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Neural correlates of antisaccade deficits in schizophrenia, an fMRI study

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Abstract

Schizophrenia patients were known to have oculomotor abnormalities for decades and several studies had found antisaccade impairment to be a biological marker of schizophrenia. In this study, we used functional magnetic resonance imaging (fMRI) to investigate the neural circuits responsible for antisaccade deficits in schizophrenia. Ten normal controls and 10 DSM-IV schizophrenia patients performed antisaccade tasks and control tasks during fMRI. Data were analyzed and task-specific activations were identified using Statistical Parametric Mapping (SPM-2). In normal subjects, antisaccade tasks activated bilateral frontal eye fields, supplementary eye fields, inferior frontal gyrus, superior parietal lobules, inferior parietal lobules, occipital visual cortex, cerebellum, thalamus, and lentiform nuclei ($P < 0.001$). By contrast, schizophrenia patients failed to show activation in bilateral lentiform nucleus, bilateral thalamus, and left inferior frontal gyrus during antisaccade performance. Our findings suggest that schizophrenic antisaccade deficits are associated with dysfunction of fronto-striatal-thalamo-cortical circuits previously demonstrated to be responsible for suppression of the reflexive saccade. Left inferior frontal gyrus, which was known to be responsible for response inhibition on ''go/no-go'' testing, also plays an important role in schizophrenic antisaccade deficit.

Keywords: fMRI; Schizophrenia; Antisaccade; Frontal eye field; Supplementary eye field; Lentiform nucleus; Thalamus; Inferior frontal gyrus

1. Introduction

Schizophrenia is a complex disorder complicated by various neuropsychological impairments. The oculomotor abnormality of schizophrenia patients was first described as a specific disorder of smooth eye tracking to a continuously oscillating visual target (Holzman et al., 1974). Recently, deficits in the antisaccade task have been proposed as another biological marker of latent liability for schizophrenia (McDowell and Zisook, 1994; Sereno and Holzman, 1995; O'Driscoll et al., 1998). In the antisaccade task, the subject fixates on a central dot that moves at random to the left or right. When the target moves into the periphery, the subjects' task is to look as quickly as possible in the opposite direction. Compared with matched controls, schizophrenic patients are reported to make more incorrect reflexive saccades toward the peripheral targets (increased error rates) and when correct antisaccades are made, the latency of these saccades is increased significantly (Fukushima et al., 1988; Crawford et al., 1995). These abnormalities were generally interpreted as increased distractibility arising from the dysfunction of inhibitory processes associated with the frontal cortices. Early studies revealed the association of saccade inhibition deficit with

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lesions in the frontal lobe, especially in the dorsolateral prefrontal cortex (DLPFC) (Guitton et al., 1985; Pierrot-Deseilligny et al., 1994; Fukushima et al., 1994).

Several cortical regions are responsible for control of saccadic eye movement (Anderson et al., 1994; Muri et al., 1996, 1998; Gaymard et al., 1998), which include frontal eye fields (FEF) in the precentral gyrus and supplementary eye fields (SEF) in the medial superior frontal cortex and posterior parietal cortex (PPC). Antisaccades may recruit additional neural structures responsible for reflexive saccade inhibition and computation of the inverse saccade vector from external visual stimuli. The neural substrates of human antisaccade eye movement were studied using various functional imaging techniques. O'Driscoll et al. (1995) used positron emission tomography (PET) to examine regional cerebral blood flow (rCBF) changes associated with antisaccade in normal subjects and found that FEF, SEF, thalamus, and putamen were more active in antisaccades than saccades. In contrast, DLPFC activation during antisaccade movements was not significantly different from that during saccade movements. It was suggested that the FEF, but not DLPFC, plays a role in antisaccade inhibition. However, later functional imaging experiments using PET (Sweeney et al., 1996) or functional magnetic resonance imaging (fMRI) (Muri et al., 1996; Matsuda et al., 2004) revealed DLPFC activation during the antisaccade tasks. Besides the DLPFC, the striatum was also found to be activated in the antisaccade task in several studies (O'Driscoll et al., 1995; Sweeney et al., 1996; Matsuda et al., 2004) and was proposed to play an important role in saccade inhibition.

