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Structural neural networks subserving oculomotor function in first-episode schizophrenia[1]

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Short title: Eye movements & MRI in first-episode schizophrenia

Key words: Eye movements; schizophrenia; structural neuroimaging; voxel-based morphometry; MTR

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ABSTRACT

Background: Smooth pursuit and antisaccade abnormalities are well documented in schizophrenia, but their neuropathological correlates remain unclear.

Methods: In this study, we used statistical parametric mapping to investigate the relationship between oculomotor abnormalities and brain structure in a sample of first-episode schizophrenia patients (n = 27). In addition to conventional volumetric magnetic resonance imaging (MRI), we also used Magnetisation Transfer Ratio (MTR), a technique that allows more precise tissue characterisation.

Results: We found that smooth pursuit abnormalities were associated with reduced MTR in several regions, predominantly in the right prefrontal cortex. Antisaccade errors correlated with grey matter volume in the right medial superior frontal cortex as measured by conventional MRI, but not with MTR.

Conclusions: These preliminary results demonstrate that specific structural abnormalities are associated with abnormal eye movements in schizophrenia.

INTRODUCTION

Eye movements can be broadly categorised into saccades, which redirect gaze to bring the image of an object onto the fovea, and smooth pursuit, which allow a moving object to remain fixed on the fovea. Schizophrenia has been associated with abnormalities of smooth pursuit (Levy et al 1994) and more recently increased antisaccadic errors, which are erroneous reflexive saccades made towards a peripheral target when subjects are instructed to direct their gaze to its mirror image location (Crawford et al 1995; Fukushima et al 1990; Katsanis et al 1997; McDowell & Clementz, 1997). Both abnormal smooth pursuit and increased antisaccade errors have been found at illness onset in medication-naïve patients (Sweeney at al, 1992; Lieberman et al 1993; Hutton et al 1998) and in first-degree relatives (Holzman et al 1988; Crawford et al 1998; Ross et al 1998). Thus, oculomotor abnormalities may represent markers of genetic vulnerability to schizophrenia.

Functional imaging studies have provided evidence for two separate but parallel cortical systems that subserve pursuit and saccadic eye movements in humans (Petit & Haxby, 1999; Berman et al 1999; Rosano et al 2002). However, few studies have used imaging techniques to examine the structural neural correlates of smooth pursuit and saccadic eye movement abnormalities in schizophrenia, although this approach has been used to investigate neural correlates of cognitive abnormalities with some success (Delisi et al 1991; Sullivan et al 1996, Stratta et al 1997; Szeszko et al 2002 and 2003; Meisenzahl et al 2004; Salgado-Pineda et al 2004).

Abnormal smooth pursuit eye movements have been associated with larger ventricles in

chronic schizophrenia in some computed tomography (CT) (Bartfai et al 1985; Smeraldi et al 1987) and magnetic resonance imaging (MRI) (Blackwood et al 1991) studies whereas antisaccadic abnormalities were found to be associated with frontal cortical atrophy on CT (Fukushima et al 1988). However, no correlation was observed between smooth pursuit and ventricular-brain ratio in medication-free schizophrenia patients (Siever et al 1986) or MRI volumetric indices of a number of brain regions including lateral ventricles, medial temporal lobe structures and fronto-parietal cortex in first-episode or established schizophrenia patients (Katsanis & Iacono, 1991; Levy et al 1992). These studies have generally used volumetric indices of brain structure. It is possible that oculomotor abnormalities reflect subtle localised neuropathological changes that do not necessarily culminate in atrophy.

Magnetisation Transfer Imaging (MTI), and the quantitative index, Magnetisation transfer ratio (MTR) (Wolf and Balaban, 1994) is based on the interaction of protons bound to macromolecular structures and free protons in tissue water. In brain tissue, the major macromolecules in the bound proton pool are thought to be cell membrane proteins and phospholipids in grey matter and myelin in white matter. Bound protons, undetected by conventional MRI because of their very short relaxation times, are preferentially saturated using an off-resonance radio-frequency pulse. Chemical exchange or direct dipolar coupling transfers macromolecular saturation from bound to free protons, causing decreased longitudinal magnetization (Henkelman et al 2001). The MT signal is closely related to macromolecular density, which is mainly dependent upon cell membrane proteins and phospholipids in grey matter and myelin in white matter. Pathological processes that damage macromolecules and brain parenchymal

integrity, particularly cell membranes and myelin, cause MTR reductions (Lexa et al 1994; Mottershead et al 1998; Van Waesberghe et al 1999; Bosma et al 2000;Van Buchem and Tofts, 2000). The specific molecules responsible for the MT signal in grey matter are yet to be specified, although creatine, choline and n-acetyl aspartate related compounds are thought to contribute (Meyerhoff, 1999). Wallerian degeneration triggered by distant axonal damage and microscopic lesions are thought to explain cortical MTR reductions in multiple sclerosis which were not detectable using conventional MRI (Cercignani et al 2001). MTR reductions in grey matter are likely to be related to decreased cell number, cell size, dendritic density or may reflect abnormal cell membrane structure. In our earlier study (Bagary et al 2003), we reported MTR abnormalities in the medial prefrontal cortex, insula and fasciculus uncinatus in first-episode schizophrenia patients compared to matched healthy control subjects, in the absence of detectable atrophy.

