Selective attention deficits reflect increased genetic vulnerability to schizophrenia

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Abstract

Background: Impairment in attention is prominent in schizophrenia and may be a valuable genetic indicator for vulnerability to this disease.
Aims: We set out to characterize the attention deficits that may be associated with genetic liability to schizophrenia.
Methods: We compared attention performance in 55 people with schizophrenia, 95 of their first-degree relatives, and 61 unrelated controls. We also segregated presumed obligate carriers of genetic risk (POCs, N=12) and compared their performance with that of controls.
Results: Although the relatives of people with schizophrenia did not significantly differ from the normal controls on the tasks of attention, their scores were significantly ordered such that patients > relatives > normal controls during tasks of sustained and selective attention as measured by the Jonckheere–Terpstra Test (p<.05). Additionally, POCs were significantly worse than normal controls during selective attention tasks such as the Stroop (p=.03) and Letter Cancellation Task (p=.04).
Conclusions: Heterogeneity in the first-degree relatives may have diluted the attention deficits present in those who are at genetic risk for schizophrenia. On the other hand, our findings in the more homogeneous group of POCs suggest that selective attention may be an indicator of genetic liability for schizophrenia.

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1. Introduction

Attention impairment is a primary symptom of schizophrenia, particularly those of the sustained and selective domains, which have been repeatedly measured using the Continuous Performance Test (CPT) and Stroop Task (Tsuang et al., 2006; Barch et al., 2004; Hepp et al., 1996). Using these two tasks, sustained and selective attention deficits have also been reported in relatives of people with schizophrenia (Chen et al., 2004; Harris et al., 1996; Sitskoorn et al., 2004; Zalla et al., 2004; Cannon et al., 1994; Asarnow et al., 2002; Mirsky et al., 1992); however, these findings have not been consistent (Cosway et al., 2002; Jones et al., 2001). Inconsistencies may be partly due to the lack of homogeneity in the relatives of people with schizophrenia that may weaken the power to
detect genetic effects. In the present study, our aim was to determine whether impaired sustained and selective attention can be used to ascertain vulnerability to schizophrenia by (1) comparing people with schizophrenia, their relatives and unrelated normal controls on tasks of sustained and selective attention, and (2) investigating the performance of some parents who appear to have transmitted the liability for the disease (Toulopoulou et al., 2005). These are parents who although not manifesting the illness themselves, are thought to be carriers of the disease, since in addition to having parent(s) or sibling(s) suffering from schizophrenia they also have at least one offspring with schizophrenia. Presumed obligate carriers are a rare sub-group of relatives and, thus, currently, only a small number of studies have measured abnormalities in this population. However, these previous studies have found that these individuals share similar neural and cognitive abnormalities as their affected relatives (Toulopoulou et al., 2005; Steel et al., 2002; Spence et al., 2000; Sharma et al., 1998; Sharma et al., 1999; Frangou et al., 1997). We hypothesized, therefore, that these presumed obligate carriers (POCs) would also show similar deficits of attention related to schizophrenia.

2. Materials and methods

2.1. Participants

The participants included in this study are members of the Maudsley Family Psychosis Study, which is a comprehensive family study of psychosis involving various investigations including neuropsychological assessment described in detail previously (Toulopoulou et al., 2003) (McDonald et al., 2006) (see Table 1). Patients were selected on the basis of having met DSM-IV criteria for schizophrenia or schizoaffective disorder. The clinical characteristics of the patient group are described in Table 2. Only individuals with at least one participating well relative were included. Table 1 describes the sociodemographic characteristics of the participants included in these experiments that include the participants’ current intellectual ability as measured by the WAIS-R (Wechsler, 1981). The mean pre-morbid IQ of the patients as ascertained by the National Adult Reading Test (NART) (Nelson HE, 1992) was above average at 109 (SD = 10).

All willing unaffected first-degree relatives of persons with schizophrenia without a reported current or past psychotic disorder as assessed by the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) (Endicott and Spitzer, 1978) were included. Of these, 56 were parents, 36 were siblings and 3 were offspring of persons with schizophrenia. The normal controls were selected based on the absence of a psychotic disorder (i.e., past or present) as well as the absence of a family history of psychosis as assessed by the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992). The exclusion criteria for the entire sample included head trauma resulting in loss of consciousness, drug or alcohol misuse (meeting DSM-IV criteria for dependency within the 12 months prior to assessment) and past or present diagnosis of neurological disorders.