Since selective antisaccade deficits presented with normal reflexive saccade in patients, functional impairment of the neural structures selectively recruited by the antisaccade task was hypothesized in schizophrenia. Crawford et al. (1996) used single photon emission tomography (SPET) to compare the rCBF change between two groups of schizophrenia patients with high and low antisaccade error rates and found that the patients with high error rates showed significantly decreased rCBF bilaterally in the anterior cingulate and insula and in the left striatum. Two recent fMRI studies compared the brain activations between schizophrenia patients and normal controls during saccade and antisaccade performance and showed conflicting results. McDowell et al. (2002) used block designs, and the subjects were required to perform blocks of either refixation saccades or antisaccades according to the color of the central cue. FEF, SEF, and PPC activation was similar in patients and normal subjects during refixation saccades, but the level of DLPFC activation differed in patients (no increase) and normal subjects (increase) during antisaccade performance, suggesting that DLPFC was responsible for schizophrenic antisaccade abnormalities. However, Raemaekers et al. (2002) used event-related designs and showed that FEF and SEF were activated by tasks involving saccade inhibition in both normal subjects and schizophrenia patients. Schizophrenia patients exhibited a selective failure to activate striatum during the inhibition of saccades. There was no significant DLPFC activation related to saccade inhibition in both normal and schizophrenia patients. Thus, the frontostriatal network dysfunction may be responsible for the saccade inhibition deficit in schizophrenia. The lack of DLPFC activation in their experiment was possibly due either to no significant activation or sustained activation during task execution.

The conflicting results of previous fMRI studies about the neural substrates of schizophrenic antisaccade deficit may be due to different experimental designs or behavioral tasks. Previous studies frequently used the reflexive saccades as the control task, and the subjects were required to perform reflexive saccades and antisaccades according to either the color of the central cue or the instructions before each experimental session. These kinds of designs made the experiments more difficult than the original antisaccade task and were biased by their additional demands on working memory or response selection during fMRI acquisition. Furthermore, without eye tracking during image acquisition, whether subjects or schizophrenia patients perform reflexive saccade and antisaccade correctly (i.e., according to the cues or instructions provided) could not be confirmed.

In this study, we used fMRI to investigate the neural correlates of schizophrenic antisaccade deficit. Because the eye movement performance of schizophrenic patients is not easily verified during the imaging process, our experimental design was different from previous studies in several ways. First, we checked the performance of antisaccades before fMRI acquisition to make sure that all of our subjects understood and executed the task according to the examiner's instructions. Second, the subjects were required to perform an alternative antisaccade/control task during fMRI acquisition. Although reflexive saccades seemed to be the ideal reference task for antisaccades because these two tasks share stimulus characteristics, schizophrenic patients may never learn to switch between antisaccade and reflexive saccades during the imaging process (McDowell et al., 2002).

2. Materials and methods

2.1. Subjects

Ten schizophrenia patients (five males and five females, mean age: 31.5 ± 4.15 y/o) were selected from outpatients of the Psychiatry Department of Taipei Veterans General Hospital. The clinical diagnosis was made by two independent psychiatrists using DSM IV criteria (eight had paranoid type schizophrenia and two had disorganized type schizophrenia). The mean illness duration was 6.3 ± 4.2 years. All patients were taking variable doses of atypical ($n = 8$, a mean daily dose of 4 mg of risperidone; $n = 1$, a daily dose of 10 mg of olanzepine) or typical ($n = 1$, a daily dose of 800 mg of sulpiril) antipsychotic medications. At the time of the imaging procedure, the schizophrenic patients

were all clinically stable, cooperative, and able to follow the requirements of the experimental tasks. The normal controls (five males and five females, mean age = 27.9 ± 3.18 y/o) were recruited through advertisement from the community. They and their first-degree relatives were screened for absence of psychiatric disorders. All subjects provided written informed consent to participate in the study, according to guidelines approved by the Institutional Medical Ethics and Radiation Safety Committees.

