Bial

153/04

The Mental Health & Neural Systems Research Unit
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Fundação Bial
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

Dear Sir/Madam

Please find enclosed my final report on the Bial Foundation project entitled: Project title: The Neural basis of attention disorder in schizophrenia

As you will see 2 further experiments have been included since my earlier report.

(i) Overall purpose of research programme:

The overall purpose of the current research programme is to investigate the hypothesis that a specific attentional dysfunction underlies the schizophrenic syndrome; namely, that sufferers experience an excessive dependence on, or sensitivity to, salient external cues, due to a failure of the brain's attentional response system to adequately redirect the focus of attention away from such stimuli. The research will investigate this hypothesis across the visual and auditory sensory modalities. One focus of the project will be to specify the nature of the deficit from the perspective of cognitive mechanisms, while another goal will be to link these mechanisms with their underlying neural substrates. This latter goal will be achieved by utilising functional magnetic resonance imaging (fMRI).

(ii) Objectives:

Objective 1

(a) The intent of the objective is to identify whether visual attention abnormalities that have been observed in schizophrenia reflect an underlying widespread deficit in the brain mechanisms of attentional control.

(b) Data collection with schizophrenic patients has commenced, and is continuing. We are currently in the process of conducting experiments with schizophrenic patients and control (i.e., neurologically normal or non-disordered) participants at the Institute of Psychiatry in London. As we are conducting five experiments with each participant, this will yield a substantial body of data from participants' single experimental sessions.

(c) Following data collection, we will undertake data analysis. Together with collaborators, the results of this research will be written-up for publication, and it is currently anticipated that four papers will result from this work.

Objective 2

(a) The intent of this objective is to explore and more accurately specify the nature of visual attention deficits in schizophrenia, in particular: (a) whether the observed deficit is due to failures in voluntary or automatic mechanisms, and (b) where the locus of the dysfunction is with respect to specific brain areas.

(b) We have obtained full NHS ethical approval for the study and have completed pilot work. It is likely that data collection on the fMRI study will, in collaboration with colleagues, be completed within the next 9-12 months.

Objective 3

(a) The intent of this objective is to clarify the nature of the cognitive dysfunction underlying the commonly observed antisaccade deficit in schizophrenia, and to determine whether this deficit can be over-ridden by task manipulations.

(b) Further to the progress previously reported, data collection with schizophrenic patients (and control participants) has commenced.

Experiment on cross-modal attention

A deficit in executing antisaccades (saccadic eye movements away from a peripheral stimulus) is commonly observed in schizophrenia. In addition, one cognitive feature of schizophrenia is a deficit in the ability to reorient attention away from salient events in peripheral vision (Maruff et al., 1996; Maruff et al., 1998). An empirical question is whether an analogous attentional deficit might occur in schizophrenia in the auditory sensory modality; i.e., whether individuals with schizophrenia may experience a difficulty shifting attention away from the location of a sound. We investigated the orienting of visual attention towards (and away from) the spatial location of an auditory stimulus, both in normal participants and individuals with schizophrenia.

Experiment 1a: Target detection task.

Three experiments with neurologically normal participants have been undertaken, and data analysis is complete. We are currently working towards writing up of these results for publication, and the results formed the basis of a poster presented at the Schizophrenia Winter Workshop in Switzerland, February 2006.

We investigated the capacity for non-disordered individuals to saccade to visual targets following auditory cues, using a technique analogous to Posner's (1980) spatial cueing paradigm.

Method

Twelve normal (i.e., non-disordered) participants. There were three conditions. Within a given block of trials, the location from which the auditory cue sounded could be either irrelevant (a 50% target at cue (TAC) contingency) or informative (20% and 80% TAC contingencies) with respect to the location of the impending visual target (Fig 1). Two blocks (of 44 trials) per condition.