All participants were informed about the purpose and the procedures involved in the study and provided signed consent. This study was approved by the ethical committee at the Institute of Psychiatry and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Tasks of attention

While there are several tasks of sustained and selective attention, we selected tasks that have frequently been used in both people with schizophrenia and their well relatives.

1. Visual CPT task — This is a 14-minute computerized test developed by Conners (1995) assessing visual sustained attention. The test involved 360 random single letter presentations with a 10% target chance. Each letter was displayed for 250 ms with random inter-stimulus intervals of 1, 2 or 4 s. Subjects were instructed to respond to every individual letter on the screen by

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**Table 1**

<table>
<thead>
<tr>
<th>Sociodemographic characteristics of the subjects per group classification</th>
<th>Patients</th>
<th>Relatives</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>55</td>
<td>95</td>
<td>12</td>
</tr>
<tr>
<td>N (males/females)</td>
<td>37/18</td>
<td>49 (15)</td>
<td>55 (5)</td>
</tr>
<tr>
<td>Age at time of testing (mean (SD))</td>
<td>35 (9)</td>
<td>49 (15)</td>
<td>55 (5)</td>
</tr>
<tr>
<td>WAIS-R Full IQ (mean (SD))</td>
<td>95 (13)</td>
<td>111 (12)</td>
<td>112 (12)</td>
</tr>
<tr>
<td>Range</td>
<td>58</td>
<td>51</td>
<td>41</td>
</tr>
</tbody>
</table>

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**Table 2**

<table>
<thead>
<tr>
<th>Clinical characteristics of the individuals with schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily chlorpromazine equivalent (in mg)</td>
</tr>
<tr>
<td>Age (in years) at first antipsychotic medication</td>
</tr>
<tr>
<td>Age (in years) at first psychiatric symptoms</td>
</tr>
<tr>
<td>Duration (in years) of medication use — meds</td>
</tr>
<tr>
<td>Duration (in years) of symptoms</td>
</tr>
</tbody>
</table>

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*a Age at testing minus age at first antipsychotic medication; *b age at testing minus age at first psychiatric symptoms.
button pressing, except when the letter is ‘X’. Variables measured include: (i) beta-value (\(\beta\)) T-score — measure of overall rate of information processing or response tendency; \(\beta = \text{Y-axis height of normal curve using proportion of commission errors} / \text{Y-axis height of normal curve using proportion of hits}\). T-scores represent the score of the subject taking the test relative to scores obtained by the comparative study group. A T-score of 50 represents the average of the comparison group with a standard deviation of 10. T-scores of <40 represent individuals who respond more frequently than normal; T-scores >60 indicate subjects who respond less frequently than normal; (ii) d-prime (\(d'\)) T-score — measure of overall perceptual sensitivity or how well subjects discriminated targets from non-targets; \(d' = \text{Z-score normal curve deviate using proportion of commission errors} / \text{Z-score normal curve deviate using proportion of hits}\). T-scores >60 indicate poor performance; (iii) index — measure of overall CPT performance; weighted sum of all variables measured: number of hits, reaction time to target, number of omission errors, number of commission errors, hit reaction time standard error, variability of standard errors, \(d'\) and \(\beta\). A score of 8–11 corresponds to borderline, while a score of >11 would suggest attention problems.

2. Auditory CPT — This task was modified from one that Faraone and colleagues used in 1995. This is a 10-minute test in which subjects were instructed to respond to the letter ‘A’ by button pressing. Three hundred single letter stimuli were presented randomly at 2-second intervals with a 10% target chance. Hit reaction time to targets was measured.

3. Stroop Color–Word Task (Trenerry et al., 1989) — This task tests the ability to attend only to the color aspect of a word while ignoring the distractor, which is how the word is read. We measured color–word score (score), which is the number of correct responses minus incorrect responses.

4. Letter Cancellation (LC) (Diller et al., 1974) — This task tests the ability to quickly select targets by performing a timed test wherein two target letters (‘E’ and ‘C’) are identified within other non-target letters (distractors). Normative data indicate a performance limit of 0–2 errors within a total performance time of 2 min. The total reaction time (RT) to complete the test was recorded.