We examine here the relationship between brain structure and oculomotor function using MTR and conventional (T1) high-resolution volumetric MRI. The combination of these techniques enhances sensitivity to atrophy and allows the detection of subtle neuropathological changes in its absence. This has been illustrated in a recent study (Davies et al 2004) that combined these techniques to explore brain abnormalities in patients with multiple sclerosis. Cortical atrophy (as measured by T1 high-resolution sequence) correlated with decreased MTR, but cortical MTR reduction was still significant after volumetric changes were taken into account, supporting the view that MTR provides additional information about intrinsic tissue pathology. We used voxel-based morphometry (VBM) to reduce observer bias, allowing whole brain analysis

without limiting correlations to pre-determined regions of interest. Both smooth pursuit and antisaccade performance were measured in a sample of first-episode schizophrenia patients wherein detectable brain abnormalities are more likely to reflect the primary disease process, diminishing confounds such as medication exposure and chronicity.

METHODS AND MATERIALS

Participants

The patients were recruited as part of a larger ongoing prospective study of first-episode schizophrenia in West London, UK. The data from twenty-seven patients were used on the basis that they had performed both imaging and oculomotor components of the study. Subjects were assessed on recruitment with the Scales for the Assessment of Positive Symptoms (SAPS, Andreasen, 1984b) and Negative Symptoms (SANS, Andreasen, 1984a). In each case the diagnosis of schizophrenia (DSM-IV) was determined at regular review meetings held by two experienced clinicians (EMJ, TREB) using the criteria of the Structured Clinical Interview for DSM-IV (SCID, First et al, 1997). Subjects with a history of neurological or systemic illness, head injury, drug abuse or alcohol intake over 240g/week were excluded. Sixteen were male; three were left-handed, as determined by Annett's (1970) questionnaire; and mean age was 26.3 ± 6.1 years (range 18-47). Mean illness duration at the time of the scan was 5.3 ± 4.3 months (range 1-14). Twenty-four patients were receiving antipsychotic medication (19 atypical and 5 typical). Twenty-seven healthy control subjects matched for age, handedness and gender underwent eye movement examination but not brain imaging (mean age 26.1 ± 5.4 years, range 18-37; two were left-handed and eighteen were male). No control subject had a history of psychiatric illness or family history of

psychosis, as assessed on clinical interview. Permission to conduct the study was obtained from the relevant Ethics Committees (Riverside; Merton, Sutton and Wandsworth; Ealing, Hammersmith and Fulham and University College Hospital Trust in London, UK). Patients and controls gave written informed consent and received a small honorarium for their time.

Procedures

Oculomotor function

Subjects were comfortably seated 1.5 meters from the screen. Head movements were minimized using an adjustable headrest. All paradigms were conducted in the dark. Eye movements were recorded using a Skalar IRIS infrared limbus reflection device. A hardware anti-aliasing filter (cut-off frequency 200 Hz) was used to filter eye position. Stimulus display and data sampling were controlled an IBM compatible PC. Each paradigm was preceded by a standard calibration trial.

Stimuli for the antisaccade tasks consisted of four red-light emitting diodes (LED) of diameter 0.25^0 located $\pm 7.5^0$ and $\pm 15^0$ either side of a central fixation LED. The LED targets were embedded in a semi-opaque screen, visible only when illuminated. Each trial started with the illumination of the central fixation LED. After 800ms, the fixation LED was illuminated and simultaneously a peripheral target LED were illuminated for 1000ms and a 200ms buzzer signal initiated. Subjects were asked to direct their gaze to the mirror image location of the peripheral stimulus (the target LED). Antisaccade errors occur when participants are unable to inhibit a reflexive saccade towards the peripheral

target. Antisaccadic errors are typically followed by a correct antisaccade in the opposite direction. Participants performed 24 trials and the percentages of antisaccade errors were measured

The smooth pursuit stimulus was a bright red laser spot back-projected onto a semi-opaque screen. The target oscillated horizontally with a triangular waveform with an amplitude of 22.5^0. Four velocities, 10, 20, 30 and 36^0 per second were used, and six full cycles recorded at each velocity. The smooth pursuit velocity gain at the four velocities was calculated as the ratio of eye velocity to target velocity. Mean values were used for the analysis. Values lower than one indicate that the eye is moving more slowly than the target.

Saccadic eye movements were analysed using software that enabled rejection of artefacts. Eye position data was filtered using a Kaiser window low-pass filter and the signal differentiated to yield eye velocity. Saccades were detected using acceleration (increased eye velocity of 30 degrees/second) and amplitude (>0.5 of a degree) criteria. Saccades were classified according to standard criteria (Abel et al 1991; Friedman et al 1992) by the operator (SBH). Smooth pursuit analysis was performed using the Eyemap analysis package (Amtech GmbH, Heidelberg, Germany). Smooth pursuit velocity gain was measured by excluding blinks and both corrective and intrusive saccadic movements from the data. In each half-cycle, a 50-ms portion of smooth pursuit eye movement were selected and expressed as peak velocity gain (eye velocity/ target velocity). This portion was always collected from the middle third of each half

cycle, to avoid acceleration and deceleration transients at the beginning and end of each ramp.

MRI

All first-episode schizophrenia patients underwent MRI examination using a GE Signa 1.5 Tesla scanner (General Electric, Milwaukee, WI) with a standard quadrature head coil. High-resolution conventional volumetric imaging was acquired using a 3-dimensional T1-weighted spoiled gradient recalled echo (SPGR) sequence generating 124 contiguous, 1.5mm coronal slices (TE 4.2ms, TR 15ms, FOV 24cm^2, 256x192 matrix, flip angle 20°). MT images were acquired using a dual spin echo based sequence (TE 30/80 ms, TR 1720 ms, 28 contiguous 5 mm axial slices, 256x128 pixel image matrix, 24cm^2 FOV) with and without a saturation pulse. A 16 ms saturation pulse (23.2T Hamming appodised 3 lobe sinc pulse) was applied 1KHz from water resonance. The sequence (TE 15/90 ms, TR 3000ms, 28 contiguous 5mm axial slices, 256x256 pixel image matrix, 24x24cm FOV) also generates T2-weighted and proton-density images sequence which are co-registered with the MT images during acquisition (Barker et al 1996). MTR was calculated on a pixel-by-pixel basis from the formula MTR = {[Mo-Ms]/Mo} x 100, where Ms and Mo are the mean signal intensities with and without the saturation pulse, respectively. A neuroradiologist reviewed MRI scans and no gross abnormalities were found.

