City Research Online

City St George's, University of London

Citation: Jarvstad, A. & Gilchrist, I. D. (2019). Cognitive control of saccadic selection and inhibition from within the core cortical saccadic network. Journal of Neuroscience, 39(13), pp. 1419-18. doi: 10.1523/jneurosci.1419-18.2018

This is the accepted version of the paper.

This version of the publication may differ from the final published version. To cite this item please consult the publisher's version.

Permanent repository link: https://openaccess.city.ac.uk/id/eprint/21150/

Link to published version: https://doi.org/10.1523/jneurosci.1419-18.2018

Copyright and Reuse: Copyright and Moral Rights remain with the author(s) and/or copyright holders. Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge, unless otherwise indicated, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way. For full details of reuse please refer to City Research Online policy.

City Research Online: http://openaccess.city.ac.uk/ publications@citystgeorges.ac.uk

RUNNING HEAD: CONTROL OF SACCADIC SELECTION AND INHIBITION

Cognitive control of saccadic selection and inhibition from within the core cortical saccadic network

Andreas Jarvstad[1,2] and Iain D. Gilchrist[1]

[1]School of Experimental Psychology, University of Bristol, United Kingdom

[2]Department of Experimental Psychology, University of Oxford, United Kingdom

46 pages; 6 Figures; 3 tables.

Number of words for Abstract: 223; Significance statement: 118; Introduction: 650; Discussion 1494.

Conflicting interests: The authors declare no conflicting interests.

Corresponding author: Dr Andreas Jarvstad, andreas.jarvstad@city.ac.uk, Department of Psychology, City, University of London, Northampton Square, EC1V 0HB, United Kingdom.

Abstract

The ability to select the task-relevant stimulus for a saccadic eye movement, while inhibiting saccades to task-irrelevant stimuli, is crucial for active vision. Here, we present a novel saccade-contingent behavioural paradigm and investigate the neural basis of the central cognitive functions underpinning such behaviour - saccade selection, saccade inhibition and saccadic choice – in female and male human participants. The paradigm allows for exceptionally well-matched contrasts, with task demands formalized with stochastic accumulation-to-threshold models. Using functional magnetic resonance imaging, we replicated the core cortical eye-movement network for saccade generation (frontal eye fields, posterior parietal cortex and higher-level visual areas). However, in contrast to previously published tasks, saccadic selection and inhibition recruited only this core network. Brain-behaviour analyses further showed that inhibition efficiency may be underpinned by white matter integrity of tracts between key saccade generating regions, and that inhibition efficiency is associated with right inferior frontal gyrus engagement, potentially implementing general-purpose inhibition. The core network, however, was insufficient for saccadic choice which recruited anterior regions commonly attributed to saccadic action selection, including dorsolateral prefrontal cortex and anterior cingulate cortex. Jointly, the results indicate that extra-saccadic activity observed for free choice, and in previously published tasks probing saccadic control, is likely due to increased load on higher-level cognitive processes, and not saccadic selection per se, which is achieved within the canonical cortical eye movement network.

Significance statement

The ability to selectively attend to, and to *not* attend to, parts of the world is crucial for successful action. Mapping the neural substrate of the key cognitive functions underlying such behaviour – saccade selection and inhibition – is a challenge. Canonical tasks, often preceding the cognitive neuroscience revolution by decennia, were not designed to isolate single cognitive functions, and result in extremely widespread brain activity. We developed a novel behavioural paradigm, which demonstrates that: the cognitive control of saccades is achieved within key cortical saccadic brain regions, individual variability in control efficiency is related to white matter connectivity between the same regions, and wide-spread activity in canonical tasks is likely related to higher-level cognitive demands and not saccadic control.

When we interact with the world, visually salient, and less salient but nevertheless task-relevant objects, compete for attention. In the driving scene in Fig. 1A, the most salient object is the road sign, yet the car on the left is the most relevant (will it pull out?). As in this example, there is often a tension between salience and task-relevance: selection must overcome salient signals (look at sign) in favour of less salient but task-relevant ones (look at car).

Compared to the modest demands in the driving example, previously published tasks involve very strong control demands. For example, the anti-saccade task, involves inhibiting the urge to look at a sudden-onset highly salient peripheral stimulus, on an otherwise empty screen, whilst making a saccade of the same amplitude to its mirror location (Hallett, 1978). Other tasks involve similarly strong demands (e.g., countermanding, Brown, et al., 2008; Xu et al., 2017; search-step, Thakkar, et al., 2014).

Saccades, including saccades directed to singly presented stimuli (prosaccades), engage a core eye-movement network, which includes posterior parietal cortex (PPC); frontal eye fields (FEF); supplementary eye fields (SEF); basal ganglia, brain stem (e.g., superior colliculus [SC]) and cerebellum (see McDowell et al., 2008; Muri & Nyffeler, 2008; Munoz & Everling, 2004; Sparks, 2002; Schall, 2015, Liversedge et al., 2011 for detailed reviews). The network largely overlaps with networks for visual attention (Corbetta & Schulman, 2002).

The core network appears insufficient for tasks with strong control demands (e.g., anti-saccades), and additional cortical regions are recruited, including dorsolateral prefrontal cortex (dlPFC), anterior singulate cortex (ACC), pre-supplementary motor area (pre-SMA) and inferior frontal gyrus (IFG) (McDowell, et al., 2008, Thakkar et al., 2014; Everling & Johnston, 2013; Chikazoe, 2010). The recruitment of regions beyond the core network is interpreted as being linked to increased action control demands. Yet, given the tasks used, it

is difficult to map regions onto unique cognitive functions (see also Xu et al., 2017; Hampshire et al., 2010; Thakkar et al., 2014, p. 8926).

For example, anti-saccades, involve both inhibition and saccade vector inversion (Ford et al., 2005). Designs to deal with this include putting hypothesized processes on hold (Curtis & Conolly, 2008; Ettinger et al., 2007) or interrupting them (Brown et al., 2008). However, changing the temporal structure of the task or response may alter the processes themselves (Mazer & Gallant, 2003). Trials can also be sorted by behavioural criteria. One might, for example, assume that differences between error-free and erroneous anti-saccades reflect inhibition. However, there is often no unique mapping of sorted trials onto single cognitive functions. For example, error-related activity may also reflect failure to switch to, or maintain, the correct task set.

Crucially, relative to the standard base-line task (prosaccades), anti-saccades are dramatically more error prone, and therefore likely engage higher-level functions, such as performance monitoring linked to ACC (Braver et al., 2001; Botvinick et al., 2001) but also to FEF (Teichert et al., 2014). Moreover, anti-saccades involve a complex task set and therefore increased memory load, both linked to dlPFC function (Curtis and D'Esposito, 2003; Everling & Johnston, 2013). rIFG activation, primarily seen in stop-signal tasks (Aron et al., 2004, but see Chikazoe et al., 2007), can similarly be given an alternative interpretation (Xu et al., 2017; Sharp et al., 2010; Koechlin et al., 2003; Levy & Wagner, 2011; Schall & Godlove, 2012). One possibility is that the recruitment of areas outside the core saccade network reflect general higher-level demands, and not saccadic control per se.

Here we introduce a novel saccade-contingent paradigm, which in combination with modest demands, allows for closely matched contrasts. We outline the paradigm and formalize its control demands with a parsimonious accumulation-to-threshold model. In addition to measuring fMRI BOLD as a function of changing action control demands, we also provide more exploratory analyses of the relationship between brain structure (white

matter integrity) and brain function (fMRI BOLD) and stable individual differences in saccadic reaction time.

Materials and Methods

Paradigm

The paradigm replaces the stop-start nature of standard tasks with a continuous sequence of saccades along a diamond configuration (see also Pertzov et al. 2011). Each sequence begins at one of four positions ('potential target locations', Fig. 1B). After a brief inter-stimulus interval, one or two stimuli (depending on condition) appear adjacent to this fixation ('target onset'). After saccade initiation, the stimuli are extinguished, and a new fixation dot is shown in place of the current target. This occurs before the saccade reaches its destination ('target offset', saccade-contingent display). Another inter-stimulus interval follows, after which new potential targets are displayed adjacent to the now current fixation (and so on). To maximize the ability to detect differences in neural substrate between conditions we use a blocked design, with periods of 20 seconds of saccades followed by periods of 20 seconds of fixation, though the paradigm is compatible with event-related designs.

###################### Insert Figure 1 about here ######################

There were four different conditions (Fig.1C), three of which included two potential targets. The conditions were designed to capture differences in action control demands, whilst minimize between-condition differences in higher-level demands. In part, this was achieved by keeping overall error rates low (~2.5%, See Results), through careful selection of stimulus parameters, and a pre-scan behavioural session (Methods).

In the 'high-contrast' condition, saliency and task-relevance overlap and participants saccade to the most salient stimulus - equivalent to looking at the road sign in the driving

scene. The ‘low-contrast’ condition involves looking at the least salient stimulus and is equivalent to looking at the car – saliency and task-relevance are in conflict. The first (pro) and the last (choice) conditions are extreme endpoints of the action selection spectrum. 'Prosaccades' provide an eye-movement baseline with minimal control demands, and 'choice' mimics saccadic selection under “normal” conditions – when saccadic selection is free and involves mixtures of target saliences.

In the two-target conditions, one target was high-contrast and the other low-contrast. In an independent pilot study, we verified that the contrast of the stimuli affected their salience. The pilot was like the main study, except that only a single target stimulus was shown on each trial. That is, participants either looked at a singly presented high-contrast stimulus or a singly presented low-contrast stimulus. Saccades to high-contrast targets were faster than saccades to low-contrast targets ($z(8) = -3$, $p = .0195$, median difference = 5 ms, Wilcoxon signed-rank test), thus confirming stimulus contrast as a determinant of stimulus salience (see also Ludwig, Gilchrist & McSorley, 2004).

Action selection can be captured with stochastic accumulation-to-threshold models (e.g., Carpenter and Williams, 1995; Bompas & Sumner, 2011; Ludwig et al., 2005; Shadlen et al., 1996; Trappenberg et al., 2001, Schall & Godlove, 2012). These models share the following assumptions: 1) potential actions compete for selection, 2) the evidence in favour of each action accumulates over time, 3) the accumulation process stops as soon as the evidence for one action reaches a decision threshold, and 4) the boundary-crossing action is selected for execution.

To formalize the demands associated with each condition (Fig. 1C), we used a parsimonious model, with minimal changes to account for differences between conditions. All conditions were modelled with two accumulators with deterministic starting points. Accumulator drift rates were proportional to the contrast of the stimulus (no distractor < low

< pro < high), and identical across conditions, subject to within- and across-trial Gaussian noise, and lateral inhibition and rectification (e.g., Usher & McLelland, 2003).

