Rightward\ Saccades + Leftward\ Saccades} \quad (1)$$

Where: *Leftward Saccades* and *Rightward Saccades* refer to the vectors of t-values obtained from the univariate analysis by contrasting respectively leftward events and rightward events against baseline. The number of voxels for each ROI gives the length of the vector. Thus, a CI close to -1 indicates a bias for leftward saccades, while a CI close to 1 indicates a bias for rightward saccades. In Experiment 1 bilateral activity was observed for both the Go and No-Go trials and so both of these conditions were included in the CI measure.

Eye movement recording

In order to check that saccades were made in the correct direction at the correct time in relation to the cue, eye position measurements were obtained with an infrared video camera positioned close to the eye (NordicNeuroLab, Norway) inside the scanner. Pupil position was continuously sampled with a frequency of 60Hz by using software (Arrington, Inc. USA) that located and tracked the pupil. Blinks were detected and the corresponding samples were excluded. Eye movements were used on-line to ensure the participant was following the task instructions but the loss of tracking for some participants means it was not analysed in detail. An EyeLink II (SR Research) was used to obtain behavioural measures on the paradigm outside the scanner that are reported here.

2.2. Results

2.2.1. ROI definition: Activation of superior colliculus during saccade execution

Figure 2 shows the location of the BOLD responses in the SC during saccade execution in go trials (leftward and rightward saccades pooled) on which the ROI definition was based for one representative participant (note the threshold used to define the SC varied across participants). The ROI locations, expressed in Talairach coordinates, of left and right SC averaged across all analysed participants (n=10) are shown in Table 1. The analysis of the voxel-wise statistical map revealed significant activation within both left and right SC in 10 participants out of 15. Failure to find significant bilateral activity resulted in exclusion, since regions of interest could not then be defined.

PLEASE INSERT FIGURE 2

PLEASE INSERT TABLE 1

2.2.2. Activation of superior colliculus during saccade preparation

Our objective was to establish whether activity occurs in SC during the preparation of saccades. Figure 3 (AC, AI) shows the mean response magnitude for saccade preparation (no-go trials), averaged across both hemispheres and participants. Responses to contralateral (C) and ipsilateral (I) saccades are shown separately. The image from the eye camera was continuously monitored during scanning and very few direction errors, or responses on no-go trials were observed. We were therefore confident that C and I were adequately separated and that errors were too few to corrupt the data significantly. Also shown, for comparison, are the magnitudes for execution of the outward Figure 3 (BC-BI) and return (CC-CI) saccades in the go trials. The results are based on beta values from the GLM, normalized in order to remove variance due to overall BOLD magnitude differences between participants. The preparatory phase of a saccade produced a significant increase in neural activity whether the cued (but not executed) saccade was ipsiversive ($t_{(9)}$ =6.06, p <0.001) or contraversive ($t_{(9)}$ =3.91, p = 0.004). The difference between ipsiversive and contraversive saccade preparation was not significant ($t_{(9)}$ =0.49, ns).

As expected, executing a saccade also produced significant activity in SC, for both ipsiversive ($t_{(9)}$ = 8.03, p < 0.001) as well as contraversive ($t_{(9)}$ = 9.65, p < 0.001) saccades, although executing contraversive saccades elicited a hemodynamic response which was 39% higher than that observed for executing ipsiversive saccades ($t_{(9)}$ =3.787, p < 0.005). Thus, the expected contralateral mapping of oculomotor activity was present for saccade execution but was not significant during saccade preparation.

Ipsiversive saccade preparation produced a response that was 62% of the response produced by executing an ipsiversive saccade, while the preparation of a contraversive saccade elicited a response that was 48% of the activity due to executing a contraversive saccade. In reality, the

response for saccade preparation is likely to be under-estimated for two reasons. Firstly, the ROIs were defined based on execution of the outward saccades in the go condition. This circularity creates a bias such that there is potential overestimation of execution activity compared to preparation activity (which is unbiased). Secondly, activity in the go trials combines preparatory activity with activity due to the execution (although the preparation component will be somewhat diminished because its timing differs from the model by 1s). Pure execution activity broadly equates to the difference between go and no-go trials. It is likely therefore that preparatory activity, although it appears less than "execution" activity in Figure 3 may be at least comparable in magnitude to execution-related activity.

Measurable responses were not observed during centripetal (return) saccades to the central fixation point, for both ipsiversive ($t_{(9)}$ = 0.07, ns) and contraversive return saccades ($t_{(9)}$ = -1.598, ns). Table 2 reports means and standard errors of normalised percentage signal change for each saccade event type.

PLEASE INSERT FIGURE 3

PLEASE INSERT TABLE 2

The increase in the BOLD response observed for both ipsiversive and contraversive saccade preparation and execution is not consistent with the expected contralateral mapping of saccades from neurophysiological studies using non-human primates. The issue of contralateral mapping was further explored therefore using a contralaterality index (CI) for all voxels (see Methods) and the results are shown in Figure 4 along with the descriptive statistics in Table 3. The distribution of CI's in the left colliculus was different (by Wilcoxon test) from that in the right colliculus for both saccade preparation (No Go trials: W = 4534, $p<0.001$) and saccade execution (Go trials: W = 1990, $p < 0.001$). Furthermore, the medians of the distributions of the CI extracted from the left SC indicate a rightward directional bias (+ve values), both when the distribution was generated with

No Go (preparation) trials (0.45) and with Go (execution) trials (0.1). The opposite pattern was observed for the right SC. In this case, the median CI's indicate a leftward bias (-ve values), both when the distribution was generated with No Go trials (-0.11) and with Go trials (-0.29).

PLEASE INSERT FIGURE 4

PLEASE INSERT TABLE 3

The activity observed during the saccade preparation period should not involve activity associated with saccades. However, it is plausible that it may include activity associated with small fixational eye movements elicited by the central cue. The spatial resolution of the eye tracker used in the scanner was not sufficient to examine this possibility. Instead the eye position of a group of six participants was examined outside the scanner using a high-resolution Eyelink II system (spatial resolution RMS 0.01^{o}). The horizontal eye position traces were examined for a period of 500ms before and after the onset of the central symbolic cue. The average eye position traces are shown in Figure 5 separately for trials on which a leftward or rightward cue was presented. This clearly shows that although eye position fluctuated around fixation (by some 0.2 deg, equally to the left and right of centre), importantly it was not modulated by the onset of the directional cue. Thus the increase in SC response observed for the preparatory period following cue onset is unlikely to reflect activity associated with small fixational eye movements.

PLEASE INSERT FIGURE 5

2.3. Discussion Experiment 1

Experiment 1 has successfully demonstrated activity associated with saccade preparation in the human SC. Unlike previous imaging studies we isolated preparatory activity associated with saccade planning and observed an increase in the BOLD response during the cue epoch when participants planned a saccade to a peripheral goal. A significant increase in SC activity was also observed for saccade execution. By contrast, activity was not observed for the return (re-centring) saccades made back to central fixation in either the contralateral or ipsilateral SC. The absence of activity associated with return saccades is superficially surprising but is consistent with the findings of Krebs and colleagues (Krebs et al. 2010a; Krebs et al. 2010).

An unexpected finding was that this increase in BOLD response for saccade preparation was not strongly lateralised, increased activity being observed in the SC both contralateral and ipsilateral to the planned response direction. A possible reason for the observed ipsilateral activity could be that it relates to inhibition of planned saccades (see also section 4.2). Significant activity was observed also for the saccade execution phase (preparatory and execution activity) and although the BOLD signal was greater for contralateral saccades, an increase in ipsilateral SC activity was again observed. As an increase in ipsilateral SC activity was observed in both the Go and NoGo trials this may not be entirely attributed to neural activity related to the inhibition of the saccade in NoGo trials. A further examination of the contralateral mapping of saccade-related activity for the preparation and execution phases was performed using a contralateral index calculated for each active voxel obtained form the univariate analysis. The CI laterality index revealed a significant contralateral bias in voxels extracted from both the left and right SC for both saccade preparation and saccade execution. Thus although the BOLD signal is not strongly lateralised, with an increase in activity also being observed for the ipsilateral colliculus there is evidence that activity is greater contralateral saccade programming. A comparative fMRI study of spatial representations in the parietal and frontal eye field regions found greater contralaterality of responses in the monkey cortex than in humans (Kagan et al. 2010). This raises the interesting possibility that this reduction in contralateral spatial representation in the human cortical eye field regions is reflected downstream in the human SC.

