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Chapter IV

The Location and Function of Parietal Cortex Supporting Reflexive and Complex Saccades, a Meta-Analysis of a Decade of Functional MRI Data

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Abstract

Saccades are rapid eye movements that move the eyes to a location of interest. Regions within posterior parietal cortex (PPC) have consistently shown activation in brain imaging studies of saccades, ostensibly reflecting shifts of visual attention and the transformation of sensory input into motor commands. Saccades range from the most basic reflexive glances toward a target to more complex saccades, which require some form of cognitive control (such as working memory or inhibition of reflexive responses). This study sought to summarize and parse the relative contribution of various brain regions (and parietal regions in particular) to reflexive and complex saccades.

We conducted an activation likelihood estimation (ALE) meta-analysis of functional MRI studies of saccades in healthy adult humans. Twenty-two studies were identified that met our criteria. These studies provided 338 participants and 375 foci for the meta-analysis, which was conducted using the GingerALE application from BrainMap. Separate analyses were conducted for all saccades, reflexive saccades only, and complex saccades only. In addition, a subtraction analysis was done to determine significant differences in activation probability between reflexive and complex saccades.

The analysis of all saccades showed activation in cortical and subcortical areas consistent with previous literature. Reflexive saccades showed a greater probability of activation than complex saccades in more superior and lateral regions of superior parietal cortex, intraparietal sulcus, middle and superior temporal cortex, cerebellum, and visual cortex. Complex saccades showed a greater probability of activation than reflexive saccades in more inferior and medial regions of superior parietal cortex, SMG in inferior parietal cortex, SEF, FEF (particularly the midline), PFC, and thalamus. Of particular interest were the differential contributions of parietal regions to the two types of saccades, specifically the SPC, IPS, IPL, and SMG. The current meta-analysis provides evidence that the posterior parietal cortex is heterogeneous, with distinct functional subregions that are differentially involved in reflexive or complex saccade performance.

Introduction

Saccades are rapid eye movements that reposition the fovea to a location of interest [1]. They range from basic visually-guided saccades (also known as prosaccades or reflexive saccades) which foveate a visual target to more complex voluntary saccades which require greater cognitive control, such as inhibition of an eye movement and/or maintenance of an internal representation of a spatial location for later eye movements. One example of a complex saccade is an antisaccade, which involves inhibition of a glance to a newly appearing cue and redirection of gaze to its mirror image (opposite side, same amplitude) [2]. Another example is a memory saccade, which involves maintenance of fixation on a central target while a peripheral cue is presented and throughout a subsequent delay period. The end of the delay period is signaled by the extinction of the central target and serves as the instruction to generate a glance to the remembered location of the peripheral cue [3]. Correct performance on all saccadic tasks, reflexive and complex, requires visual perception, visuospatial attention and motor responses. Complex saccade task performance also requires inhibitory control, working memory and generation of a saccade to a specific spatial location in the absence of a visual target. Complex saccade performance can be used as a measure of cognitive control and flexibility.

The same basic neural circuitry supporting saccade generation is utilized for both reflexive and complex saccadic responses [1; 4], with evidence that complex saccade performance requires greater activity in the same circuitry and/or recruitment of additional neural regions [5]. Regions included in these networks are: brainstem, cerebellum, superior colliculus, basal ganglia, thalamus, visual cortex, frontal eye fields (FEF), supplementary eye field (SEF), prefrontal cortex (PFC), cingulate cortex, and posterior parietal cortex (PPC) [1; 2; 6; 7]. Subcortically, the brainstem generates saccadic eye movements, which are coordinated by the superior colliculus, while the cerebellum is important in determining the amplitude of the saccades [1; 8]. Nuclei of the basal ganglia project to the superior colliculus and may support target selection and saccade initiation, particularly when responses are rewarded [1; 9]. The caudate nucleus of the basal ganglia may also be involved in saccade suppression [10], and evidence suggests that the thalamus is involved in the control of antisaccades specifically [11].

Within the cortex, occipital areas (specifically, the cuneus and lingual gyrus) support visual perception and may play a role in presaccadic remapping processes (i.e., the shifting of receptive fields to future spatial locations) [12]. The FEFs are involved in generating saccadic

movements and may be more important for complex than reflexive saccades. The SEF may be involved in target selection based upon previously rewarded performance and in making sequences of learned saccades [1]. The PFC may mediate both inhibition and maintenance of remembered target locations [1; 2]. The cingulate cortex is likely involved in error monitoring, learning rewarded sequences of saccades, and other more complex saccade tasks [1; 13; 14].

The relative contribution of parietal cortex regions to reflexive and complex saccade performance is of particular interest in the current analysis. Regions within PPC show activation in brain imaging studies during saccadic performance [15; 16]. The PPC ostensibly supports shifts of visual attention [1; 17] and the transformation of sensory input into motor commands [2]. One region of the PPC, the superior parietal cortex (SPC), has been shown by many studies to be associated with saccade tasks [18]. While the SPC is activated with reflexive saccades [19], its role in mediating attention may increase activity in this region for more complex saccadic tasks [20]. A medial region of the SPC, which is also known as the precuneus, has been reported in many neuroimaging studies of saccades. This region may show more activation for complex than reflexive saccades [2], although the reverse also has been reported [21].

Still in parietal lobe, but positioned inferior to the SPC and precuneus regions is the intraparietal sulcus (IPS) [1; 22; 23]. Projections from the IPS have been mapped to the FEF and superior colliculus, suggesting a role in saccade execution [23; 24; 25]. The role of the IPS in saccadic performance is a topic of ongoing study, but it has been suggested that IPS is involved in visuospatial integration and reflexive saccade triggering [1; 22]. At least one study has found that reflexive saccades elicit greater activation in the IPS than complex saccades [21], suggesting that while this region is important for saccades in general, it may be more critical for supporting reflexive than complex saccades. In addition to its potential role in saccade generation, the IPS appears to be important in attentional processes. For instance, there is evidence that IPS is involved in spatial updating of visual information [26]. It has been suggested that human IPS is the analogue of monkey parietal eye field (PEF), which is positioned in lateral intraparietal area [27; 28].

