BRIEF COMMUNICATIONS

Do antisaccade deficits in schizophrenia provide evidence of a specific inhibitory function?

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Abstract

Background: Despite its inhibitory control requirements, antisaccade deficits have been consistently associated with working memory impairments in schizophrenia. We investigated whether variance in antisaccade performance could be better accounted for in terms of a specific inhibitory function. Method: We assessed 48 clinically stable out-patients with schizophrenia on an antisaccade task, as well as on measures of spatial and verbal working memory, sustained selective attention, and a simple motoric go/no-go measure of response inhibition. Results: In a stepwise multiple regression analysis, go/no-go task performance accounted for a considerably greater percentage of variance in antisaccade performance (25.3%) than either working memory (8.4%) or sustained selective attention task (9.1%). Discussion: We conclude that antisaccade deficits in schizophrenia appear to be better understood in terms of a specific deficit of inhibitory control than in terms of more general difficulties with context maintenance or goal neglect. (*JINS*, 2006, *12*, 901–906.)

Keywords: Antisaccade, Schizophrenia, Working memory, Inhibitory control, Attention, Cognition

INTRODUCTION

The ability to inhibit irrelevant responses and ignore irrelevant information is essential to human thinking and behaviour. In disorders where deficits in "inhibitory control" are present, the impact is significant. In schizophrenia, an inability to control attention and inhibit pre-potent responses has been described as a core characteristic of the disorder (Brownstein et al., 2003), associated with greater symptom severity (Donohoe et al., 2006), and prognostic of poorer social and occupational outcome (Reeder et al., 2004). Such inhibitory deficits are particularly evident in patients' performance on the antisaccade task, and have been consistently associated with hypo-functioning of the dorsolateral

prefrontal cortex (DLPFC) in schizophrenia (see McDowell and Clementz, 2001 for a review).

There has however been much debate over whether these deficits result from a specific mechanism of inhibitory control, or to deficits in working memory more generally, also involving DLPFC. At a behavioural level, a number of studies have replicated a correlation between antisaccade and working memory performance in samples of both controls (Roberts et al., 1994) and patients with schizophrenia (Broerse et al., 2001; Gooding & Tallent, 2001; Hutton et al., 2004; Nieman et al., 2000). Furthermore, in schizophrenia this association has been reported and replicated in the absence of correlations with other tasks of spatial attention and inhibitory control such as Stroop and trail making tasks (Broerse et al., 2001; Hutton et al., 2004; Nieman et al., 2000). This has led to the view that antisaccade deficits in schizophrenia overlap with working memory tasks in indexing general difficulties with context maintenance (Cohen

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and Servan-Schreiber, 1992), rather than a specific inhibitory mechanism per se (Hutton et al., 2004).

Against this view, traditional pre-frontal tasks such as the stroop are unlikely to selectively measure response inhibition, and the absence of a correlation may be due to the involvement of additional cognitive domains, particularly of selective attention, rather than the lack of a common inhibitory function. Using a simple go/no-go measure of response inhibition in which working memory load was parametrically varied, we (Hester et al., 2004) recently showed that the functions of working memory and response inhibition were associated with discrete as well as overlapping patterns of prefrontal cortical activation in healthy controls using f MRI. While inhibitory control decreased under conditions of increased working memory load, inhibitory control was still maintained, reflected in increased dorsolateral pre-frontal cortex and anterior cingulate activation during stop trials which was not evident during working memory rehearsal. This evidence of regional activations that appeared specific to inhibitory control seem to support the view that inhibitory control overlapped with, but is also discrete from working memory. This view is further supported by a recent study by Barton et al. (2006) in which the inter-trial effects of antisaccade performance was behaviourally similar the inter-trial effects during a go/no-go task in a sample of healthy controls.

The Present Study

In the present study we investigated the relationship between antisaccade performance and measures of both spatial and verbal working memory, sustained selective attention, and a selective go/no-go measure of response inhibition in a group of chronic but stable outpatients with schizophrenia. We hypothesised that a significant proportion of variance in antisaccade deficits would be accounted for by go/no-go task performance, independently of that accounted for by working memory. We further hypothesised that variance in antisaccade performance would be accounted for by go/no-go performance independently of that accounted for by more general deficits in sustained/selective attention.