General Methodological Details:

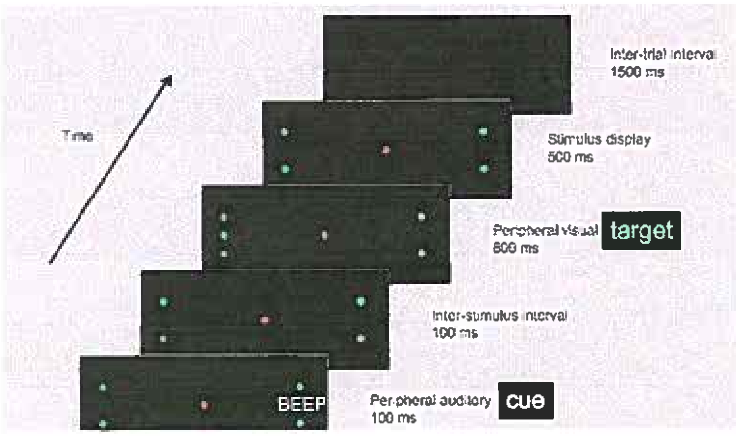
A 200ms stimulus onset asynchrony (SOA) between the auditory cue and the visual target (an LED) was employed. Cues: 2 buzzers (1 left and 1 right) presented in free-field form, 0.5° from target LED. Each was a pure tone with a frequency of 2.3 kHz, presented for 100 ms at a sound level of 75 dB measured from participants' position. Order of exposure to the 3 conditions was counterbalanced. Darkened, sound attenuated room.

Experiments 1a and 1b
Participants were seated 168cm from a board from which auditory cues were emitted and visual targets appeared. Cues and targets could each be presented at one of two peripheral locations, 17.5° to the left or right of central fixation. Participants were informed of the relationship between the cue and the target.

Experiment 1b
Any trials with eye movements (>1° within 700 ms of tone onset), or not fixating centrally at tone onset) excluded from analysis. Proportion correct calculated (out of all possible responses). Binary logistic regression analysis.

Experiments 1a and 2
Latency to initiate a saccadic eye movement to the visual target was measured, using a Skalar IRIS eye monitoring system with a 500 Hz sampling rate. Participants were warned about catch trials. Only saccadic latencies > 80 ms and < 700 ms included in the analysis. Latencies of saccades (in the correct direction) entered into an ANOVA with 2 within-subject factors: Condition (20%, 50%, & 80% TAC) and Validity (target same side as cue vs target opposite cue).