Previous reviews and meta-analyses on saccadic circuitry have been conducted [29; 30], although the most recent analysis was inclusive of studies only through 2004 [31]. The current meta-analysis expands upon these earlier findings by incorporating the recent literature from this rapidly expanding area (see Figure 1; McDowell et al., 2008 showing a doubling of the number of neuroimaging and saccade studies available via PubMed roughly every 4 years between 1988 and 2007). Given this recent increase in relevant publications, the current meta-analysis can be conducted based solely on fMRI studies instead of relying on a mixture of PET and fMRI studies. PET and fMRI are characterized by differing temporal resolution (with fMRI data capturing shorter time periods) and spatial resolution (with fMRI typically having finer spatial resolution) [32; 33]. Thus, including only one imaging modality ensures the most comparable contingent of studies. Further, improved identification of saccadic circuitry is realized by including only studies with a passive fixation baseline (i.e., excluding studies that had active baselines, which were usually reflexive saccades). Finally, only those studies that reported results based on whole brain analyses are used. These later characteristics adhere to the best practice recommendations made by the authors of the meta-analytical software [34; 35]. It is anticipated that the current available advances will provide more precise localization of overlapping and differential circuitry supporting reflexive and

complex saccades. Of particular interest is the identification of various parietal regions, particularly the IPS, in these two types of saccadic tasks. The current meta-analysis investigates brain activation associated with both types of saccades collapsed together, as well as for each type separately, in order to further clarify the circuitry involved in each type of saccade.

Methods

Study Selection

fMRI studies comparing patterns of activity in healthy adult participants were found by searching the MEDLINE (PubMed) database using the keywords: saccade, fMRI and “functional magnetic resonance”. We placed no limit on the year of publication and the search was completed in October 2011. Articles were included in the analysis only if they met all of the following criteria: a) journal articles available in English, b) full text available, c) results reported for healthy adult participants alone, and d) whole brain analyses (>80 mm brain coverage and non-ROI analyses) with reported MNI (Montreal Neurological Institute) or Talairach coordinates. We also included data from one previously published study from our laboratory, which was re-analyzed using a whole brain analysis (rather than the published ROI analysis) [3]. The 22 studies identified are listed in Table 1.

Whole Brain fMRI Data Collection and Analysis

The literature search revealed that there were relatively more studies available of reflexive than complex saccades. In order to increase the number of foci in the complex saccade analysis (and therefore make the analyses more comparable), we conducted an additional whole brain re-analysis of data from our laboratory that have been previously published as a regions-of-interest analysis [3]. Fifteen healthy participants were analyzed. All participants underwent a three-dimensional T1-weighted structural MRI scan for definition of anatomical structures (spoiled gradient-recall protocol: echo time = 2.8 msec, repetition time = 10.8 msec, flip angle = 20°, number of excitations = 2, matrix = 256 x 256, field of view = 24, slice thickness = 1.5 mm, sagittal acquisition, 124 contiguous slices, scan time 5 min 41 sec). Then, two functional runs were conducted. For each, a series of T2*-weighted functional images were obtained (spoiled-gradient pulse sequence with a spatial readout pattern in k-space: echo time = 40 msec, repetition time = 1912 msec with two interleaves resulting in an image acquisition time of 3.8 sec, flip angle = 77°, matrix = 64 x 64, field of view = 24, slice thickness = 4 mm, axial acquisition, 24 contiguous slices). Functional scan time was 5 min 8 sec for the antisaccade task and 6 min 9 sec for the memory saccade task.

Analyses were conducted with Analysis of Functional NeuroImages (AFNI) [54]. For each functional run, despiking was performed to reduce noise. Volumes were registered to a middle volume to correct for minor head movement and aligned to the anatomical images. A 4-mm full-width at half-maximum Gaussian filter was applied to each dataset and then each run was scaled by its mean to allow for group comparison. Multiple linear regression was

Table 1 Data sources. Studies were conducted at 1.5 Tesla unless otherwise indicated. * indicates 3 T, † indicates 2 T, ‡ indicates 4 T

Study and Year	<i>n</i>	Contrast
Corbetta, et al., 1998 [36]	5	Reflexive saccades > fixation
Perry and Zeki, 2000 [37]†	7	Reflexive saccades > fixation
Simó et al., 2005 [6]*	10	Reflexive saccades > fixation
Nelles et al., 2007 [38]	10	Reflexive saccades > fixation
de Haan et al., 2008 [39]	10	Reflexive saccades > fixation
Ettinger et al., 2008 [40]	36	Reflexive saccades > fixation
Haller et al., 2008 [41]	14	Reflexive saccades > fixation
Ettinger et al., 2009 [42]	24	Reflexive saccades > fixation
Nelles et al., 2009 [43]	11	Reflexive saccades > fixation
Petit et al., 2009 [44]	27	Reflexive saccades > fixation
Schraa-Tam et al., 2009 [21]	18	Reflexive saccades > fixation
van Broekhoven et al., 2009 [45]	17	Reflexive saccades > fixation
Krebs et al., 2010 [46]*	16	Reflexive saccades > fixation
Grosbras et al., 2001 [47]*	9	Memory-guided saccades > fixation
Matsuda et al., 2004 [5]	21	Antisaccades > fixation
Sugiura et al., 2004 [48]	19	Memory-guided saccades > fixation
Camchong et al., 2006 [49]	14	Memory-guided saccades > fixation
Tu et al., 2006 [50]*	10	Antisaccades > fixation
Ettinger et al., 2008 [51]	17	Antisaccades > fixation
Fukumoto-Motoshita et al., 2009 [52]	18	Antisaccades > fixation
Camchong et al., 2008 [3]	15	Antisaccades + memory-guided saccades > fixation
DeSouza et al., 2003 [53]‡	10	Antisaccades + reflexive saccades > fixation

performed and for each voxel, the beta coefficient was obtained for the stimulus timing as convolved with the hemodynamic response. The anatomical and functional images were warped to Talairach space. Then, the stimulus-related activation in the two functional runs was averaged together for each participant. Finally, a one-sample *t*-test was conducted across the participants to identify the significantly activated circuitry for complex saccades. To protect against false positives, a threshold/cluster method derived from Monte Carlo simulations (accounting for the 4-mm full-width half-maximum Gaussian filter and with a connectivity radius of 5.7 mm) was applied to the *t*-map. The center of mass of each cluster was identified and included in the meta-analysis.