A further possibility is that the bilateral increase in saccade-related responses observed in SC may include visual drive from the cues used to direct the participant's gaze in the superficial layers of the SC, rather than saccade-related activity in the intermediate layer saccade-related neurons. We think this is unlikely as care was taken to minimize the visual cues, which consisted in each case of a

small single line element appearing or disappearing, making it unlikely that they would elicit detectable sensory responses in SC. It remains a possibility that some visual drive may have modulated the collicular response and that this might explain the low degree of laterality seen in the execution and planning activity. However, a visual fixation stimulus was continuously presented throughout each event and would therefore be expected to drive both hemispheres equally. Furthermore, the absence of a significant response for the return saccades (made after a long period of fixation) would suggest that the bilateral collicular activity observed for saccade preparation and execution does not reflect fixation-related activity. Why return saccades generate smaller BOLD responses than outward saccades (Krebs et al., 2010a; Krebs et al., 2010b) is not fully understood (see General Discussion) but it seems likely to be related to saccade generation mechanisms and most unlikely to be related to visual asymmetries, since the cues were essentially the same. We therefore think that any sensory activity caused by our cues in SC is insufficient to contribute significantly to our results.

Another consideration is that the bilateral BOLD response observed in the saccade preparation and execution phases may be due to the small eccentricity of the saccade goals used in Exp 1. It has been estimated that a population of around one quarter of saccade-related neurons are active for any one saccade (Lee et al. 1988; Sparks et al. 1990) and the centre of this population of activity extends in a continuum from micro-saccades at the rostral pole to larger saccades encoded caudally. Hafed et al. (2009) described neurons in the rostral pole that showed an increase in firing rate for micro-saccades and in some cases also for larger voluntary saccades (up to 5^{o} amplitude). Some neurons showed ipsilateral responses, indicating that the foveal retinotopic map may be encoded to some extent across both colliculi. In our study saccades were prepared towards a goal located 3^{o} from fixation and it is plausible that the bilateral increase in BOLD response reflects activity of neurons with bilateral response fields. We investigated this possibility in a second study designed to explore the effect of saccade magnitude on the laterality of the response in SC using a range of saccade amplitudes of 2, 8 or 20 deg. It would be predicted on the above account that bilateral activity would be found for smaller saccades, while larger saccades should produce only contralateral responses, arising from more caudal populations of neurons.

3. Experiment 2: Activity in the human SC for different saccade amplitudes

In this second study we measured the hemodynamic response in the SC while participants executed saccades with three different magnitudes. If the bilateral increase in BOLD response observed in Experiment 1 was related to rostral pole activity associated with a bilateral foveal representation then we would predict that small amplitude saccades will increase activity in both colliculi, while larger amplitude saccades should produce only contralateral activity. Thus the BOLD response in the ipsilateral SC should decrease with increasing saccade eccentricity, while the BOLD response in the contralateral SC should have the same amplitude irrespective of eccentricity.

3.1. Materials and Methods

3.1.1. Participants

Nine healthy participants (7 females) took part in this experiment. Of these five had participated in Experiment 1. All had normal or corrected to normal vision.

3.1.2. Stimuli and task

Visual stimuli were generated as described for Experiment 1 (see Stimuli and task) and were similar to those from Experiment 1 in terms of dimensions and brightness. The display sequence used to generate saccades of different amplitudes is displayed schematically Figure 6. Two white circular targets (outside diameter of 0.5°, inside diameter of 0.05°) were presented on a black background. The two targets were separated by a variable distance of 2°, 8° and 20°. There were six conditions, defined in terms of saccade direction (leftward, rightward) and saccade magnitude (2°, 8°, 20°). Saccade magnitude was manipulated between runs, while saccade direction was manipulated within runs. In the 'leftward saccade', the participant moved the gaze from the right target toward the left one, following an auditory cue. In the 'rightward saccade', the participant moved the gaze from the left to the right target, again following an auditory cue. The auditory cue was a brief sound delivered via MRI compatible earphones (Sensimetrics, Model S14). We decided to use two auditory cues corresponding to the two saccade directions. The sound had either a high (800Hz) or a low pitch (400Hz), and the mapping between cue and target location was counterbalanced across participants: in half of the participants, the high pitch sound indicated a

leftward saccade, while in the remaining half it indicated a rightward saccade. This mapping guarded against the participants losing track of which target to fixate, allowing them to know when and where to move their gaze at any time. The task of the participant was to perform a saccade toward the cued location as quick and as precise as possible.

PLEASE INSERT FIGURE 6

As in the previous experiment, the ITI between trials had a duration drawn from a Poisson probability distribution (Hagberg et al. 2001) with an average of 4 seconds, a minimum of 2 seconds and a maximum of 12 seconds. Each scan run contained 40 trials (20 leftward saccades, 20 rightward saccades), all of them with the same saccade magnitude. We repeated each saccade magnitude 3 times, leading our experiment to have 9 runs.

3.1.3. Data acquisition and analysis

Data were acquired and preprocessed as in Experiment 1 (see Data acquisition and Data analysis). The preprocessed data were analyzed by running a General Linear Model (GLM) analysis with separate predictors for the six events (2° leftward saccade, 8° leftward saccade, 20° leftward saccade, 2° rightward saccade, 8° rightward saccade, 20° rightward saccade). Each event was modelled by convolving the predictor time course with a dual-gamma hemodynamic impulse response function (HRF) (Friston et al. 1998) and then scaling to unity. As in the first experiment, we optimized the signal estimation within the SC by using a HRF with an early peak (4.5 seconds) (Wall et al. 2009).

In Experiment 2, we defined two ROIs corresponding to left and right SC by selecting the voxels overlapping the anatomical location of each colliculus. In the current experiment the ROIs were defined anatomically instead of functionally, as done in the previous experiment. In Experiment 1 we were able to localize the colliculi functionally as we were primarily interested in exploring neural activity associated with saccadic preparation and were therefore able to use execution-related activity to define our ROIs. By contrast, in Experiment 2 we were interested in all the six conditions and so all of the events were included in the analysis. We therefore chose to define our ROIs anatomically, in order to keep the selection of voxels as independent as possible.

Having identified the ROIs, the mean BOLD response magnitudes (β values) corresponding to each condition were calculated by averaging across all voxels in the ROI. The resulting parameter estimates were normalized in order to remove any between subjects bias, and then tested for significant activity across participants by *t*-tests.

3.1.4. Eye movement recording

Eye movements were again monitored on-line to ensure participants were following the task instructions as for Exp 1.

3.2. Results

3.2.1. ROI definition: Activation of superior colliculus during saccade execution

The mean position across participants of our anatomically defined ROIs are reported in Table 4.

PLEASE INSERT TABLE 4

3.2.2. Hemodynamic response as a function of saccade amplitude

Our aim was to establish whether neural activity in SC occurring during saccade execution was affected by the size of the saccade. Figure 7 shows the mean response magnitudes for saccades with different amplitudes, combined in terms of ipsiversive and contraversive saccade direction. There was no main effect of saccade size on amplitude. More importantly, responses were again bilateral and there was no indication that the BOLD response became more lateralized for larger saccades. Executing a saccade produced responses in the SC that reached statistical significance for four out of the six conditions. The hemodynamic activity for executing a 2°, saccade was significant in both the ipsiversive ($t_{(8)}$=2.8842, p = 0.020) and contraversive ($t_{(8)}$=3.2008, p = 0.012) SC. A significant increase in activity was also found when participants executed a contraversive saccade of 8°

($t_{(8)}$=4.2735, p = 0.002) and an ipsiversive saccade of 20° ($t_{(8)}$=2.8467, p = 0.021). Activity associated with ipsiversive saccades of 8° ($t_{(8)}$=2.1657, ns) and 20° ($t_{(8)}$=2.0004, ns) was comparable in magnitude to the other conditions although was not significant.

PLEASE INSERT FIGURE 7

3.3. Discussion Experiment 2

Experiment 2 was performed to examine the possibility that the elevated saccade-related activity in the ipsilateral colliculus seen in Experiment 1 may reflect rostral pole activity associated with smaller saccades. Here three different saccade amplitudes were used, including large saccades of 20^{o} that should produce caudal activity that should be more clearly localised to the contralateral SC. The results, however, revealed a broadly similar pattern of activity with both ipsilateral and contralateral activity irrespective of saccade amplitude. The observed increase in BOLD response associated with ipsilateral saccades is unlikely to reflect rostral pole activity. As discussed above this activity is unlikely to reflect visual fixation-related activity as the visual stimuli were small and activity was not observed for return saccades (c.f. Krebs et al., 2010a; Krebs et al., 2010b) even though fixation of similar visual stimuli was involved. The lack of any change in response with saccade size is also of interest because it contrasts with reports that BOLD activity increases with saccade amplitude in the visual cortex (Tse et al 2010). In the colliculus, saccades of different sizes simply activate different neurons, in different parts of the retinotopic map, and there is no reason to expect the summed BOLD response to vary in amplitude.

