Neuronal Substrate of the Saccadic Inhibition Deficit in Schizophrenia Investigated With 3-Dimensional Event-Related Functional Magnetic Resonance Imaging

Mathijs Raemakers, MSc; Johannus M. Jansma, PhD; Wiepke Cahn, MD; Josef N. Van der Geest, PhD; Jeroen A. van der Linden, MD; René Kahn, MD, PhD; Nick F. Ramsey, PhD

Background: Several studies have shown that the ability to suppress automatic saccadic eye movements is impaired in patients with schizophrenia as well as in their first-degree relatives, and suggest that this impairment is a potential vulnerability marker for schizophrenia. The neurobiological mechanisms underlying normal saccade production and inhibition, revealed in primate studies, indicate that the impairment may result from a failure of the oculomotor system to effectively exert inhibitory control over brainstem structures. Functional localization of the affected brain structure(s) potentially provides a physiological measure for the investigation of vulnerability markers in schizophrenia.

Methods: The hemodynamic response to discrete visual stimuli was measured during prosaccades (saccades toward a peripheral stimulus), antisaccades (saccades toward a position opposite to a peripheral stimulus), and active fixation (holding fixation and ignoring a peripheral stimulus) in 16 patients with schizophrenia receiving atypical neuroleptics and 17 healthy control subjects using an event-related functional magnetic resonance imaging task design.

Results: Brain responses were detected in the frontal and parietal regions of the oculomotor system in all 3 tasks. Patients made more errors during inhibition tasks and exhibited a selective failure to activate the striatum during the inhibition of saccades. In other regions that were active during inhibition, specifically the supplementary and frontal eye fields, no difference was found between patients and control subjects.

Conclusions: A frontostriatal network is engaged in the suppression of automatic eye movements. The results indicate that abnormalities in this network, rather than the selective dysfunction of prefrontal brain regions, underlie the saccade inhibition deficit in schizophrenia.

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SMOOTH PURSUIT eye movement1 and the inhibition of automatic saccades2 is impaired in patients with schizophrenia, their healthy first-degree relatives,3,4 and healthy subjects with high scores on a measure of schizotypy.5 This suggests that eye movement deficits are a vulnerability marker6,7 or reflect an endophenotype8 for schizophrenia. A common feature of both smooth pursuit eye movements and antisaccade tasks is the requirement to avoid automatic intruding saccades. The failure to effectively inhibit saccades may explain the oculomotor impairments observed in patients with schizophrenia.9 A potential link has been reported between the antisaccade deficit and a genetic marker on chromosome 22q.10 The neural correlate of the antisaccade deficit in schizophrenia has not yet been identified. The elucidation of the neural correlate could provide a physiological measure of saccade inhibition, which could in turn prove to be a better endophenotype marker than the behavioral measure.

In the antisaccade task,12 subjects have to suppress saccades that are triggered by a peripherally presented stimulus (prosaccades) and instead have to generate a saccade toward a location in the opposite direction (hence, antisaccade). Patients with schizophrenia fail to suppress the reflexive saccades more often than healthy controls and exhibit longer saccade onset latencies of correct responses, whereas prosaccade performance is well within normal range.13-17 The deficit in saccade suppression in schizophrenia has been attributed to prefrontal dysfunction, a postulated key feature of schizophrenia.18 Some reported correlations between saccade inhibition, dorsolateral prefrontal cortex (DLPFC) function, and working memory support this theory.19,20 However, the notion of DLPFC involvement in saccade inhibition is primarily based on lesion studies.21,22
SUBJECTS AND METHODS