2.2. Experimental design

The subjects were asked to perform two experimental tasks during functional image acquisition. (A) Control task: no stimulus was presented on the screen. The subjects were instructed to see the blank screen and refrain from eye movements. (B) Antisaccade task: the subjects fixated on a cross 1 × 1 in visual angle at the center of the screen. After a random interval (0.8–1.2 s), the target moved horizontally to a position 5° to the right or left of the fixation point. The subjects needed to make a saccade toward the mirror location on the opposite side after the target position changed and then to return their eye immediately to the center and wait for the reappearance of the next fixation point. The direction of target movement was pseudorandom, with the numbers of left and right movements being equal. The inter-trial intervals are varied so that each trial lasted for 2.5 s. Each block of control or antisaccade tasks lasted for 30 s (about 10 scans) and these two conditions were presented in sequences of ABABABAB and then BABABABA in two separate runs and each run consisted of 80 scans. The visual stimuli were generated by a PC using STIM software and presented through goggles connected to the PC.

2.3. Behavioral measurement

The behavioral performances of antisaccade tasks were acquired before MR scanning using the infrared eye tracking system (Ober2, Permobil Meditech, Timra, Sweden). In the process of measurement, subjects were restrained from movement using a dental bite-bar and a chest support bar. Horizontal eye position was sampled at 240 Hz. One hundred antisaccade trials were presented and they had the same stimulus characteristics as those presented in the imaging procedure. Eye movement recordings were transferred to a computer and analyzed offline. An initial reflexive saccade toward the cue followed by corrective antisaccade constituted an error and the error rate was calculated for each subject. The behavioral measurements provided the behavioral data and ensured that each subject did the antisaccade task according to the examiner's instructions.

2.4. Image acquisition and scanning

Scanning was performed on a 3.0 T Bruker MedSpec300 system (Bruker, Kalsrube, Germany). Twenty slices were acquired every 2.96 s. The T2-weighted functional images were acquired using an echo-planar (EPI) pulse sequence (TR = 200 ms, TE = 70 ms, flip angles = 90°, matrix size = 128 × 128, and FOV = 250 × 250 mm). Following functional scanning, the anatomical image was acquired using a T1-weighted, 3D gradient-echo pulse sequence (MDEFT, Modified Driven Equilibrium Fourier Transform, TR/TE/TI = 88.1/4.12/650 ms).

2.5. Image analysis

Using the Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, UK), the original images were first corrected for head motion, re-sampled every 4 mm using sinc interpolation, normalized to the standard brain space as defined by the Montreal Neurological Institute, and spatially smoothed with an isotropic Gaussian filter of 8 mm full width and half maximum. Statistical parametric maps were calculated for the condition-specific effects within a general linear model. Statistical threshold for those voxels identified as activations was set at $P < 0.001$ (uncorrected for multiple comparisons).

3. Results

Behavioral pretests were administered before imaging procedures to get the behavioral data and ensure that all subjects understood the examiner's instructions sufficiently. The error rate of patients was 33.9 ± 12.5% and normal controls 9.4 ± 6.4%. The patients were characterized by significantly higher rates ($F_{1,18} = 29.84$, $P < 0.01$) of initial reflexive saccades and later corrective antisaccades.