METHOD

Participants

Our sample consisted of 48 patients with schizophrenia who gave written informed consent to participate in the study, and all data was obtained in accordance with the guidelines of the Helsinki declaration. Consensus diagnosis was made by three clinicians using DSM-IV criteria based on all available information (SCID interview, family or staff report, and chart review). All patients were aged between 18 and 60 years, screened for current substance abuse, other psychiatric disorders, head injury with loss of consciousness, or a history of seizures. Additional information gathered on participants included current symptomatology (assessed using the positive and negative symptom scale; PANSS) and prescribed neuroleptic and anticholinergic medication.

Antisaccade Task

Antisaccade performance was assessed using a portable EOG eye tracking apparatus. Grass Ag/AgCI electrodes were placed close to the canthus of each eye and horizontal eye movement was measured with respect to a reference electrode placed on the centre of the forehead. To reduce unwanted EEG interference a butterworth low pass filter was applied with a cut-off frequency of 38Hz. Presentation of stimuli and recording of EOG were made using two interfaced laptop computers (both models: Dell latitude D600).

Antisaccade stimuli were presented using an overlap design suggested by McDowell et al. (1999) to be an optimal method of task presentation in schizophrenia studies. In this version participants are required to attend to a continually illuminated central fixation point and, when a peripheral cue is illuminated at either $\pm 16°$ on the horizontal from the central fixation point, to generate an antisaccade (a saccade towards the cue's mirror location). Preceding the block of antisaccade trials, a pre-potent response to look towards the cue was established during a block of trials in which participants were instructed to make prosaccades towards the peripheral cue. Antisaccade accuracy was defined as an eye movement in the correct direction and with amplitude greater than 50% of the individuals' averaged eye movement (calculated during the prosaccade trials). This was identified using custom software which yielded a total percentage correct response.

Neuropsychological Tests

Spatial working memory was assessed using the *Spatial Working Memory Task* from the Cambridge Automated Neuropsychological Test battery (CANTAB). On this task, presented using a laptop computer with touch screen, patients are required to "open" sets of boxes, varying between three and eight in number, and "find" a blue token hidden in one of the boxes. Participants were instructed that each box only contains a token once, and so an error is made when boxes in which tokens have been previously found on that trial are reopened. Verbal working memory was assessed using the Wechsler *Letter Number Sequencing task*. This requires participants to listen to a string of letters and numbers of increasing length and then to repeat the string by arranging the numbers numerically and the letters alphabetically.

Sustained attention was assessed using the distractibility version of the Gordon's *Continuous Performance Task* (Gordon, 1996). In this version, participants are required to attend to numbers between one and nine presented randomly, and respond by pressing a response key whenever a 1 is followed by a 9. To increase the attentional demands of the task, subjects must selectively attend to the centre of the screen while ignoring flanker numbers presented concur-

rently on either side. Number of correct responses to 1–9 sequences was taken as the dependent variable.

Inhibitory control was assessed using the *XY task*, a simple go/no-go measure of response inhibition (Garavan et al., 1999). In this task participants attended to a series of alternating stimuli ('X' or 'Y') presented on screen with the requirement to respond by button press for each stimulus except where the same stimulus is presented twice ('X' followed by 'X' or 'Y' followed by 'Y'). On these occasions participants must withhold (or inhibit) the usual response. Proportion of correct responses was taken as the dependent variable.

Statistics

Correlation coefficients (Pearson's r) were calculated between each of the tasks used. To test the hypothesis that antisaccade performance could be explained in terms of an 'inhibitory control' function we undertook a multiple regression analysis in which antisaccade performance was the dependent variable. Go/no-go performance (our inhibitory control measure) was entered on the first step as an index of response inhibition. This was followed by spatial working memory (the working memory index most likely associated with antisaccade performance), followed by verbal working memory, and followed by sustained selective attention. All analyses were carried out using SPSS 12 for windows.

RESULTS

The means and standard deviations for demographic and clinical data on all participants are presented in Table 1. The majority of the sample was male and while all had attended second level education approximately only half had completed final year state exams. All patients were medicated and clinically stable, with many patients receiving atypical neuroleptics either alone or in combination with another neuroleptic. 18% of patients were receiving clozapine. Despite this, participants' performance on the spatial working memory task fell just over 1 SD below age corrected norms for this task. Similarly, on the occulomotor tasks, patients responded incorrectly to over 30% of antisaccade trials. These results were broadly similar to those observed in previous studies (Maruff et al., 1998).