SUBJECTS

Sixteen patients with schizophrenia (13 men and 3 women; mean ± SD age, 27.9 ± 5.3 years) from the Department of Psychiatry at the University Medical Center Utrecht, Utrecht, the Netherlands, participated in this study. All patients met the criteria for schizophrenia according to the DSM-IV, as assessed with the Comprehensive Assessment of Symptoms and History (1 patient had disorganized schizophrenia, 11 had paranoid schizophrenia, 3 had schizophreniform disorder, and 1 was undifferentiated; mean ± SD duration of illness, 29 ± 19 months), and were screened for severity of present symptoms using the Positive and Negative Syndrome Scale (PANSS) (mean ± SD sum of positive items, 13.3 ± 3.9; sum of negative items, 15.2 ± 3.9; sum of generalized items, 29.9 ± 6.6). Every patient was taking a stable dose of atypical neuroleptic medication (clozapine: n = 7, with a mean ± SD daily dose of 200 ± 87 mg; olanzapine: n = 8, with a mean ± SD daily dose of 11.3 ± 6.4 mg; quetiapine fumarate: n = 1, with a daily dose of 450 mg). The control group consisted of 17 healthy subjects (10 men, 7 women; mean ± SD age, 25.9 ± 4.1 years). None of the subjects in the control group exhibited any signs of a major psychiatric disorder according to the Mini-International Neuropsychiatric Interview. All participants were right-handed according to the Edinburgh Handedness inventory (mean ± SD number of patients, 0.84 ± 0.14; number of controls, 0.84 ± 0.18). There was no significant difference in educational level between the groups (mean ± SD number of patients, 12.1 ± 2.3 years; number of controls, 13.1 ± 2.0 years). A history of substance abuse or major neurologic illness resulted in exclusion from the experiment, as did metal implants. All subjects gave their informed consent for participation, approved by the Human Ethics Committee of the University Medical Center Utrecht.

Alternatively, studies in nonhuman primates indicate that saccade inhibition involves more complex hierarchical networks. In a recent study on the functioning of the superior colliculus (SC) in primates, neuronal activity in the SC was reduced immediately before antisaccades, but not before prosaccades, indicating that the SC must be suppressed by this network to prevent an automatic saccade. The failure to inhibit a saccade can be caused by any one of the brain structures forming the neural network that projects to the SC. The saccadic inhibition deficit in schizophrenia could therefore be associated with cortical as well as basal ganglia dysfunction, or disconnection, because both have been implicated in schizophrenia.

To our knowledge, only 2 functional imaging studies have investigated the saccade inhibition deficit in schizophrenia. The deficit was associated with reduced blood flow in the DLPFC and frontal eye fields (FEF) in one study and with reduced blood flow in the insula, anterior cingulate cortex, and striatum in the other study. In both studies, single measurements of brain perfusion required sustained periods (minutes or longer) during specific events in time, which provides the opportunity for prolonged measurements are predominantly sensitive to tonic levels of activity. Brain regions that exhibit a change in tonic activity may be directly involved not in saccade inhibition but rather in sustained attention and effort. To investigate the specific neuronal correlates of the saccadic inhibition deficit in schizophrenia, we used a new experimental design that differs from the previous studies in 2 ways. First, to focus on the inhibition of saccades, an active fixation task was added to the experiment; subjects were required to ignore distracting visual stimuli. The antisaccade task is not sufficient because it involves other processes in addition to inhibition, particularly those that are required for the deliberate initiation of a saccade toward another predetermined location. Patients with schizophrenia are more easily distracted by stimuli when the task requires active fixation. Second, the tasks were adapted for event-related functional magnetic resonance imaging (ERfMRI). This technique has the advantage of coupling changes in the BOLD (blood oxygenation level–dependent) signal with specific events in time, which provides the opportunity for the response of interest, namely the first eye movement (in the image analysis, the BOLD curves were mathematically uncorrelated). A new stimulus was triggered by the scanner for every ninth scan, thereby generating a fixed stimulus interval of 12.9 seconds and giving the stimulus-related BOLD signal time to return to baseline.