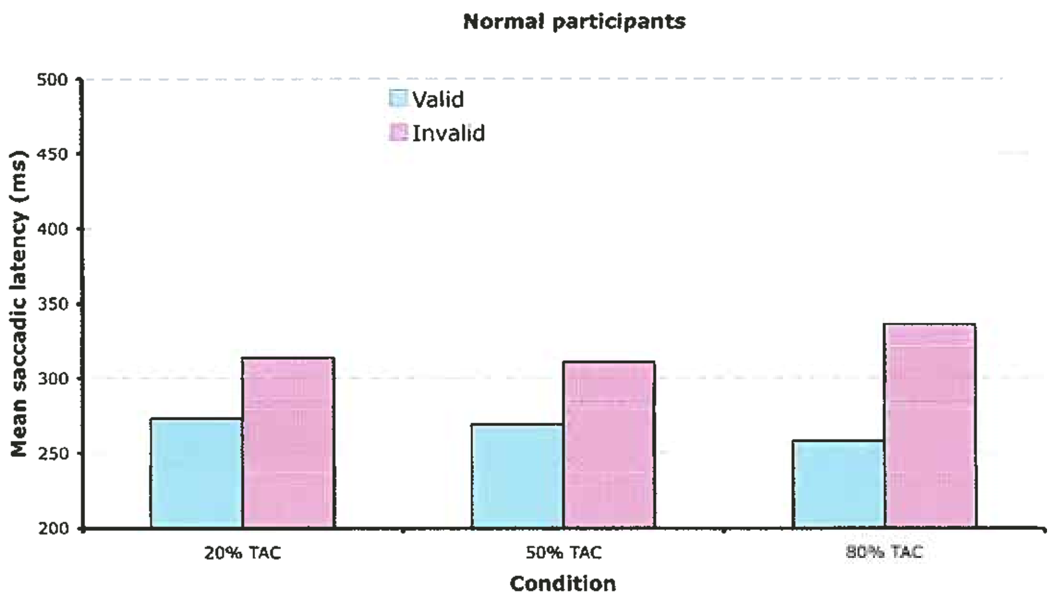
Figure 1



Results

There was significant main effect of Validity: $F(1,11)=39.82$, $p<.001$ (Figure 1.2). Saccades to targets ipsilateral to the auditory cue (266 ms) were significantly faster than saccades to targets contralateral to the cue (320 ms). There was a significant interaction of Condition & Validity: $F(2,22)=7.53$, $p<.01$. To explore this interaction further, Simple Effects Analyses were conducted separately for the valid and the invalid data: No significant effect for valid: $F(2,22)=1.40$, $p>.05$. There was a nonsignificant effect for a trend in the invalid data: $F(2,22)=3.12$, $p=.06$. The main effect of Condition (i.e. 20% vs 50% vs 80%) was not significant ($F<1$). Experiment 1a demonstrated faster eye movements to visual target presented on same side as auditory cue.

Figure 1.2



Experiment 1b: Discrimination task.

The aim of this experiment was to determine whether the effects of the auditory cue on visual attention could also improve performance in a visual discrimination task, independent of reaction times. The task required an elevation judgement (up vs. down) of a visual target presented to the left or right. In Experiment 1b, participants were required to keep their eyes still (i.e., maintain central fixation) while making a difficult up/down discrimination of the position of the peripheral target – i.e., the response required was orthogonal to the side on which the target appeared – and orthogonal to the direction from which the cue was presented, so the cue could not preactivate one of the possible responses.

Method

The number of participant was N=12 (same 12 participants as in Expt 1a). Again there were 3 conditions: 20%, 50%, and 80% target at cue (TAC) contingency. 2 blocks (of 40 trials) per condition.

Results

There was a significant Validity effect: $\chi^2 = 6.09$, df=1, p=.014
Proportion correct: same side (0.7) better than opposite (0.66).
There was a significant Condition effect: $\chi^2 = 9.56$, df=2, p<.01
Performance better in 50% TAC condition (0.71) than both 20% (0.67) and 80% (0.65) conditions, which did not differ.

Discussion

Discrimination performance was significantly better for the side from which the auditory cue had sounded. These results support an attentional explanation of the findings of Experiment 1a, rather than simply ipsilateral response preparation (priming of an ipsilateral response by the cue), or simply a criterion shift. The results provide evidence for crossmodal attention capture. Covert visual attention shifts to the spatial location of an auditory stimulus (facilitating the difficult up/down discrimination, or, in the case of

Expt 1a, facilitating target detection and faster saccadic responses). This occurs even when the visual target is unlikely to appear near the auditory cue (in the 20% TAC condition). Results have implications for the existence of "hardwired, structural links between audition and vision in the control of covert attention" (Spence & Driver, 1997).

Experiment 2: Orienting to/from auditory cues in schizophrenia

An investigation into schizophrenic patients' performance on a task with peripheral auditory cues, and peripheral visual targets, to which a saccadic eye movement response was required.

Method

So far we have tested 6 patients with schizophrenia (mean age = 37.2 yrs, mean education = 14 yrs, all male, all right handed, (2 Caucasian, 1 Afro-Caribbean, 1 Asian, 2 other ethnicity (e.g. mixed)). 11 controls (mean age = 32.3 yrs, mean education = 17.7 yrs, 6 male, all right handed, (8 Caucasian, 2 Afro-Caribbean, 1 Asian). Similar to Experiment 1a (above). Three differences: Participants seated 140cm from the LED board, and participants not informed of the relationship between cue and target (in the 3 different conditions). Fewer trials (only one block (of 44 trials) for each of the three conditions).

Results

Results are shown in Fig 1.3. Control participants and patients with schizophrenia show similar responses when the target is preceded by a valid cue. However schizophrenics are slowed when the are required to re-orient visual attention, following an invalid cue.