Meta-Analytic Techniques

Analyses were performed using the activation likelihood estimation (ALE) technique in GingerALE [55; 56]. ALE is a coordinate-based quantitative meta-analysis method that identifies consistent brain activations elicited across studies employing similar tasks. In ALE,

activation foci (reported coordinates which are extracted from tables or text of manuscripts and entered into a database for analysis) are treated as probability distributions centered at the reported coordinates. Activation probabilities are then calculated for each standard-space voxel to construct ALE maps for contrasts of interest. A statistical test of values in the observed ALE distribution is then performed by comparing them with values in a null distribution to assign p values to the observed values. False discovery rate correction is used in determining the p values, with two options provided by the software for determining the p value thresholds. The first option is the pN method, which is nonparametric, makes no correlation assumptions, and is more conservative. The other option is the pID method, which assumes independence or positive correlation. In practice, it is a more lenient method of thresholding (although it is still approved by the developers of the GingerALE software). A detailed description of the ALE process and analysis procedures can be found on the BrainMap website (<http://brainmap.prg/ale/manual.pdf>).

For the current meta-analysis, the p values were calculated using the random-effects method generated by Eickhoff, et al. [34]. The resulting ALE maps were then thresholded at the recommended minimum cluster size threshold (2168 mm³ for the overall analysis, 1288 mm³ for the analysis of reflexive saccades alone, and 672 mm³ for the analysis of complex saccades alone). The p value threshold was determined by a false discovery rate of 0.05. For the overall, reflexive, and complex meta-analyses, the pN method of p value thresholding was used. For the subtraction analyses (i.e., investigating significant differences in a direct comparison between reflexive and complex saccades), the pID method of p value thresholding was used.

Results

The final meta-analysis study pool for overall reflexive and complex saccades (total $N = 338$) included 22 studies (details in Table 1) from which a total of 375 foci (Talairach or converted MNI coordinates) were entered into the ALE analysis. The following results are from one of three levels of analysis: (1) probability of activation associated with all saccades combined, (2) probability of activation associated with either a) reflexive saccades versus fixation or b) complex saccades versus fixation, or (3) direct subtraction of probability of activation associated with one type of saccade (reflexive or complex) as compared to the other type of saccade. The regions found in the second and third levels of analysis may differ because while the second level used a conservative method of p -thresholding, the third level used a more liberal method. Both methods are approved by the authors of the meta-analytical software, but using a more liberal thresholding method in some analyses allowed for exploration of additional potential differences. In the first level of analysis, combined reflexive and complex saccades elicited a greater probability of activation than fixation in a variety of regions, including SPC (bilateral precuneus, left postcentral gyrus, and right superior parietal lobule (SPL)), SEF (left medial frontal gyrus), FEF (bilateral precentral gyrus and right middle frontal gyrus (MFG)), visual cortex (bilateral lingual gyrus and left cuneus), and cerebellum (left declive) (see Figure 1 and clusters meeting ALE criteria in Table 2).