4. General Discussion

The functional and anatomical properties of the superior colliculus have been well characterized and described in non-human primates (for reviews see: Munoz 2002; Sparks 1999; 1989; 1991; 1986; Wurtz 2000). Much less is known about the functional properties of human SC. Some of these properties have been confirmed for human SC, such as a role in processing visual stimuli (DuBois and Cohen 2000; Schneider and Kastner 2005; Sylvester et al. 2007; Wall et al. 2009) and in generating endogenous saccadic eye movement (Gitelman et al. 1996; Himmelbach et al. 2007; Krebs et al. 2010a; Krebs et al. 2010b), which suggests that the human SC may be organized similarly to the monkey. If this is correct then other crucial functional properties should also be observed, such as the involvement of SC in target selection processes prior to saccadic movements and potentially the modulation of neural activity due to higher-level cognitive functions. Activity relating to saccade preparation has been revealed in oculomotor regions of the frontal and parietal cortex that project to the SC (Curtis and Connelly, 2008). In the current studies, we first measured the hemodynamic activity within SC while participants were preparing to make a saccade in a go/no-go task that enabled preparatory activity to be dissociated from that relating to saccade execution (Experiment 1). We then examined the hemodynamic activity within SC related with saccades of different magnitude (Experiment 2). The main findings are summarised below.

4.1. Hemodynamic activity associated with saccade preparation

Our work provides the first evidence that the neural activity produced in the superior colliculus during the preparatory target selection period can be measured in humans. A significant increase in BOLD was observed during the delay period prior to saccade initiation and a greater increase observed for the combined preparation and execution phases. The SC is a layered structure and the spatial resolution of fMRI is not able to dissociate neural activity from the visual superficial layers from that of the deeper saccade-related activity. Here visual drive was minimised by the use of small stimuli and limiting the effects of visual transient onset/offset effects. The increase in BOLD response observed during the saccade preparation (cued) phase is therefore unlikely to reflect increased activity in the superficial visual layers but is predicted on the basis of a rise in activity for visuomotor or ‘ build-up’ neurons located in the deeper layers of the SC. Build-up neurons show a continuous discharge of low-frequency activity, from the signal to make a movement of the target until saccade execution, that has been attributed to preparation to make a saccade and can be observed prior to the appearance of the actual saccade target, which is suggestive of a generalised preparatory response (Munoz and Wurtz 1995a). An additional burst of activity is observed in

populations of burst neurons just prior to and during saccade execution. The additional BOLD response observed during the saccade execution phase could reflect the additional contribution of burst neuron activity combined with that associated with build-up neurons.

4.2. Saccade-related activity was observed in both contralateral and ipsilateral SC

A finding unexpected on the basis of monkey neurophysiology was that the increase in BOLD response observed in both experiments here did not reveal the expected contralateral dominance for saccade direction. In Experiment 1, a bilateral increase in BOLD was observed during the saccade preparation and execution phases. The contralateral increase in BOLD was found to be significantly greater than the ipsilateral response only for the saccade execution phase. This was further examined using a contralaterality index (CI) calculated on the t-values for each voxel associated with leftward and rightward saccades extracted from the univariate analysis. This provided evidence of a bias in the SC for contralateral saccades. The increase in ipsilateral collicular response is inconsistent with neurophysiological evidence of contralateral mapping of saccade direction as revealed by electrical stimulation (Robinson 1972) and single cell recording (Wurtz and Goldberg, 1972). A similar ipsilateral increase in BOLD, with a small contralateral bias, has however also been found in fMRI studies of the human frontal eye fields (FEF) (Connolly et al. 2005; Curtis and Connolly, 2008; Krebs et al. 2010a). The difference between the results from neurophysiological and neuroimaging studies may, in part, reflect the different methods used (but see: Kagan et al. 2010 and below). Specifically, the difference may arise because the BOLD signal is sensitive not only to neural spiking but also to synaptic activity (Logothesis et al. 2001; Logothetis and Wandell 2004), leading the BOLD signal to be potentially sensitive to post-synaptic potentials related to inhibition. In our case, the increased BOLD response in ipsilateral SC might reflect inhibitory inputs while the response in contralateral SC may reflect a mixture of inhibitory and excitatory inputs. Van Horn et al. (2010) recorded both spike rate and local field potentials (LFP) of saccadic neurons in the brainstem. Increased spiking rate was associated with saccades made in the neurons preferred direction and was absent for saccades in the non-preferred direction. The response of LFPs was consistent with depolarization associated with spiking activity, and with hyperpolarization when saccades were made in the non-preferred direction. Both hyperpolarization and depolarization were found to be equally associated with the encoding of movement dynamics. The wider implication of this for our study is that the BOLD response may be sensitive to increased blood flow associated with spiking activity (output) and also with inhibitory

inputs that modulate synaptic activity during response suppression, making it an insensitive measure of saccade direction.

Connolly et al. (Connolly et al. 2005) similarly noted that functional imaging studies have often failed to demonstrate a clear relationship between FEF activity and saccade direction, despite overwhelming evidence of contralateral mapping in the monkey. They measured the hemodynamic activity in FEF during a short time prior to saccade execution and showed that the FEF hemodynamic activity correlated with saccadic reaction time (SRT). Specifically, they observed that SRT was predicted by the preparatory activity of contraversive but not of ipsiversive saccades. Saccadic latency reflects sensory processing delays and the accumulation of a decision process (Hanes and Schall 1996), which is dependent on higher-level cognitive processes. Therefore, the nature of the hemodynamic response in FEF for contraversive saccades is attributed to activity associated with short-latency saccades that is dependent on higher cognitive functions. If this were correct, then the same prediction would hold for subcortical regions such as the SC that is heavily innervated by the FEFs. Therefore, the same neural processes that generate the contralatateral activity in the FEF could generate a similar contralateral activity in the SC. If so, the contralateral bias should emerge only during certain saccades i.e. those with specific latencies, leading to a modest mean bias averaged over all trials. However, this hypothesis cannot easily be tested with our data due to the small number of data points available if a median split analysis is performed.

The superior colliculus is often referred to as a phylogenetically older subcortical brain structure (e.g. Foreman and Stevens 1987). Our assumption was that the human SC would be functionally similar to the monkey and we therefore expected to observe clear evidence of contralateral mapping of saccade-related activity. Direct comparisons between species are hindered by differences in the techniques used and the bilateral increase in signal observed may reflect the nature of the BOLD response as discussed. An interesting possibility that cannot be excluded is that space representation may be more strongly lateralized in monkey than humans even at the level of the SC. Kagan et al. (2010) report evidence that human frontoparietal oculomotor regions are less lateralized than in the monkey in an imaging study of monkey and human participants. Activity associated with memory-guided saccades was examined using event-related fMRI study. Activity in monkey frontal (FEF) and parietal (LIP/IPS) cortex was strongly contralateral, by contrast contralaterality was much reduced in the putative human homologue regions. The reduction in contralateral mapping in human cortical visual areas may be due to the increase in lateralization of higher-level cognitive functions (right-hemisphere dominance in attention, left hemisphere for

601 language) in the human brain. Although the SC is a lower-level structure it is thought to: "*act as a*
602 *funnel through which much of the input from the cortical reaches the brainstem"* (Wurtz, 2000).
603 Projections from the frontal eye fields to the SC convey signals relating to a range of cognitive
604 aspects of oculomotor behavior (Sommer and Wurtz, 2000) thus it is plausible that the reduced
605 contralaterality in the cortex is reflected downstream in the human SC.

606 ## 4.3. Hemodynamic activity associated with return saccades is small

607 Similar to Krebs et al. (Kreb 2010a; Kreb 2010b) we found that activity associated with return
608 saccades made back to central fixation did not produce a significant hemodynamic response
609 (Experiment 1). The reasons for the low-level of response for return saccades is as yet unclear, but
610 it may be due to their highly predictable nature that requires less 'processing effort' involving
611 reduced attentional and computational demands resulting in reduced cortical drive to the SC for
612 these responses (Krebs et al 2010b). The low-level of activity for centripetal saccades has also been
613 attributed to a natural tendency to return the eyes to the central position during eye-hand
614 coordination in the natural environment. This 're-centering bias' may account for the reduced
615 latency of return saccades compared to outwardly directed centrifugal responses (see: Krebs et al.
616 2010a for further discussion of the re-centering bias).

617 # 5. Conclusions

618 We used functional magnetic resonance imaging to examine the hemodynamic responses in human
619 SC while participants were either preparing or executing saccadic eye movements. We observed
620 increases in hemodynamic response related both to presaccadic preparatory saccade programming
621 and to saccade execution. The presaccadic response is consistent with increased activity associated
622 with saccade target selection and motor preparation in buildup neurons in the intermediate layers
623 of the SC. To the best of our knowledge, we have presented the first evidence of presaccadic activity
624 in human SC measured with functional magnetic resonance imaging. The BOLD response did not
625 show a strong contralateral mapping and increased for both ipsilateral and contralateral saccades.
626 Similar to other reports return saccades produced little BOLD response.

627

6. Acknowledgements

This work was supported by a grant from the Leverhulme Trust to RW and ATS.