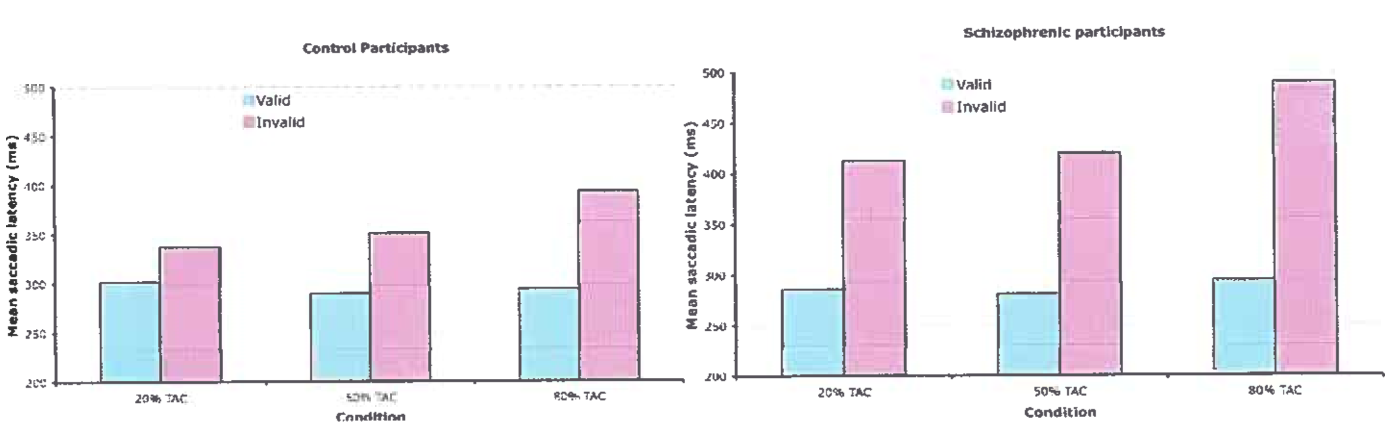


Fig 1.3.

Conclusions:

In non-disordered individuals, visual attention is reflexively drawn to the spatial location of an auditory stimulus, even if the target visual event is unlikely to occur at that location.

The preliminary results reported here have implications for potential cross-modal attentional abnormalities in schizophrenia. In Figure 1.3, we do not see evidence for abnormal crossmodal attention-*capture* (individuals with schizophrenia are just as fast to respond to the visual target when it is presented near the auditory cue). Rather, relative to control participants, schizophrenic participants exhibit slower responses when attention needs to be redirected to the other side of the display - contralateral to the auditory cue. In schizophrenia, there appears to be a deficit in the disengagement of attention from an auditory stimulus (equivalent to the previously reported deficit (Maruff et al., 1996; 1998) in the disengagement of attention from a visual stimulus).

Experiment 3. Can a deficit in spatial attention account for the abnormality of antisaccades in schizophrenia?

There is extensive evidence that patients with schizophrenia and their biological relatives are impaired in the ability to generate an eye movement away from a target (i.e.antisaccades), although a saccade towards a target remains intact.

Why are antisaccades slow?
It is thought that the slower latency for antisaccades partly reflects the delay in moving attention away from the target location. When the target is presented, this automatically draws our attention to this location, similar to an exogenous cue. It is thought that prior to any eye movement, attention must first be focused on the destination of the saccade.

HYPOTHESES
If we can facilitate the transfer of spatial attention to the opposite hemifield we should accelerate the antisaccade.

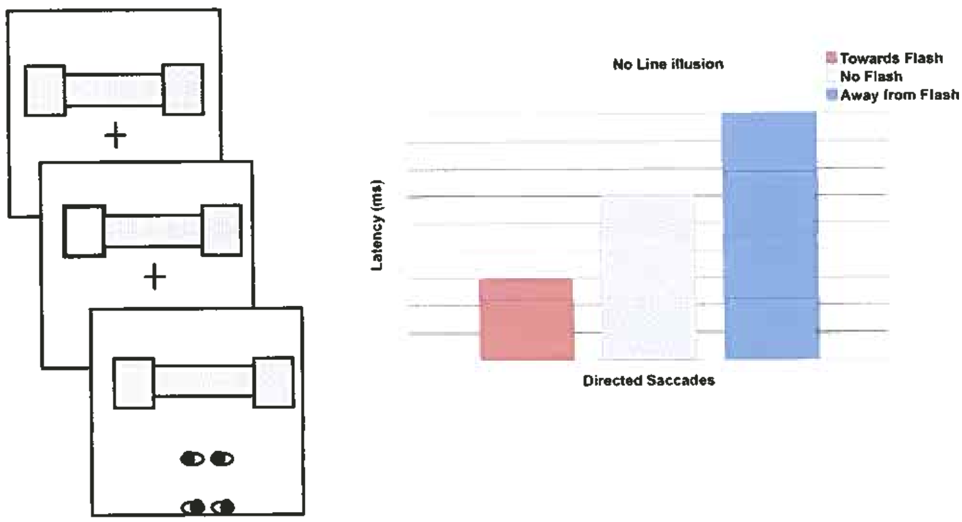
If we remove attention from the target then prosaccades should be impeded.

