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Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis

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Abstract

Background: Schizophrenia is characterized by a generalized cognitive impairment with pronounced deficits in the domains of verbal memory, executive functioning and attention. Aim: To investigate whether cognitive deficits found in patients with schizophrenia are also found in non-affected relatives. Method: A meta-analytic review of the published literature on cognitive performance between relatives of schizophrenic patients and healthy controls. Results: The meta-analyses yielded nine weighted effect sizes from 37 studies comprising 1639 relatives of schizophrenia patients and 1380 control subjects. The largest differences were found on verbal memory recall \( (d = 0.54, 95\% \text{ CI} = 0.43–0.66) \) and executive functioning \( (d = 0.51, 0.36–0.67) \). Attentional functioning showed smaller effect sizes \( (d = 0.28, 0.06–0.50) \). These effect sizes are in the moderate range. Conclusion: Cognitive deficits found in patients with schizophrenia are also found in non-affected relatives. This finding is consistent with the idea that certain cognitive deficiencies in relatives are caused by familial predisposition to schizophrenia and that these deficiencies might be putative endophenotypes for schizophrenia. However, our results do not address genetic causes directly. Further work is needed to determine whether certain cognitive traits are familial and whether there is co-inheritance of these traits with schizophrenia within families.

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Keywords: Endophenotype; Marker; Cognition; Schizophrenia; Relatives

1. Introduction

Schizophrenia is characterized by a generalized cognitive impairment, with varying degrees of deficit in all domains (Heinrichs and Zakzanis, 1998). Deficits are especially pronounced in the domains of verbal memory, executive functioning and attention (e.g. Albus et al., 1997; Aleman et al., 1999; Bilder, 1996; Censits et al., 1997; Heinrichs and Zakzanis, 1998; Saykin et al., 1994; Sitskoorn et al., 2002) and less attenuated in the domains of perceptual- and basic language processes (Goldberg and Gold, 1995; Heinrichs and Zakzanis, 1998).

The most pronounced deficits are already recorded early in the course of the illness (Saykin et al., 1994; Albus et al., 1997; Censits et al., 1997) and thus may, at least partly, be independent of factors such as
medication or duration of illness. Furthermore, family studies have demonstrated that there is a substantial genetic contribution to the etiology of schizophrenia (Cardno et al., 1999; McGuffin et al., 1995) and that some cognitive deficits in schizophrenia are heritable (e.g. Cannon et al., 2000; Goldberg et al., 2003; Tuulio-Henriksson et al., 2002). Therefore, one might hypothesize that cognitive deficits not only occur in patients but that non-affected relatives of patients exhibit similar cognitive deficiencies.

Indeed, most studies that investigated cognitive traits in relatives of patients with schizophrenia report cognitive deficiencies in relatives when compared to healthy controls (see for e.g. Appels et al., 2003; Faraone et al., 1995; Kremen et al., 1994). However, results of individual studies are contradictory (see e.g. Chen and Faraone, 2000; Faraone et al., 1995; Kremen et al., 1994) and although a narrative review has appeared some years ago (Kremen et al., 1994) no quantitative review of the literature on cognitive test performance in relatives of schizophrenic patients exists yet. It is therefore, not unequivocal clear which cognitive functions are deficient in relatives and whether deficiencies parallel the deficits found in patients.

If cognitive deficits found in relatives parallel the deficits found in patients, they might be putative endophenotypic markers for schizophrenia. Endophenotypic markers are characteristics that mark the presence of a genetic predisposition to a certain disease or disability (e.g. de Geus et al., 2001). They reflect a biological variable that is along the pathway between disease and distal genotype. Therefore they represent simpler clues to the genetic underpinnings of a disease than the disease syndrome (Gottesman and Gould, 2003) and may yield greater statistical power in genetic studies. Gottesman and Gould (2003) describe criteria useful for the identification of endophenotypes: The endophenotype is associated with the illness in the population, is heritable, primarily state-independent and endophenotype and illness co-segregate within families. In addition, the endophenotype, found in affected family members is also found in nonaffected family members at a higher rate than in the general population. This last criterion may be especially useful for identifying endophenotypes of diseases that display complex inheritance patterns, such as schizophrenia.

With an emergent body of literature on cognitive test performance in relatives of schizophrenic patients, a quantitative review of cognitive traits of relatives of patients with schizophrenia becomes possible. Such a review can reveal whether cognitive deficits found in patients with schizophrenia are also found in their non-affected relatives.