Instructions for all tasks were given verbally prior to the start of the experiment and included the following: (1) PRO: “From central fixation look toward the square as quickly as possible when it appears. Look back to the fixation cross when the square disappears and the fixation cross reappears in the center”; (2) ANT: “When the square appears, look in the opposite direction as quickly as possible, without looking toward the square. Look back to the fixation cross when the square disappears and the fixation cross reappears in the center”; and (3) FIX: “Keep looking at the location of the fixation cross when it disappears, and do not move toward the square.” At the beginning of each new block of 17 stimuli, the task instructions were changed. There were 3 blocks per task making a total of 9 blocks, which were presented in a semirandomized sequence (PRO-ANT-FIX-ANT-PRO-FIX-PRO-FIX-ANT). A similar oculomotor task with EOGs immediately followed the fMRI session to measure subject task performance. Stimulus visual size was slightly reduced (0.8° visual angle), as was visual distance between central fixation and the peripheral square (7.0° visual angle). To avoid fatigue, the interstimulus interval was shortened to 3 seconds, of which 1.8 seconds were used for central fixation and 1.2 seconds for peripheral visual stimuli. The antisaccade task is not sufficient because it involves other processes in addition to inhibition, particularly those that are required for the deliberate initiation of a saccade toward another predetermined location. Patients with schizophrenia are more easily distracted by stimuli when the task requires active fixation. Second, the tasks were adapted for event-related functional magnetic resonance imaging (ERfMRI). This technique has the advantage of coupling changes in the BOLD (blood oxygenation level–dependent) signal with specific events in time, which provides the opportunity for the response of interest, namely the first eye movement (in the image analysis, the BOLD curves were mathematically uncorrelated). A new stimulus was triggered by the scanner for every ninth scan, thereby generating a fixed stimulus interval of 12.9 seconds and giving the stimulus-related BOLD signal time to return to baseline.

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square display. All 51 stimuli for each task were presented in 1 block. Blocks were presented in a PRO-ANT-FIX sequence. Subjects were seated in a near-dark room in front of a VGA monitor. Electro-oculographic data for horizontal saccades were acquired using surface electrodes at a sampling rate of 500 Hz. Data were processed offline with the aid of a custom nonautomated EOG analysis program. Onset latencies were determined for all saccades. Any initial movement of the eyes in the wrong direction (depending on the task) with a latency longer than 100 ms was counted as an error. Any stimulus-related saccades during FIX were counted as errors.

IMAGE ACQUISITION
All images were obtained with a clinical scanner (ACS-NT 1.5T; Philips Medical Systems, Best, the Netherlands) with fast gradients (PT6000). The head was held in place with a strap and padding. Structural and functional images were acquired in transverse orientation from the same section of the brain (Figure 2). For functional scans, a 3D-PRESTO pulse sequence was used with following parameters: echo time, 36 milliseconds; repetition time, 24 milliseconds; flip angle, 10°; matrix, 48 × 64 × 24; field of view, 192 × 256 × 96 mm; voxel size, 4-mm isotropic; scan duration, 1.43 seconds per 24-slice volume. Immediately after functional scans, an additional PRESTO scan of the same volume of brain tissue was acquired with a high (30°) flip angle (FA30) for the image registration routine. A total of 1620 functional volumes were acquired per subject.

DATA ANALYSES
Data analysis of fMRI scans was done with custom-written programs in PV-Wave using the International Mathematical and Statistical Library routines (Visual Numerics Inc, Boulder, Colo). The last functional volume was registered to the FA30 scan, thereby providing spatial alignment to the last functional volume using a least-squares difference criterion. The structural scan was also registered to the FA30 scan, thereby providing spatial alignment between the structural scan and the functional volumes. Only the scans acquired during stimulus trials were analyzed. A 3-dimensional gaussian filter (8-mm full width at half maximum; Visual Numerics Inc) was applied to all fMRI volumes. To decrease low-frequency noise, for each voxel the offset and linear trend were calculated for every set of 9 scans belonging to a single stimulus, using a standard registration procedure. The residuals were used for further analyses.

Next, 3 t values per voxel were obtained from a standard linear multiple regression procedure with a factor matrix that contained the 3 factors representing stimulus-related changes in BOLD signal during PRO, ANT, and FIX, respectively. For each trial in the matrix, the BOLD curve was modeled using a curve derived from a previous (unpublished) study. This curve has a skewed gaussian shape (with a kernel of 6 seconds) that peaks at 5 seconds. Thus, the 3 t values for each voxel represented the presence and magnitude of the stimulus-contingent BOLD response during the 3 tasks for each subject. Finally, all the now coregistered t values and structural scans were spatially normalized in Talairach orientation to enable groupwise comparisons.