In terms of demographic and illness characteristics, significant negative correlations were observed between age and response accuracy on each of the occulomotor tasks (prosaccade: $r = -.36$, $p = .006$; antisaccade $r = -.47$; $p < .001$), CPT performance ($r = -.49$; $p = .001$), and XY task performance ($r = -.31$; $p = .023$), verbal working memory ($r = -.230$; $p = .02$) and a trend towards correlation with spatial working memory errors ($r = .22$; $p = .08$). For symptom severity, no significant correlations were observed between positive symptom severity and performance on any task. Negative symptom severity correlated with spatial working memory ($r = .406$; $p < .001$), but not with measures of attention or response inhibition.

Table 1. Demographic, clinical, neuropsychological, and antisaccade characteristics of the study sample

Variable	N	Percentage
Male	36	74.7
Receiving atypical neuroleptics	32	66.3
Receiving anticholinergics	1	3.4
	M	**SD**
Age (years)	45.2	10.2
Years in education	12.8	2.9
Symptom severity		
Positive symptoms (PANSS)	27.46	6.18
Negative symptoms (PANSS)	19.57	6.13
Neuropsychological measures		
Pre-morbid IQ (WTAR estimate)	95.2	10.6
CPT (percentage correct)	62.8	27.9
CANTAB SWM (z-scores from norm)	−1.07	1.16
Letter number sequence performance	7.26	3.45
XY performance (percentage correct)	19.1	25.3
Occulomotor task		
Pro-saccade percentage correct	85.6	20.4
Antisaccade percentage correct	68.9	30.7

Antisaccade performance accuracy significantly correlated with performance on each of the behavioural tasks (go/no-go task accuracy $r = .56$; spatial working memory errors $r = .48$; verbal working memory accuracy $r = .40$; CPT accuracy $r = .61$, all at $p < .01$). In addition, spatial working memory errors were significantly negatively correlated with CPT accuracy ($r = -.34$, $P < .01$). Go/no-go performance did not correlate with spatial working memory performance or CPT performance, but did correlate with verbal working memory accuracy ($r = .329$, $p < .01$)

In our regression analysis, once the effects of age had been partialled out of the equation, response inhibition (measured by the XY go/no-go task) accounted for 25.3% of variance in antisaccade performance. Spatial working memory accounted for a further 8.4% of variance in performance. Verbal working memory did not contribute significantly to the regression equation. Sustained selective attention (CPT with distractors) accounted for 9.1% of variance in performance (see Table 2). On this basis, response inhibition was a more effective predictor of antisaccade performance than either working memory or sustained selective attention. Finally, when the regression equation was re-run with response inhibition performance entered on the last step of the analysis (after all other variables had been entered), response inhibition continued to be the most effective variable in explaining antisaccade performance.

DISCUSSION

We investigated the hypothesis that antisaccade deficits in schizophrenia would be better accounted for by perfor-

Table 2. A Stepwise Multiple Linear regression analysis of antisaccade performance based on measures of response inhibition (XY go/no-go task), working memory (CANTAB SWM and Letter Number sequencing), and selective attention (CPT with distractors)

Variable Entered	R	R Square	Change Statistics				
			R Square Change	F Change	df1	df2	Sig. F Change
1) Age	.403	.162	.162	6.39	1	33	.016
2) XY accuracy	.644	.415	.253	13.841	1	33	.001
3) CANTAB SWM errors	.707	.499	.084	5.204	1	32	.030
4) Letter number accuracy	.708	.501	.001	.074	1	31	.787
5) CPT accuracy	.769	.592	.091	6.490	1	30	.016

mance on a selective measure of inhibitory control than by performance on working memory tasks or tasks of sustained selective attention. We found that response inhibition (measured by a simple go/no-go task) explained just over a quarter of the variance in antisaccade performance. While variance in antisaccade performance did correlate with working memory performance and with sustained selective attention, these variables accounted for a much smaller percentage of variance in antisaccade performance (8% and 9% respectively).

These findings can be contrasted with previous evidence that antisaccade performance correlated with working memory tasks performance but not with performance on 'traditional' pre-frontal tasks presumed to have an inhibitory component. The lack of correlation previously seen is likely to have resulted from the use of non-specific tasks of inhibitory control such as Stroop. As well as typically requiring a verbal rather than a motoric response to presented stimuli (unlike antisaccade performance), Stroop performance involves aspects of attentional control that are additional to inhibitory control (e.g. selective attention). This difficulty of cognitive interference is widely reported in studies using "traditional" pre-frontal measures to fractionate individual domains of higher level function (Burgess, 1997).