The Line Motion Illusion

Illusory line motion occurs when a bar is presented in it's entirety next to an exogenous cue (a periferal flash). It is known that attention follows illusory line motion. Under these circumstances, the bar appears to "lazer beam" away from the flashed location. Therefore Illusory Line Motion (ILM), should remove the difference in latencies between pro and anti-saccades

Experiment 3: Pro and anti saccades in the absence of illusory line motion. As shown in Fig. 1.4 a trial began with the presentation of a grey 'barbell' for a period of 500 ms, together with a central fixation cross. On the 'Flash' trials a luminance increment was applied to one of the boxes for 50 ms, so that it appeared to flash briefly. Immediately, the fixation cross changed colour to either red or blue. On the 'No Flash' trials there was no luminance increment.

Fig 1.4

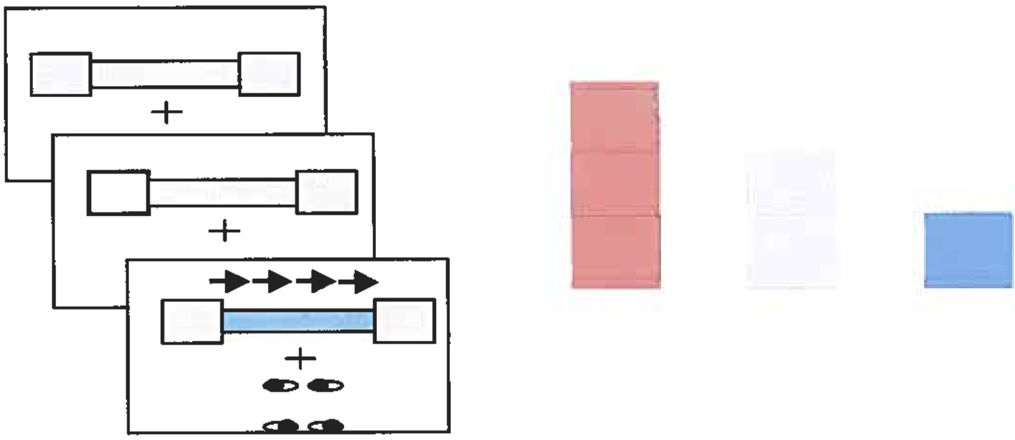


Experiment 1 confirmed that prosaccade latencies were faster than antisaccade latencies ($F(1,14) = 19.84$, $p = 0.0005$). As expected there were also fewer correctly directed saccades on the antisaccade trials (mean = 79.7%) in comparison to prosaccades (mean=91.6%), ($F(1,14)=15.35$, $p=0.002$).

Experiment 4: Line motion illusion

The same general procedure was employed, with one critical change to produce the illusion of line motion. In contrast to experiment 1, where the direction of the eye movement was supplied by the colour change of the fixation cross, in experiment 2 this information was supplied by a colour change of the central bar. On 'Flash' trials the change of colour in the bar was characterised by a compelling impression of motion away from the flash. The objective was to generate a saccade, as quickly and as accurately as possible, to either the left or the right box, depending upon the colour of the bar.