Image processing

Data were processed on a Sun Ultra workstation (Sun Microsystems, Mountain View, CA) using SPM99 (Wellcome Department of Cognitive Neurology, London, UK) working in MATLAB (MathWorks, Natick, MA) unless otherwise stated.

MTR

Spatial normalization involved registration of the T2-weighted images into standard space using a modified (Symms et al 1997) version of the Automated Image Registration software (Woods et al 1992). A masking procedure was used to remove non-brain tissue and linear transformations were used to normalize T2-weighted scans to the Montreal Neurological Institute (MNI) template in SPM. The normalization parameters were then applied to MTR images (Bagary et al 2003).

Volumetric imaging

Total brain, grey matter and white matter volumes were calculated according to methods described by Chard and colleagues (2002). For regional correlations, images were spatially normalized to the standard T1-template in SPM99, following a method that optimises segmentation accuracy for VBM (Good et al 2001). Images were aligned and spatially normalized to the standard T1 template in SPM99 using affine registration and flipped to neurological space. Images were then segmented into grey matter, white matter and CSF. Grey and white matter segments were extracted to remove non-brain voxels. The extracted brain images were subject to non-linear normalization to the grey-and-white image template in SPM99 using 7x8x7 basis functions. The resulting images were segmented to produce grey matter, white matter and CSF tissue maps in MNI space having excluded non-brain voxels. A modulation step was used to preserve

within-voxel volumes that may have been altered during non-linear normalization (Ashburner and Friston, 2000, 2001) allowing subsequent correlations between eye movements and absolute regional brain volume.

Smoothing of volumetric and MTR data

Taking account of voxel size and the size of structures within which abnormalities were predicted, images were smoothed to 12mm (volumetric) and 15mm (MTR) using a full-width-half-maximum Gaussian filter to improve signal-to-noise ratio and to allow for inter-subject anatomical variability.

Statistical analysis

Volumes of total grey and total white matter as a fraction of total brain volume were correlated with oculomotor indices using Spearman's rank order correlation. For regional correlations, smoothed MTR and volumetric data from first- episode schizophrenia patients were subject to covariate analysis based upon the general linear model and the theory of random Gaussian fields (Worsley et al 1992; Friston et al 1996). Thresholds for both MTR and SPGR data were set at 40% of mean image intensity to minimize low signal-to-noise voxels. Only voxels exceeding this intensity threshold (40% of mean image intensity) were included in the analyses. As calculation of mean intensity includes all the (very low intensity) voxels outside the head, the cut-off of 40% of this value should not exclude any voxels that are fully brain tissue. This procedure excluded noise areas outside the brain and/or in the ventricles. Proportional scaling was used to normalize image intensity in SPGR grey and white matter maps. Smooth pursuit velocity gain and antisaccade errors were selected as covariates of

interest with three nuisance variables (gender, age and handedness). In order to minimise the risk of Type 1 errors, we focussed on antisaccade errors and smooth pursuit velocity gain as these two measures are the most robust and reliably reported indices of oculomotor dysfunction in schizophrenia. For regional correlations, we selected a voxel-level study threshold of $p<0.001$, uncorrected to avoid an overly conservative correction for family-wise type 1 error in a structural VBM analysis. SPM was originally designed to analyse functional data and correction for multiple comparisons can be considered overly conservative when applied to structural data (Sowell et al 1999). The study threshold was based on analysis parameters validated using healthy control subjects (n = 30) divided into two subgroups matched for age, handedness and gender. At the threshold of $t > 3.24$, $p < 0.001$, uncorrected there were no voxel-level differences in MTR or SPGR (both grey and white matter) between the two subgroups of healthy controls, suggesting this threshold minimizes false positives (Bagary et al 2003). Small clusters (<25 contiguous voxels) were also excluded to further minimise false positives (Wilke et al 2001). Results were then subjected to correction for multiple comparisons ($p<0.05$) using Random Field Theory (Worsley et al 1992). Spatial MNI co-ordinates were transformed into Talairach-brain co-ordinates using transformations (see www.mrccbu.cam.ac.uk/imaging/mnispace) to allow Talairach anatomical localization (Talairach and Tournoux, 1988). Comparisons between control and patients were performed using x^2 and t-tests.

RESULTS

There were no differences for age ($t = 0.03$, $df = 51$, $p = 0.976$), gender ($x^2 = 0.153$, p

= 0.696) and handedness (x^2 = 0.181, p = 0.670) between first-episode schizophrenia patients and controls.

Smooth pursuit velocity gain was significantly reduced and the percentage of antisaccadic errors significantly increased in first-episode schizophrenia patients compared to matched controls (see table 1).

Correlations between brain parenchymal tissue fractions and oculomotor measures

There were no significant correlations (Spearman's rho) between either total grey or total white matter volumes, as a fraction of total brain volume and oculomotor indices measured i.e. smooth pursuit velocity gain or percentage of antisaccadic errors (see table1).

Correlations between brain regions and oculomotor measures (see table 2)

i) Percentage of antisaccade errors

There were no significant correlations between percentage of antisaccade errors and MTR. However, antisaccade errors were negatively correlated with grey matter volume in the right medial superior frontal cortex (fig.1) suggesting worse performance on the antisaccade task was associated with reduced grey matter volume in this cortical region.

ii) Smooth pursuit velocity gain

Smooth pursuit velocity gain was positively correlated with MTR in the right post-

central gyrus, right cingulate gyrus, right precentral gyrus, right middle frontal gyrus and left inferior frontal gyrus (fig.2). Thus, worse performance in the smooth pursuit velocity gain task was associated with reduced grey matter integrity, as measured by MTR, largely in the right prefrontal cortex. No correlations were found between smooth pursuit velocity gain and regional grey matter volume.