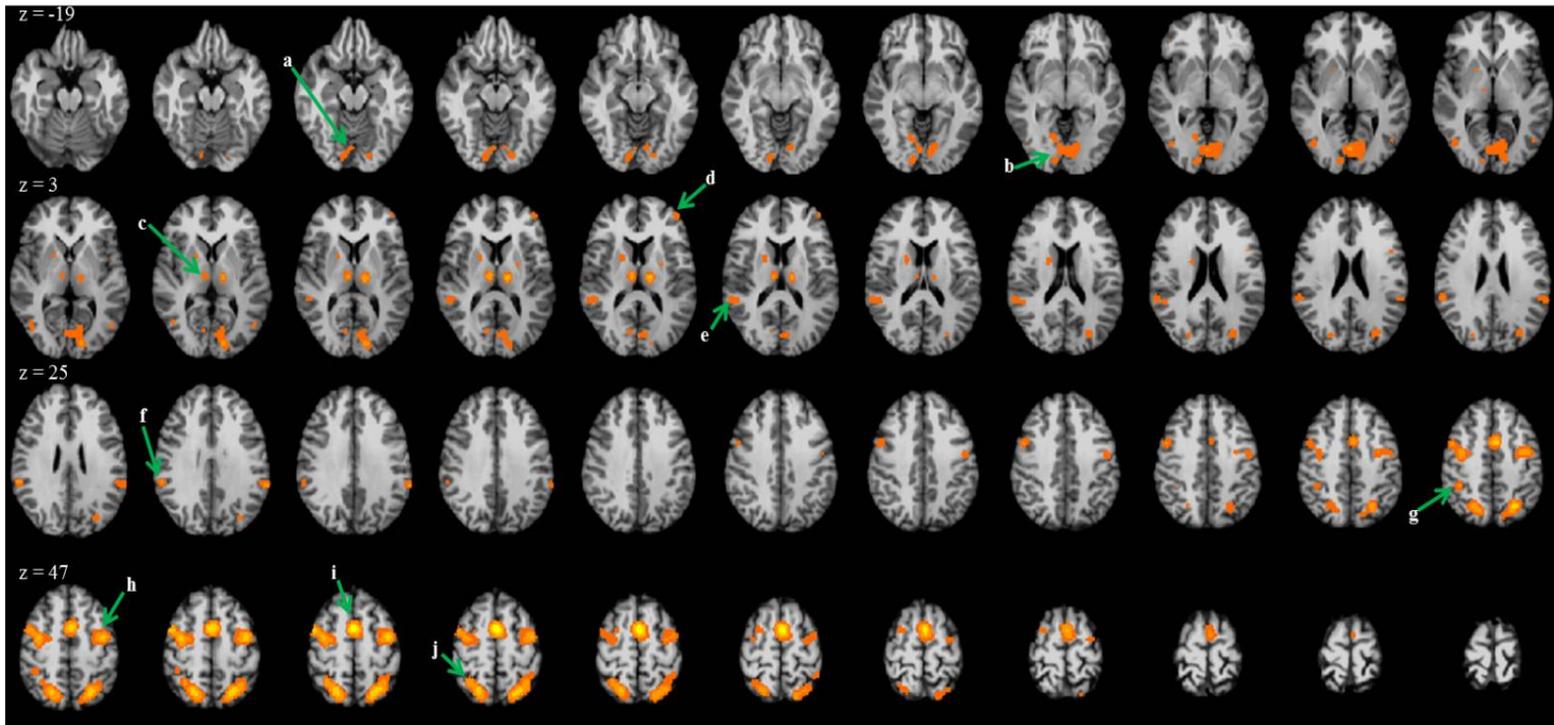


Figure 1. Regions of significantly elevated probability of activation in the overall saccade > fixation contrast. Images are oriented in the radiological convention (the left hemisphere is shown on the right side of the figure). a: cerebellum; b: visual cortex; c: thalamus; d: PFC; e: MTG/STG; f: IPL/SMG; g: IPS; h: FEF; i: SEF; j: SPC.

Table 2 Regions of significantly elevated probability of activation in the overall saccade > fixation contrast. Coordinates are the maxima within the cluster and are in Talairach space. SMG is the supramarginal gyrus, IPL is the inferior parietal lobule, and BA is Brodmann area

Region	Sub-region	x	y	z	Cluster size (mm ³)	Label on Fig. 1
SPC	L precuneus (BA 7)	-22	-64	50	6440	j
	L postcentral gyrus (BA 5)	-38	-46	56		
	R precuneus (BA 7)	22	-62	52	5168	
	R SPL (BA 7)	32	-54	54		
SEF	L medial frontal gyrus (BA 6)	0	2	56	6264	i
FEF	R precentral gyrus (BA 6)	36	-8	50	5416	h
	R precentral gyrus (BA 6)	46	0	52		
	R MFG (BA 6)	48	2	40		
	R MFG (BA 6)	26	0	60		
	L precentral gyrus (BA 6)	-38	-8	50	4840	
	L precentral gyrus (BA 4)	-46	-10	40		
Visual Cortex	R lingual gyrus (BA 18)	2	-78	0	5688	b
	R lingual gyrus (BA 19)	16	-64	-4		
	L lingual gyrus	-8	-80	0		
	L cuneus (BA 17)	-12	-86	6		
	L cuneus (BA 17)	-4	-78	12		
Cerebellum	L declive	-8	-76	-10		a

The overall meta-analysis was separated to allow for more specific meta-analyses of reflexive and complex saccades. In the second level of analysis, the reflexive saccade study pool (total N = 205) included 13 studies and a total of 235 foci. Reflexive saccades elicited a greater probability of activation than fixation in visual cortex, regions of SPC (left inferior parietal lobule (IPL) and bilateral SPL), right superior temporal gyrus (STG), SEF (left medial frontal gyrus), FEF (left precentral gyrus and left MFG), visual cortex (bilateral lingual gyrus and left cuneus), and cerebellum (left declive) (see Figure 2 and Table 3 for all clusters identified as meeting ALE criteria).

Another comparison within the second level of analysis, the complex saccade study pool (total N = 123) included 8 studies and a total of 131 foci. Complex saccades elicited a greater probability of activation than fixation in SPC (bilateral precuneus), SEF (right medial frontal gyrus and left SFG), FEF (bilateral precentral gyrus), and right thalamus (see Figure 2 and Table 4 for clusters identified as meeting ALE criteria).

Table 3 Regions of significantly elevated probability of activation in the reflexive saccade > fixation contrast. Coordinates are the maxima within the cluster and are in Talairach space

Region	Sub-region	x	y	z	Cluster size (mm ³)	Label on Fig. 2
SPC	L SPL (BA 7)	-24	-64	50	4928	j
	L SPL (BA 7)	-18	-68	54		
	L IPL (BA 40)	-30	-50	54	2888	
	R SPL (BA 7)	22	-64	54		
	R SPL (BA 7)	32	-54	52		
MTG/STG	R STG (BA 13)	58	-42	16	1680	e
	R STG (BA 13)	50	-44	18		
SEF	L medial frontal gyrus (BA 6)	0	0	58	2976	i
FEF	L precentral gyrus (BA 6)	-38	-6	52	2936	h
	L precentral gyrus (BA 4)	-46	-10	40		
	L MFG (BA 6)	-30	-8	46		
Visual Cortex	R lingual gyrus (BA 18)	14	-84	-12	5184	b
	R lingual gyrus (BA 18)	6	-80	-2		
	R lingual gyrus (BA 18)	12	-68	-4		
	L lingual gyrus (BA 18)	-16	-84	-12		
	L lingual gyrus (BA 18)	-10	-78	-2		
	L cuneus (BA 17)	-12	-88	8		
Cerebellum	L declive	-8	-74	-10		a

Table 4 Regions of significantly elevated probability of activation in the complex saccade > fixation contrast. Coordinates are the maxima within the cluster and are in Talairach space

Region	Sub-region	x	y	z	Cluster size (mm ³)	Label on Fig. 2
SPC	R precuneus (BA 7)	22	-60	50	1976	j
	R precuneus (BA 7)	16	-68	48		
	L precuneus (BA 7)	-12	-72	46	960	
	L precuneus (BA 7)	-20	-64	50		
SEF	L SFG (BA 6)	-2	4	48	3168	i
	R medial FG (BA 6)	4	2	52		
FEF	R precentral gyrus (BA 6)	36	-8	48	1520	h
	L BA 6	-28	0	52	1040	
	L precentral gyrus (BA 6)	-36	-6	50		
Thalamus	R thalamus	8	-16	10	848	c