In the prosaccade condition (Fig. 1C-D), there is only one target, but two potential target locations. The target accumulator (blue line) is driven by a strong signal and the distractor accumulator (red line) has close to zero-mean signal. Under these conditions, the threshold (dashed line) can be set very low: the absence of a distractor stimulus means that the risk of the wrong accumulator reaching threshold is negligible. The resulting saccades are both accurate and fast.

In the 'high-contrast' condition (Fig. 1C-D), the task is to select the most salient stimulus (blue line). Unlike the prosaccade condition, the distractor stimulus now has non-zero mean signal, which means that maintaining the same threshold would lead to frequent errors. The threshold is therefore elevated, which causes more evidence to be accumulated prior to action selection, thus avoiding premature selection of the less salient target. This, in turn, leads to longer response times with maintained accuracy.

Selecting the least salient target (Fig. 1C-D), however, cannot be achieved by threshold adjustment alone. On average, the low-contrast accumulator will not reach the threshold before the high-contrast accumulator. Thus, this condition necessitates a different kind of control. A mechanism that modulates the relative gain of the two accumulators; such that the weaker signal can overcome the stronger signal, allows the less salient stimulus to be selected. Here this is achieved after an initial accumulation stage, after which the action for which there is more evidence is inhibited. It is these processes that are candidates for being implemented from outside the primary cortical saccade network.

Although the previous example relies on actively inhibiting the stronger signal, and the contrast is labelled 'inhibition', other mechanisms for modulating the relative strength of each accumulator, some of which do not (or do not only) rely on modulating the distractor accumulator, are also feasible. Additionally, inhibition is a multi-faceted concept, both on the

neural (e.g., lateral vs feedforward inhibition; different types of inhibitory interneurons) and the functional level (e.g., inhibition of pre-potent responses, modulation of decision-relevant activity, global break-type inhibition, inhibition to step persevering). All our conditions minimally involve some form of global break-type inhibition – to stop participants returning to neutral straight-ahead fixation (and/or move eyes freely). Importantly, only the low-contrast and the choice condition involve inhibition as in the anti-saccade and other tasks.

The fourth and final condition is ‘choice’. Unlike the ‘high contrast’ and ‘low contrast’ conditions, this task involves decisions about which of two decision-rules to implement (possibly whilst considering the recent history of past choices). Participants were instructed not to pre-plan their saccades, or respond according to simple rules (e.g., alternating between low- and high-contrast stimuli), but to make a genuine choice on each trial. The main purpose of this instruction was to ensure that participants did not end up choosing only, or mostly, the high-contrast target. Due to the saccade-contingent display, any differences between this condition and the previous ones will be due to such decision-related processes.

As far as we are aware, there is no existing accumulator model for free saccadic choice. It is possible that participants simply switch randomly between ‘selection’ and ‘inhibition’ (Fig. 1D). However, this model is likely too simplistic. Moreover, because errors are ill defined, the modelling of the cost of switching between mechanisms render predictions very flexible, and because it is unclear how to model demands on performance monitoring and memory (e.g., remembering past choices) we refrain from specifying a full model for this condition.

The following contrasts between tasks may now be specified: prosaccades contrasted against fixation quantifies the demands of making saccades. [High-contrast – prosaccades] quantifies additional demands, over and above those required for making saccades, imposed by ‘selection’, modelled as a threshold adjustment. 'Inhibition' - [low-contrast - high-contrast]

– reflects demands imposed by ‘selection’ and additionally the control process allowing the least salient signal to be selected. 'Choice' [choice – low-contrast] represents the additional demands imposed by freely selecting between the two stimuli. Note that each consecutive contrast also captures the demands of the previous contrast(s). ‘Inhibition’, for example, also involves ‘selection’.

Based on extant literature, prosaccades should engage the following cortical areas: PPC, FEF and SEF, and visual cortex (McDowell et al., 2008). We expect demands associated with ‘selection’ and ‘inhibition’ to be met by the cortical saccadic network and higher-level visual areas (V4, Mazer & Gallant, 2003). For the anti-saccade task specifically, it has been hypothesized that the increased fMRI BOLD in FEF (e.g., Curtis & D’Esposito, 2003) reflects inhibitory processes (possibly increased firing rates of fixation-holding neurons, Hanes et al., 1998), that the increased activity in PPC may reflect the vector inversion necessary for successful anti-saccades (e.g., Medendorp et al., 2005), and that SEF may contribute by slowing saccadic onsets (e.g., Boxer et al., 2006). Although our tasks do not require re-mapping, the PPC is more generally thought to provide salience signals for action selection (Pare & Dorris, 2011), and is thus likely to be involved in the encoding and modulation of target-relevant signals in our task.

As noted initially, other tasks including the anti-saccade task, which target the same functions as the current tasks, also engage regions outside the primary cortical saccade network (e.g., dlPFC, ACC, IFG). The dominant view of dlPFC function is that it is directly involved in inhibiting saccades (e.g., Mueri & Nyffeler, 2008; McDowell et al., 2008). However, more recently Everling and Johnston (2013) proposed that the anti-saccade deficits observed in patients with dlPFC lesions (e.g., Pierrot-Deseilligny et al., 1991), and the increased fMRI BOLD for anti-saccades in dlPFC (e.g., Ettinger et al., 2008), is more consistent with the dlPFC implementing task sets. If the classical view of dlPFC is correct we should observe dlPFC activity for the ‘inhibition’ contrast here. More generally, if any extra-

saccadic region is directly involved in saccadic selection and/or inhibition they should be recruited for the current tasks also. Conversely, if the involvement of these regions in published tasks is due to increased higher-level demands (such as maintaining task sets), we should not be able to detect effects in extra-saccadic regions.

For choice one might predict activations which look like a mixture of 'selection' and 'inhibition'. However, because choice is involved, areas more typically involved in decision-making tasks, such as ACC and dlPFC, should be engaged (e.g., Hare et al., 2011). Significant effects in these extra-saccadic regions for this contrast, in conjunction with no detectable effects for the inhibition and selection contrasts, would strongly suggest that these extra-saccadic regions do not implement selection or inhibition per se, but reflect higher level cognitive functions (e.g., error-monitoring, memory, see also Xu et al., 2017 and Discussion).

Procedure

Participants took part in two sessions: a behavioural session (~60 min) and a scanning session (~90 min). In both sessions, each participant performed two runs of the experimental tasks. In each run, participants performed six consecutive blocks of 20 seconds of fixation followed by 20 seconds of saccades, for each of the four conditions. Each six-block sequence was preceded by a 5-second condition-cue. Condition order was randomized across runs and participants. For the three first conditions (Fig 1) participants were instructed to look at the appropriate target. For 'choice', participants were told to make a genuine choice on each trial and to not pre-plan their eye-movements. The behavioural session also included a familiarization phase to ensure compliance and understanding. The familiarization phase allowed participants to practise the tasks in a relaxed state and its length was flexibly adjusted based on individual participant needs. Data from the familiarization phase was not recorded.

Stimuli

Targets were grey discs subtending 1º visual angle presented on a light grey background (346 cd/m^2) at an eccentricity of 11.3 on the four cardinal axes (8º from the

centre of the screen). The fixation dot subtended .15º. The high-contrast target was dark grey (28 cd/m^2), the low-contrast target was light grey (192 cd/m^2), and the prosaccade target was intermediate between the high and the low contrast target (71 cd/m^2). To reduce memory load, the fixation dot luminance matched the luminance of the current target, except in the choice condition where the luminance was intermediate between the two targets (71 cd/m^2).

Apparatus

The experiment was written in MATLAB using Psychtoolbox (Kleiner, Brainard & Pelli, 2007). In the behavioural session the stimuli were shown on a CRT monitor (1152x864@85hz). In the fMRI session the stimuli were back-projected using a DLP projector (F22 SX+ VisStim, ProjectorDesign) onto a custom screen (1400x900@60hz) and viewed through a front-silvered head coil mounted mirror. Eye movements in both the behavioural and fMRI sessions were recorded at 1000hz with an EyeLink 1000 (SR Research Ltd.).

Image acquisition

Magnetic resonance images were acquired with a 32-channel head coil on a Siemens Skyra 3T scanner. For each participant, we recorded functional data, anatomical data, field maps and diffusion tensor images (DTI). Echo-planar images (EPI) were acquired with the following parameters: field of view=192mm, TR=2000ms, TE=30ms, flip-angle=90deg, 3mm isotropic voxels with a 25% distance factor. Each volume consisted of 36 slices. T1 anatomical scans were acquired with the following parameters: field of view=240mm, TR=1800ms, TE=2.25ms, flip-angle=9deg. Forty-nine field map slices were recorded with the following parameters: field of view=192mm, flip-angle=60deg, TR=520ms, TE=4.92ms. For each EPI sequence, we also recorded physiological variables (cardiac and respiratory phase). 130 diffusion volumes, one without diffusion weighting, were acquired with Siemens Multi Directional Diffusion Weighting (MDDW) with an acceleration factor of 2, 2mm slice

thickness and a 30% distance factor, bValue=1400 s/mm, FOV 192 x 192 x 130 mm, TR=6500ms, TE=70ms.

Experimental Design and Statistical Analyses

The study was approved by the local ethics board and participants gave written consent. Twenty-four healthy human participants of both sexes were paid £7/hr for the behavioural session of testing and £10/hr for the fMRI session (except for the first author who also took part). The sample size is consistent with the standard sample size for a study of this kind at the time of data collection. One of the participants was excluded as an outlier: in three of four conditions, this participant's median SRT was >3 inter-quartile range relative to the other participants. This was a within-subject design with each participant taking part in all four conditions, 'pro-saccade', 'high-contrast', 'low-contrast' and 'choice' (see Fig 1). The study was not pre-registered.

Behavioural analyses: Saccades, fixations and blinks were extracted using SR Research's algorithms. Valid trials were defined as trials which involved only one large saccade (> 50% of the distance between fixation and target, or > 5.5°), for which the saccade start coordinate was within 3° of the fixation dot and for which the saccade end coordinate was within 4° of the target. The mean and the standard deviation of the percentage of trials classified as invalid were as follows: prosaccade M=10%, SD=8%; high-contrast M=8%, SD=5%, low-contrast M=9%, SD=5%; choice M=13%, SD=9%. Saccade errors were defined as saccades that fulfilled the criteria for valid saccades except were directed at the wrong target (landing within 4º of the non-target stimulus). Errors are undefined in the choice task.