Fig 1.5

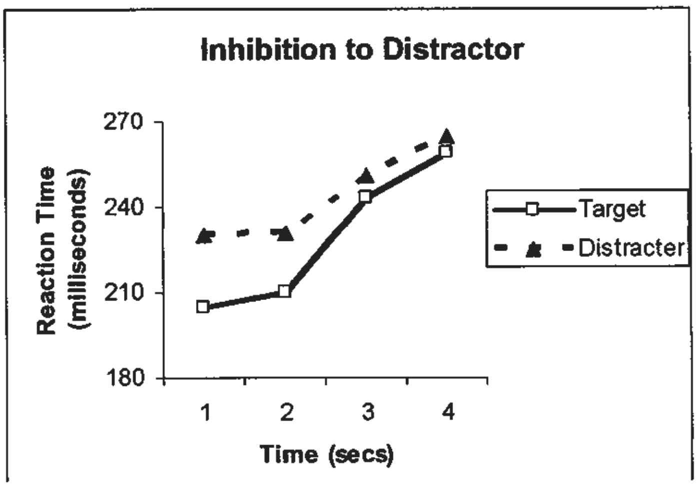


Illusory line motion. With Illusory line motion prosacade latencies were now *slower* than antisaccade latencies ($F(1,30) = 4,15$, $p=0.05$) (Figure 1.5) . In fact there was a reverse effect, with more correctly directed antisaccades (mean=89.3%) than prosaccades (mean=82.5%). These result support the hypothesis that attentional reorientation is a major factor in the control of antisaccades, and a critical factor in the deficit of antisaccade in schizophrenia.

(5) Experiment 5. Inhibition of distracters.

Research on the behavioural inhibition in schizophrenia is heavily dependent on the antisaccade task. We have recently developed a novel task at Lancaster University that will enable us to characterise inhibition more precisely.[46] Although, there is extensive clinical research on the antisaccade task, the task may not be ideally suited to all patients with a cognitive impairment. The antisaccade task may be problematic for patients since it represents a departure from everyday behaviour, where saccades in the opposite direction to a novel stimulus are uncommon. The task does not easily lend itself to parametric manipulation, thus the role of important factors in relation to the specific nature of inhibition (e.g. object features vs spatial location, & temporal characteristics) are unknown. We have recently developed an alternative paradigm for the exploration inhibitory control[46] that avoids many of the limitations inherent in the antisaccade task. Individuals are presented with 2 critical displays. The first display contains a red target and an irrelevant green distracter. The observer's task is to look from the starting point of eyes at the centre of the screen to the target, while ignoring the distracter, before returning back to the central fixation. A single target is then presented in the second display. The observer again looks at the target, and then returns back to the fixation point. The critical manipulation is the relation of the target in display 2 to the target and distracter in display 1. The display 2 target can be presented at the location of the previous target, the previous distracter or a new location. Saccades are slowed if the target appears at the location of the previous distracter, relative to the situation when the target appears at the previous target or a new location. In healthy participants, the size of the inhibition effects depends on the interval between the 2 displays, the effect declines for intervals longer 5 seconds (Figure 1.6).

Figure 1.6



This novel test has the following features:

(1) Eye movements are naturalistic; (2) Spatial field of inhibition is readily mapped; (3) Temporal duration of inhibition easily measured; (4) Distinguishes between inhibition of object features and spatial location.

Most importantly, the failure of inhibitory control is indexed by faster saccade responses to the critical stimulus display. Thus, in contrast to the majority of available behavioural tasks, a functional impairment in the patients is indexed by 'better/faster' performance in this group. This is important because it ensures that any abnormality is not a non-specific effect of poor task compliance, task complexity or poor motivation.