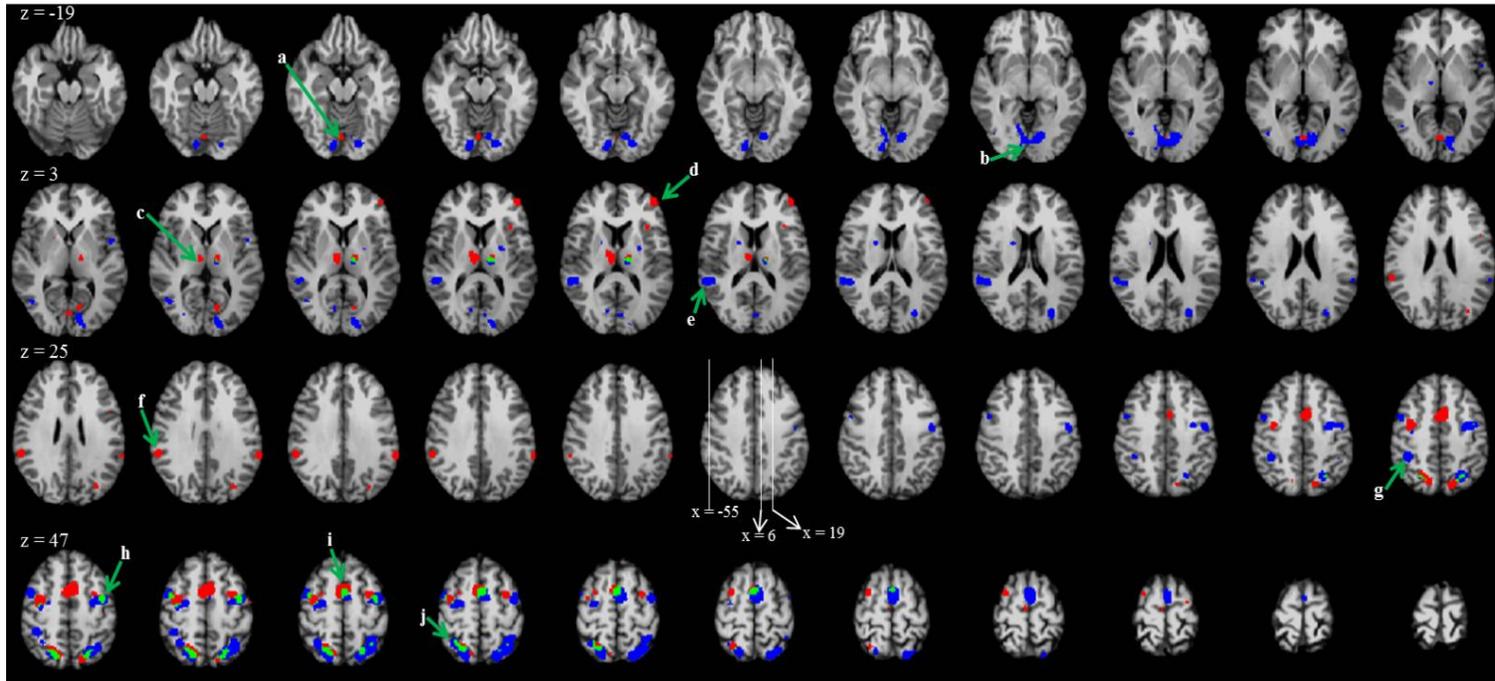


Figure 2a. Regions of significantly elevated probability of activation specific to reflexive saccade contrasts (in blue), specific to the complex saccade contrast (in red) or common to both the reflexive and complex contrasts (in green). Images are oriented in the radiological convention (the left hemisphere is shown on the right side of the figure). Vertical white lines indicate sagittal slice positions for Figures 2b (SPC), 2c (MTG/STG and IPL/SMG), and 2d (SEF). a: cerebellum; b: visual cortex; c: thalamus; d: PFC; e: MTG/STG; f: IPL/SMG; g: IPS; h: FEF; i: SEF; j: SPC.

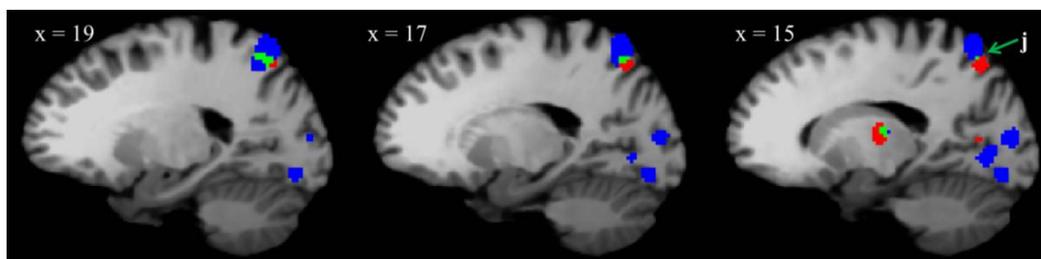


Figure 2b. Sagittal view of SPC.

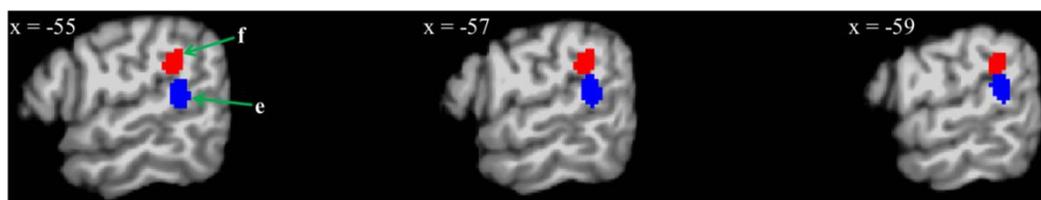


Figure 2c. Sagittal view of MTG/STG and IPL/SMG.

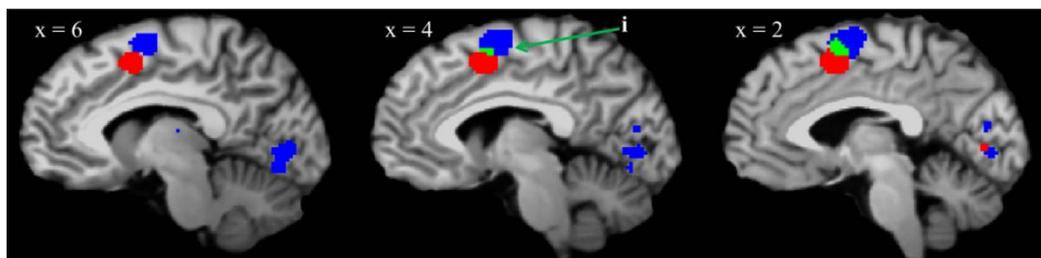


Figure 2d. Sagittal view of SEF.