In the present study we present a meta-analysis of the published literature on cognitive performance as measured by standard clinical tests between relatives of schizophrenic patients and healthy comparison subjects. We hypothesize that, cognitive deficits found in patients with schizophrenia are also found in their non-affected family members. Confirmation of this hypothesis is consistent with the idea that certain cognitive deficiencies in relatives are caused by familial predisposition to schizophrenia and that these deficiencies might be putative endophenotypes for schizophrenia.

2. Method

2.1. Data sources

Articles considered were identified through an extensive literature search in MEDLINE and PsycLIT in the period between 1980 and July 2002. The key words were neuropsychol* and relative* and schizophren*. An additional search was done with the key words neuropsychol* and sib* and schizophren*. Combinations of relative*, sib* and schizophren* were also made with cogniti* and neurocogniti*. The search produced over 260 unique studies. Titles and abstracts of the articles were examined for possible inclusion in our analysis. Additional articles were obtained from the reference lists of these articles and from a journal by journal search from September 2001 through July 2002 of journals that most frequently published articles on cognition in relatives of schizophrenic patients. This strategy was adopted to minimize the possibility of overlooking studies that may not yet have been included in computerized databases. The journals included the following: American Journal of Psychiatry, American Journal of Medical Genetics, Archives of General Psychiatry, Journal of Abnormal Psychology, Psychiatry Research, Schizophrenia Bulletin, and Schizophrenia Research.
2.2. Study selection

The identified studies had to meet the following inclusion criteria: First, each study had to report on one of the following cognitive constructs, which have most consistently been implicated in schizophrenia (Heinrichs and Zakzanis, 1998): verbal/nonverbal memory, psychomotor performance, attention, intelligence, spatial ability, executive functioning and language functioning.

Second, studies had to compare the performance of relatives; this could be offspring, parents and/or siblings, with the performance of healthy comparison subjects.

Third, studies had to be published in English-language international, peer reviewed journals. Finally, studies had to report sufficient data for the computation of a $d$-value. This implies that means and standard deviations, exact $p$-values, $t$-values, or exact $F$-values and relevant means had to be reported.

2.3. Data extraction

For each study Cohen’s $d$, the difference between the mean of the experimental group and the mean of the comparison group, divided by the pooled standard deviation (Shadish and Haddock, 1994; cf. Aleman et al., 1999) was calculated. When means and SDs are not given, $d$-values can be computed from exact $p$-values, $t$-values or $F$-values. Data extraction and calculation of effect sizes was performed independently by two authors (A.A., S.E.), who reached consensus in case of discrepancies. The effect sizes were corrected for upwardly biased estimation of the effect in small sample sizes using the procedure described by Hedges and Olkin (1985). After computing individual effect sizes for each study, meta-analytic methods were applied in order to obtain a combined effect size, weighted for study variance, which indicated the magnitude of the association across all studies (cf. Lipsey and Wilson, 2001). We also calculated a homogeneity statistic, $Q$, to test whether the studies can be taken to share a common population effect size. A significant $Q$-statistic indicates heterogeneity of the individual study effect sizes, which poses a limitation to a reliable interpretation of the results. A $t$-test was subsequently done on the null hypothesis that the effect is nil, i.e. a $d$-value of 0.00, with the associated $p$-value. All analyses were carried out in the random effects model, using Comprehensive Meta-analysis™ (BioStat, 1999).

Ten standard clinical cognitive tests were reported by an adequate number of studies. We report nine weighted effect sizes from the relevant variables of these 10 tests. For neurocognitive tests and variables, see Table 1. We included perseverative errors, perseverative responses and the number of categories completed as Wisconsin Card Sorting Test (WCST)