Experiment 6. fMRI Experiment

Functional and structural magnetic resonance imaging scans at the Centre for Neuroimaging Sciences, Institute of Psychiatry (using a 1.5-tesla General Electric, Milwaukee WI, USA) will be employed to localise the brain areas which may not be functioning normally when schizophrenic individuals are engaged in shifting visual attention. The study is concerned with the visual attention reorienting deficit which has already been noted, and will comprise two experimental conditions. One condition will investigate consciously-directed shifts of attention and the other will address the potential contribution of automatically-acting processes. The primary difference between the two conditions will be the length of the inter-stimulus interval (i.e., time elapsed between the peripheral cue and the target stimulus). When this interval is relatively extended (approximately 300 msec), attention shifts are thought to be consciously-directed; when the inter-stimulus interval is brief (approximately 150 milliseconds), the processes responsible for redirecting attention operate independently of conscious control.[5,8] Consciously controlled attention shifts are subserved primarily by cortical brain areas such as the dorsolateral prefrontal cortex and the posterior parietal cortex, while non-conscious, automatic, or 'implicitly-derived' attentional allocation appears to be modulated primarily by subcortical brain structures including the superior colliculus.[7,40-43] It is presently unclear whether the specific attentional deficit observed in schizophrenia is due to failures in the voluntary attentional control system or reflexive / automatic mechanisms. Maruff *et al*. speculated that the problem may be due to dysfunctional voluntary mechanisms mediated by the frontal lobes.[22] However, attention shifts away from peripheral stimulation do not necessarily involve this type of 'higher level' control.[4,44] Alternative explanations include, for instance, over activation of the automatic mechanism responsible for reflexive shifts of attention to the peripheral cue, or diminished involuntary inhibition of the source of peripheral stimulation, relative to normal cognitive functioning.

The fMRI experiment will allowed us to study the neural sites involved in processing specific cognitive abnormalities in schizophrenia, such as the inhibition of an oculomotor response or the deployment of overt visual attention. We will employ an event-related fMRI design to study these individual cognitive component processes. We have obtained first imaging data from antisaccades in healthy volunteers in the Centre for Neuroimaging Sciences. Figure 2 depicts the brain areas that show significantly stronger activation during antisaccades compared to prosaccades.

Figure 2
Activation during Antisaccade Eye Movements

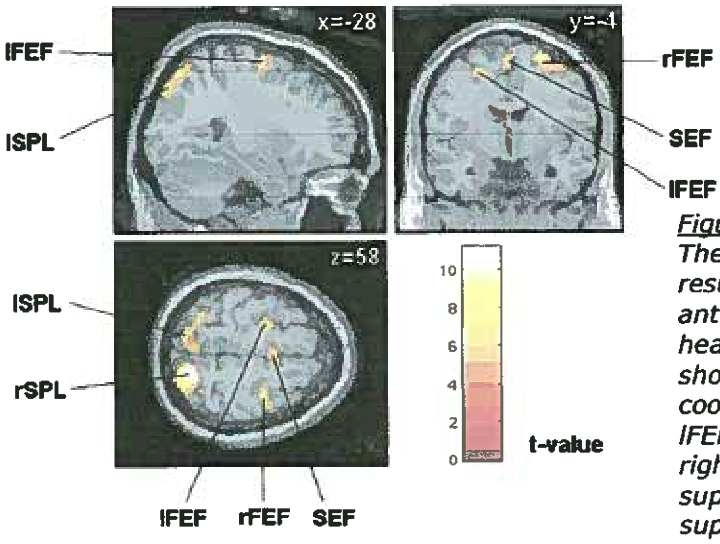
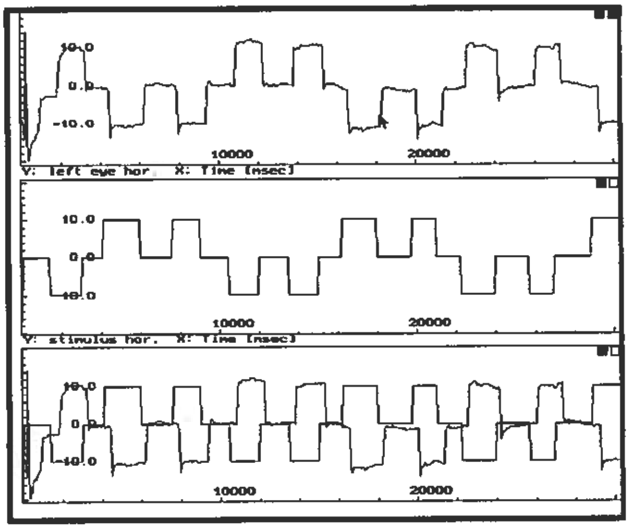


Figure Legend: The figure represents the group results of a contrast between antisaccades and prosaccades in 13 healthy volunteers. The sections shown are centred at Talairach coordinates x=-28, y=-4, and z=58. lFEF, left frontal eye field; rFEF, right frontal eye field, lSPL, left superior parietal lobule, rSPL, right superior parietal lobule; SEF, supplementary eye field.