The tasks in the fMRI and behavioural sessions were identical, with periods of 20 seconds of saccades followed by periods of 20 seconds of fixation (see *Procedure*). Thus, time-on-task was time-limited with fast participants completing, on average, more trials than slow participants. To account for this variation, regressors capturing saccade frequency and saccade errors were included in the GLM for the fMRI analyses (see below). We observed no

quantifiable improvements (in SRT or error frequency) during the behavioural session, and report data from this session only to evaluate the association between behavioural and fMRI performance.

For behavioural analyses of SRTs and saccadic errors non-parametric tests of differences (paired Wilcoxon) and tests of association (Pearson's r) were used. All tests used conventional thresholds ($p<.05$). To explore participants choice sequences, we tested whether sequences were different from random (runs test, MATLAB, Bonferroni corrected for number of runs). We also assessed whether the average autocorrelation coefficients of participants choice sequences differed from zero by one-sample t-tests (uncorrected).

fMRI analyses: Imaging data was analysed with FSL (version 5.06-1, FMRIB's software library, www.fmrib.ox.ac.uk/fsl). EPI data was corrected for head-movements (Jenkinson, Bannister, Brady & Smith, 2002), non-brain removal was performed with BET (Smith, 2002) and data was spatially smoothed using a 5mm full width at half maximum Gaussian kernel. Data was filtered with a high-pass filter (1/100 Hz) and pre-whitened (Woolrich, 2001). EPI data was corrected for distortions using field maps (Jenkinson, 2004) and was registered to participant anatomical space (Jenkinson, Bannister, Brady & Smith, 2002), which in turn was registered to MNI space (non-linear registration, Anderson, Jenkinson & Smith, 2007).

Statistical inference on EPI data was performed with a general linear model. The design matrix was constructed as follows. Four regressors, one for each condition, specified the saccade blocks (with fixation blocks as the implicit baseline). Two further regressors specified eye blinks and the instruction periods respectively. These regressors were convolved with a double-gamma function and its temporal derivative. Estimated head movement regressors were also included, as were regressors that removed the influence of volumes estimated to contain large head-movements. Finally, voxel-wise physiological

regressors, modelling the measured cardiac and the breathing cycle, were included (Brooks, Beckman, Miller et al., 2008).

First-level (each run), second-level (the average of two runs) and third-level (participant-level) modelling involved six contrasts: 1) the prosaccade condition was contrasted with the implicit baseline, targeting regions that are more active for mixtures of saccades and fixations compared to fixation; 2-4) conditions with increasing demands on action selection were contrasted with those with lower demands: selection 2) high-contrast-prosaccade, inhibition 3) low-contrast-high-contrast, and choice 4) choice-low-contrast. We also included two control contrasts: 5) block-wise errors (number of valid saccades directed at the wrong target) and 6) block-wise saccade frequency (number of valid saccades), each modelled by a single regressor parametrically modulated by error and saccade frequency respectively. All regressors were entered competitively.

Second-level effects were modelled as fixed effects and third level effects were modelled using FSL's FLAME (1+2) and FSL's automatic outlier de-weighting (Woolrich, Beherens, Beckman, Jenkinson & Smith, 2004). Statistical maps were cluster-corrected at $z > 2.3$ and $p < .05$, and cluster information is provided in tables. Brain areas were labelled using FSL's Harvard-Oxford Cortical and Subcortical atlases, the Cerebellar Atlas in MNI152 (FNIRT) and the Juelich Histological Atlas. Areas not labelled in these atlases (e.g., the hypothesized human homologue of the frontal eye fields [FEF]), were localized anatomically and verified with published coordinates.

We also tested how individual differences in saccadic reaction time (SRT), and saccadic reaction time differences between pair-wise contrasts (ΔSRT), relate to functional activity and white-matter structure. Given the relatively low sample size (N=23) these analyses should be viewed as exploratory. For functional analyses, standardized SRTs/ ΔSRTs were entered as third-level covariates.

Voxelwise statistical analysis of the diffusion data was carried out using TBSS (Tract-Based Spatial Statistics, Smith, 2006). Fractional anisotropy (FA) images were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using BET. All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT, which uses a b-spline representation of the registration warp field (Rueckert 1999). The mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxel-wise cross-subject statistics. Participants were median-split into low/high SRT and ΔSRT groups. Non-parametric permutation testing with threshold-free clustering (Winkler et al., 2014) was used to test for differences between groups.

Results

Behaviour

The demands of successive conditions were reflected behaviourally in the fMRI session (Fig. 2A). Both selection and inhibition was associated with increased saccadic reaction time (SRT, Fig. 2B), as shown by highly significant paired-Wilcoxon tests (selection: $Z(22)=-4.2$, $p < .0001$; inhibition: $Z(22)=-3.9$, $p=.0001$). That is, although there were moderately large individual differences (see IQRs Fig 2A), there was highly reliable slowing down as control demands increased. The choice condition, however, did not result in statistically detectable change relative to the low-contrast condition (choice, $Z(22)=-.183$, $p=.855$).

Consistent with the paradigm targeting more modest control demands, SRT differences between conditions were smaller than those reported in the literature. For example, the behavioural cost of inhibition was ~11ms (low-contrast – high-contrast SRT), with the reported behavioural cost of anti-saccades 6-10 times larger (anti-pro SRTs, e.g., 60ms, Brown et al., 2006; >100ms Curtis & Connolly, 2008). The overall very low error rate

(~2.6%, c.f., ~10% in Brown et al,. 2006) is also consistent with the paradigm being less demanding than other tasks. Nonetheless, small but significant increases in error rates (Fig. 2 C) were observed for both the selection and inhibition contrasts ($Z(22)=-4.11$, $p<.0001$ and $Z(22)=-2.524$, $p=.0116$, respectively).

###################### Insert Figure 2 about here ######################

In the choice task, participants were effectively instructed to randomise their response from one trial to the next (see Methods). The purpose of this instruction was to avoid strong biases in favour of the high-contrast stimulus. Even so, there was a weak trend towards choosing the high-contrast target more than the low-contrast target (proportion of high-contrast choices $M=.52$, $SD=.77$), but it failed to reach significance ($t(22)=1.4$, $p=.17$, one-sample t-test against a choice proportion of .5). Jointly with the small increases in SRT with increasing demands, and very small increases in errors, the approximately equal choice proportion, shows that, although the high-contrast stimulus was more salient than the low-contrast stimulus (*Methods: Paradigm*), its pre-potency was comparatively weak (c.f., Brown et al., 2006; Curtis & Connolly, 2008).

Testing for systematicity in response sequences is non-trivial, partly because tests are imperfect, we have limited data, but also because there is no single a priori definition of systematic/random given our task. Nonetheless, in addition to evaluating the overall choice proportion, we also explored participants choice sequences in each run (the sequence of low- and high-contrast target decisions).

First, we performed runs tests, which test the null hypothesis that the sequence of low- and high-contrast target choices was random. The null hypothesis was rejected in 4 of 46 tests (23 participants, 2 runs) at $p <.025$ (Bonferroni corrected for runs). Thus, only .087 of the choice sequences were classed as non-random, which is close to the expected Type I error

rate ($p<.05$). Second, we computed the autocorrelation of the choice sequence with a lag up to 21 for each run and participant. One-sample t-tests on the autocorrelation coefficients showed that responses at trial 3 and 4 were negatively correlated with responses at trial 1 – but only for the first run. However, these effects were comparatively weak (average autocorrelation coefficient: trial 3 $r=-.10$, trial 4 $r=-.11$).

In summary, participants chose the low- and high-contrast target in approximately equal proportion, choice sequences were consistent with random choice, though there were weak temporal dependencies in the first run. A choice strategy based on randomly switching between the low- and the high-contrast choice rules, might be expected to result in SRT's in-between that of the low- and high-contrast conditions. This was not observed, suggesting that choice was not achieved by a simple mixing of selection mechanisms.

Not only were average SRTs similar across the sessions and the runs (Table 1), SRT was highly correlated both across conditions and the two sessions (behaviour and fMRI). Participants who were slow in one condition were also slow in others (pro-high, $r(21)=.83$, $p<0.0001$; high-low, $r(21)=.79$, $p<.0001$; choice-high $r(19)=.63$, $p=.0025$, two participants with exaggerated slowing for choice excluded for the choice-high correlation). Furthermore, SRTs in the behavioural and the imaging session were highly correlated (Prosaccade: $r(20)=.89$, $p<.0001$, High-Contrast: $r(20)=.89$, $p<.0001$, Low-Contrast $r(20)=.88$, $p<.0001$, Choice $r(20)=.47$, $p=.024$, N=22 due to missing behavioural data for one participant). We explore the functional and structural correlates of these apparently stable individual differences below.

################# Insert Table 1 about here ####################

Prosaccade contrast

The control of saccadic selection and inhibition

As expected, prosaccades (Fig. 3), implicitly contrasted with fixation, recruited key saccadic cortical regions: posterior parietal cortex (PPC), the hypothesized human homologue of the frontal eye fields (FEF, at the junction of the prefrontal sulcus and the precentral sulcus Luna et al., 1998; Amiez et al., 2006), and supplemental eye fields (SEF), as well as visual areas (Table 2 for cluster details). Within the FEF cluster we observed typical lateral and medial peaks of activity (e.g., Amiez et al., 2006; Ettinger et al. 2008),

The weak ventromedial prefrontal cortex (vmPFC) activation may be due to the relative demanding peripheral fixation baseline (deactivation of default network, Raichle, 2015), which is consistent with greater vmPFC engagement for prosaccades than for anti-saccades (Pierce & McDowell, 2016). We also observed, within the left FEF cluster (Figure 3; Table 2), a significant but relatively weak pre-frontal activation. This activation was substantially more ventral and anterior than pre-frontal activation commonly associated with higher-level control of saccades (e.g., Curtis & Connolly, 2008; Ettinger et al., 2008), and consistent with previously observed pre-frontal pro-saccade activation (e.g., Brown et al., 2006).

All regressors were entered competitively, which explains the relative absence of sub-cortical, cerebellar and brain-stem activations. These regions become highly significant when control regressors are orthogonalized with respect to task regressors.

###################### Insert Figure 3 about here ######################

Pair-wise condition contrasts

As can be seen in Figure 3, each additional demand, from an increase in decision threshold (‘Selection’), to a modulation of the integrated signals (‘Inhibition’), to free choice (‘Choice’), resulted in increased recruitment of key cortical saccade regions (PPC/FEF) and higher level visual areas (see especially MNI Z=52mm, and Table 2).

The control of saccadic selection and inhibition

The absence of significant activation outside the key cortical saccade regions for 'selection' and 'inhibition' suggests that action selection processes are implemented from within the cortical saccadic network, or at the very least, that action selection recruits saccadic regions to a much greater extent than extra-saccadic regions.