<table>
<thead>
<tr>
<th>Test (version CPT; CPT 1.9; CPT-IP; DS-CPT)a</th>
<th>Test domain</th>
<th>Recorded test variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLTb,c</td>
<td>Verbal memory</td>
<td>Immediate and delayed free recall: list A</td>
</tr>
<tr>
<td>RBMTc,d</td>
<td>Verbal memory</td>
<td>Immediate and delayed free recall score</td>
</tr>
<tr>
<td>Stroop</td>
<td>Selective attention/executive functioning</td>
<td>Time color–word task</td>
</tr>
<tr>
<td>TMT Ae</td>
<td>Visuomotor tracking</td>
<td>Time part A</td>
</tr>
<tr>
<td>TMT Bf</td>
<td>Visuomotor speed/executive functioning</td>
<td>Time part B or interference score: time part B–time part A</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>Language function/executive functioning</td>
<td>Number of responses</td>
</tr>
<tr>
<td>WAIS(-R)g</td>
<td>Attention/verbal memory span</td>
<td>Digit span forwards and digit span backwards</td>
</tr>
<tr>
<td>WCSTh</td>
<td>Executive functioning</td>
<td>Categories achieved; number of perseverative responses; number of perseverative errors</td>
</tr>
<tr>
<td>WMS(-R)i Logical Memory</td>
<td>Verbal memory</td>
<td>Immediate and delayed recall score: story A and story B</td>
</tr>
<tr>
<td>WMS(-R)j Visual Reproduction</td>
<td>Visual memory</td>
<td>Immediate and delayed recall score</td>
</tr>
</tbody>
</table>

a CPT: Continuous Performance Test.
b CVLT: California Verbal Learning Test.
c Analysed together as domain “verbal memory.”
d RBMT: Rivermead Behavioral Memory Test.
e TMT A: Trail Making Test—Part A.
f TMT B: Trail Making Test—Part B.
g WAIS(-R): Wechsler Adult Intelligence Scale (-Revised).
h WCST: Wisconsin Card Sorting Test.
i WMS(-R): Wechsler memory Scale (-Revised).
performance measures (cf. Nieuwenstein et al., 2001). Factor analyses have indicated that these variables load on one single factor that has been denoted “perseveration” and that this factor differentiates well between patients with schizophrenia and normal comparison subjects (Cuesta et al., 1995; Koren et al., 1998). When multiple WCST variables were reported in one study, we computed a pooled effect size. Thus, only one effect size was included for each study in the meta-analysis.

We included Wechsler Memory Scale-R logical memory, and California Verbal Learning Test (CVLT) and Rivermead Behavioral Learning Test (RBMT) free recall as verbal recall measures (see also Aleman et al., 1999; Heinrichs and Zakzanis, 1998). Again, when multiple variables were reported in one study, we computed a pooled effect size.

Krabbendam et al. (2001) reported data for domains of neurocognitive functioning (in which individual tests were pooled), however, data for individual tests could be extracted from Krabbendam et al. (2000).

3. Results

The articles included in the meta-analyses are listed in Table 2, while the results of the meta-analyses are given in Table 3. Thirty-seven studies, comprising 1639 relatives of schizophrenia patients and 1380...
comparison subjects were included in the analyses, with some studies, which contained results of multiple relevant tests, participating in more than one analysis. The largest difference between relatives and comparison subjects was for verbal recall (15 effect sizes), mean weighted $d=0.54$, 95% Confidence Interval $0.43-0.66$. This effect size is in the moderate range, according to the nomenclature of Cohen (1988). The $Q$ (12.3) statistic was not significant, which implies that the studies can be reliably interpreted as indicators of the same estimated population effect size. Fig. 1 plots the individual studies (effect size, confidence interval and $N$) that were included in this analysis. As can be seen in the figure, all $d$-values were larger than $d=0$.

The mean weighted effect size for Trailmaking Test B (TMT B) also fell within the moderate range ($d=0.51$, confidence interval $0.36-0.67$). Fig. 2 plots the individual studies (effect size, confidence interval and $N$) that were included in this analysis. As can be seen in the figure, most $d$-values were larger than $d=0$.

As can be seen in Table 3, performance differences on all other tests showed effect sizes in the small to moderate range, if their confidence intervals are also