DISCUSSION

In this study we have demonstrated that oculomotor function in patients with first-episode schizophrenia correlates with measures of brain structure derived from high-resolution MRI and MTR using VBM. We found that increased antisaccade errors were associated with decreased right superior medial frontal cortical volume. Additionally, decreased smooth pursuit velocity gain was associated with cortical MTR reductions in several areas, predominantly in the right frontal lobe.

Previous studies have found significant relationships between oculomotor function and indices of whole brain or frontal lobe volume in patients with established schizophrenia (Bartfai et al 1985; Smeraldi et al 1987; Fukushima et al 1988; Blackwood et al 1991). In first-episode patients, no such relationships have been found (Levy et al 1992). Our study, which employed imaging techniques with better spatial resolution, also failed to find correlations between eye movements and both total grey and total white matter volumes in a sample of first-episode patients. This suggests that the relationships between eye movement performance and brain structure are regionally specific, at least in the early stages of the illness.

Functional neuroimaging studies of smooth pursuit, visually-guided saccades (pro-saccades) and antisaccades in healthy volunteers have found common activations in areas which have been shown to subserve oculomotor function in non-human primate electrophysiological studies (e.g. Gottlieb et al 1993; Gottlieb and Goldberg, 1999; Schlag-Rey et al 1997; Schlack et al 2003; Tian & Lynch, 1995). These are two frontal areas, the supplementary eye fields (SEF) and the frontal eye fields (FEF), and the posterior parietal cortex (PPC) (Berman et al 1999; Petit and Haxby 1999; O'Driscoll et al 1998). In our study, the cortical area associated with antisaccade performance was in the right superior frontal cortex within Brodmann's area 6. This was a highly circumscribed area and it is difficult to be more precise about the exact location as image normalisation procedures inevitably blur individual differences in anatomical boundaries. Nevertheless this area almost certainly corresponds to an area within the oculomotor circuitry relevant to antisaccade performance. For example, Dorricchi and colleagues (1997) found that the same area was activated on the right during antisaccades compared to pro-saccades and suggested that this corresponded to the supplementary motor area (SMA), which contains the SEF. Medial prefrontal cortex activation in functional studies using saccadic and antisaccadic paradigms varies considerably however, and the majority would suggest that the SMA is more medially situated on the wall of the paracentral lobule (Luna et al 1998; Grosbras et al 1999). An alternative possibility is that the area we have identified corresponds to the medial aspect of the frontal eye field (FEF) which lies in the dorsal aspect of the precentral sulcus near the junction with the superior frontal sulcus (Paus, 1996).

Over and above the ability to perform a saccadic eye movement, the antisaccade

paradigm requires the inhibition of a reflex pre-potent saccade towards the target and the computation of the co-ordinates required to generate a saccade to the mirror image location. The neural mechanisms for inhibition and vector transformation are not entirely clear. It has been argued that both of these processes depend on working memory resources mediated by the dorsolateral prefrontal cortex (DLPFC) (Roberts et al 1994; Stuyven et al 2000; Hutton et al 2002). This is supported by imaging studies which have found that, in addition to activation of the oculomotor circuitry described above, the DLPFC is activated during antisaccades but not pro-saccades performance (Sweeney et al 1996; Dorricchi et al 1997; Muri et al 1998; McDowell et al 2002) and evidence showing increased antisaccade errors following DLPFC damage (Guitton et al 1985; Pierrot-Deseilligny et al 1991; Fukushima et al 1994). Thus one hypothesis is that a signal from DLPFC to FEF activates an inhibitory mechanism within FEF, which results in suppression of a reflex pro-saccade and generation of an antisaccade (Munoz and Everling, 2004). Alternatively, inhibition and vector transformation may be a function of the oculomotor circuitry itself (Munoz and Everling, 2004). Curtis and D'Esposito (2003) showed that an area near the SMA (pre-SMA) and the SEF, but not the DLPFC, is maximally active prior to the generation of an antisaccade and therefore 'prepares' other regions so that a reflex pro-saccade is less likely when the target appears. Other imaging studies have also failed to find activation in DLPFC in relation to antisaccade performance (O'Driscoll et al 1995; Raemaekers et al 2002).

There have been relatively few functional imaging studies comparing antisaccade peformance in patients with schizophrenia and healthy controls. Again the evidence is conflicting. For example, McDowell and colleagues (2002) found that antisaccade

performance activated oculomotor circuitry in both patients and controls but DLPFC activation was evident only in controls, whereas Raemaekers and colleagues (2002) did not find DLPFC activation at all, either in patients or controls. Rather, the latter study found that oculomotor circuitry in general was less active in patients compared to controls during saccades. We found no correlation between structural measures of DLPFC integrity and antisaccade errors. There are two possible explanations for this finding. One is that abnormalities in DLPFC early in the course of schizophrenia, if present, are beyond the resolution of the techniques used in this study. The other is that the SEF/FEF area identified in our study is a more relevant frontal area than DLPFC for the performance of antisaccades and therefore emerges as a correlation.

The reasons why antisaccades were correlated with a volumetric measure and not with MTR remain unclear. A possible explanation in need of further confirmation is that SPGR and MTR may be sensitive to different neuropathogical processes or, alternatively, to the same neuropathological changes at different stages of evolution.