The neural structures activated by antisaccade tasks in normal and schizophrenia subjects are shown in Fig. 1 and Table 1. In normal subjects, comparison of antisaccade tasks with control tasks demonstrated significant activations in the medial frontal gyrus at the level of the supplementary motor area, corresponding to the SEF, and the activation extended to the anterior cingulate cortex (ACC). Significant bilateral activation was noticed in the precentral gyrus corresponding to the FEF. Bilateral activations of the bilateral inferior frontal gyrus (IFG), bilateral superior parietal lobules (SPL), inferior parietal lobules (IPL), and primary visual cortex. Subcortically, activations occurred in the bilateral lentiform nucleus, thalamus, and cerebellum. Schizophrenia subjects showed significant activations in bilateral FEF, SEF/anterior cingulate, SPL, primary visual cortex, cerebellum, and right IPL. But in contrast to normal subjects, no significant activations in the bilateral lentiform nucleus and thalamus, left inferior frontal gyrus, and left IPL occurred in patients.

4. Discussion

In our studies, patients showed significantly higher behavioral pretest error rates, in agreement with results

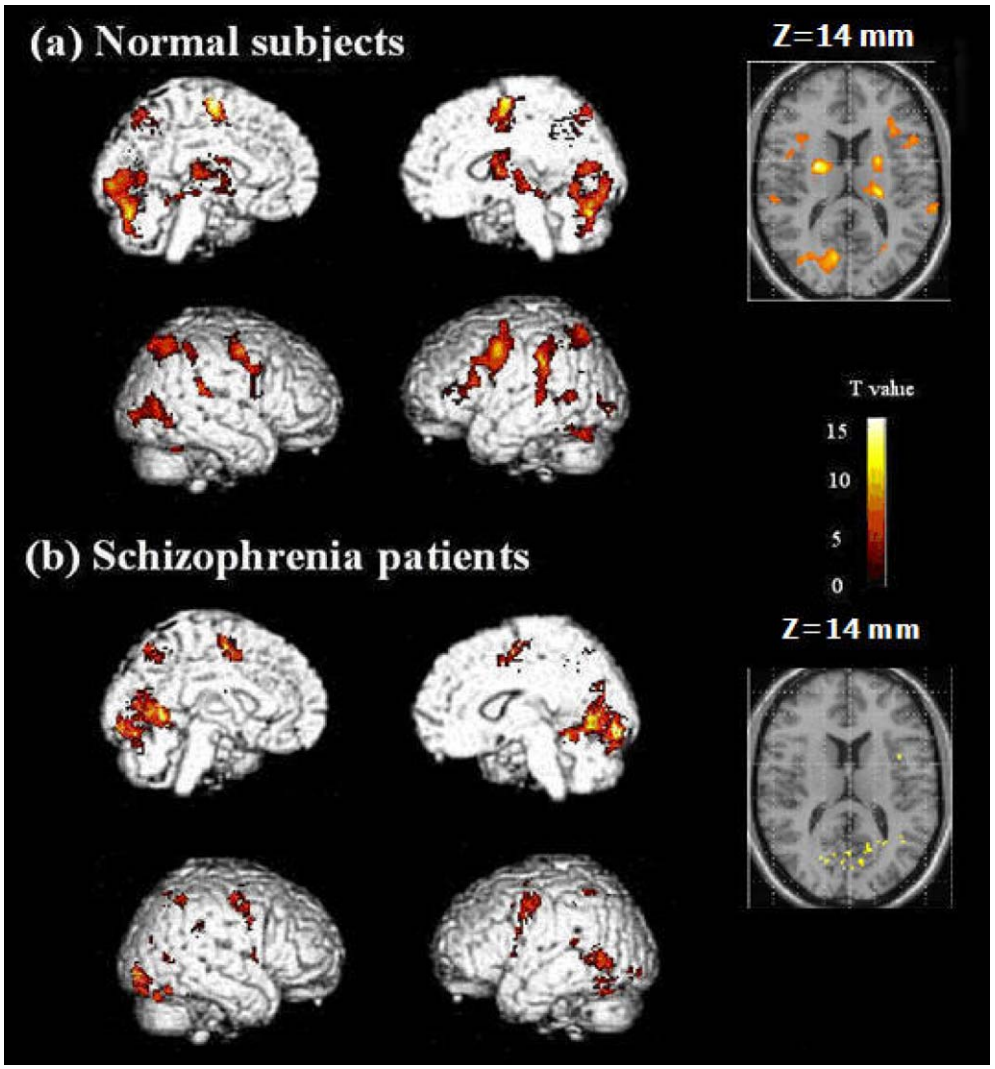

Fig. 1. Statistical parametric maps of brain regions displaying significant activations when antisaccade tasks were compared with rest conditions. Group results of 10 normal volunteers and schizophrenic patients, $P < 0.001$, uncorrected for multiple comparisons.

of previous behavioral studies (Fukushima et al., 1988; Crawford et al., 1995). Using fMRI, antisaccade impairments in patients were associated with lack of activation in the bilateral lentiform nucleus, thalamus, left IFG, and left IPL. No obvious activation of the DLPFC was noted in both patients and normal subjects. Our result is consistent with the results of a recent fMRI study (Raemaekers et al., 2002) and provides evidence for a role of the fronto-striato-thalamo-cortical circuits in antisaccade deficit in schizophrenic patients.