Finally, in the third level of analysis, subtraction analyses were conducted to examine whether the differences in probabilities of activation were significant between reflexive and complex saccades. Complex saccades elicited a significantly greater probability of activation than reflexive saccades in right IPL, SEF (left SFG, bilateral medial frontal gyrus, and left cingulate gyrus), FEF (bilateral SFG and MFG), PFC (left MFG), and right thalamus (see Figure 3 and Table 5 for all clusters identified as meeting ALE criteria).

An additional subtraction analysis was conducted for the reverse contrast. Reflexive saccades elicited a significantly greater probability of activation than complex saccades in IPS (right IPL), right middle temporal gyrus (MTG) and STG, visual cortex (left lingual and middle occipital gyri), and cerebellum (left declive) (see Figure 3 and Table 6 for all clusters identified as meeting ALE criteria). The fact that there are a larger number of reflexive saccade studies available for this meta-analysis may be contributing to the size of some of these effects; however, it is likely not the only factor behind these differences. Even when studies were eliminated from the reflexive saccade analysis in order to match it to the complex saccade analysis in terms of number of foci, the probability of activation of these regions remained larger than in the complex analysis.

Table 5 Regions of significantly greater probabilities of activation in the complex saccade analysis as compared to the reflexive saccade analyses. Coordinates are the maxima within the cluster and are in Talairach space

Region	Sub-region	x	y	z	Cluster size (mm ³)	Label on Fig. 3
IPL/SMG	R IPL (BA 40)	54	-34	28	752	f
	R IPL (BA 40)	60	-34	30		
	R IPL (BA 40)	60	-41	31		
SEF	L SFG (BA 6)	-8	12	50	2792	i
	L SFG (BA 6)	0	4	48		
	L medial frontal gyrus (BA 32)	-6	12	46		
	R medial frontal gyrus (BA 6)	4	4	52		
	L cingulate gyrus (BA 24)	-6	4	46		
FEF	R SFG (BA 6)	30	-2	64	1704	h
	R SFG (BA 6)	26	0	66		
	R MFG (BA 6)	32	0	50		
	L MFG (BA 6)	-26	2	58	840	
	L MFG (BA 6)	-30	4	52		
	L SFG (BA 6)	-28	-4	64		
PFC	L MFG (BA 46)	-43	40	14	656	d
	L MFG (BA 10)	-37	43	15		
	L MFG (BA 10)	-36	44	10		
	L MFG (BA 10)	-39	49	15		
Thalamus	R thalamus	12	-8	14	464	c
	R thalamus	10	-11	13		
	R thalamus	8	-10	8		

Table 6 Regions of significantly greater probabilities of activation in the reflexive saccade analysis as compared to the complex saccade analyses. Coordinates are the maxima within the cluster and are in Talairach space

Region	Sub-region	x	y	z	Cluster size (mm ³)	Label on Fig. 3
IPS	R IPL (BA 40)	38	-48	42	1344	g
	R IPL (BA 40)	45	-41	48		
	R IPL (BA 40)	42	-47	50		
	R IPL (BA 40)	32	-42	48		
MTG/STG	R MTG (BA 37)	51	-52	3	1800	e
	R MTG (BA 22)	52	-44	12		
	R STG (BA 13)	46	-48	20		
Visual Cortex	L lingual gyrus (BA 18)	-14	-78	-6	1168	b
	L lingual gyrus (BA 18)	-16	-80	-14		
	L middle occipital gyrus (BA 18)	-22	-82	-8		
Cerebellum	L declive	-12	-82	-16	464	a
	L declive	-12	-74	-9		