To test for specific effects of inhibition and of illness on inhibition in the brain activity maps, a multivariate repeated-measures analysis was applied. Four independent comparisons were tested for significance for each voxel by first calculating the within-subject contrast value and subsequently comparing these contrast values between the groups. Four comparisons of interest represented overall activity (activity during all conditions for both groups), overall effect of illness (differences between groups for all conditions), overall effect of inhibition (ANT and FIX combined vs PRO for both groups), and effect of illness on inhibition (differences in effect of inhibition between groups). The group effects were converted to t values were subsequently tested for significance (P < .05) with Bonferroni correction for the number of voxels (approximately 14000), resulting in a critical t value of 4.51 for each voxel. Thus, for the assessment of significant effects, a threshold of t = 4.51 was applied to all of the image analysis results.

RESULTS
EOG PERFORMANCE
The EOG results indicate that patients did not perform worse than controls on the PRO task in terms of reaction time (t29 = 0.38; P = .71) or error rate (t29 = −0.23; P = .82). However, in the ANT task the error rate was significantly increased (Figure 3A), in the window of 100 to 180 milliseconds (t29 = 1.90; P = .03), but not in other time windows. In addition, patients made more saccades (distraction) during FIX (t29 = 1.70; P = .03) (Figure 3B). The reaction time of correct antisaccade responses was increased (t29 = 1.92; P = .05) (Figure 3C). Thus, patients were moderately impaired in inhibiting saccades. When the data were summed across all tasks, patients made more eye movements overall, within a time window of −100 to 500 milliseconds (Mann-Whitney U test: z = 2.36; P = .02).

IMRI: SACCADe-RELATED ACTIVITY
The maps corresponding to the tested contrasts are shown in Figure 4. The overall activity pattern, including all tasks and subjects, is extensive (Figure 4A). In addition to extensive occipital activation, the detected regions of the oculomotor system included the PEF in Brodmann area (BA) 39 and BA 40, FEF at the intersection between the superior frontal and precentral fissure extend-
ing dorsally into the lateral part of BA 6, and SEF in the medial part of BA 6. Further activity was found in the anterior cingulate cortex and anterior insula.

Compared with controls, patient brain activity was significantly reduced in the visual cortex and, to a lesser extent, in all other oculomotor regions (PEF, FEF, and SEF) as well as the anterior cingulate cortex (Figure 4A). However, when examining the overall group map, significant activity was found in all of these regions, indicating that activity was relatively reduced but not absent. This is shown for the visual cortex in Figure 5.

fMRI: Inhibition-Related Activity

In the overall inhibition map, a significant BOLD response occurred in the lateral occipital lobe (visual area [V] 5), FEF, and SEF (Figure 3B). Interestingly, the BOLD response decreased in some subregions of the occipital lobe (V1 and V2). The interaction between inhibition and illness was significant only in the striatum bilaterally. More specifically, 4 areas were found with the following Talairach x, y, and z coordinates: left putamen (−23, 8, 7); right putamen (26, 4, −3); left caudate body (−10, 1, 10); and right caudate body (13, 1, 10).

Further inspection revealed that in controls the striatum responded (selectively) to the inhibition tasks but that this response was absent in patients (Figure 6). This difference was also present in the individual inhibition t maps. Whereas 12 of 17 control subjects showed activated voxels (t > 3.0) in the striatum, the same was true for only 5 of 16 patients (χ² = 3.69; P = .03). In further exploring the data, we looked at lower thresholds in the inhibition maps (t > 3.5) and observed additional reduced responses in patients in the thalamus, intraparietal area, and BA 44.

Clinical Variables

Clinical variables (positive, negative, and general PANSS scores as well as type and dose of medication) did not correlate significantly with measures of performance or striatal activity.