<table>
<thead>
<tr>
<th>Test</th>
<th>$K$</th>
<th>$n$ control group</th>
<th>$n$ relative group</th>
<th>$d$</th>
<th>$t$</th>
<th>$p$</th>
<th>95% CI</th>
<th>$Q$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory</td>
<td>15</td>
<td>397</td>
<td>600</td>
<td>0.54</td>
<td>9.1</td>
<td>&lt; 0.0001</td>
<td>0.43–0.66</td>
<td>12.3</td>
</tr>
<tr>
<td>TMT B</td>
<td>12</td>
<td>608</td>
<td>816</td>
<td>0.51</td>
<td>6.5</td>
<td>&lt; 0.0001</td>
<td>0.36–0.67</td>
<td>12.9</td>
</tr>
<tr>
<td>TMT A</td>
<td>10</td>
<td>360</td>
<td>483</td>
<td>0.38</td>
<td>5.0</td>
<td>&lt; 0.0001</td>
<td>0.23–0.53</td>
<td>9.3</td>
</tr>
<tr>
<td>Digit Span</td>
<td>10</td>
<td>239</td>
<td>391</td>
<td>0.35</td>
<td>4.4</td>
<td>&lt; 0.0001</td>
<td>0.19–0.50</td>
<td>4.4</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>13</td>
<td>373</td>
<td>514</td>
<td>0.35</td>
<td>3.2</td>
<td>0.001</td>
<td>0.14–0.56</td>
<td>30.6**</td>
</tr>
<tr>
<td>CPT</td>
<td>11</td>
<td>406</td>
<td>545</td>
<td>0.33</td>
<td>2.7</td>
<td>0.006</td>
<td>0.09–0.57</td>
<td>27.6**</td>
</tr>
<tr>
<td>WMS visual reproduction</td>
<td>8</td>
<td>401</td>
<td>747</td>
<td>0.30</td>
<td>3.0</td>
<td>0.003</td>
<td>0.10–0.50</td>
<td>11.2</td>
</tr>
<tr>
<td>WCST</td>
<td>19</td>
<td>310</td>
<td>550</td>
<td>0.29</td>
<td>3.8</td>
<td>0.0001</td>
<td>0.14–0.43</td>
<td>33.2*</td>
</tr>
<tr>
<td>Stroop</td>
<td>8</td>
<td>798</td>
<td>891</td>
<td>0.28</td>
<td>2.5</td>
<td>0.01</td>
<td>0.06–0.50</td>
<td>11.8</td>
</tr>
</tbody>
</table>

$k=$ number of studies; $N=$ number of subjects; $d=$ mean weighted effect size; $Q=$ within-category homogeneity statistic.

**$p<0.01$.

*p < 0.05.

Fig. 1. Mean effect size ($d$-value) and confidence intervals for each study in the verbal memory meta-analysis. Magnitude of symbols depicting the individual effect sizes is proportional to the number of subjects included in the study.

Fig. 2. Mean effect size ($d$-value) and confidence intervals for each study in the Trail Making Test B meta-analysis. Magnitude of symbols depicting the individual effect sizes is proportional to the number of subjects included in the study.
taken into account. All measures showed significant differences between relatives and comparison subjects. Most $Q$-values were nonsignificant.

4. Discussion

We presented a meta-analysis of the published literature on cognitive performance of relatives of patients with schizophrenia. The results of the meta-analysis indicate that relatives of patients show less cognitive efficiency than healthy controls on several cognitive measures. The mean effect sizes can be considered in the moderate range. Differences between relatives and controls were largest on verbal recall ($d=0.54$) and trails B ($d=0.51$). Importantly, these variables are among those that are most impaired in schizophrenic patients themselves. In patients, deficits are especially prone in the domains of verbal memory, executive functioning and attention (e.g. Saykin et al., 1994; Bilder, 1996; Albus et al., 1997; Censits et al., 1997; Heinrichs and Zakzanis, 1998; Aleman et al., 1999; Sitskoorn et al., 2002), and measures/tests like verbal memory and TMT B discriminate highly between patients and controls (Heinrichs and Zakzanis, 1998; Aleman et al., 1999; Zakzanis et al., 1999). The differences between relatives and controls was smallest on the Stroop ($d=0.22$) which is in concordance with the relative small difference found between patients and controls on variables of this test (Zakzanis et al., 1999). The data support our hypotheses that cognitive deficits found in patients with schizophrenia are also found in their non-affected relatives.

In a narrative review of family studies by Kremen and colleagues conducted in 1994 (Kremen et al., 1994), it was concluded that the strongest impairment in relatives was in sustained attention (see also Cornblatt and Keilp, 1994), perceptual motor speed and concept formation. Our conclusion is somewhat in contrast with the conclusion from this narrative review. However, as Kremen and colleagues already mentioned, impairments in verbal memory and verbal fluency were also found, but these cognitive functions were less well studied at the time (respectively two and three studies then in contrast to 13 and 12 studies now). Furthermore, since 1994 several studies found no or a negative effect on certain versions of the test used mostly to measure sustained attention in schizophrenics and their relatives, i.e. the Continuous Performance Test (e.g. Egan et al., 2000; Laurent et al., 2000; Jones et al., 2001). Additional data collected over the last 8 years made it possible to refine the conclusions from the narrative review from Kremen and colleagues.