We also found that impaired smooth pursuit was related to cortical MTR reductions, predominantly in the right frontal lobe in two clusters of voxels: A medial cluster corresponding to the right anterior and posterior cingulate gyrus (Brodmann areas 24, 31, 32) and a lateral cluster corresponding to the post- and pre-central and the middle frontal gyri (Brodmann areas 3, 6 and 9). A small focal area of MTR reduction on the left corresponded to the inferior frontal gyrus. Although its localization is imprecise, the lateral cluster was in the vicinity of the frontal eye fields. There was no overlap between this area and that related to antisaccade errors. However, activation studies show that

although saccades and smooth pursuit activate the same oculomotor regions, the areas mediating saccades and pursuit are actually distinct and are located in near-by but different areas (Berman et al 1999, Petit and Haxby, 1999; Rosano et al 2002). Berman et al (1999) demonstrated that smooth pursuit and saccades activated the anterior and posterior cingulate cortex with the spatial extent being greater for pursuit in the posterior cingulate, which may have a role in integrating sensory and motor signals, which is especially important for sustained pursuit performance. This is a possible explanation of why we found structural correlations with the cingulate gyrus for pursuit but not with antisaccades.

There has been only one functional neuroimaging study examining smooth pursuit on both patients with schizophrenia and healthy controls (Tregellas et al 2004). This found that the greatest distinction between patients and controls was that the former showed greater activations in the posterior hippocampus bilaterally and in the right fusiform gyrus, which they attribute to an illness effect rather than a performance effect. In addition patients tended to show lower activations in the right frontal eye fields, the cingulate gyrus and medial occipital region.

The significant correlations we observed were predominately right-sided. The reasons for this are not clear. Functional imaging studies of pursuit (e.g. Rosano et al 2002; Petit & Haxby, 1999) and antisaccade performance (e.g. Curtis & D'Esposito, 2003; O'Driscoll et al 1995) in healthy controls do not report significant laterality effects for SEF and FEF oculomotor areas. One speculative interpretation is that our findings reflect neural immaturity in first-episode schizophrenia patients. Directional asymmetry

observed in young primates (human and nonhuman) may reflect a different neural organization of the pursuit system with a presumed maturational compensation (Takeichi et al 2003). Further studies will be required in order to determine whether this lateralization is specific to patients with first-episode schizophrenia.

The effects of neuroleptics on MTR have not been studied and could be a potential confound although there is little evidence from experimental animal studies to suggest that neuroleptic medication contributes to the neuropathology of schizophrenia (Harrison, 1999). The main limitation to the study is the lack of imaging data on control subjects, which makes it impossible to confirm whether oculomotor neuronal circuits are abnormal in schizophrenia. The full significance of the correlations reported in this study may become apparent in planned longitudinal studies with appropriate control subjects, which should also explore other eye movements known to be abnormal in schizophrenia, such as antisaccade latency and increased anticipatory saccades during pursuit (Hutton et al 1998; Tregellas et al 2004).

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Abel LA, Friedman L, Jesberger J, Malki A, Meltzer HY (1991): Quantitative assessment of smooth pursuit gain and catch-up saccades in schizophrenia and affective disorders. *Biol Psychiatry* 29:1063-72.

Andreasen NC (1984a): Schedule for the Assessment of Negative Symptoms (SANS).

University of Iowa Press: Iowa City.

Andreasen NC (1984b): Schedule for the Assessment of Positive Symptoms (SAPS). University of Iowa Press: Iowa City.

Annett MA (1970) A classification of hand preference by association analysis. *Br J Psychol* 61:303-21.

Ashburner J, Friston KJ (2000): Voxel based morphometry- the methods. *Neuroimage* 11:805-21.

Ashburner J, Friston KJ (2001): Why voxel-based morphometry should be used. *Neuroimage* 14:1238-43.

Bagary MS, Symms MR, Barker GJ, Mutsatsa SH, Joyce EM, Ron MA (2003): Gray and white matter brain abnormalities in first-episode schizophrenia inferred from magnetization transfer imaging. *Arch Gen Psychiatry* 60:779-88.

Barker GJ, Tofts PS, Gass A. (1996): An Interleaved Sequence for Accurate and Reproducible Clinical Measurement of Magnetization Transfer Ratio. *Magn. Reson. Imag* 14:403-411.

Bartfai A, Levander SE, Nyback H, Berggren BM, Schalling D (1985): Smooth pursuit eye tracking, neuropsychological test performance, and computed tomography in

schizophrenia. *Psychiatry Res* 15:49-62.

Berman RA, Colby CL, Genovese CR, Voyvodic JT, Luna B, Thulborn KR, Sweeney JA (1999): Cortical networks subserving pursuit and saccadic eye movements in humans: an FMRI study. *Hum Brain Mapp* 8:209-25.

Blackwood DH, Young AH, McQueen JK, Martin MJ, Roxborough HM, Muir WJ, St Clair DM, Kean DM (1991): Magnetic resonance imaging in schizophrenia: altered brain morphology associated with P300 abnormalities and eye tracking dysfunction. *Biol Psychiatry* 30:753-69.

Bosma GP, Rood MJ, Zwinderman AH, Huizinga TW, van Buchem MA (2000): Evidence of central nervous system damage in patients with neuropsychiatric systemic lupus erythematosus, demonstrated by magnetization transfer imaging. *Arthritis Rheum* 43:48-54.

Cercignani M, Bozzali M, Iannucci G, Comi G, Filippi M (2001): Magnetization transfer ratio and mean diffusivity of normal appearing white and grey matter from patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 70:311-7.

Chard DT, Parker GJ, Griffin CM, Thompson AJ, Miller DH (2002): The reproducibility and sensitivity of brain tissue volume measurements derived from an SPM-based segmentation methodology. *J Magn Reson Imaging*. 15:259-67.