Comment

In accordance with other studies, patients with schizophrenia were impaired on the ANT task, which requires the inhibition of prepotent saccades. The imaging results suggest that this impairment is associated with a failure to engage striatal structures. In healthy volunteers, we demonstrated significant activation in a network of regions that subserve saccadic eye movements.16,31,34,36,37,39 Furthermore, the inhibition of saccades was found to involve the SEF (the anterior aspect of the supplementary motor area), FEF, and striatum, confirming previous studies.19,27 Thus, the obtained brain activity maps for each task demonstrated that the event-related fMRI procedure was adequate.

Although patients with schizophrenia showed activity in the same regions as the controls during all tasks combined, overall the magnitude of activity was smaller. Because reduced activity occurred in all oculomotor-
related areas; patients with schizophrenia generally exhibited either lower amplitudes of, or more variability in, the BOLD response. The latter explanation is supported by the finding that the patients made more eye movements in the period between 100 milliseconds before and 500 milliseconds after a stimulus during the EOG test. A higher incidence of random eye movements during the fMRI experiment may have increased variability by adding BOLD responses to the data, resulting in increased noise. The fact that inhibition-related brain activity was present in FEF and SEF in both patients and controls indicates that patients complied with the tasks when undergoing scans. This further indicates that the observed difference between patients and control subjects in the striatum does not reflect merely a behavioral difference caused by a higher percentage of incorrect prosaccades in patients during inhibition.

The relevance of the striatum for oculomotor functioning has been studied extensively. The striatum represents the major input site of the subcortical oculomotor circuit. These subcortical regions transfer input from the frontal cortex downward to the substantia nigra pars reticulata (SNr). From the SNr, ascending fibers feed back to the cortex through the thalamus, whereas the descending efferents provide an escape route from the basal ganglia-thalamocortical loop by projecting to the SC.

The striatum is capable of exerting both an inhibitory and an excitatory influence on the SNr by means of 2 parallel pathways. The inhibitory pathway projects to the SNr directly, and the excitatory pathway passes through the external globus pallidus and subthalamic nucleus. With these 2 connections, the striatum can facilitate or suppress overt oculomotor behavior and does so by transiently modulating the tonic inhibitory control that is exerted by the SNr on the SC. The suppressed neuronal activity in the SC during saccadic inhibition probably reflects an effort to avoid fast reflexive saccades triggered by the SC through afferents of the nuclei of the optic tract or parietal regions. Accordingly, the inhibition of saccades requires adequate input from a network that feeds into the SNr, which is most likely initiated in the frontal cortex.

Indirect evidence of the striatum’s possible role in saccade inhibition in human subjects is provided by the fact that distractibility rates are increased in patients with degenerative diseases affecting the basal ganglia, such as Huntington disease. This indicates that although direct connections also exist between the frontal cortex and the SC (and the reticular formation), providing an alternative means of inhibitory control, impaired striatal function does affect saccadic inhibition. Tardive dyskinesia in patients with schizophrenia has been shown to enhance distractibility, which has been ascribed to altered γ-aminobutyric acid and dopamine function in the basal ganglia. The striatum has been implicated in schizophrenia in other studies. The clinical efficacy of neuroleptics is linked to dopamine D2 receptors, which are present in high concentrations in the striatum, and both medicated and unmedicated patients demonstrate abnormal striatal metabolic rates.

Alternatively, dysfunction of the frontostriatal-thalamic loops could contribute to cognitive and psychotic symptoms of schizophrenia. Because the frontal regions are involved in the generation of a “stop” signal, frontostriatal connections play an important role in the downward transmission of this signal. A deficit in functional connectivity between the frontal lobes and the striatum has been demonstrated in schizophrenia in concordance with a reduction in interconnecting white matter between these areas.

Surprisingly, in this study there was no indication that abnormal activity in the frontal lobes contributed to the deficit. Healthy volunteers did not exhibit a BOLD response in the DLPFC despite of its postulated involvement in saccade inhibition. Because the DLPFC did not respond to the stimuli in a transient manner, it may have been constantly active during inhibition tasks, thereby remaining unnoticed in this experiment and making the detection of abnormal activity in patients difficult. However, the role of the DLPFC in saccadic inhibition has not been consistently confirmed by imaging studies.