As initially noted, 'choice' could be solved by mixing 'selection' and 'inhibition' mechanisms. However, the choice contrast evokes a much wider network than that one might expect by such mixing. Instead, many of the additional regions are also those extra-saccadic regions engaged by decision-making tasks (e.g., Hare et al., 2011), including dlPFC, ACC, SEF, preSMA, OFC and insula.

##################### Insert Table 2 about here ###################

The observed main effects were not accounted for by differences in error rates or saccade frequency. Error frequency was associated with right lateral FEF extending down into right IFG/OFC and a separate cluster in cerebellum (Fig. 4). Saccade frequency was associated with SEF/ACC (Talanow et al., 2016) and some posterior visual activity (Fig. 4). Both of these results were comparatively weak (peak z=4.04 in cerebellum for error and peak z=3.89 for frequency, compared to e.g., peak pro-saccade z=5.72).

###################### Insert Figure 4 about here ######################

Neural correlates of individual differences in saccadic reaction time

We also investigated how individual differences in saccadic reaction time (SRT) relate to BOLD (Fig. 5, Table 3). Effects of basic prosaccade SRT were largely absent. The apparent lack of a significant association may be due to total on-task duration being fixed.

This meant that faster participants completed more trials than slower participants, possibly masking BOLD-related efficiency differences (c.f., Özyurt & Greenlee, 2011).

###################### Insert Figure 5 about here ######################

Nevertheless, pair-wise task contrasts revealed associations between the behavioural cost of action selection (i.e., differences in SRT between conditions, ΔSRT) and BOLD. Greater saccadic slowing for 'Selection' was associated with greater left dorsal IFG, PPC and OFC activity (red heatmap, Fig. 5). Faster participants (blue heatmap), on the other hand, engaged vmPFC more, suggesting a greater investment in the task relative to fixation.

For 'inhibition' and 'choice' those with larger behavioural costs showed increased activity in PPC and right insula/IFG. Thus, although our participants did not engage rIFG *on average* when having to inhibit a pre-potent response (Fig. 3), there was nevertheless a relationship between the behavioural cost of inhibition and rIFG activity (Aron et al., 2004).

As can be seen in Fig 5., some white matter voxels were significant. It is not unusual to observe significant BOLD responses outside the brain and/or in white matter in published work. Such activation may be a result of smoothing or imperfect mapping of EPI data onto the MNI template. To establish the extent of white-matter activations for these contrasts, we visually inspected the whole volume of each statistical map, and ran FSLs 'atlasquery' on the Harvard Oxford Subcortical Structural Atlas. Although a proportion of the significant voxels lay in white matter, the majority of significant voxels (for all contrasts) were classed as grey matter.

############### Insert Table 3 about here #######################

White-matter integrity and saccadic reaction time

We further performed whole-brain TBSS analyses exploring the relationship between SRT and fractional anisotropy (FA). We observed no significant effects for 'selection' or 'choice' (not shown). For prosaccades, FA was higher for white matter tracts between PPC and FEF for *slower* participants. The effect was largely left-lateralized, and extended dorsally to basal ganglia (incl. thalamus, pallidum and putamen) and anteriorly towards orbitofrontal cortex. For these analyses participants were median-split in low/high SRT groups, but post-hoc inspection reveals a non-linear relationship between FA and prosaccade SRT (Fig. 6, Table 3), with a positive association between FA and SRT emerging for participants with prosaccade SRT >~ 190ms.

For 'inhibition', the effects were predominantly in the brainstem extending dorsally through thalamus and towards FEF. Specifically, participants with the smallest difference between low- and high-contrast SRT, that is those with the smallest behavioural cost of inhibition, had higher FA between cortical and sub-cortical eye movement regions. The relationship between mean FA and median SRT appears non-linear here also, with the association levelling off for participants who pay the largest behavioural cost (largest ΔSRT).

###################### Insert Figure 6 about here ######################

Discussion

Salient stimuli have the capacity to drive saccadic selection, however salient stimuli are not always task-relevant. When relevance and salience do not overlap, action selection mechanisms must overcome salient signals to select appropriate actions. Previous work has used tasks with very strong control demands, often capturing multiple cognitive functions. Here we introduced a novel paradigm involving more moderate demands allowing for well-matched contrasts.

Whilst replicating key results, we also observe striking differences. The baseline condition (prosaccades), engaged known cortical substrate for controlling eye movements. Compared to tasks which involve more extreme control demands, such as the anti-saccade task, however, both the 'selection', and 'inhibition' contrasts engaged a much smaller network including PPC, FEF and higher-level visual areas. These results suggest that cortical mechanisms for 'selection' and 'inhibition' are implemented within sensori-motor and integration regions, without strong reliance on more anterior regions.

The focal recruitment of PPC and FEF for selection and inhibition contrasts with the regions engaged when participants freely choose between targets, for which activations extend far beyond the core cortical saccade network (including dlPFC, ACC, insula, pre-SMA, SEF and IFG). Although 'choice' effectively involved switching between two task sets, the recruited networks are more extensive than those seen for task switching, or switching between trial types (Pierce & McDowell, 2017), and closely match those recruited for decision-making (e.g., Hare et al., 2011 Fig. 3 & Table S3). Importantly, choice-related activations shows that the absence of extra-saccadic cortical involvement for the preceding contrasts ('selection', 'inhibition') was not due to a general inability to detect activity in these regions.

One explanation for the recruitment of extra-saccadic regions (e.g., dPFC, ACC) for previously published tasks, and their apparent lack of recruitment for selection and inhibition here, is that these regions are only engaged when control demands are more extreme. However, the joint result of no detectable SEF, ACC, dlPFC or IFG engagement for the inhibition and selection contrasts, but very strong effects for the choice contrast – a condition with greater memory load and a more complex task set – is consistent with the hypothesis that effects in more typical tasks are due to higher-level processes, rather than saccadic action selection per se (see also Mostofsky et al., 2003, Everling & Johnston, 2013; Xu et al., 2017; Erika-Florence, Leech & Hampshire, 2014; Pierce & McDowell, 2016; 2017), which in turn

is consistent with the reliable activation of these regions in tasks directly targeting these higher-level functions (e.g., Curtis & D'Esposito, 2003; Braver et al., 2001). This is especially noteworthy for dlPFC, because it is consistent with recent rethinking of dlPFC function - not as an inhibitory control region per se (Pierrot-Deseilligny et al., 1991; McDowell et al., 2008; Müri & Nyffeler, 2008) - but as a region involved in maintaining and implementing task sets (Johnston et al., 2013; Everling & Johnston, 2013).

One possible exception is rIFG. Although, the inhibition contrast did not result in significant rIFG engagement, the strength of rIFG activation correlated with ΔSRT for the two contrasts which do involve inhibition ('inhibition', 'choice'), but not significantly so for the contrasts which do not involve inhibition ('prosaccades', 'selection'). This is consistent with reported rIFG involvement in inhibition (e.g., Aron et al., 2007). Note, however, that the rIFG effect does not necessarily reflect a direct causal role in inhibition but may instead reflect broader inhibition-related demands (Erika-Florence et al., 2014; Xu et al., 2017). Post-hoc tests showed a very strong relationship between ΔSRT cost for inhibition and prosaccade SRT ($r(21)=.56$, $p=.0059$). That is, those who made fast prosaccades also paid the highest cost for inhibition. rIFG activation may therefore reflect a compensatory mechanism in those who make fast prosaccades, perhaps because they exhibit a lower base-line inhibition of all eye movement (e.g., less strong control of fixation).

Relatively little is known about the relationship between white-matter integrity and behavioural markers of saccadic control in humans (Manoach et al., 2007; Thakkar et al., 2016). We observed higher fractional anisotropy (FA) in white matter tracts between PPC, FEF and basal ganglia, for those who made slower prosaccades. Higher FA is typically associated with improved task performance. However, higher FA has also been associated with poorer behavioural outcomes (Tuch et al., 2004; Hoeft et al., 2007) and neuropathology (Douaud et al., 2011). There are at least two possibilities for the current positive association: one related to what FA measures, and the other related to the task itself. FA is affected by

several properties of white matter structure (Alexander et al., 2007), including myelination, fiber density, axonal diameter and fiber crossings. Increased myelination leads to both higher FA and increased nerve conduction, the latter which should improve SRT. However, as Tuch et al. outline, crossing fibres and other factors may invert the relationship leading to a positive association.

Alternatively, slow prosaccade SRT may be a sign of efficient task performance. All conditions involved relatively demanding fixation control. Stronger fixation holding is expected to result in slower release from fixation and therefore slower SRT. If stronger fixation is partly due to a task-wide strategy for avoiding premature responses, slower SRT should be correlated with performance. Post-hoc analyses show that participants with slower prosaccade SRT paid a smaller ΔSRT cost for 'selection' ($r(21)=-.65$, $p<.0001$). Thus, slow prosaccade SRT, associated with higher FA, may reflect more efficient fixation holding mechanisms, allowing for better saccadic selection.

Moreover, participants who exhibited lower behavioural costs for inhibition had higher FA in tracts from the brainstem to FEF. These results are consistent with known white matter tracts between saccade generating regions in cortex, sub-cortex and brain-stem (e.g., Helminski & Segraves, 2003, see Schall, 2015 for review). A recent tractography study showed that a fronto-striatal network is related to speed of inhibition and speed of selection in a search-step task (Thakkar et al., 2016). This is consistent with weak effects close to rIFG observed here, but direct comparisons are difficult because Thakkar et al. did not analyse whole-brain data and used a different task. Nevertheless, the observed effects suggest that individual differences in efficiency of inhibition may have structural origin.

Brain-behaviour correlations are often explored in fMRI studies with sample sizes of ~20 participants. However, given recent problems in replicating brain-behaviour correlations (Boekel et al., 2015), some caution is warranted in interpreting both the reported FAxSRT, and the BOLDxSRT associations. Nonetheless, data on functional and structural origins of

individual differences in saccadic action selection is sparse, and our results tentatively show that structural differences may underpin individual variability in action selection efficiency.

Whilst the current paradigm achieves good mapping of hypothesized functions onto fMRI BOLD contrasts (inhibition and selection, see also Xu et al., 2017), the accumulator formalization is likely too simplistic. The inhibition contrast, for example, was modelled as a modulation of the relative gain of two accumulators. However, the inhibition contrast strongly engaged FEF, PPC and V4, and these regions perform overlapping but separable functions (Schall, 2015). Thus, a formalization which more closely captures how the brain solves this task, will likely involve representing visual signals (V4), integrated decision-variables (PPC), and motor-plans (FEF) separately; all of which are modulated by the need to inhibit salient stimuli to select less salient but nevertheless task-relevant stimuli. At the level of individual neurons, we may speculate that the activity in some regions are supported by functional sub-classes of neurons. Activity in FEF, may for example, be a result of an increase in the recruitment of fixation-holding neurons, but also a direct modulation of visuo-motor neurons (Hanes et al., 1998).