Frontal oculomotor areas project to the caudate nucleus and then exert their effects on the thalamus or superior colliculus (SC) through parallel direct and indirect pathways (Alexander et al., 1986). Cortical inputs into the direct pathway disinhibit SC and thalamus and facilitate the generation of saccades, while cortical inputs to the indirect pathway, which inhibit SC and thalamus, inhibit saccade generation. Our study found that dysfunction of the fronto-striato-thalamo-cortical pathway in schizophrenia may reduce inhibitory ability and produce more reflexive saccade errors in antisaccade tasks. The striatum and thalamus in normal subjects are more activated during antisaccades than during reflexive saccades (Matsuda et al., 2004; O'Driscoll et al., 1995) and may be responsible for the inhibitory component of antisaccade tasks. A SPET study (Crawford et al., 1996) found that significantly decreased regional cerebral blood flow (rCBF) occurred in the left striatum of those schizophrenia patients with more rather than less distractible errors in antisaccade tasks. In our studies, during antisaccade performance, the bilateral lentiform nucleus and thalamus were activated in normal subjects but not in patients. Previous as well as our present results showing the role of the striatum and thalamus in antisaccade generation support the hypothesis that dysfunction of the fronto-striato-thalamo-cortical is associated with the deficit in antisaccade task performance.

In our study the significant activations in the left inferior frontal gyrus shown in normal but not schizophrenia

Table 1
Identification of brain activations in normal subjects and schizophrenia patients when brain activities during antisaccade performance was contrasted with rest condition ($P < 0.001$, uncorrected for multiple comparison)

Brain regions	Left			*T* values	Right			*T* values
	X	*Y*	*Z*		*X*	*Y*	*Z*	
A: Normal subjects								
FEF	−46	−2	32	8.1	44	−8	48	9.34
SEF	−10	−6	64	14.65	6	−10	64	9.87
SPL(BA 7)	34	−62	50	8.52	−24	−70	48	8.41
IPL	−54	−38	30	15.41	28	−60	32	14
STG	−58	−34	6	8.28	58	−28	14	5.64
Visual cortex	−6	−90	−2	6.64	6	−80	−12	10.34
Lentiform nucleus	−22	2	16	8.24	24	−2	16	11.94
Thalamus	−22	−22	14	10.20	12	−20	8	7.77
Cerebellum	−6	−74	−22	9.09	6	−80	−12	10.34
Insula					−36	24	10	6.4
IFG	−46	16	16	8.55	38	6	26	7.25
B: Schizophrenia patients								
FEF	−40	−6	44	12.22	−46	−2	32	8.1
SEF	−12	−6	52	8.92	4	−6	56	7.23
SPL(BA 7)	−12	−66	56	8.92	28	−60	46	6.15
IPL					44	−42	22	6.94
STG					52	6	2	6.36
Visual cortex	−18	−76	−14	16.72	14	−70	0	12.97
Lentiform nucleus								
Thalamus								
Cerebellum	−38	−58	−16	7.36	36	−72	−24	10.08
Insula	−38	8	16	5.84				
IFG					50	4	8	7.49