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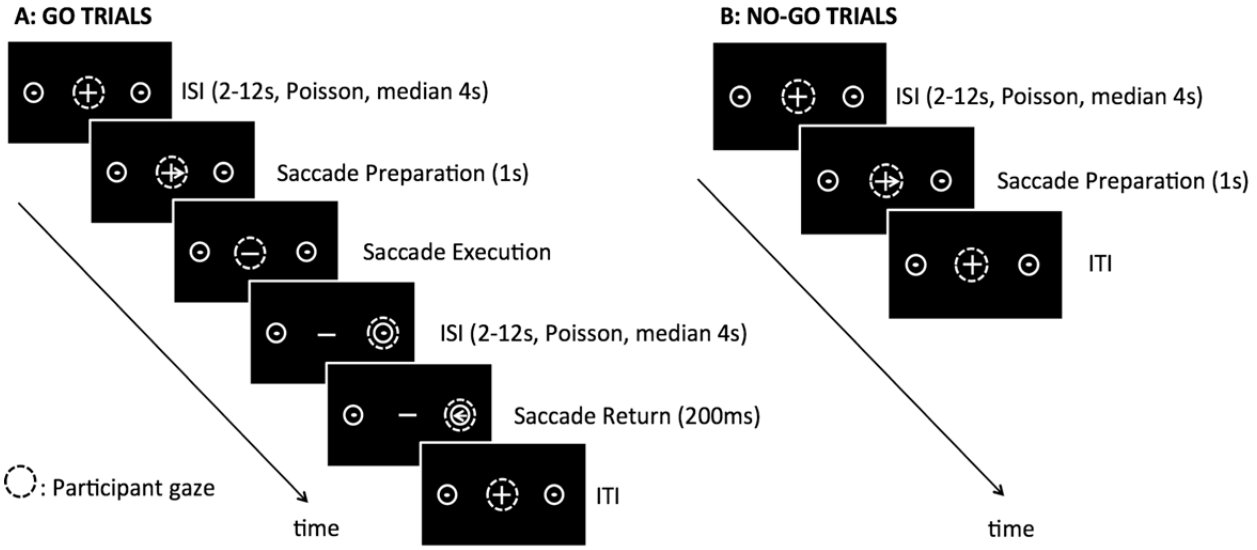
Figures



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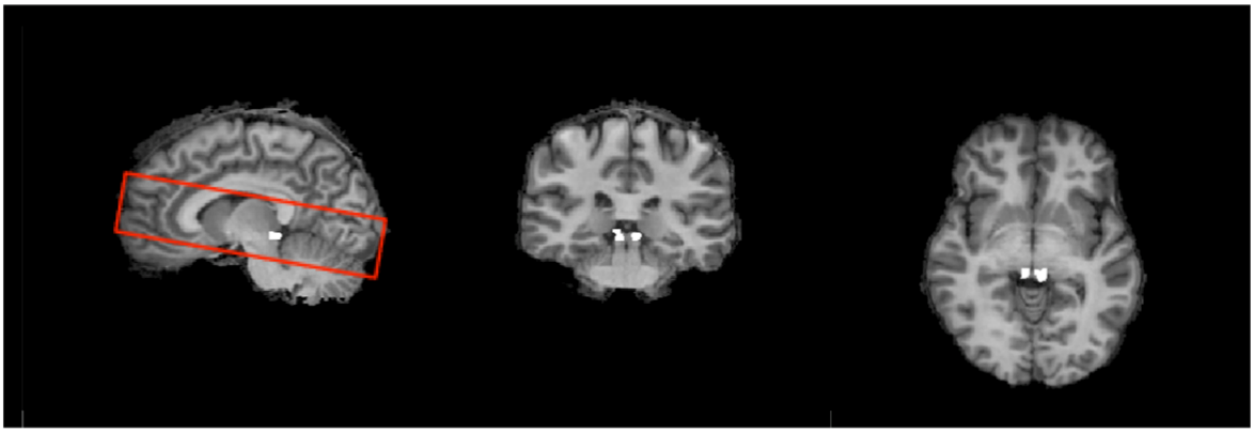

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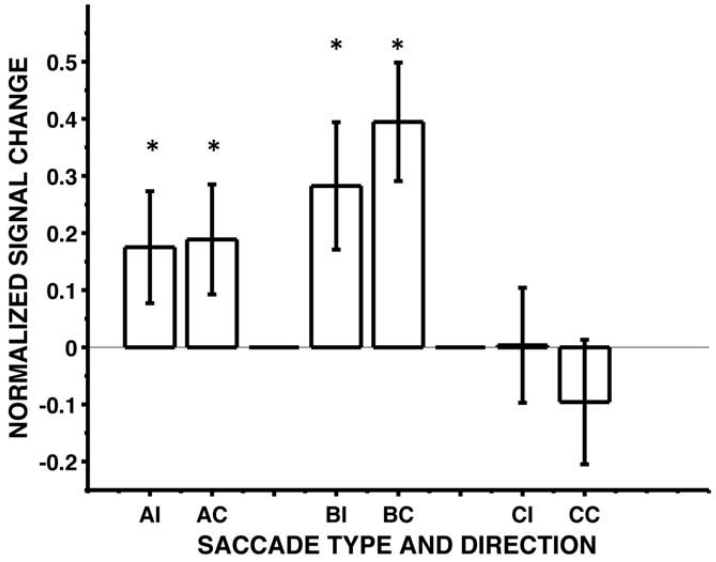

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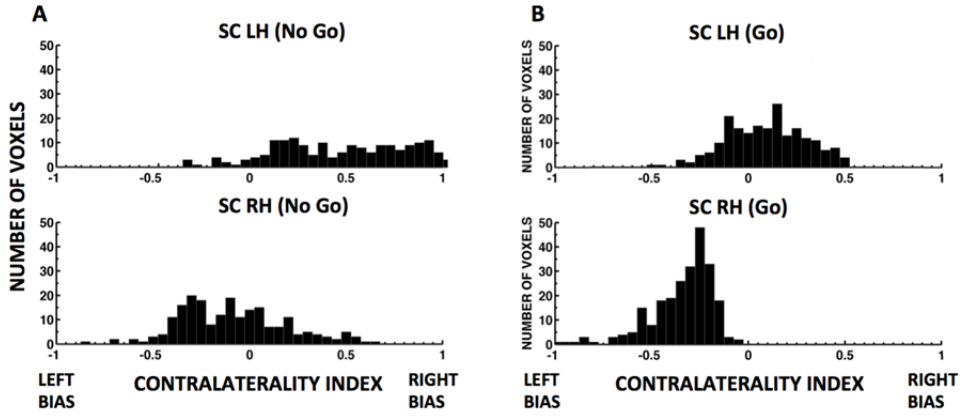
749 Figure 3



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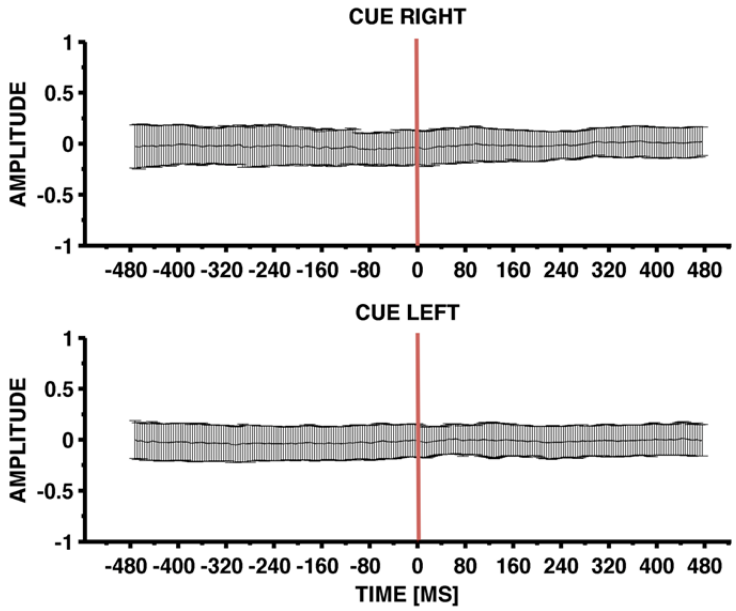

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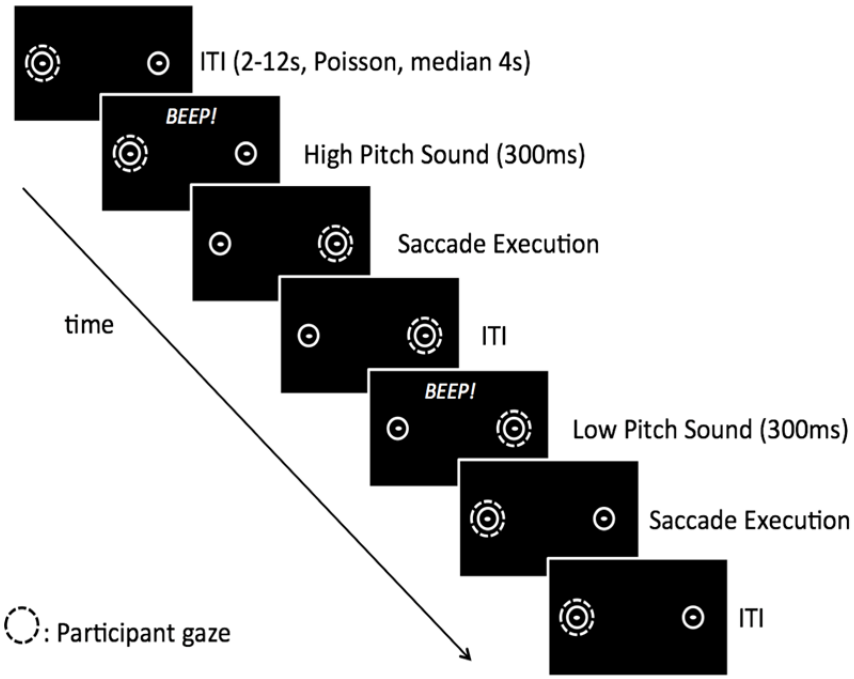