Our paradigm could be used to explore distinct functions in different regions. One approach would be to use methods allowing for greater temporal specificity (MEG/neurophysiology) thus allowing the characterisation of how signals in V4, PPC and FEF evolve over the period of a single trial. Such approaches will necessarily involve event-related designs, which could also be used with fMRI to further probe processes involved in saccadic control. We also recognize that the choice contrast is not as optimal, in isolating function, as the other contrasts are. Of course, in some sense, the choice contrast provided the most interesting results. Nonetheless, future work is required to tease apart its wide-spread effects.

We presented a novel saccade-contingent paradigm for saccadic action selection under moderate demands, allowing for a very close mapping between hypothesized cognitive

functions and fMRI BOLD contrasts. The results replicated the known network for simple eye movements (prosaccades). However, 'selection' and 'inhibition' engaged a substantially more well-defined network than seen with alternative tasks. In contrast, when participants freely choose between targets, a substantially wider network is engaged; a network which overlaps with that seen in alternative tasks. Differences between the current and previous results can be accounted for, if it is assumed that extra-saccadic activity in standard paradigms are largely driven by higher-level demands associated with task complexity – not saccadic action-selection per se. Finally, we observed associations between FA and behaviour, which suggest that individual differences in saccadic action selection may be underpinned by individual differences in white matter structure.

Acknowledgements

This research was supported by the EPSRC (EP/1032622/1), a BBSRC Research Development Fellowship awarded to Iain Gilchrist (BB/H021574/1), and a British Academy Postdoctoral Fellowship awarded to Andreas Jarvstad (D-MAD, PF150005).

References

Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics, 4(3),* 316-329.

Amiez, C., Kostopoulos, P., Champod, A. S., & Petrides, M. (2006). Local morphology predicts functional organization of the dorsal premotor region in the human brain. *Journal of Neuroscience, 26(10),* 2724-2731.

Andersson, J. L., Jenkinson, M., & Smith, S. (2007). Non-linear registration, aka Spatial normalisation *FMRIB technical report TR07JA2*. FMRIB Analysis Group of the University of Oxford, 2, 1-21.

Aron, A. R., Robbins, T. W., Poldrack, R. A., (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences*, *8*, 170–177.

Boekel W, Wagenmakers EJ, Belay L, Verhagen J, Brown S, Forstmann BU (2015): A purely confirmatory replication study of structural brain-behavior correlations. *Cortex 66*:115–133.

Bompas, A., & Sumner, P. (2011). Saccadic inhibition reveals the timing of automatic and voluntary signals in the human brain. *The Journal of Neuroscience, 31(35),* 12501-12512.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological review, 108(3),* 624.

Boxer, A. L., Garbutt, S., Rankin, K. P., Hellmuth, J., Neuhaus, J., Miller, B. L., & Lisberger, S. G. (2006). Medial versus lateral frontal lobe contributions to voluntary saccade control as revealed by the study of patients with frontal lobe degeneration. *Journal of Neuroscience, 26(23),* 6354-6363.

Braver, T.S., Barch, D.M., Gray, J.R., Molfese, D.L, Snyder, A. (2001). Anterior cingulate cortex and response conflice: Effects for frequency, inhibition and errors. *Cerebral Cortex, 11(9),* 825 - 914.

Brooks, J. C., Beckmann, C. F., Miller, K. L., Wise R. G., Porro C. A., Tracey I., Jenkinson M. (2008). Physiological noise modelling for spinal functional magnetic resonance imaging studies. *Neuroimage, 39*, 680-692.

Brown, M. R. G., Vilis, T., Everling, S. (2008). Isolation of saccade inhibition processes: Rapid event-related fMRI of saccades and nogo trials. Neuroimage, 39, 793-804.

Carpenter, R. H. S., and Williams, M. L. L. (1995). Neural computation of log likelihood in the control of saccadic eye movements. *Nature 377*, 59-62.

Chikazoe, J. (2010). Localizing performance of go/no-go tasks to prefrontal cortical subregions. *Neuropsychiatry, 23,* 267-272.

Chikazoe, J., Konishi, S., Asari, T., Jimura, K., Miyashita, Y. (2007). Activation of right inferior frontal gyrus during response inhibition across response modalities. The *Journal of Cognitive Neuroscience, 19(1),* 69-80.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3(3),* 201.

Curtis, C. E., & Connolly, J. D. (2008). Saccade preparation signals in the human frontal and parietal cortices. *Journal of Neurophysiology, 99*, 133 - 145.

Curtis, C. E., & D'Esposito, M. (2003). Success and failure suppressing reflesxive behavior, *Journal of Cognitive Neuroscience, 15*, 409-418.

Douaud, G., Jbabdi, S., Behrens, T. E., Menke, R. A., Gass, A., Monsch, A. U., ... & Smith, S. (2011). DTI measures in crossing-fibre areas: increased diffusion anisotropy reveals early white matter alteration in MCI and mild Alzheimer's disease. *Neuroimage, 55(3),* 880-890.

Erika-Florence, M., Leech, R., Hampshire, A. (2014). A functional network perspective on response inhibition and attentional control. *Nature Communications, 5:4073,* DOI: 10.1038.

Ettinger, U., Ffytche, D. H., Kumari, V., Kathman, N., Reuter, B., Zelaya F., Williams, S. C. R. (2007). Decomposing the neural correlates of antisaccade eye movements using event-related fMRI. *Cerebral Cortex, 18*, 1148-1159.

Everling, S., & Johnston, K. (2013). Control of the superior colliculus by the lateral prefrontal cortex. *Philosophical Transactions of the Royal Society: Biological Sciences, 368*, 1-11.

Ford, K. A., Goltz, H. C., Brown, M. R. G., Everling, S. (2005). Neural processes associated with antisaccade task performance investigated with event-related fMRI. Journal of *Neurophysiology, 94,* 429-440.

Hampshire, A., Chamberlain, S. R., Monti, M. M., Duncan, J., Owen, A. M. (2010). The role of the right inferior frontal gyrus: Inhibition and attentional control. *Neuroimage, 50,* 1313-1319.

Hare, T. A., Schultz, W., Camerer, C. F., O'Doherty, J. P., & Rangel, A. (2011). Transformation of stimulus value signals into motor commands during simple choice. *Proceedings of the National Academy of Sciences, 108(44),* 18120-18125.

Harel, J., Koch, C., Perona, P. (2006). Graph-based visual saliency. *Proceedings of Neural Information Processing Systems (NIPS)*.

Helminski, J. O., & Segraves, M. A. (2003). Macaque frontal eye field input to saccade-related neurons in the superior colliculus. *Journal of Neurophysiology, 90(2),* 1046-1062.

Hoeft, F., Barnea-Goraly, N., Haas, B. W., Golarai, G., Ng, D., Mills, D., ... & Reiss, A. L. (2007). More is not always better: increased fractional anisotropy of superior longitudinal fasciculus associated with poor visuospatial abilities in Williams syndrome. *Journal of Neuroscience, 27(44),* 11960-11965.

Jenkinson, M. (2004). Improving the registration of B0-disorted EPI images using calculated cost function weights. Tenth Int. Conf. on Functional Mapping of the Human Brain.

Jenkinson, M., Bannister, P., Brady, M., Smith, S. (2002). Improved optimisation for the robust and accurate linear registration and motion correction of brain images. *NeuroImage, 17,* 825-841.

Jenkinson, M., Beckmann, C.F., Behrens ,T.E., Woolrich, M.W. Smith, S.M. (2012). FSL. *NeuroImage, 62*, 782-790.

Johnston, K., Koval, M. J., Lomber, S. G., & Everling, S. (2013). Macaque dorsolateral prefrontal cortex does not suppress saccade-related activity in the superior colliculus. *Cerebral Cortex, 24(5),* 1373-1388.

Kleiner, M., Brainard, D., Pelli, D., (2007). What's new in Psychtoolbox-3? *Perception, 36*, ECVP Abstract Supplement

Koechlin, E., Ody, C., & Kouneiher, F. (2003). The architecture of cognitive control in the human prefrontal cortex. *Science, 302(5648*), 1181-1185.

Levy, B. J., & Wagner, A. D. (2011). Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action updating. *Annals of the New York Academy of Sciences, 1224(1),* 40-62.

Liversedge, S. P., Gilchrist, I. D., & Everling, S. (2011). *Oxford handbook on eye movements.* Oxford University Press, Oxford, UK

Ludwig, C.J.H., Gilchrist, I.D. & McSorley, E. (2005). The remote distractor effect in saccade programming: Channel interactions and lateral inhibition. *Vision Research, 45,* 1177-1190.

Ludwig, C.J.H., Gilchrist, I.D., & McSorley, E. (2004). The influence of spatial frequency and contrast on saccade latencies. *Vision Research, 44*, 2597-2604.

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

Manoach, D. S., Ketwaroo, G. A., Polli, F. E., Thakkar, K. N., Barton, J. J., Goff, D. C., ... & Tuch, D. S. (2007). Reduced microstructural integrity of the white matter underlying anterior cingulate cortex is associated with increased saccadic latency in schizophrenia. *Neuroimage, 37(2),* 599-610.

Mazer, J. A., & Gallant, J. L. (2003). Goal-related activity in V4 during free viewing visual search: Evidence for a ventral stream visual salience map. *Neuron, 40,* 1241-1250.

McDowell, J. E., Dyckman, K. A.., Austin, B. P., Clementz, B. A. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades: Evidence from studies of humans. *Brain and Cognition, 68,* 255-270.

Mostofsky, S. H., Schafer, J. G., Abrams, M. T., Goldberg, M. C., Flower, A. A., Boyce, A., ... & Pekar, J. J. (2003). fMRI evidence that the neural basis of response inhibition is task-dependent. *Cognitive brain research, 17(2),* 419-430.

Munoz, D. P., & Everling, S. (2004). Look away: The anti-saccade task and the voluntary control of eye movement. *Nature Reviews Neuroscience, 5,* 218-228.

Müri, R. M., & Nyffeler, T. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades as revealed by lesion studies with neurological patients and transcranial magnetic stimulation (TMS). *Brain and cognition, 68(3),* 284-292.