Crawford TJ, Haeger B, Kennard C, Reveley MA, Henderson L (1995) Saccadic abnormalities in psychotic patients. I. Neuroleptic-free psychotic patients. *Psychol Med* 25:461-71.

Crawford TJ, Sharma T, Puri BK, Murray RM, Berridge DM, Lewis SW (1998): Saccadic eye movements in families multiply affected with schizophrenia: the Maudsley Family Study. *Am J Psychiatry* 155:1703-10.

Curtis CE, D'Esposito M (2003): Success and failure suppressing reflexive behavior. *J Cogn Neurosci* 15:409-18.

Davies GR, Ramio-Torrenta L, Hadjiprocopis A, Chard DT, Griffin CM, Rashid W, Barker GJ, Kapoor R, Thompson AJ, Miller DH (2004): Evidence for grey matter MTR abnormality in minimally disabled patients with early relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* 75:998-1002.

DeLisi LE, Hoff AL, Schwartz JE, Shields GW, Halthore SN, Gupta SM, Henn FA, Anand AK (1991): Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. *Biol Psychiatry* 29:159-75.

Doricchi F, Perani D, Incoccia C, Grassi F, Cappa SF, Bettinardi V, Galati G, Pizzamiglio L, Fazio F (1997): Neural control of fast-regular saccades and antisaccades: an investigation using positron emission tomography. *Exp Brain Res* 116:50-62.

First MB, Gibbon M, Spitzer RC, Williams JBW, Benjamin LS (1997): Structured Clinical Interview for DSM-IV Axis 1 Disorder, research version, patient edition. Washington DC. American Psychiatric Press Inc.

Friedman L, Abel LA, Jesberger JA, Malki A, Meltzer HY (1992): Saccadic intrusions into smooth pursuit in patients with schizophrenia or affective disorder and normal controls. *Biol Psychiatry* 31:1110-8.

Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD (1996): Detecting activations in PET and fMRI: levels of inference and power. *Neuroimage* 4:223-35.

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

Fukushima J, Morita N, Fukushima K, Chiba T, Tanaka S, Yamashita I (1990): Voluntary control of saccadic eye movements in patients with schizophrenic and affective disorders. *J Psychiatr Res*. 24: 9-24.

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

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS

(2001): A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14:21-36.

Gottlieb J, Goldberg ME (1999): Activity of neurons in the lateral intraparietal area of the monkey during an antisaccade task. *Nat Neurosci* 2:906-12.

Gottlieb JP, Bruce CJ, MacAvoy MG (1993): Smooth eye movements elicited by microstimulation in the primate frontal eye field. *J Neurophysiol* 69:786-99.

Grosbras MH, Lobel E, Van de Moortele PF, LeBihan D, Berthoz A (1999): An anatomical landmark for the supplementary eye fields in human revealed with functional magnetic resonance imaging. *Cereb Cortex* 9:705-11.

Guitton D, Buchtel HA, Douglas RM (1985): Frontal-lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp Brain Res* 58: 455-472.

Harrison P (1999): The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* 122:593-624.

Henkelman RM, Stanisz GJ, Graham SJ (2001): Magnetization transfer in MRI: a review. *NMR Biomed* 4:57-64.

Holzman PS, Kringlen E, Matthysse S, Flanagan SD, Lipton RB, Cramer G, Levin S,

Lange K, Levy DL (1988): A single dominant gene can account for eye tracking dysfunctions and schizophrenia in offspring of discordant twins. *Arch Gen Psychiatry* 45:641-7.

Hutton SB, Crawford TJ, Puri BK, Duncan LJ, Chapman M, Kennard C, Barnes TR, Joyce EM (1998): Smooth pursuit and saccadic abnormalities in first-episode schizophrenia. *Psychol Med* 28:685-92.

Hutton SB, Joyce EM, Barnes TR, Kennard C (2002): Saccadic distractibility in first-episode schizophrenia. *Neuropsychologia* 40:1729-36.

Katsanis J, Iacono WG (1991): Clinical, neuropsychological, and brain structural correlates of smooth-pursuit eye tracking performance in chronic schizophrenia. *J Abnorm Psychol* 100:526-34.

Katsanis J, Kortenkamp S, Iacono WG, Grove WM (1997): Antisaccade performance in patients with schizophrenia and affective disorder. *J Abnorm Psychol*.106: 468-72.

Levy DL, Bogerts B, Degreef G, Dorogusker B, Waternaux C, Ashtari M, Jody D, Geisler S, Lieberman JA (1992): Normal eye tracking is associated with abnormal morphology of medial temporal lobe structures in schizophrenia. *Schizophr Res*. 8:1-10.

Levy DL, Holzman PS, Matthysse S, Mendell NR (1994): Eye tracking and schizophrenia: a selective review. *Schizophr Bull* 20:47-62.

.

Lexa FJ, Grossman RI, Rosenquist AC (1994): MR of wallerian degeneration in the feline visual system: characterization by magnetization transfer rate with histopathologic correlation. *Am J Neuroradiol* 15:201-12.

Lieberman JA, Jody D, Alvir JM, Ashtari M, Levy DL, Bogerts B, Degreef G, Mayerhoff DI, Cooper T (1993): Brain morphology, dopamine, and eye-tracking abnormalities in first-episode schizophrenia. Prevalence and clinical correlates. *Arch Gen Psychiatry* 50:357-68.

Luna B, Thulborn KR, Strojwas MH, McCurtain BJ, Berman RA, Genovese CR, Sweeney JA. Luna B, Thulborn KR, Strojwas MH, McCurtain BJ, Berman RA, Genovese CR, Sweeney JA (1998): Dorsal cortical regions subserving visually guided saccades in humans: an fMRI study. *Cereb Cortex* 8:40-7.