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755 Figure 6

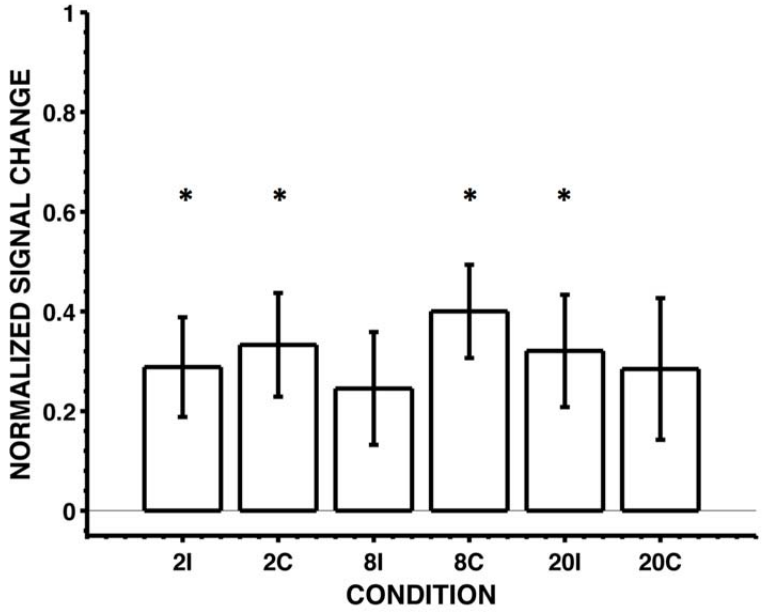
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Figure 7

Tables

Hemisphere	X(μ±σ)	Y(μ±σ)	Z(μ±σ)	Size (mm^3)	Size (Voxels)
SC RH	4±1	-27±1	-2±1	270±55	34±7
SC LH	-4±1	-28±1	-2±1	310±73	39±9

Table 1

		Saccade type		
		Preparation	Execution	Return
SC	Ipsilateral	0.175±0.098	0.2825±0.111	0.004±0.100
	Contralateral	0.189±0.096	0.395±0.104	-0.096±0.102

Table 2

Distribution	Max	Min	Mean	Median	Sd	Skew
SC LH (No Go)	0.98	-0.36	0.44	0.45	0.34	-0.23
SC RH (No Go)	0.64	-0.84	-0.08	-0.11	0.28	0.37
SC LH (Go)	0.5	-0.52	0.09	0.1	0.2	-0.17
SC RH (Go)	-0.03	-1	-0.34	-0.29	0.16	-1.33

Table 3

Hemisphere	X(μ±σ)	Y(μ±σ)	Z(μ±σ)	Size (mm^3)
SC RH	5±2	-28±3	-3±2	399
SC LH	-5±3	-28±2	-3±2	538

Table 4

Figure captions

Figure 1: Diagram illustrating the two conditions used in the experiment. Panel A ('go' trials): participants were initially asked to fixate the central fixation cross. The dotted circle indicates eye position at any given time and was not present on the screen. After a variable ISI, an arrow overlapped the fixation cross, pointing to the left or to the right (right shown in the figure). After a 1 second delay, the participant was cued to perform a saccade toward the cued target. The participant then had to maintain fixation on the target until s/he saw an arrow pointing toward the central fixation cross, which cued a return saccade back to the centre. Panel B ('no-go' trials): This stimulus was initially the same as the 'Go' Trials but following saccade preparation, participants were cued to keep their gaze on the central cross.

Figure 2. Location of the superior colliculus in one representative participant. Executing a saccade ('go' trial) was used as an event to functionally identify the two ROIs (left and right colliculi). The red box represents the outline of the acquisition volume.

Figure 3: BOLD responses in the superior colliculus, averaged across 20 hemispheres from 10 participants for contraversive and ipsiversive responses. Left: activity from no-go trials only, time-locked to the onset of the arrow cue in the contralateral (AC) and ipsilateral (AI) Saccade Preparation phase (see Fig. 1). This represents preparation activity isolated from saccade execution. Centre: activity from go trials only, time-locked to the contralateral (BC) and ipsilateral (BI) Saccade Execution cue. Because execution followed preparation by only 1s, this may encompass both preparation and execution activity. Right: activity for the return saccade made back to fixation on go trials only, time-locked to the peripheral arrow cueing contralateral (CC) and ipsilateral (CI) responses. The asterisks ('*') indicate activity time locked to saccade execution that is significantly different from baseline activity. This reflects the combined preparation and execution activity for the return saccade.

Figure 4. Contralaterality Index (CI) calculated in Experiment 1. The number of voxels is shown as a function of CI in both the left (upper row) and right SC (bottom row). Panel A shows the distribution of CI calculated on t-values extracted from No Go trials alone (saccade preparation), while Panel B shows the distribution of CI calculated on t-values extracted from Go trials alone (preparation plus execution).

Figure 5. Eye position along the horizontal axis for a period of 500ms before and after the onset of the cue, averaged across subjects as a function of time. The vertical red line depicts the onset of the cue. The standard deviation in gaze position was calculated across trials for each subject and averaged across subjects as indicated by the grey border.

Figure 6. Schematic diagram illustrating the procedure used in the Experiment 2. At the beginning of each run, participants were asked to fixate either the left or the right peripheral target (left in the figure). After a variable ISI, a tone (high pitch in the example) was sent via earphones to the participants, indicating to execute a saccade to the right peripheral target. The sound was followed by another ISI, during which participants had to keep their gaze on the right peripheral target. After a variable time, a different tone (low pitch in the example) was sent to the participants, cueing them to execute a saccade toward the left peripheral target.

Figure 7. Hemodynamic activity in the superior colliculus averaged across 18 hemispheres from 9 participants. BOLD response expressed in Percentage Signal Change is shown separately for each saccade magnitude (2°, 8°, 20°) for both ispiversive ('I') and contraversive ('C') saccades. The asterisks ('*') indicate activity time locked to saccade execution that is significantly different from baseline activity. Error bars represent ±SEM.