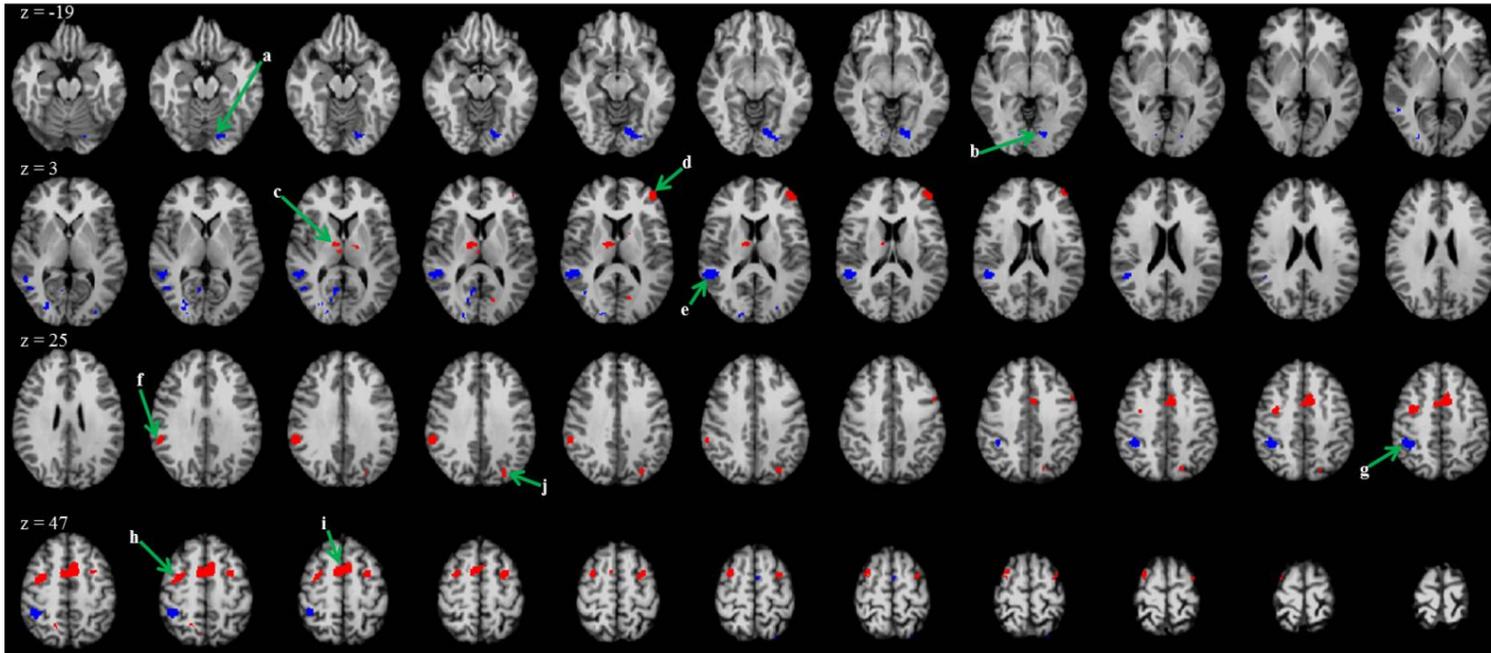


Figure 3. Significant differences found in the subtraction analyses. Reflexive saccade > complex saccade contrast is in blue. Complex saccade > reflexive saccade contrast is in red. Images are oriented in the radiological convention (the left hemisphere is shown on the right side of the figure). a: cerebellum; b: visual cortex; c: thalamus; d: PFC; e: MTG/STG; f: IPL/SMG; g: IPS; h: FEF; i: SEF; j: parieto-occipital junction.

Discussion

Saccadic circuitry was precisely localized using a meta-analysis [55; 56] with informative differences indicated for reflexive and complex saccades. These results are based exclusively on over 20 whole brain fMRI studies (N = 338) with passive task baselines (usually simple fixation). Combined reflexive and complex saccades were associated with a significantly greater probability of activation relative to fixation in regions that are well-known as supporting saccadic performance. These regions have been previously identified as saccadic circuitry in many human neuroimaging studies [3; 57; 58], and have analogues in studies of saccades in non-human primates [59; 60; 61; 62].

Of particular interest in this study was summarizing and parsing the contribution of various parietal regions to reflexive and complex saccades. This direct integration of numerous studies is critical because the field suffers from a lack of consistent terminology (see Table B, Mort et al., 2003 for a list of fMRI studies showing PPC activity, that includes Talairach coordinates and the inconsistent terminology used to refer to those areas). The saccade-related regions in the resulting meta-analyses included bilateral superior parietal cortex (SPC) both medially (BA 7, commonly referred to as precuneus) and laterally (BA 7 and to a lesser extent 5). Other areas included the area around the intraparietal sulcus, localized to the right side, as well as more bilateral inferior parietal lobe regions.

The SPC showed strong and persistent probability of activation in the overall saccade contrast. Activity in this region is reported in many saccade studies [18]. Activity also has been shown in this region during other eye movement tasks (smooth pursuit and optokinetic nystagmus), suggesting that it may be invoked with general ocular motor function [63]. Despite the similarity of activity in this area across different eye movements, detailed analysis of a direct comparison of these three types of movements demonstrated that regions of SPC activation did not completely overlap. In fact, there was enough systematic offset in activation patterns to suggest the existence of parallel circuits within SPC that differentially subserved various eye movements [63]. The current analyses provided evidence of SPC subregions, as well; the extent of activation probability in this region appeared to be localized more superiorly in the reflexive saccades, and more inferiorly and perhaps medially for the complex saccades (see Fig 2b). The latter more inferior and medial aspect of SPC is the precuneus (the mesial extent of BA 7 [64]). This area has widespread connections to a variety of cortical and subcortical structures, and is reported to be involved in higher-order cognitive functions in response to external and self-generated stimuli, including shifting of attention [64], which requires a sensorimotor transformation to generate an antisaccade to the correct location [2], opposite a visual target.

Inferior parietal regions also showed saccade-specific behavior that persisted in the direct subtraction maps. Reflexive saccades were associated with a region around IPS [1]. Greater activation of IPS for reflexive than complex saccades has been seen in some studies [21; 31] but not all [18]. The anatomical location of the IPS in humans is similar to what has been called parietal eye field (PEF) in non-human primates [28], an area which supports visuospatial integration and reflexive saccade triggering [1; 21; 22]. This has led to the suggestion that the IPS is the human analogue of the monkey PEF. While the anatomical label "PEF" has been applied to parietal activation across many human saccadic imaging studies, the coordinates of those anatomical regions vary greatly and suggest conflation of different

subregions subserving different circuitry (see Mort et al., Table 4 for an example culled from various studies). Of course, another possibility is that PEF may show high inter-individual variability in its precise location [65]. Given the lack of agreement about the location and function of PEF in humans, we have chosen to present the parietal regions and their respective patterns of activation without delineating PEF, per se, which we think is reasonable given that not only the location, but the existence of human PEF is a topic of current debate [66].

In more inferior regions of parietal cortex, clusters were found in the inferior parietal lobule/supramarginal gyrus (IPL/SMG) in the complex saccade analysis only. Although they did not pass cluster thresholding, the bilaterality makes it less likely that these are false positives, and the subtraction analysis revealed a significantly greater probability of activation in the right hemisphere for complex relative to reflexive saccades. This region (which overlaps IPL and SMG in this meta-analysis) is anatomically separate from the IPS region that showed greater probability of activation in the reflexive saccade analysis, suggesting that these regions may perform different functions. The SMG has previously been associated with saccades and specifically in the inhibition required by antisaccades and other more complex saccadic tasks [51; 67; 68]. It also may facilitate stimulus detection, saccade generation, and attention shifts [37; 51; 69; 70]. Further support for a greater role of the SMG in complex saccades comes from studies of verbal, auditory, and spatial working memory tasks [70; 71]. These tasks have been shown to activate SMG; therefore, it is possible that complex saccades recruit SMG due to additional working memory requirements.