Özyurt, J., & Greenlee, M . W. (2011). Neural correlates of inter- and intra-individual saccadic reaction time differences in the gap/overlaps paradigm. *Journal of Neurophysiology, 105,* 2438-2447.

Pertzov, Y., Avidan, G., Zohary, E. (2011). Multiple reference frames for saccadic planning in the human parietal cortex. *Journal of Neuroscience, 31(3),* 1059-1068.

Pierce, J. E., & McDowell, J. E. (2017). Contextual effects on cognitive control and BOLD activation in single versus mixed saccade tasks. *Brain and cognition, 115,* 12-20.

Pierce, J.E., & McDowell, J.E., 2016, Modulation of cognitive control levels via mnaipulation of saccade trial-tupe probability assessed with event-realted BOLD fMRI, *Journal of Neurophysiology, 115*, 763-772.

Pierrot-Deseilligny, C. H., Rivaud, S., Gaymard, B., & Agid, Y. (1991). Cortical control of reflexive visually-guided saccades. *Brain, 114(3),* 1473-1485.

Raichle, M. E. (2015). The brain's default mode network. *Annual review of neuroscience, 38,* 433-447.

Rueckert, D., Sonoda, L. I., Hayes, C., Hill, D. L., Leach, M. O., & Hawkes, D. J. (1999). Nonrigid registration using free-form deformations: application to breast MR images. *IEEE transactions on medical imaging, 18(8),* 712-721.

Schall, J. D. (2015). Visuomotor functions in the frontal lobe. *Annual Review of Vision Science,* 1, 469-498.

Schall, J. D., & Godlove, D. C. (2012). Current advances and pressing problems in studies of stopping. *Current opinion in neurobiology, 22(6),* 1012-1021.

Shadlen, M. N., Britten, K. H., Newsome, W. T., Movshon, J. A. (1996). A computational analysis of the relationship between neuronal and behavioural responses to visual motion. *Journal of Neuroscience, 16,* 1486-1510.

Sharp, D. J., Bonnelle, V., De Boissezon, X., Beckmann, C. F., James, S. G., Patel, M. C., & Mehta, M. A. (2010). Distinct frontal systems for response inhibition, attentional capture, and error processing. *Proceedings of the National Academy of Sciences, 107(13),* 6106-6111.

Smith, S. (2002). Fast Robust Automated Brain Extraction. *Human Brain Mapping, 17,* 143-155.

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., ... & Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage, 31(4),* 1487-1505.

Sparks, D. L. (2002). The brainstem control of saccadic eye movements. *Nature Reviews Neuroscience, 3,* 952-964.

Talanow, T., Kasparbauer, A. M., Steffens, M., Meyhöfer, I., Weber, B., Smyrnis, N., & Ettinger, U. (2016). Facing competition: Neural mechanisms underlying parallel programming of antisaccades and prosaccades. *Brain and cognition, 107,* 37-47.

Teichert, T., Yu, D., & Ferrera, V. P. (2014). Performance monitoring in monkey frontal eye field. *Journal of Neuroscience, 34(5),* 1657-1671.

Thakkar, K. N., van den Heiligenberg, F. M., Kahn, R. S., & Neggers, S. F. (2014). Frontal-subcortical circuits involved in reactive control and monitoring of gaze. *Journal of Neuroscience, 34(26),* 8918-8929.

Thakkar, K. N., van den Heiligenberg, F. M., Kahn, R. S., & Neggers, S. F. (2016). Speed of saccade execution and inhibition associated with fractional anisotropy in distinct fronto-frontal and fronto-striatal white matter pathways. *Human brain mapping, 37(8),* 2811-2822.

Trappenberg, T. P., Dorris, M. C., Munoz, D. P., Klein, R. M. (2001). A model of saccade initiation based on the competitive integration of exogenous and endogenous signals in the superior colliculus. *Journal of Cognitive Neuroscience, 13,* 256-271.

Tuch, D. S., Salat, D. H., Wisco, J. J., Zaleta, A. K., Hevelone, N. D., & Rosas, H. D. (2005). Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. *Proceedings of the National Academy of Sciences of the United States of America, 102(34),* 12212-12217.

Usher, M., & McClelland, J. L. (2001). The time course of perceptual choice: the leaky, competing accumulator model. *Psychological review, 108(3),* 550.

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *Neuroimage, 92,* 381-397.

Woolrich, M. W., Behrens, T. E. J., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modeling for fMRI group analysis using Bayesian inference. *Neuroimage, 21,* 1732–1747.

Woolrich, M. W., Ripley, , B.D., Brady, J.M., Smith, S.M. (2001). Temporal Autocorrelation in Univariate Linear Modelling of FMRI Data. *NeuroImage, 14,* 1370-1386.

Xu, K. Z., Anderson, B. A., Emeric, E. E., Sali, A. W., Stuphorn, V., Yantis, S., & Courtney, S. M. (2017). Neural Basis of Cognitive Control over Movement Inhibition: Human fMRI and Primate Electrophysiology Evidence. *Neuron, 96(6),* 1447-1458.x

Figure legends

Figure 1. A: A driving scene, low-level visual salience map (Harel, et al., 2006), and salience map overlaid on scene. The most salient part of the image is the road sign. The task-relevant car on the left has very low salience. B: Trial structure. Each block of saccades begun with fixation at one of the four possible target locations. After an inter-stimulus interval in the .75-1.25 second range (shifted and truncated exponential distribution) target stimuli were displayed. Once the eyes deviated by more than 3° from the current fixation, the targets were extinguished and replaced by a fixation dot at the target location. Blocks of 20 seconds of saccades were interleaved with blocks of 20 seconds of continuous fixation. C: Conditions: Prosaccades involve saccading to a single target, high-contrast involves saccading to the most salient of two targets, low-contrast involves saccading to the least salient of two targets, and choice involves a free choice between the targets. Pair-wise contrasts reflect: selection, inhibition, and choice. D: Stochastic accumulator model: Blue traces represent the target accumulator and red traces the distractor. The dashed line is the threshold at which a decision is made. The grey line for the low-contrast condition shows the distractor without inhibition. The model includes within- and across trial Gaussian noise and lateral inhibition.

Figure 2. fMRI session behaviour: A) median saccadic reaction time (SRT) as a function of condition. Error bars represent IQR; B) Boxplots of differences in SRT (ΔSRT) as a function of contrasts between pair-wise conditions, C) Boxplots of differences in error rates (Δerror rate) between pair-wise conditions (errors are undefined for the choice condition and therefore for the choice contrast).

Figure 3. BOLD effects of prosaccades and pair-wise task contrasts. ‘Prosaccades’ shows regions with greater activation for prosaccades than fixation. ‘Selection’ shows regions with greater activity for high-contrast blocks than for prosaccade blocks. ‘Inhibition’ shows

regions with greater activity for low-contrast blocks than for high contrast blocks. 'Choice' shows regions with greater activity for choice blocks than for low-contrast blocks. Heat-maps were cluster-corrected at $z > 2.3$ and $p < .05$, and scaled to lie in the Z=2.3–4 interval. Slice coordinates are in MNI space.

Figure 4. BOLD effects of error frequency and saccade frequency control regressors. Cooler colours represent greater activation. Maps were cluster-corrected at $z > 2.3$ and $p < .05$, and heat maps are scaled to lie in the Z=2.3–4 interval. Slice coordinates are in MNI space.

Figure 5. Individual differences in SRT and BOLD effects. For prosaccades the blue colourmaps indicate areas in which faster SRT was associated with greater activation. For pair-wise contrasts the red heatmaps indicate areas for which greater difference in SRT (ΔSRT) was associated with greater activation, and blue heatmaps indicate areas for which smaller ΔSRT was associated with greater activation. Maps were cluster-corrected at +-z 2.3 and $p < .05$, and heat maps are scaled to lie in the Z=[-4—2.3, 2.3–4] interval. Slice coordinates are in MNI space.

Figure 6. TBSS analyses of the relationship between SRT for prosaccades, and ΔSRT for inhibition, and fractional anisotropy (FA). Participants were median split into high and low SRT groups, and inferences performed on positive and negative associations between SRT and FA. Scatter plots show the underlying continuous relationship between SRT (prosaccades) and FA, and ΔSRT (inhibition) and FA averaged across all clusters of significant activity. Heatmaps are probability maps thresholded at $p < .05$ (corrected).

Table legends

Table 1. Saccadic reaction time (SRT) in milliseconds as a function of session type and run number. Median SRT with IQR SRT in parentheses.

Table 2. Local maxima in clusters of positive brain activation. Cluster forming threshold z=2.3 and $p < .05$ (corrected).

Table 3. Positive BOLD x SRT and FA x SRT cluster details. Cluster forming threshold z=2.3 and $p < .05$ (corrected) for SRT x BOLD, and threshold free clustering permutation testing for SRT x FA at $p < .05$ (corrected).

Table 1.

		Condition			
		pro-saccades	high-contrast	low-contrast	choice
Behaviour	Run1	188 (48)	221 (35)	251 (50)	257 (80)
	Run2	196 (36)	226 (21)	245 (27)	237 (71)
fMRI	Run1	192 (29)	226 (35)	238 (36)	253 (69)
	Run2	201 (37)	228 (34)	240 (26)	236 (70)