FEF: frontal eye field, SEF: supplementary eye field, SPL: superior parietal lobule, IPL: inferior parietal lobule, IFG: inferior frontal gyrus, MFG: middle frontal gyrus, ACC: anterior cingulated gyrus.

subjects also suggest that the left inferior frontal gyrus plays a role in antisaccade deficit. Although rarely discussed in previous imaging studies of antisaccades, left inferior frontal gyrus activation has been demonstrated using the tasks of covert attention (Corbetta et al., 1998) and saccade imagination (Law et al., 1997) in which saccade suppression is required. Several imaging studies of go/no-go tasks (Konishi et al., 1998, 1999; Menon et al., 2001) requiring subjects to inhibit their motor responses to experimental cues also found that the inferior frontal gyrus was involved in response inhibition. Therefore, left inferior frontal gyrus may be not only responsible for the suppression of reflexive saccades, but also involved in various tasks in which response inhibitions are required. Our suggestion is compatible with a recent diffusion tensor imaging study (Hoptman et al., 2004) that showed compromised white matter integrity in inferior frontal areas was associated with impulsivity in schizophrenia patients.

The bilateral IPL were demonstrated to be involved in antisaccade or saccade suppression tasks in previous studies (Doricchi et al., 1997; Law et al., 1997). In the antisaccade task, IPL were supposed to subserve operations of sensory-motor integration dealing with attentional disengagement from the initial peripheral cue and with the computation of the antisaccadic vector on the basis of external visual stimuli. In our study, schizophrenia subjects failed to show activation in left IPL while normal controls showed significant activation in the bilateral IPL. IPL dysfunction may contribute to other behavioral impairments like increased saccade latency in antisaccades. In the antisaccade task, subjects had to voluntarily reorient their covert attentional and overt oculomotor response in the opposite direction after initial inhibition of overt orientation toward the peripheral cue. Thus, IPL dysfunction makes response reorientation more difficult for schizophrenic patients. This conclusion is compatible with the finding of a close relationship between schizophrenic antisaccade impairments and covert attention deficit (Maruff et al., 1998), suggesting the ability to utilize the voluntary orientating mode to control or inhibit reflexive orientation is reduced in schizophrenic patients, and this impairment of voluntary control is evident for both overt and covert attention shifts.

DLPFC, SEF, and FEF project to the SC directly or via the striatum and play important roles in antisaccade tasks. In our study, both patients and normal subjects showed significant activation in the bilateral FEFs and SEFs during antisaccade. No obvious DLPFC activations occurred in both patients and normal subjects. No DLPFC activation was also found in a previous event-related MRI study (Raemaekers et al., 2002). Although they suggested that the possibility of a sustained effect of DLPFC, which event-related designs failed to demonstrate, our study found no DLPFC activation even when using a block design.

The aim of this study was to investigate the neural circuits associated with antisaccade impairment in schizophrenia. Our interpretation is constrained by the limitations of

our study. First, technical limitations prevented the monitoring of the online antisaccade performance of subjects during image acquisition. Yet behavioral performances before the imaging procedure showed that all subjects understood and engaged in our experimental tasks. Further use of MRI-compatible eye trackers and designs of event related paradigms to separate correct from incorrect antisaccades (Cornelissen et al., 2002; Curtis and D'Esposito, 2003) will further our understanding of the neural substrate and time course of saccade inhibition in schizophrenia patients. Secondly, a visually guided saccade task was not included in our fMRI study because the schizophrenia patients' ability to switch between a visually guided task and antisaccade task in the same fMRI experiment could not be verified. Thus, our designs failed to evaluate the neural networks of the visually guided pathway and to see whether they were intact in schizophrenia. Thirdly, the subjects were instructed to see the blank screen and refrain from eye movement in the control condition of our study. The control task has been used in several functional imaging studies of saccades in normal subjects (Petit et al., 1996; Matsuda et al., 2004). However, a previous behavioral study (Matsue et al., 1986) showed that schizophrenia patients had higher frequency of saccades than normal subjects during fixation on a target or blank screen. Although the neural substrates of these involuntary saccades were unclear, it is possible that our results were confounded by these involuntary saccades. Further online monitoring of eye movements during fMRI is required to exclude their possible effects.