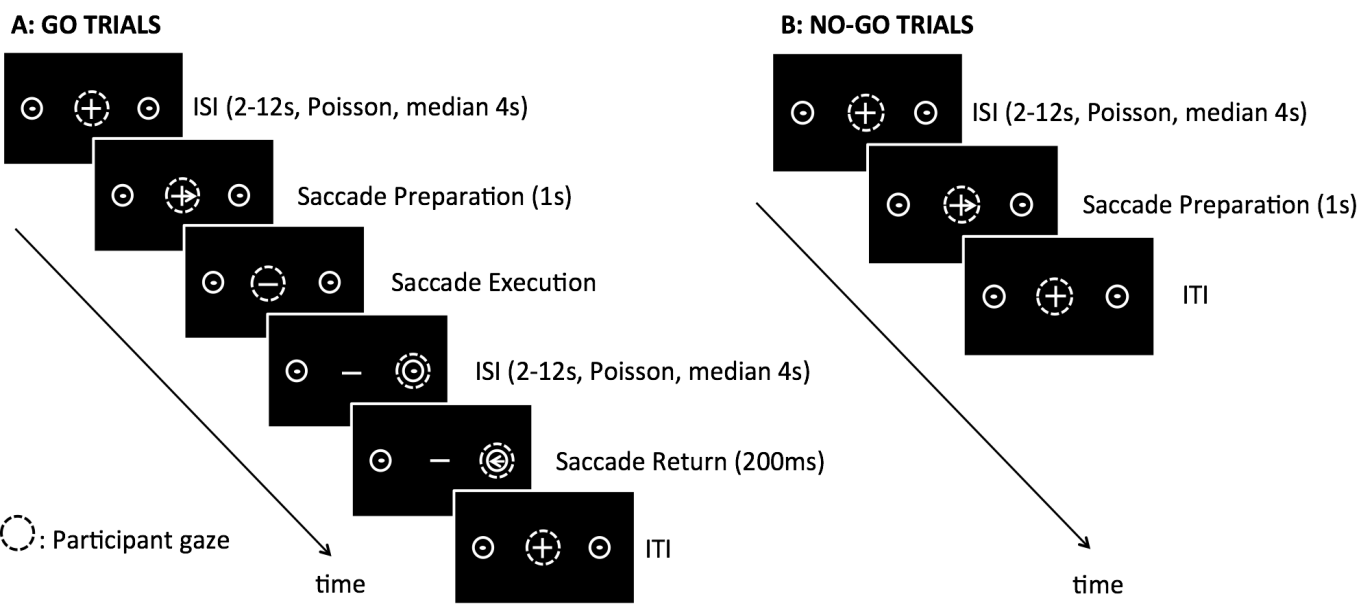
Table captions

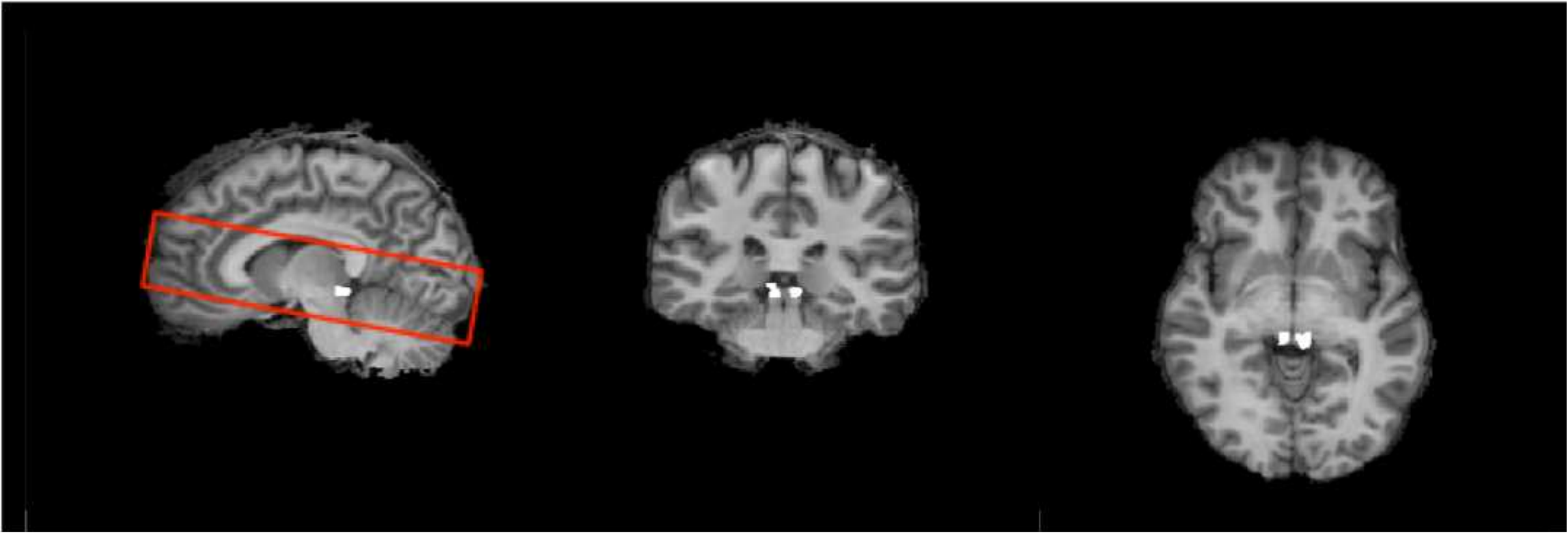
Table 1. Talairach coordinates (μ± σ x, y, z, volume) averaged across ten participants included in the final analysis.

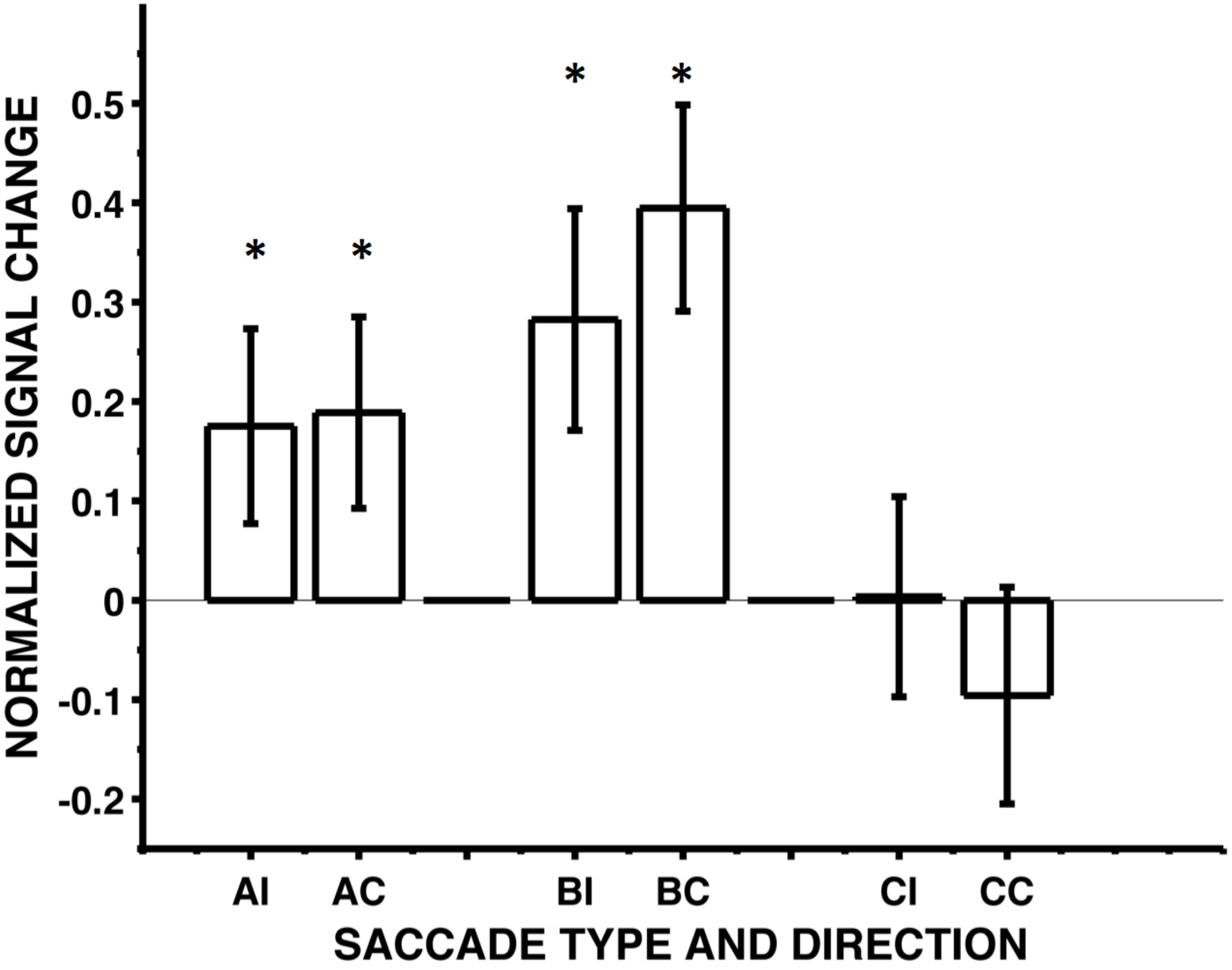
Table 2: Mean and standard error of normalised signal change for each saccade event type.