These are fronto-parietal networks comprising frontal eye fields, supplementary eye fields, and superior parietal lobule, known to be involved in the control of overt and covert attention and thought to be impaired in schizophrenia.Eye movements will be recorded during the fMRI scans using a state-of-the-art, high-speed infrared oculographic device (Cambridge Research Systems Ltd., Rochester, UK) with a sampling frequency of 500Hz. This system is compatible with the magnetic field of the scanner due to its lack of ferromagnetic materials and its reliance instead on fibre-optic cables for signal transduction. We have successfully implemented this method in our fMRI scanner. Figure 3 shows the recordings of a healthy participant during a series of antisaccade trials recorded in the fMRI environment.

Figure 3
Antisaccade Eye Movement Recordings during fMRI



<u>Figure Legend</u>:
This figure depicts one antisaccade block (30 seconds) of the block design fMRI task. Horizontal movements of the left eye were recorded from a single participant while performing the task. Top panel: eye; middle panel: target. Bottom panel: both. Vertical axis in each panel represents degree of visual angle; horizontal axis in each panel depicts time in milliseconds.

Publications:

(1) Crawford, T.J., Hill, S., Higham, S. (2005). The inhibitory effect of a recent distracter. Vision Research, 45, 3365-3378.

(2) Crawford, T. J., Kean, M., Klein, R. M., & Hamm, J. P. (2006). The effects of illusory line motion on incongruent saccades: Implications for saccadic eye movements and visual attention. *Experimental Brain Research, 173,* 498-506.

<u>Submitted</u>

Kean, M., & Crawford, T. Cueing eye movements (and visual attention) to spatial locations with auditory cues. Paper submitted to *Acta Psychologica*.

<u>In preparation</u>

Kean, M., & Crawford, T. Eye movements in response to auditory stimuli: A prosaccade versus antisaccade advantage.

The financial support of the Bial Foundation is acknowledged in these papers.

Conference presentations:

(1) Crawford, T., Kean, M., Hamm, J., & Klein, R. (2005). Illusory line motion reverses the processing advantage of prosaccades over antisaccades. Paper presented at the 16th British Ocular Motor Group meeting, University College London, United Kingdom.

(2) Crawford, T.J., Kean, M., Klein, R.M., Hamm, J.P. Can a deficit in spatial attention account for the abnormality of antisaccades in Schizophrenia? 13th Biennial Winter Workshop on Schizophrenia Research, Davos, Switzerland, 4-10th Feb 2006.

(3) Saccadic latencies to visual targets following auditory cues. Kean, M., Ettinger, U., Kumari, V., Williams, S.C.R., Anilkumar, A., Crawford, T.J. 13th Biennial Winter Workshop on Schizophrenia Research, Davos, Switzerland, 4-10th Feb 2006

(4) Kean, M., Crawford, T.J. **Eye movements in response to auditory stimuli: A prosaccade versus antisaccade advantage.** Abstract submitted for BPS Annual Conference,

York 2007 (21-23 March). Submitted on the 1st of December 2006

(5) Kean, M., Ettinger, U., Kumari, V., Williams, S.C.R., Anilkumar, A., Crawford, T.J **Cross-modal attention capture in schizophrenia. Abstract submitted to 2nd International Congress of Biological Psychiatry, Santiago, Chile** 17-21 April 2007.

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Maruff, P., Pantelis, C., Danckert, J., Smith, D., & Currie, J. (1996). Deficits in the endogenous redirection of covert visual attention in chronic schizophrenia. *Neuropsychologia, 34 (11),* 1079-1084.

Posner, M. I. (1980). Orienting of attention. *Quarterly Journal of Experimental Psychology, 32,* 3-25.

Spence, C., & Driver, J. (1997). Audiovisual links in exogenous covert spatial orienting. *Perception and Psychophysics, 59,* 1-22.