1

1

1 **Table 2.**
2

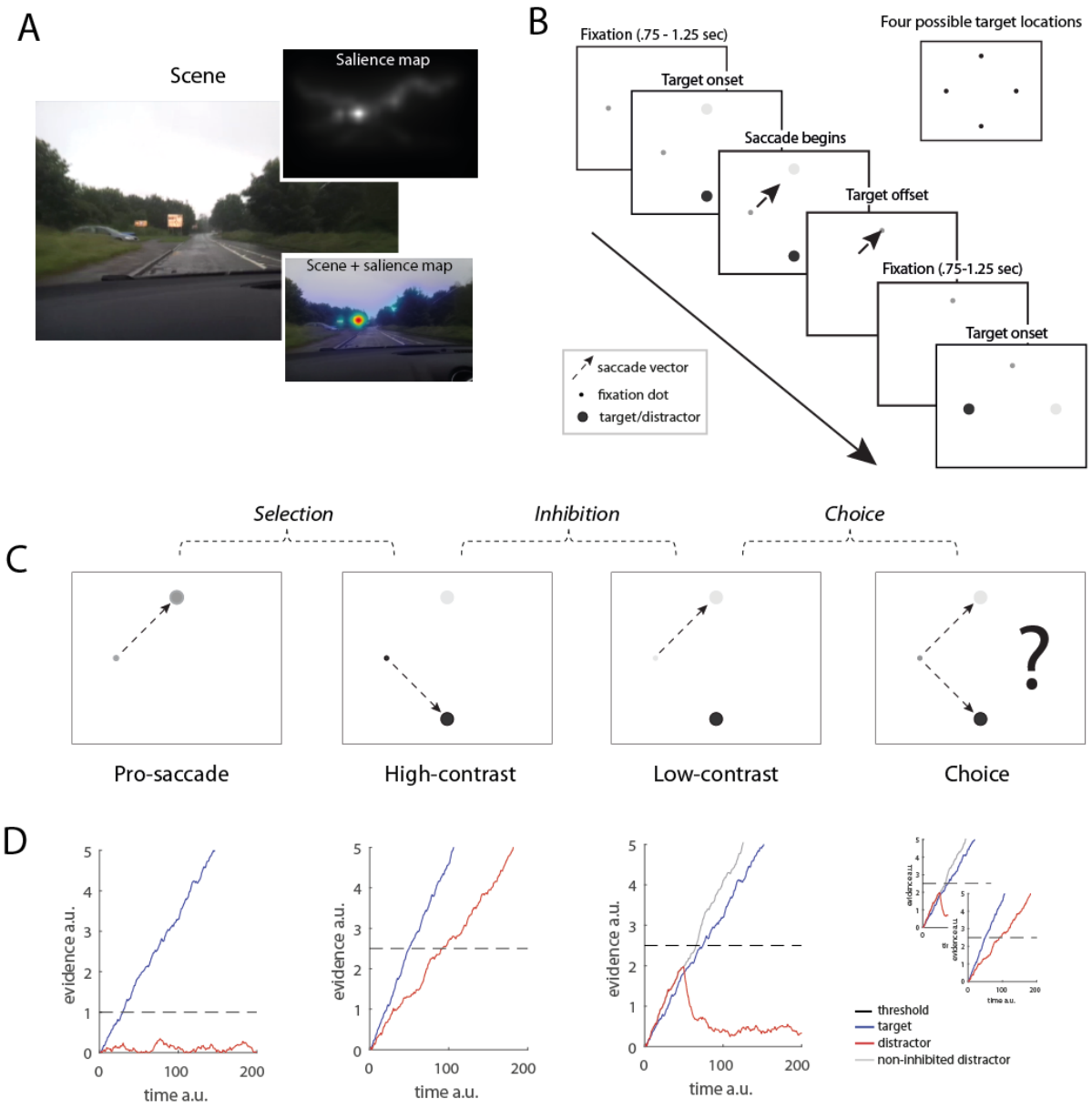
Contrast	Cluster size (voxels)	Peak Z	Peak X (mm)	Peak Y (mm)	Peak Z (mm)	Peak region (MNI)
Prosaccades	15674	6.35	4	-72	14	Occipital lobe (V1/V2)
	3196	4.77	8	2	58	SEF
	1195	5.62	48	-2	48	FEF
	782	4.29	6	56	-14	vmPFC
	419	3.85	-24	-8	12	Putamen
	360	4.09	62	-52	14	Parietal/temporal lobe
Selection	4507	7.09	-20	-70	50	PPC
	1295	4.94	26	-62	48	PPC
	784	3.74	34	-66	-14	Occipital lobe (V4)
	718	4.21	-26	-4	50	FEF
	385	3.93	-38	4	34	Precentral gyrus/MFG/BA44
	289	4.2	28	-2	52	FEF
Inhibition	6537	5.68	-18	-56	56	PPC
	552	4	-20	2	56	FEF
	347	3.74	20	-86	-6	Occipital lobe (V2/V3)
	285	3.57	24	4	48	FEF
Choice	21133	7.87	36	44	36	dlPFC (incl. FEF, SEF, ACC, IFG)
	9172	6.36	-28	-54	44	PPC
	1830	5.92	-34	-58	-32	Cerebellum (Crus I)
	1406	4.58	36	-48	-32	Cerebellum (VI)
	437	3.75	-6	-20	-4	Brain-stem (thalamus/SC)
	358	4.46	22	56	-4	OFC

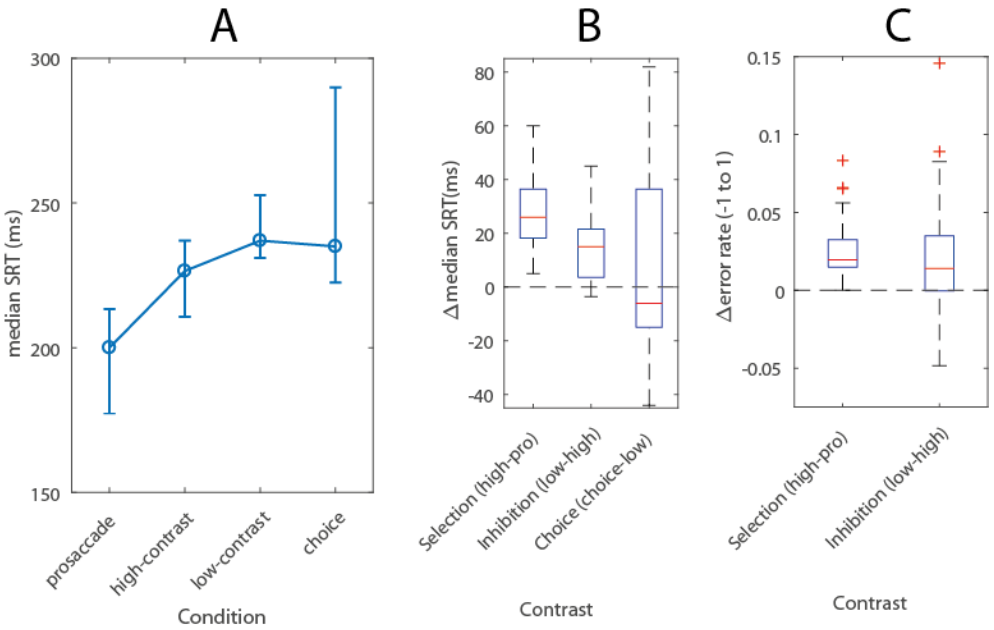
SEF=supplementary eye field, vmPFC=ventro-medial prefrontal cortex, PPC-posterior parietal cortex, FEF=frontal eye field, OFC=orbitofrontal cortex, SC=superior colliculus.

1 **Table 3.**

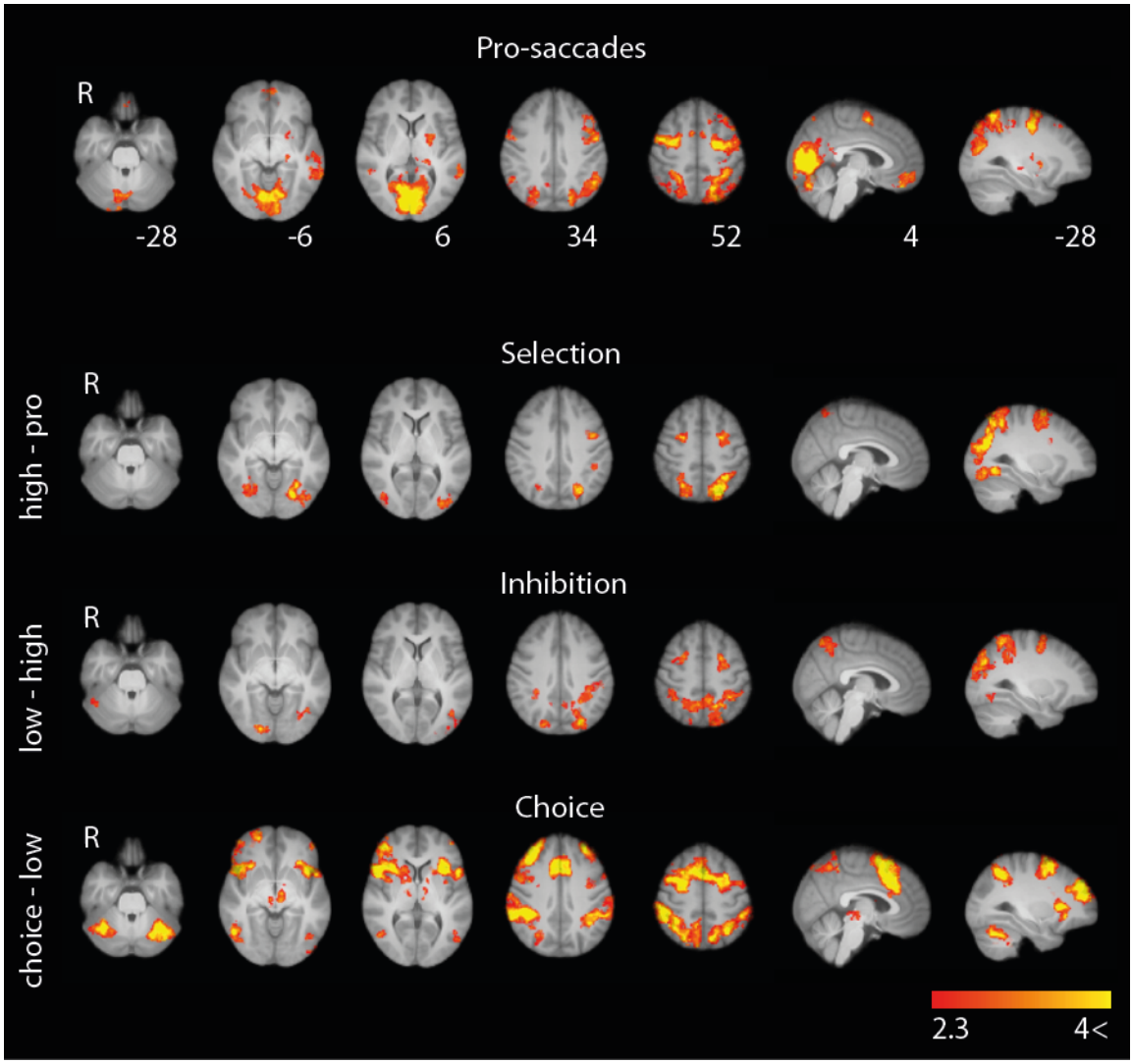
	Size (voxels)	Peak Z	Peak X (mm)	Peak Y (mm)	Peak Z (mm)	Peak region (MNI)
dSRT x selection	409	3.58	-54	-54	-8	middle temporal gyrus
	332	3.85	-30	-70	58	PPC
	330	3.76	-42	8	28	left IFG, pars opercularis
	321	3.28	-50	44	-10	left frontal pole
dSRT x inhibition	651	3.89	-28	-72	28	PPC ext. to V4
	368	3.73	12	-66	68	PPC
	254	3.39	56	16	12	right IFG,,pars opercularis
dSRT x choice	564	3.97	48	42	-8	right frontal pole ext to rIFG
	436	3.89	-44	-86	-6	lateral occipital cortex, inferior division