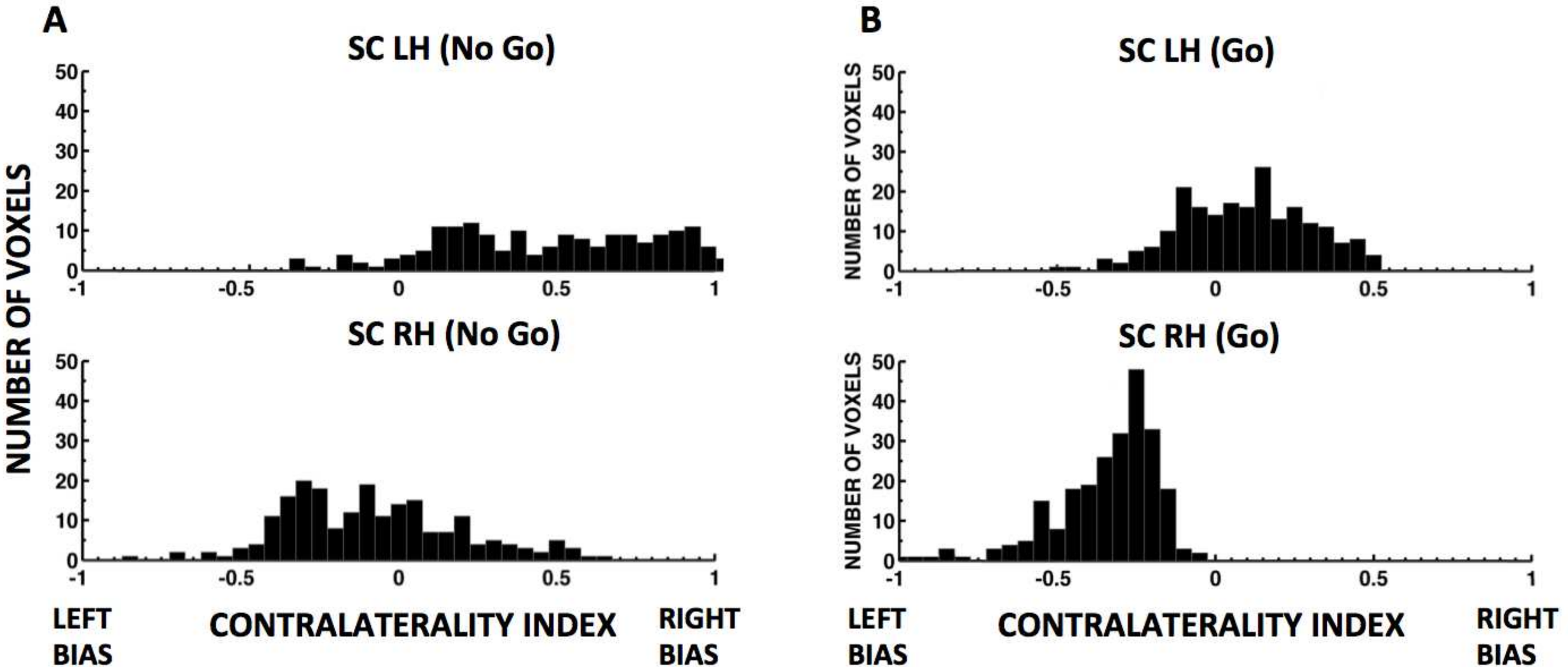
Table 3. Descriptive statistics for the CI's calculated for the left (LH) and right (RH) SC from No Go and Go trials in Experiment 1.

Table 4: Talairach coordinates (μ± σ x, y, z, volume) for participants included in the analysis.

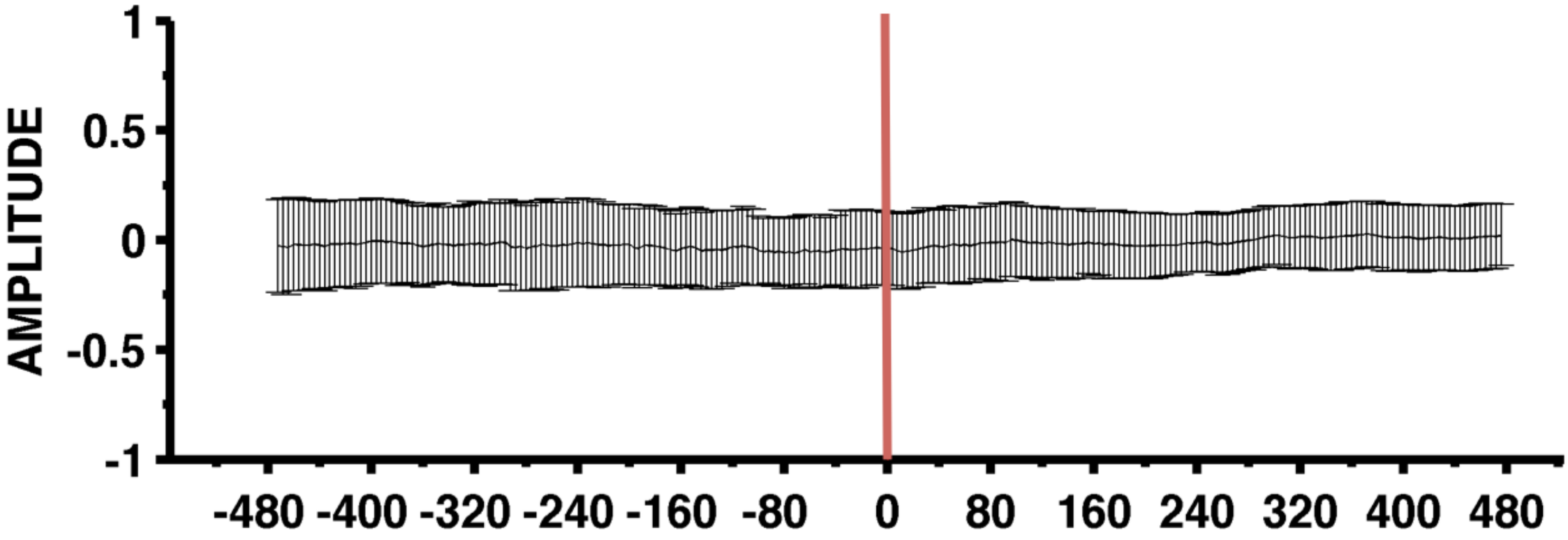

A: GO TRIALS
ISI (2-12s, Poisson, median 4s)
Saccade Preparation (1s)
Saccade Execution
ISI (2-12s, Poisson, median 4s)
Saccade Return (200ms)
ITI
: Participant gaze
time
B: NO-GO TRIALS
ISI (2-12s, Poisson, median 4s)
Saccade Preparation (1s)
ITI
time



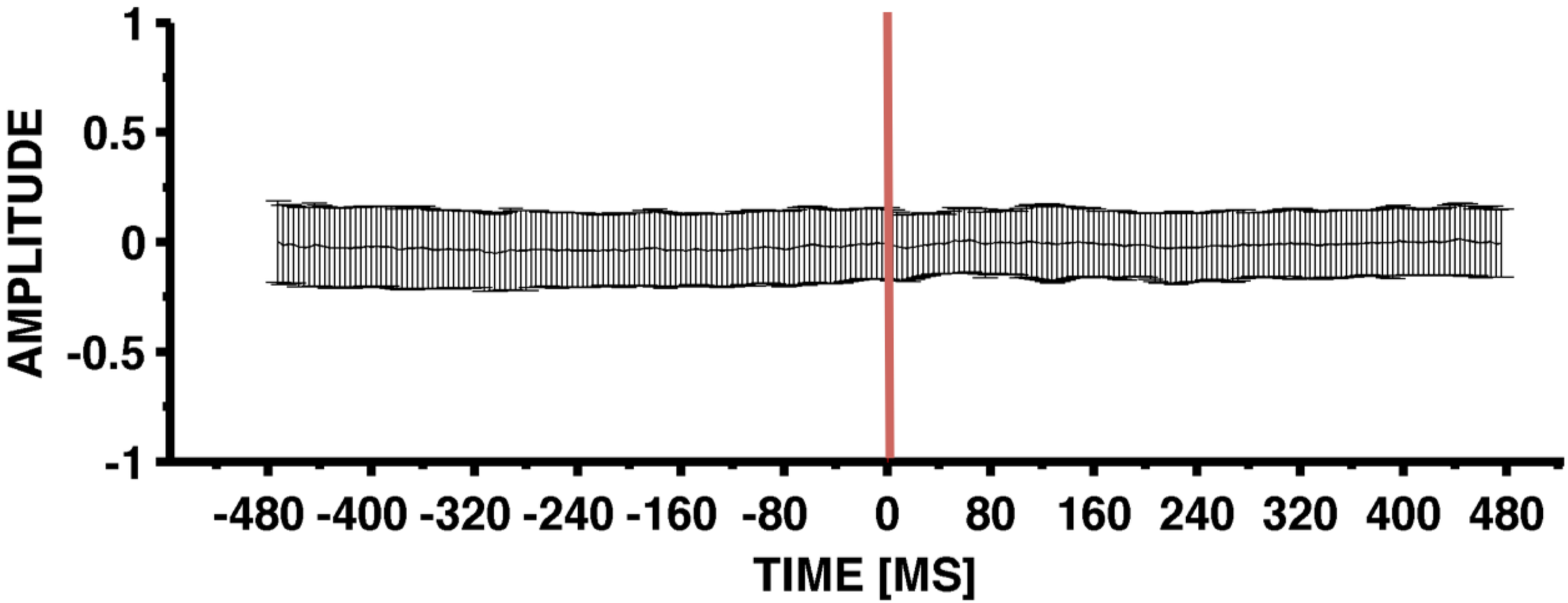

NORMALIZED SIGNAL CHANGE
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
*
*
*
*
AI
AC
BI
BC
CI
CC
SACCADE TYPE AND DIRECTION