Before discussing the implications of our results that antisaccade performance is indexing an inhibitory control function, a number of limiting factors should be noted. First, the lack of a control group limits our ability to generalize from these results, and although similar results have recently been reported in a sample of healthy controls (Barton et al., 2006) the use of identical antisaccade and cognitive measures would help to further elucidate this relationship. Second, given the chronic nature of this sample, differences in drug treatment are likely to have affected individual patient performance. Third, while our data is derived from one measure of each cognitive function, multiple measures of each function would help to confirm the construct validity of the cognitive constructs used. For working memory, although we used both a visuo-spatial and a verbal task, the requirement of 'automated' alphabet knowledge in the verbal working memory task may have been an unwanted contributor of variance in relation to antisaccade performance. Fourth, the fact that only one of our cognitive measures correlated with negative symptoms suggest that our study may have been underpowered to explore the influence of symptom severity on antisaccade performance.

Response Inhibition and Attentional Control

This study also addressed whether antisaccade deficits in schizophrenia are specifically due to deficits of inhibitory control or to more global deficits in attentional control. Some reviewers have suggested that antisaccade deficits in schizophrenia index deficits in attentional control leading to difficulties with goal directed behaviour more generally (Nieuwenhuis et al., 2004; Reuter & Kathmann, 2004). In this view, antisaccade deficits may arise from a general difficulty with goal neglect, operationalised by Duncan (1995) as the tendency to disregard task requirements even though they are understood and remembered. As applied to our study this would presumably mean that while a go/no-go task may account for variance in antisaccade performance, a different measure of attention may well have done so as effectively.

To test this possibility, we also assessed patients on a CPT task, which involves attending to a long series of both targets to be remembered and targets to be ignored (hence indexing both sustained and selective aspects of attention). This contrasts with our go/no-go XY task which involves sustained attention to only two alternating stimuli (X and Y) with the requirement to inhibit a pre-response to either two X's or two Y's appearing in a row. While performance on both tasks correlated with antisaccade performance, XY task performance accounted for more than twice as much variance in antisaccade performance as CPT performance, irrespective of which variable was entered into the equation first. This difference may be taken as evidence that it is the function of inhibitory control specifically, rather than attentional control more generally, that is being indexed by antisaccade performance in schizophrenia. This conclusion is strengthened by the strong correlation between antisaccade and CPT performance, suggesting that although the two tasks made similar attentional demands on participants, this was not adequate to explain variance in antisaccade performance.

Cortical Correlates of Response Inhibition

In summary, in the present sample of patients with chronic schizophrenia, the shared variance in go/no-go and anti-saccade performance deficits evidences a particular inhibitory function common to both tasks and which overlaps with but is also independent of working memory deficits. This view of overlap but also separability between inhibitory control and working memory is consistent with our earlier neuro-imaging work showing evidence of shared but also discreet cortical areas associated with these functions (Hester et al., 2004). In this imaging study we found that while increasing working memory load led to interference in response inhibition, subjects maintained a reasonable level of inhibitory control nonetheless. Further, successful inhibition during WM interference appeared to be facilitated by increased activation of common regions (activated during both working memory rehearsal and during successful response inhibition) but also by inhibitory specific regions (regions of the dorsolateral prefrontal cortex and anterior cingulate that were activated during response inhibition only).

CONCLUSIONS

The present study is consistent with the view in contemporary cognitive neuroscience of a separate function of inhibitory control, and that deficits in this function are being indexed by antisaccade performance. Antisaccade deficits in schizophrenia are well established, show evidence of familiality (Calkins et al., 2004; Malone & Iacono, 2002), and have been proposed as a potential endophenotype in schizophrenia molecular genetics studies (Freedman et al., 1999). Other cognitive phenotypes for schizophrenia include working memory and attention. The present study suggests that antisaccade deficits are unlikely to be simply another index of working memory in schizophrenia genetics. This view is supported by a recent study in which the COMT VAL158MET polymorphism, which has been repeatedly associated with variance in working memory tasks such as the n-back task, was not associated with variance in antisaccade performance in a large (n=543) sample of healthy males (Stefanis et al., 2004). Instead, the present study suggests that antisaccade performance is indexing a more specific deficit of response inhibition, a function which overlaps with but is also separate to working memory.

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