McDowell JE, Clementz BA (1997): The effect of fixation condition manipulations on antisaccade performance in schizophrenia: studies of diagnostic specificity. *Exp Brain Res* 115:333-44.

McDowell JE, Brown GG, Paulus M, Martinez A, Stewart SE, Dubowitz DJ, Braff DL (2002): Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. *Biol Psychiatry* 51:216-23.

Meisenzahl EM, Frodl T, Muller D, Schmitt G, Gallinat J, Zetzsche T, Marcuse A,

Juckel G, Leinsinger G, Hahn K, Moller HJ, Hegerl U (2004): Superior temporal gyrus and P300 in schizophrenia: a combined ERP/structural magnetic resonance imaging investigation. *J Psychiatr Res* 38:153-62.

Meyerhoff DJ (1999): Proton magnetization transfer of metabolites in human brain. *Magn Reson Med* 42:417-20.

Mottershead JP, Thornton JS, Clemence M, Scaravilli F, Newcombe, Cuzner ML, Barker GJ, Tofts PS, Parker GJM, Ordidge RJ, Miller DH, McDonald WI (1998): Correlation of spinal cord axonal density with post mortem NMR measurements in multiple sclerosis and controls. *Proc Intl Soc Mag Res Med* 8: 2163.

Munoz DP, Everling S (2004): Look away: the anti-saccade task and the voluntary control of eye movement. *Nat Rev Neurosci* 5:218-28.

Muri RM, Heid O, Nirkko AC, Ozdoba C, Felblinger J, Schroth G, Hess CW (1998): Functional organisation of saccades and antisaccades in the frontal lobe in humans: a study with echo planar functional magnetic resonance imaging. *J Neurol Neurosurg Psychiatry* 65:374-7.

O'Driscoll GA, Alpert NM, Matthysse SW, Levy DL, Rauch SL, Holzman PS (1995): Functional neuroanatomy of antisaccade eye movements investigated with positron emission tomography. *Proc Natl Acad Sci*. 92:925-9.

O'Driscoll GA, Strakowski SM, Alpert NM, Matthysse SW, Rauch SL, Levy DL, Holzman PS (1998): Differences in cerebral activation during smooth pursuit and saccadic eye movements using positron-emission tomography. *Biol Psychiatry* 44:685-9.

Paus T (1996): Location and function of the human frontal eye-field: a selective review. *Neuropsychologia* 34:475-83.

Petit L, Haxby JV (1999): Functional anatomy of pursuit eye movements in humans as revealed by fMRI. *J Neurophysiol* 82:463-71.

Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y (1991): Cortical control of reflexive visually-guided saccades. *Brain* 114:1473-85.

Raemaekers M, Jansma JM, Cahn W, Van der Geest JN, van der Linden JA, Kahn RS, Ramsey NF (2002): Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. *Arch Gen Psychiatry* 59: 313-320.

Roberts RJ, Hager LD and Heron C (1994) Prefrontal Cognitive Processes: Working Memory and Inhibition in the Antisaccade Task. J Exp Psychol: Gen 123: 374-393.

Rosano C, Krisky CM, Welling JS, Eddy WF, Luna B, Thulborn KR, Sweeney JA (2002): Pursuit and saccadic eye movement subregions in human frontal eye field: a

high-resolution fMRI investigation. *Cereb Cortex*12:107-15.

Ross RG, Olincy A, Harris JG, Radant A, Adler LE, Freedman R (1998): Anticipatory saccades during smooth pursuit eye movements and familial transmission of schizophrenia. *Biol Psychiatry* 44:690-7.

Salgado-Pineda P, Junque C, Vendrell P, Baeza I, Bargallo N, Falcon C, Bernardo M (2004): Decreased cerebral activation during CPT performance: structural and functional deficits in schizophrenic patients. *Neuroimage* 21:840-7.

Schlack A, Hoffmann KP, Bremmer F (2003): Selectivity of macaque ventral intraparietal area (area VIP) for smooth pursuit eye movements.
J Physiol 551:551-61

Schlag-Rey M, Amador N, Sanchez H, Schlag J (1997): Antisaccade performance predicted by neuronal activity in the supplementary eye field. *Nature* 390:398-401.

Siever LJ, van Kammen DP, Linnoila M, Alterman I, Hare T, Murphy DL (1986): Smooth pursuit eye movement disorder and its psychobiologic correlates in unmedicated schizophrenics. *Biol Psychiatry* 21:1167-74.

Smeraldi E, Gambini O, Bellodi L, Sacchetti E, Vita A, di Rosa M, Macciardi F, Cazzullo CL (1987): Combined measure of smooth pursuit eye movements and ventricle-brain ratio in schizophrenic disorders. *Psychiatry Res* 21:293-301.

Sowell ER, Thompson PM, Holmes CJ, Batth R, Jernigan TL, Toga AW (1999): Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *Neuroimage* 9:587-97.

Stratta P, Mancini F, Mattei P, Daneluzzo E, Casacchia M, Rossi A (1997): Association between striatal reduction and poor Wisconsin card sorting test performance in patients with schizophrenia. *Biol Psychiatry* 42:816-20.

Stuyven, E. Van der Goten, K., Vandierendonck, A. Claeys, K and Crevits, L (2000): The effect of cognitive load on saccadic eye movements. *Acta Psychologica Scandinavica* 104:69-85.

Sullivan EV, Shear PK, Lim KO, Zipursky RB, Pfefferbaum A (1996): Cognitive and motor impairments are related to gray matter volume deficits in schizophrenia. *Biol Psychiatry* 39:234-40.

Sweeney JA, Haas GL, Li S (1992): Neuropsychological and eye movement abnormalities in first-episode and chronic schizophrenia. *Schizophr Bull* 18:283-93.

Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL, Rosenberg DR, Carl JR (1996): Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *J Neurophysiol* 75:454-68.

Symms M, Barker G, Holmes A: (1997): A rapid automated system for detection of serial changes in transient ischaemic attack using registration and subtraction of three dimensional images. *Proc Intl Soc Mag Res Med* 584.

Szeszko PR, Strous RD, Goldman RS, Ashtari M, Knuth KH, Lieberman JA, Bilder RM (2002): Neuropsychological correlates of hippocampal volumes in patients experiencing a first episode of schizophrenia. *Am J Psychiatry. 2002* 159:217-26.

Szeszko PR, Gunning-Dixon F, Goldman RS, Bates J, Ashtari M, Snyder PJ, Lieberman JA, Bilder RM (2003): Lack of normal association between cerebellar volume and neuropsychological functions in first-episode schizophrenia. *Am J Psychiatry* 160:1884-7.

Takeichi N, Fukushima J, Kurkin S, Yamanobe T, Shinmei Y, Fukushima K (2003): Directional asymmetry in smooth ocular tracking in the presence of visual background in young and adult primates. *Exp Brain Res* 149:380-90.

Talairach J, Tournoux P (1988): Co-planar stereotaxic atlas of the human brain. New York: Thieme Medical Publisher.

Tian JR, Lynch JC (1995): Slow and saccadic eye movements evoked by microstimulation in the supplementary eye field of the cebus monkey. *J Neurophysiol* 74:2204-10

Tregellas JR, Tanabe JL, Miller DE, Ross RG, Olincy A, Freedman R (2004): Neurobiology of smooth pursuit eye movement deficits in schizophrenia: an fMRI study. *Am J Psychiatry* 161:315-21.

van Buchem MA, Tofts PS (2000): Magnetization transfer imaging. *Neuroimaging Clin N Am* 10:771-88.

van Waesberghe, Kamphorst W, De Groot CJ, van Walderveen MA, Castelijns JA, Ravid R, Lycklama a Nijeholt GJ, van der Valk P, Polman CH, Thompson AJ, Barkhof F (1999): Axonal loss in multiple sclerosis lesions: magnetic resonance imaging insights into substrates of disability. *Ann Neurol* 46:747-54.

Wilke M, Kaufmann C, Grabner A, Putz B, Wetter TC, Auer DP (2001): Gray matter-changes and correlates of disease severity in schizophrenia: a statistical parametric mapping study. Neuroimage 13:814-24.

Wolff SD, Balaban RS (1994): Magnetization transfer imaging: practical aspects and clinical applications. *Radiology* 192:593-9.

Woods R, Cherry S, Mazziotta J: (1992): Rapid Automated Algorithm For Aligning And Reslicing PET Images. *J Computer Assisted Tomography* 16:620-33.

Worsley KJ, Marrett S, Neelin P, Evans AC (1992): A three-dimensional statistical analysis for CBF activation studies in human brain. *J Cereb Blood Flow Metab*

12:900-918.

Table 1 Oculomotor function in first-episode schizophrenia and correlation with brain parenchymal volume

Oculomotor Index	mean ± SD (range)			Correlations with white matter as % of total brain volume in first-episode schizophrenia	Correlations with grey matter as % of total brain volume in first-episode schizophrenia	First-episode
	Schizophrenia (n = 27)	Controls (n = 27)	t-test			
% Antisaccade Errors	0.35 ± 0.25 (0.04-1.0)	0.16 ± 0.14 (0.00-0.54)	t = 2.947 p = 0.005*	r = 0.14 p = 0.49	r = -0.07 p = 0.75	
Smooth Pursuit Velocity Gain	0.88 ± 0.07 (0.71-0.99)	0.95 ± 0.04 (0.81-1.03)	t = -4.001 p = 0.000*	r = -0.32 p = 0. 88	r = -0.33 p = 0. 11	

r = Spearman's rho
p = 2-tailed significance
* = significant differences between first-episode schizophrenia patients and controls
Smooth pursuit velocity gain was significantly reduced and percentage of antisaccadic errors significantly increased in first-episode schizophrenia. There were no significant correlations between brain parenchymal tissue fraction and oculomotor indices

Table 2 Regional MTR and volume correlations with oculomotor function

Oculomotor Test	Correlation	Structural	Index	Voxel	Level (t)		Talairach Coordinates	Region (Brodmann Area)
					X	Y Z		

% Antisaccadic Errors	Negative MTR	-	-	-	-		GM		
						Right medial superior frontal gyrus (6)		4.38	38
								-	-
Smooth Pursuit Velocity Gain	Positive MTR	4.5 4.3 4.1 3.9 3.9 3.8 3.7	45 3 11 7 60 -5 0 49	-1 9 4 -3 7 11 -7 20 22	51 37 43 41 32 -1 3 40	Right post-central gyrus (3) Right anterior cingulate gyrus (24) Right posterior cingulate gyrus (31) Right anterior cingulate gyrus (32) Right precentral gyrus (6) Left inferior frontal gyrus (47) Right middle frontal gyrus (9)	GM		
								-	-
								-	-

N=27
Degrees of freedom = 20
MTR-magnetization transfer ratio
GM- grey matter
WM- white matter
Voxel-level study threshold of $p<0.001$, uncorrected. Regions did not survive correction for multiple comparisons.
Co-ordinates have been converted from MNI space to Talairach space using transformations (see www.mrc-cbu.cam.ac.uk/imaging/mnispace) to allow Talairach anatomical localization (Talairach and Tournoux, 1988)

Figure 1

Glass brain view of negative correlations between regional grey matter volume and antisaccade errors

Figure 2

Glass brain view of positive MTR correlations with smooth pursuit velocity gain in first-episode schizophrenia