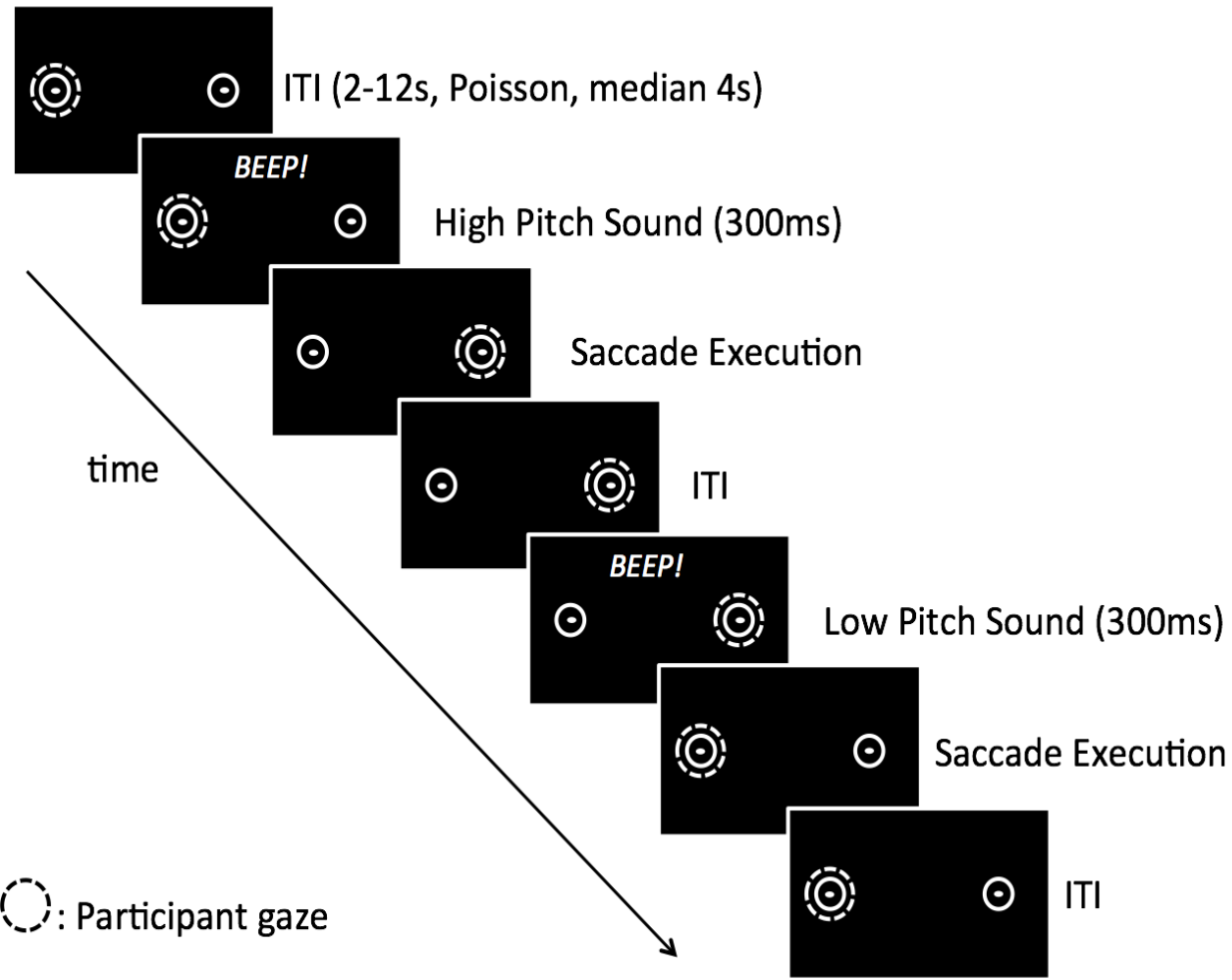

A
SC LH (No Go)
SC RH (No Go)
NUMBER OF VOXELS
50
40
30
20
10
0
-1
-0.5
0
0.5
1
LEFT BIAS
CONTRALATERALITY INDEX
RIGHT BIAS
B
SC LH (Go)
SC RH (Go)
NUMBER OF VOXELS
LEFT BIAS
CONTRALATERALITY INDEX
RIGHT BIAS

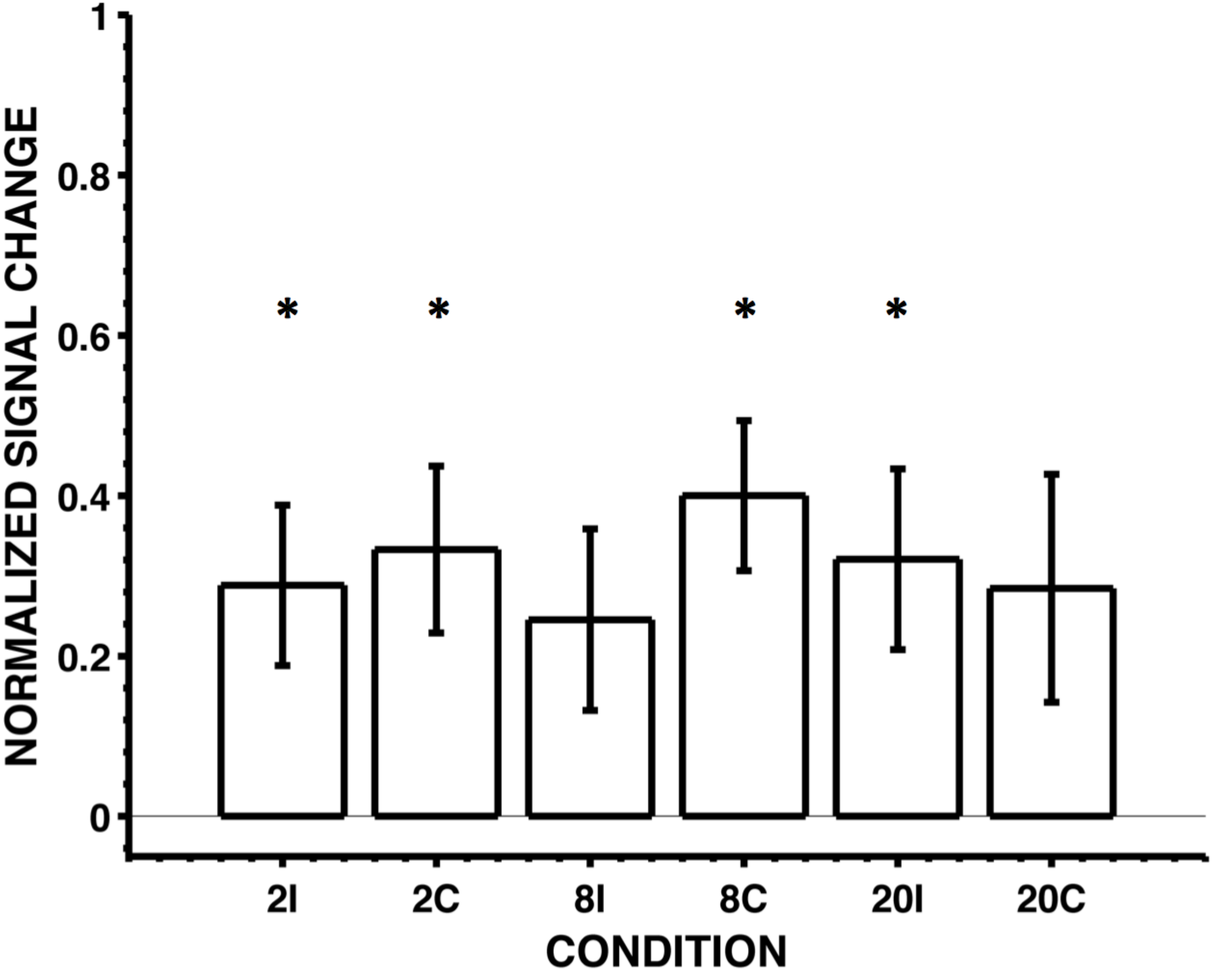
CUE RIGHT



CUE LEFT




ITI (2-12s, Poisson, median 4s)
BEEP!
High Pitch Sound (300ms)
Saccade Execution
time
ITI
BEEP!
Low Pitch Sound (300ms)
Saccade Execution
ITI
: Participant gaze


NORMALIZED SIGNAL CHANGE
1
0.8
0.6
0.4
0.2
0
*
*
*
*
2I
2C
8I
8C
20I
20C
CONDITION

Hemisphere	X(μ±σ)	Y(μ±σ)	Z(μ±σ)	Size (mm^3)	Size (Voxels)
SC RH	4±1	-27±1	-2±1	270±55	34±7
SC LH	-4±1	-28±1	-2±1	310±73	39±9

		Saccade type		
		Preparation	Execution	Return
SC	Ipsilateral	0.175±0.098	0.2825±0.111	0.004±0.100
	Contralateral	0.189±0.096	0.395±0.104	-0.096±0.102

Distribution	Max	Min	Mean	Median	Sd	Skew
SC LH (No Go)	0.98	-0.36	0.44	0.45	0.34	-0.23
SC RH (No Go)	0.64	-0.84	-0.08	-0.11	0.28	0.37
SC LH (Go)	0.5	-0.52	0.09	0.1	0.2	-0.17
SC RH (Go)	-0.03	-1	-0.34	-0.29	0.16	-1.33

Hemisphere	X(μ±σ)	Y(μ±σ)	Z(μ±σ)	Size (mm^3)
SC RH	5±2	-28±3	-3±2	399
SC LH	-5±3	-28±2	-3±2	538