Our study is limited in several respects. For one, eye movements were not recorded in the scanner. Perfor-
mance measurements were acquired outside the scanner immediately after the fMRI session because at the time of the fMRI experiment, we did not have access to an MRI-compatible eye-tracking device. Also, the task was not the same during and after scanning; the interstimulus interval was shortened to minimize the overall length of the experimental session. This shorter interval may have affected performance because it may be more stimulating and alerting for subjects. However, the main reason for the offline recording of eye movements was to determine whether all subjects were capable of performing the task as intended and whether the patient group would display a deficit, as was expected on the basis of reported findings in the literature. The results indicated that all subjects were capable of performing the tasks and that the patients made more errors. The brain activity maps showed that most of the brain regions that were active in controls were also active in patients during all tasks, albeit at lower levels, providing indirect evidence that patients did perform the tasks and that the difference in brain activity was not due to noncompliance. Another limitation is that in maximizing sensitivity to transient brain responses to examine the dynamics of the involved network, we did not measure sustained brain activity during the tasks. It would be worthwhile to design studies that allow the assessment of both types of responses simultaneously. Responsivity of one region can conceivably depend on the tonal activity of another.65

Figure 4. Active voxels superimposed on the averaged anatomical scan. The numbers displayed in the top left corner of each slice correspond to Talairach z coordinates. Only the most informative slices are shown. Colored voxels represent significant effects at \( P < .05 \) (Bonferroni-corrected). A, Response pattern for all 3 tasks combined. Red voxels are those that were active in both groups (patients and controls, main effect of visual processing). Yellow indicates regions where there is a difference between patients and controls (in which controls were more active than patients). Analyses of each group showed that patients exhibited significant activity in the yellow regions but less than the controls. B, Response pattern for the inhibition conditions. Red voxels are those that were selectively active during saccadic inhibition (as opposed to prosaccades) in both patients and controls. Blue indicates the regions where activity decreased during inhibition in both groups. Yellow voxels represent the key finding, namely the significant difference between patients and controls during the inhibition of saccades (in which patients were less active than controls).

Figure 5. Averaged blood oxygenation level-dependent (BOLD) responses and corresponding \( t \) values during prosaccades and antisaccades, averaged across the activated voxels in the occipital lobe for control subjects (n=17) and patients with schizophrenia (n=16). Because of the normalization of values in multiple regression analyses, the BOLD response amplitude is presented in arbitrary units (AU).

Figure 6. The scanner plot shows the mean \( t \) value in the striatum of the difference in brain activity between antisaccades (ANT) and prosaccades (PRO) and between fixation (FIX) and prosaccades for each subject. For these mean \( t \) values, voxels were selected only if an interaction between illness and inhibition was found in the group comparison. The plot shows that the patients fail to activate the striatum during both inhibition tasks (ANT and FIX). Controls are indicated with triangles; patients, with squares.
Finally, because we tested patients who were receiving medication, one could argue that the results are associated with medication effects. Although we do not know whether the observed abnormalities of brain function in the striatum in our patients are the result of medication, we do know from the literature that the behavioral saccade inhibition abnormality observed in patients with schizophrenia are not explained by medication. Therefore, if the brain activity effect were attributed to medication, the observed abnormality in brain function would bear no relevance to the behavioral deficit in saccadic inhibition. However, we show that the striatum is actively involved in saccade inhibition in healthy subjects, so any medication effects on this region would be expected to have behavioral consequences.

In summary, we have shown that the network that subserves the inhibition of prepotent saccades may be dysfunctional in schizophrenia at the level of the striatum. Because saccade inhibition deficits may be regarded as biological markers for schizophrenia, IMRI images of the neuronal circuits underlying saccade inhibition could be a useful tool to identify those at risk for schizophrenia.

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Corresponding author and reprints: Nick F. Ramsey, PhD, Department of Psychiatry, University Medical Center, 3584 CX, the Netherlands.

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