Interestingly, the right IPL/SMG region that showed a greater probability of activation in the complex saccade analysis is distinct from the right middle and superior temporal gyrus (MTG/STG) region that showed a probability of activation only in the reflexive analysis. This region was also found to have a greater probability of activation for reflexive than complex saccades in the subtraction analysis. While the role of this region in saccades is not as clear, at least one study suggests that superior temporal regions may be particularly important for reflexive saccades relative to other types of eye movements [72]. This study found that the medial superior temporal region was more activated by reflexive saccades than by exploratory saccades. Evidence to the contrary also is available, showing increased MTG and STG on a visual exploration task as compared to saccades [73]. The right lateralization of the activation in these temporal regions is consistent with at least some previous neuroimaging research of reflexive saccades, which also found activation in this region in the right (but not left) hemisphere [44].

In addition to parietal and temporal regions, saccade-specific differences were identified in several frontal regions. For example, the cluster encompassing the supplementary eye field (SEF) showed a significantly greater probability of activation in the complex saccade analysis than in the reflexive saccade analysis, which persisted after the subtraction analysis. This was expected, given that SEF has been previously suggested to be more important for complex saccades [12], particularly in sequencing of saccades [74] and perhaps in inhibition of reflexive saccades [75]. SEF differs from other eye fields in that it may be more concerned with internally guided target selection and generation of saccades that are not guided by a visual target stimulus [1; 12]. Another interesting difference observed in the SEF is that the location of activation was slightly different for complex and reflexive saccades. SEF activation appears more anterior and inferior for complex saccades relative to reflexive saccades (Figure 2d).

Bilateral frontal eye fields (FEFs), known to support saccade preparation and generation [76], also showed a significantly greater probability of activation for complex compared to reflexive saccades in the subtraction analysis. FEF activation probability was localized more midline for complex saccades and lateral for reflexive saccades, a feature that has been observed before. This pattern suggests a functional distinction between medial and lateral FEF, with medial being more associated with complex saccades [77; 78]. FEF activity may be modulated based on task demands, perhaps particularly when inhibition of incorrect reflexive responses is required [79].

Left middle frontal gyrus (MFG), a region of prefrontal cortex (PFC), also was found to have a significantly greater probability of activation in the direct comparison of complex to reflexive saccades. This is consistent with the putative role of PFC in higher-order executive function processes, including but not limited to working memory and inhibition [80; 81]. There is evidence in studies of both humans and non-human primates that PFC must be functionally intact for correct performance of various types of complex saccades [82; 83; 84]. In non-human primates, PFC deactivation has been shown to cause slower reaction times and more errors on an antisaccade task [85]. There is evidence that the PFC plays an important role in suppressing reflexive responses.

The thalamus has strong reciprocal connections to the PFC and other regions of the cortex. It did not demonstrate a significant probability of activation in the reflexive saccade-only analysis but did in the complex saccade-only analysis, and this difference remained significant in the direct subtraction between the two types of saccades (i.e., it demonstrated an increased probability of activation for complex relative to reflexive saccades). Consistent with our results, a previous study of reflexive saccades compared to antisaccades demonstrated that thalamus activation is greater during antisaccades than during reflexive saccades when either is compared to fixation [2]. Studies indicate that the thalamus is involved in visual attention and could play a greater role in complex saccades due to its importance for spatial working memory [5].

While several regions involved in higher-order cognitive control were found to be more involved in complex saccades, other regions showed greater probability of activation for reflexive saccades. The cerebellum was found in the reflexive-only analysis (and not in the complex-only analysis) and a significant difference also remained in the subtraction analysis. Studies show that regions in cerebellum fine-tune eye movements and thus determine the amplitude of saccades [1; 87]. Structural neuroimaging also provides evidence for a role of the cerebellum in saccades. One study found that reflexive saccade gain (i.e., accuracy in foveating the visual target) was associated with grey matter volume in the left cerebellar hemisphere and cerebellar vermis, extending into the lingual gyrus, which may support our fMRI-based findings [88]. The cerebellum is involved in saccadic circuitry [86], but whether its contribution varies by saccade type has not yet been demonstrated.

The cluster which encompassed the cerebellum also included the visual cortex (specifically, the middle occipital and lingual gyri), meaning that this region also demonstrated a significant probability of activation for reflexive saccades relative to complex saccades. This difference was significant in the direct subtraction analysis. The lingual gyrus is involved in bottom-up mechanisms that are important for detecting visual stimuli. In the context of saccades toward a cue, it has been suggested that lingual gyrus activation during saccade generation could be associated with a forthcoming shift of the cue (that is, the visual image) on the retina. There may be a neural remapping prior to this shift which preserves the

perception of the visual image [12]. The middle occipital gyrus may show greater activation during reflexive saccades due to the greater visual stimulation that occurs during the reflexive saccades (because participants have the visual stimulus on their retina for a greater percentage of the time than during the antisaccade task) [2]. More reflexive saccade and less complex saccade activation in early visual cortex may reflect the influence of top-down control mechanisms. In this model, during complex, but not reflexive saccades, signals from other neural regions (potentially frontal regions) may suppress primary visual cortex responsiveness. Decreasing the response of sensory cortex to relevant stimuli may in turn decrease the probability of generating an incorrect response to a visual cue (i.e., looking at the cue) [89].

In summary, reflexive saccades showed a greater probability of activation than complex saccades in more superior and lateral regions of superior parietal cortex, intraparietal sulcus, middle and superior temporal cortex, cerebellum, and visual cortex. Complex saccades showed a greater probability of activation than reflexive saccades in more inferior and medial regions of superior parietal cortex, SMG in inferior parietal cortex, SEF, FEF (particularly the midline), PFC, and thalamus.

Conclusion

Due to the rapidly increasing number of relevant results from fMRI studies of saccadic circuitry, the current meta-analysis provides updated information with improved spatial localization. Patterns between reflexive and complex saccades were largely, although not completely overlapping, and as such, the results illuminate several areas for further study. Of particular interest were the differential saccade-specific contributions of parietal regions, specifically the SPC, IPS, IPL, and SMG. While many studies have reported posterior parietal cortex activation during saccade tasks, the localization of regions within PPC has lacked consensus. The current meta-analysis suggests that despite commonalities in PPC activation across saccade types, there also is evidence that the region is heterogeneous with distinct functional subregions that are differentially involved in reflexive or complex saccade generation.

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