### 2.3 Analyses

Demographic differences between the patients, relatives and controls were examined using analyses of variance (ANOVA) and variables that significantly differed from normal controls were co-varied for in subsequent analyses. For each test of difference in attention between the groups, a series of separate analyses was conducted to compare performance between three groups (patients with schizophrenia, relatives, and controls). To adjust for the effect of covariates, a regression model was employed with each test score as the dependent variable and group, gender and age as the predictor variables. In addition, since we were interested in identifying dysfunctional cognitive systems that exist even when differences in general intellectual function are accounted for, all results presented are adjusted for current IQ. As with any family study, observations of family members who belong to the same family are not likely to be independent (i.e. they share a similar value of the variable). Ignoring within-family correlations would

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Table 3

<table>
<thead>
<tr>
<th></th>
<th>Patients mean (SD) t, p</th>
<th>Relatives mean (SD) t, p</th>
<th>Controls mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ALL</td>
<td>POCs</td>
</tr>
<tr>
<td>CPT(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d')</td>
<td>56 (14) t=0.01, p=1.0</td>
<td>49 (11) t=1.33, p=0.2</td>
<td>53 (11) F=.01, p=.98</td>
</tr>
<tr>
<td>(\beta)</td>
<td>69 (23) t=2.85, p&lt;0.01</td>
<td>59 (20) t=1.24, p=.2</td>
<td>57 (16) F=.53, p=.59</td>
</tr>
<tr>
<td>Index</td>
<td>6.1 (5.6) t=2.06, p&lt;0.05</td>
<td>3.6 (4.1) t=1.37, p=0.2</td>
<td>4.2 (3.9) F=.5, p=.58</td>
</tr>
<tr>
<td>A-CPT(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>149 (151) t=1.78, p=0.08</td>
<td>125 (88) t=1.84, p=0.07</td>
<td>97±(93) F=.19, p=.82</td>
</tr>
<tr>
<td>Stroop Score LC(^c)</td>
<td>102 (90) t=4.23, p&lt;0.001</td>
<td>102 (13) t=1.1, p=0.3</td>
<td>97 (17) F=3.7, p=.03</td>
</tr>
<tr>
<td>RT</td>
<td>144 (51) t=3.81, p&lt;0.001</td>
<td>126 (36) t=.84, p=0.4</td>
<td>132 (39) F=3.4, p=.04</td>
</tr>
</tbody>
</table>

\(^a\) CPT = continuous performance test.

\(^b\) A-CPT RT = auditory continuous performance test mean reaction time to hits in ms.

\(^c\) LC RT = letter cancellation total response time in seconds.
inflate the significance of between-group differences. To account for this, the regression equation had a component for clustered observations using a robust estimator for the variances of the regression coefficient estimates (Binder, 1983) (Toulopoulou et al., 2005) (Bramon et al., 2005).

As a further investigation, we carried out a trend analysis, the Jonckheere–Terpstra (J–T) test to examine whether the performance of each group was significantly ordered (Jonckheere, 1954) (Terpstra, 1952).

For the comparisons between the POCs and the normal controls, differences in demographic variables were investigated using ANOVA. Differences in demographic characteristics were then controlled for by adding them as covariates during the task performance analyses between these two groups using analysis of covariance (ANCOVA).

3. Results

Results indicated that the patients were significantly younger than controls \( (t=2, p<.05) \) and their well relatives \( (t=6, p<.001) \) at assessment. The patient group also had significantly less females than the relatives \( (\chi^2 = 9, p<.001) \) and the control group \( (\chi^2 = 4, p<.05) \). The relatives and the smaller group of POCs were significantly older than controls at assessment \( (t=3, p<.001) \), but were both similar in IQ and gender distribution compared to the normal controls (see Table 1).

During the visual CPT, the patients had \( \beta \) that indicated a response pattern less frequent than normal (>60). None of the groups had \( d' \) that indicated poor perceptual sensitivity (>60) or indicated attention problems as measured by the CPT-visual index (>11) (see Table 3).