	Size (voxels)	Peak T	peak p	Peak X (mm)	Peak Y (mm)	Peak Z (mm)	Peak region (MNI)
FA x prosaccade SRT	4145	3.79	0.03	-26	-30	19	Superior corona radiata L
	788	4.64	0.037	26	-23	26	Posterior corona radiata R
FA x inhibition dSRT	2048	5.3	0.036	-9	-20	8	thalamus/Cerebral peduncle
	540	3.9	0.044	35	-29	36	Superior longitudinal fasciculu
	282	4.04	0.044	-27	-20	-7	Fornix (cres) / Stria terminalis
	139	4.23	0.046	30	13	14	anterior corona radiata
	114	5.47	0.046	31	-2	17	External capsule R
	74	3.42	0.048	-25	23	13	Anterior corona radiata L
	63	3.42	0.049	-28	-29	9	internal capsule L
	39	4.42	0.048	-23	29	1	Anterior corona radiata L

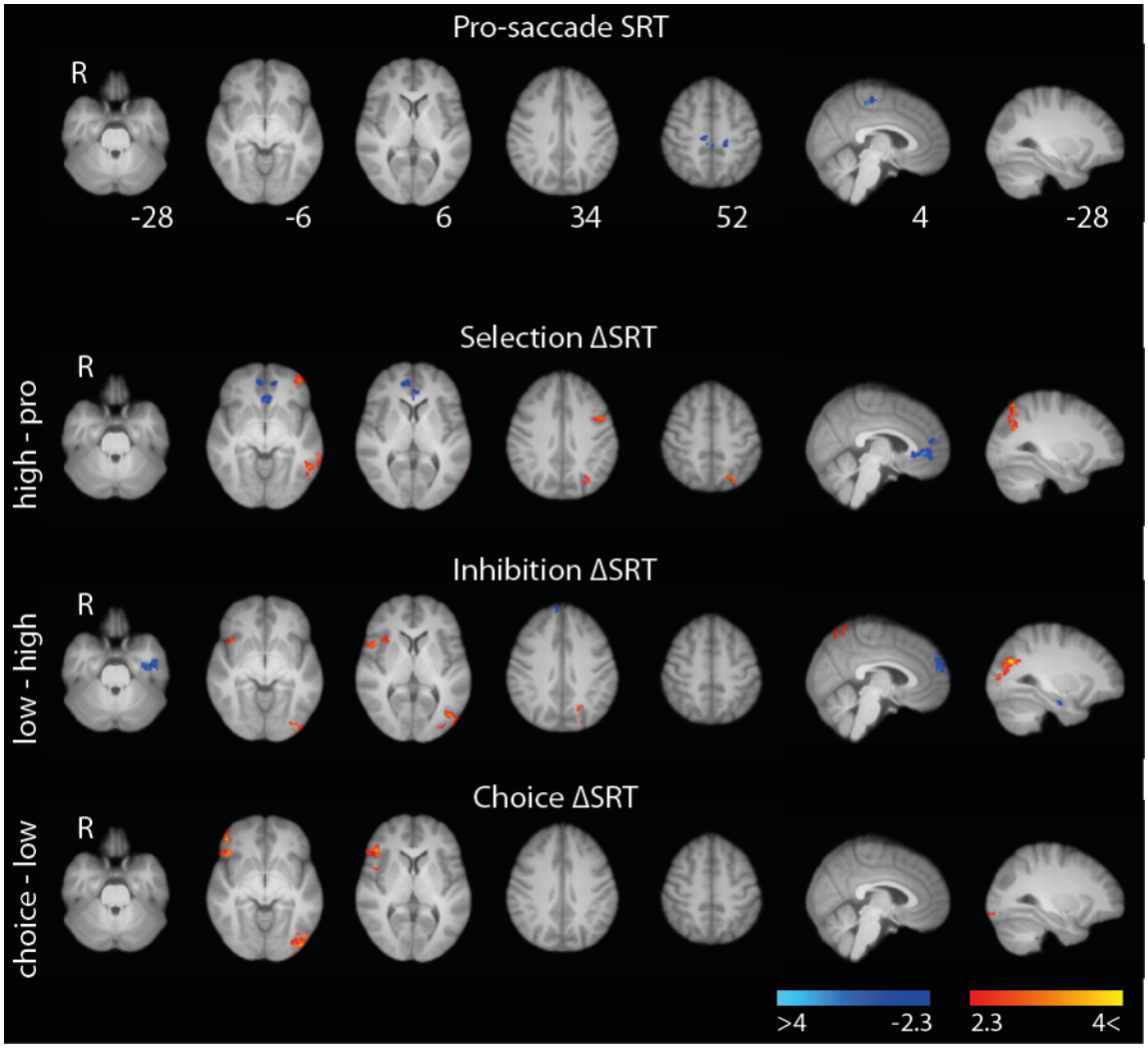

A
Scene
Salience map
Scene + salience map
B
Fixation (.75 - 1.25 sec)
Target onset
Saccade begins
Target offset
Fixation (.75-1.25 sec)
Target onset
Four possible target locations
saccade vector
fixation dot
target/distractor
C
Selection
Inhibition
Choice
Pro-saccade
High-contrast
Low-contrast
Choice
D
evidence a.u.
time a.u.
threshold
target
distractor
non-inhibited distractor

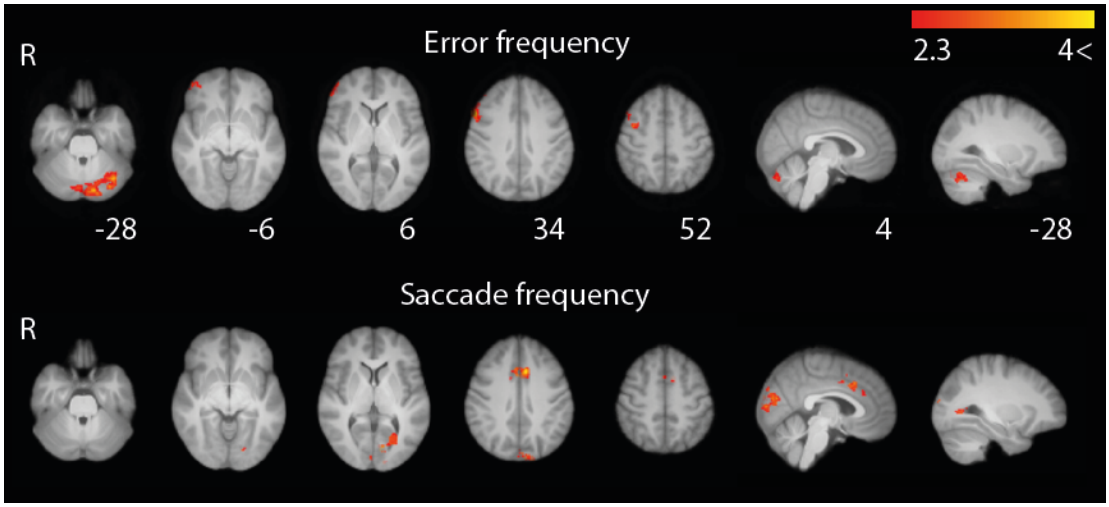

A
B
C
median SRT (ms)
300
250
200
150
prosaccade
high-contrast
low-contrast
choice
Condition
Δmedian SRT(ms)
80
60
40
20
0
-20
-40
Selection (high-pro)
Inhibition (low-high)
Choice (choice-low)
Contrast
Δerror rate (-1 to 1)
0.15
0.1
0.05
0
-0.05
Selection (high-pro)
Inhibition (low-high)
Contrast

1

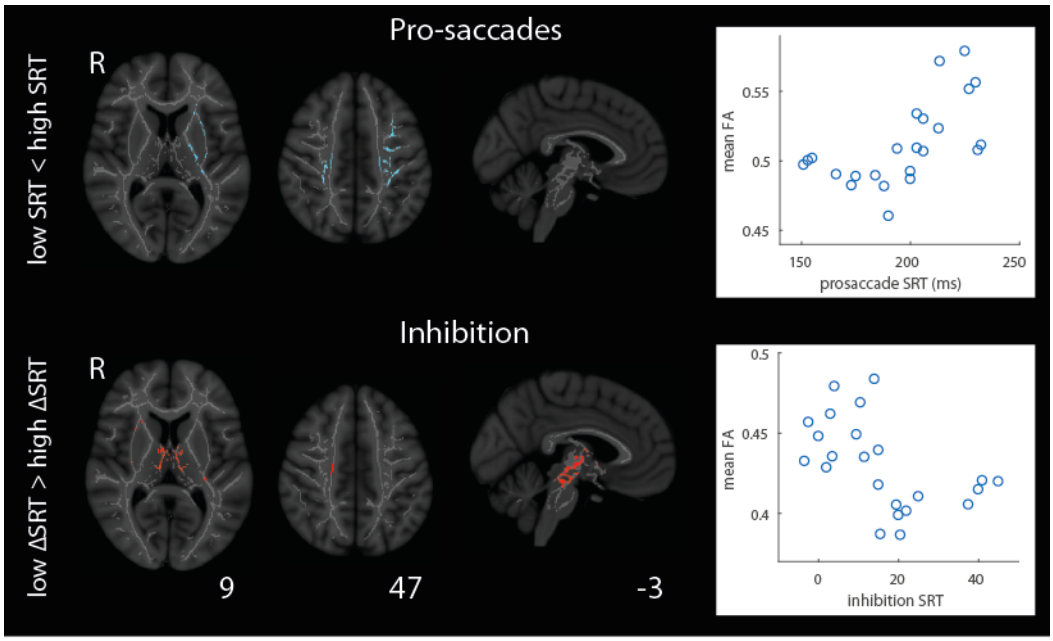

Pro-saccades
R
-28
-6
6
34
52
4
-28
Selection
high - pro
R
Inhibition
low - high
R
Choice
choice - low
R
2.3
4<

1


Pro-saccade SRT
R
-28
-6
6
34
52
4
-28
Selection ΔSRT
high - pro
R
Inhibition ΔSRT
low - high
R
Choice ΔSRT
choice - low
R
>4
-2.3
2.3
4<


R
Error frequency
2.3
4<
-28
-6
6
34
52
4
-28
Saccade frequency
R

1


Pro-saccades
low SRT < high SRT
R
mean FA
0.55
0.5
0.45
150
200
250
prosaccade SRT (ms)
Inhibition
low ΔSRT > high ΔSRT
R
9
47
-3
mean FA
0.5
0.45
0.4
0
20
40
inhibition SRT

2