In conclusion, antisaccade tasks activated bilateral FEF, SEF, inferior frontal gyrus, SPL, IPL, thalamus, and lentiform nuclei in normal subjects. In contrast to normal subjects, schizophrenic patients failed to show significant activations in the bilateral lentiform nucleus, thalamus, inferior frontal gyrus, and left IPL. Our results suggest that schizophrenic antisaccade deficits are associated with dysfunction of fronto-striatal-thalamo-cortical circuits and fronto-parietal circuits. These circuits are important for reflexive saccade inhibition and generation of the volitional saccade from computation of the inverse saccade vector. Therefore, the oculomotor paradigms used in clinical neural imaging may not only help us to evaluate the functions of a single localized area and disorders of neural circuits or connections, but also may provide us insight into the neuropathology of various psychiatric illnesses.

References

Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual Review of Neuroscience 1986;9:357–81.

Anderson TJ, Jenkins IH, Brooks DJ, Hawken MB, Frackowiak RS, Kennard C. Cortical control of saccades and fixation in man. A PET study. Brain 1994;117:1073–84.

Corbetta M, Akbudak E, Conturo TE, Snyder AZ, et al. A common network of functional areas for attention and eye movements. Neuron 1998;21:761–73.

Cornelissen FW, Kimmig H, Schira M, Rutschmann RM, et al. Event-related fMRI responses in the human frontal eye fields in a randomized pro- and anti-saccade task. Experimental Brain Research 2002;145(2):270–4.

Crawford TJ, Haeger B, Kennard C, Reveley MA, Henderson L. Saccadic abnormalities in psychotic patients. I. Neuroleptic-free psychotic patients. Psychological Medicine 1995;25:461–71.

Crawford TJ, Puri BK, Nijran KS, Jones B, Kennard C, Lewis SW. Abnormal saccadic distractibility in patients with schizophrenia: a 99mTc-HMPAO SPET study. Psychological Medicine 1996;26:265–77.

Curtis CE, D'Esposito M. Success and failure suppressing reflexive behavior. Journal of Cognitive Neuroscience 2003;15(3):409–18.

Doricchi F, Perani D, Incoccia C, Grassi F, Cappa SF, Bettinardi V, et al. Neural control of fast-regular saccades and antisaccades: an investigation using positron emission tomography. Experimental Brain Research 1997;116(1):50–62.

Fukushima J, Fukushima K, Chiba T, Tanaka S, Yamashita I, Kato M. Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. Biological Psychiatry 1988;23(7):670–7.

Fukushima J, Fukushima K, Miyasaka K, Yamashita I. Voluntary control of saccadic eye movement in patients with frontal cortical lesions and parkinsonian patients in comparison with that in schizophrenics. Biological Psychiatry 1994;36(1):21–30.

Gaymard B, Ploner CJ, Rivaud S, Vermersch AI, Pierrot-Deseilligny C. Cortical control of saccades. Experimental Brain Research 1998;123:159–63.

Guitton D, Buchtal HA, Douglas RM. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal directed saccades. Experimental Brain Research 1985;58:455–74.

Holzman PS, Proctor LR, Levy DL, Yasillo NJ, Meltzer HY, Hurt SW. Eye-tracking dysfunctions in schizophrenic patients and their relatives. Archive of General Psychiatry 1974;31:143–51.