As expected, compared to normal controls, the patients performed significantly worse on the visual CPT \( \beta(t=2.85, p<0.01) \) and index \( (t=2.06, p<0.05) \), Stroop score \( (t=4.23, p<0.001) \) and LC RT \( (t=3.81, p<0.001) \) despite controlling for age, gender and IQ. The patients’ CPT index and A-CPT RT did not differ from the normal controls. The performance of the relatives as measured by the attention variables did not significantly differ from the normal controls. The performance of the relatives was significantly ordered, such that the patients < relatives < normal controls (see Fig. 1).

Comparisons between the POCs and the normal controls indicated that the POCs performed more poorly than the normal controls during the Stroop \( (F=3.7, p=.03) \) and LC tasks \( (F=3.4, p=.04) \) despite controlling for age differences.

4. Discussion

We found that, as expected, the patients performed more poorly than the normal controls on most attentional measures. However, their well relatives did not share any of these attention deficits to a significant degree. Of interest, however, is that the relatives’ performance on several attention measures was intermediate to patients and normal controls, which is consistent with reports from other studies (Laurent et al., 1999; Mirsky et al., 1995). The low alpha levels from the trend test suggest that these attention deficits are indeed present in the relatives although to a lesser extent than the patients with schizophrenia.

A possibility for the absence of greater disparity between the relatives and the normal controls using direct contrasts may be the non-homogeneity of the relatives group. To circumvent this issue, we segregated the POCs...
and compared their performance on the attention tasks with the normal controls. The results of this contrast indicated that this more homogeneous group of relatives indeed performed more poorly during tasks of selective attention. Our paradigm consisted of inhibiting a response, which might indicate that the slower reaction time in the POCs during the Stroop and LC may reflect poor perceptual sensitivity. Although these significance levels are modest, these results are in the hypothesized direction. This finding in conjunction with the J–T test findings of significantly ordered performance of the relatives such that the POCs are intermediate to the patients and the normal controls suggest the possibility that selective attention deficits over sustained attention deficits may be a better predictor of genetic susceptibility to schizophrenia.

These findings are in accord with past literature that report that the ability to focus and selectively attend to relevant stimuli while ignoring irrelevant stimuli is a key dysfunction in schizophrenia (Egeland et al., 2003) (Lussier and Stip, 1999) (Klemm et al., 2006). Visual search tasks such as the LC have also been shown to discriminate high-risk subjects from normal controls (i.e., high-risk subjects are much slower at finding target stimuli) (Winters et al., 1981). In an interesting study using a visual search task involving visual discrimination among simultaneous stimuli called Embedded Figures Test, deficits were found in children as young as three years of age of mothers with schizophrenia (Gamer et al., 1977).

The nature of these selective attention deficits in schizophrenia remains unknown. While many theories propose that selective attention deficits in persons with schizophrenia are due to abnormalities in filtering and inhibiting irrelevant stimuli as early as the sensory level, others contend that the deficit in inhibitory processes actually occur at a later stage of processing (Salo et al., 1996). However, investigations examining the basic operations of selective attention have provided evidence of problems of attentional selectivity in individuals with schizophrenia at all levels of information processing—sensory (Braff et al., 1991), perceptual (Nestor et al., 1992), cognitive and response selection (Spitzer et al., 1994a,b). Neuroimaging studies have posited that these deficits may be related to hypofrontality, particularly of the anterior cingulate and dorsolateral prefrontal cortices (Weiss et al., 2007).

The findings in the POC group should be interpreted with caution given the small sample size. However, given the likely high genetic loading in these individuals, separate analyses were warranted. Lastly, addressing the genetic causes was beyond the scope of this study, however, if attentional deficits are indeed associated with genetic risk for schizophrenia, whether the mechanisms that underlie this association are similar across families or individuals should be addressed in future studies.

In conclusion, we found that there are selective attention deficits akin to prodromal schizophrenia in a sub-population of relatives that may carry the genes for schizophrenia, which suggests that selective attention may be associated with the genetic liability for schizophrenia.

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CMcD and EB were supported by the Wellcome Trust; The Wellcome Trust had no further role in the study.

Contributors

FF conceived the design of the study, collected, analyzed and interpreted the data, and drafted the manuscript. TT analyzed the data and provided assistance in the interpretation of the data. RGM made contributions to the design of the study. CMcD and EB provided the clinical diagnoses, screening and categorization of the participants. MW assisted in the data management. RMM conceived of the study and made substantial contributions in the drafting of the manuscript. All authors assisted in the revisions of the manuscript and have read and approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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