Hoptman MJ, Ardekani BA, Butler PD, Nierenberg J, Javitt DC, Lim KO. DTI and impulsivity in schizophrenia: a first voxelwise correlational analysis. Neuroreport 2004;15(16):2467–70.

Konishi S, Nakajima K, Uchida I, Sekihara K, Miyashita Y, et al. No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. European Journal of Neuroscience 1998;10:1209–13.

Konishi S, Nakajima K, Uchida I, Kikyo H, Kameyama M, Miyashita Y. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related fMRI. Brain 1999;122:981–91.

Law I, Svarer C, Holm S, Paulson OB. The activation pattern in normal humans during suppression, imagination and performance of saccadic eye movements. Acta Physiologica Scandinavica 1997;161(3):419–34.

Maruff P, Danckert J, Pantelis C, Currie J. Saccadic and attentional abnormalities in patients with schizophrenia. Psychological Medicine 1998;28(5):1091–100.

Matsuda T, Matsuura M, Ohkubo T, Ohkubo H, Matsushima E, Inoue K, et al. Functional MRI mapping of brain activation during visually guided saccades and antisaccades: cortical and subcortical networks. Psychiatry Research 2004;131(2):147–55.

Matsue Y, Okuma T, Saito H, Aneha S, Ueno T, Chiba H, et al. Saccadic eye movements in tracking, fixation, and rest in schizophrenic and normal subjects. Biological Psychiatry 1986;21(4):382–9.

McDowell JE, Zisook S. Saccadic system functioning among schizophrenia patients and their first-degree biological relatives. Journal of Abnormal Psychology 1994;103(2):277–87.

McDowell JE, Brown GG, Paulus M, Martinez A, et al. Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. Biological Psychiatry 2002;51(3):216–23.

Menon V, Adleman NE, White CD, Glover GH. Error-related brain activation during a go/no-go response inhibition task. Human Brain Mapping 2001;12:131–43.

Muri RM, Iba-Zizen MT, Derosier C, Cabanis EA, Pierrot-Deseilligny. Location of the human posterior eye field with functional magnetic resonance imaging. Journal of Neurology, Neurosurgery, and Psychiatry 1996;60:445–8.

Muri RM, Heid O, Nirkko AC, Ozdoba C, et al. Functional organization of saccades and antisaccades in the frontal lobe in humans: a study with echo planar functional magnetic resonance imaging. Journal of Neurology, Neurosurgery, and Psychiatry 1998;65:374–7.

O'Driscoll GA, Alpert NM, Matthysse SW, Levy DL, Rauch SL, Holzman PS. Functional neuroanatomy of antisaccade eye movements investigated with positron emission tomography. Proceedings of the National Academy of Sciences of the USA 1995;92:925–9.

O'Driscoll GA, Lenzenweger MF, Holzman PS. Antisaccades and smooth pursuit eye tracking and schizotypy. Archive of General Psychiatry 1998;55(9):837–43.

Petit L, Orssaud C, Tzourio N, Crivello F, Berthoz A, Mazoyer B. Functional anatomy of a prelearned sequence of horizontal saccades in humans. Journal of Neuroscience 1996;16:3714–26.

Pierrot-Deseilligny C et al.. Saccade and smooth pursuit impairment after cerebral hemispheric lesions. European Neurology 1994;34:121–34.

Raemaekers M, Jansma JM, Cahn W, Van der Geest JN, Van der Linden JA, Kahn RS, et al. Neural substrate of the saccadic inhibition deficit in schizophrenia investigated with three-dimensional event-related functional magnetic resonance imaging. Archives of General Psychiatry 2002;59:313–20.

Sereno AB, Holzman PS. Antisaccades and smooth pursuit eye movements in schizophrenia. Biological Psychiatry 1995;37:394–401.

Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL. Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. Journal of Neurophysiology 1996;75(1):454–68.