Our results show that certain cognitive deficits that are found in patients with schizophrenia are found in their non-affected family members as well. This is consistent with the idea that certain cognitive deficits are familial and possibly co-segregate with schizophrenia within families. However, our study did not investigate familial effects and co-inheritance directly. In fact, little is known about the inheritance of neurocognitive traits in healthy people and about co-inheritance of cognitive traits with schizophrenia.

One study by Shedlack et al. (1997) observed a familial effect for tests of reading ability, attention, some syntactic measures, and short-term memory. However, these were not the measures that distinguished patients with schizophrenia from controls. It can be concluded from these results that some cognitive traits are heritable but do not co-segregate with schizophrenia while others may distinguish patients with schizophrenia from controls but are not familial and directly related to the genetics of the disorder. In the quest for endophenotypes, further work is needed to determine whether certain cognitive traits are familial and whether there is co-inheritance of these traits with schizophrenia within families.

Our results have several additional implications. Firstly, it is clear from the comparison of our results and the results from meta-analyses on cognitive impairments in patients (e.g. Aleman et al., 1999; Zakzanis et al., 1999) that patients are more impaired than their relatives. In patients, large effect sizes on several cognitive measures have been found while in relatives we only found some moderate effect sizes. This suggests that a significant portion of the variance in cognitive performance in patients with schizophrenia is closely associated with variables that are associated to the illness itself (see also Egan et al., 2001).

Secondly, even though our quantitative review shows that relatives of schizophrenic patients show deficiencies on several neurocognitive measures when compared to controls, no single test adequately dis-
criminates relatives from control subjects, although there is variability in the magnitude of deficiency. The largest mean effect sizes that are also reported by adequate numbers of studies include verbal recall ($d = 0.54$) and TMT B ($d = 0.51$). These effects are associated with approximately 65% overlap between groups. This means that substantial numbers of relatives of patients with schizophrenia must function within a normal range with regard to specific neurocognitive measures. Neurocognitive deficiency can therefore not be considered a defining characteristic for each relative of a patient with schizophrenia. However, even though there is a considerable percentage of overlap between relatives and controls, the cognitive performance of first degree relatives of schizophrenic patients is more than half a standard deviation lower than that of healthy comparison subjects on some measures. In comparison, inspection of the results of a meta-analytic review of cognitive dysfunction in mild head trauma patients (Binder et al., 1997) shows that relatives of schizophrenic patients show more profound deficiencies on for example memory and attention than mild head trauma patients. In the mild head trauma study, measures of attention had the largest effect of all studied measures ($d = 0.22$) which is as high as the smallest difference between relatives of patients and controls in our meta-analysis. It can be concluded that the cognitive deficiencies in relatives of schizophrenic patients seem substantial greater than the deficiencies that occur after mild traumatic head injury.

It is possible that those relatives that exhibit cognitive deficiencies will develop schizophrenia later on. In other words, that cognitive deficiencies are predictive for later illness. It would be interesting to analyze studies including relatives who are above the age of risk and those including relatives still at risk, separately as the magnitude of deficiency might differ between these two groups. Unfortunately, it was not possible to divide the included studies in the meta-analysis clearly on basis of age of onset of the included relatives. However, a recent study (Appels et al., 2003) showed that parents of patients who were well above the age of risk, differed from control couples on some other cognitive constructs on which patients show a smaller but also significant difference compared to healthy controls. These results suggest that cognitive deficiencies are not solely predictive of later illness, but also exist in relatives that will never be affected.

Finally, cognitive deficits that are consistently found in patients and their relatives can provide us with hypotheses about the brain regions involved in schizophrenia. The results of our meta-analysis show that deficiencies in relatives of patients are especially pronounced in the domains of memory, executive functioning and attention. These cognitive functions are associated with frontal and temporal lobe dysfunction (e.g. Stuss, 1993; Naatanen, 1988; Goldberg and Seidman, 1991; Squire et al., 1992; Nestor et al., 1993; Ungerleider, 1995; Wheeler et al., 1995; Squire and Zola, 1996; Yener and Zafos, 1999). Our results are therefore indicative for fronto-temporal dysfunction in schizophrenia and consistent with studies that report dysfunction of frontal—temporal circuits in schizophrenia (e.g. McGuire and Frith, 1996; Weinberger et al., 1992; Weinberger, 1995a,b; Friston et al., 1996; Fletcher et al., 1998; Dolan et al., 1999; Laurent et al., 1999a). Additionally, they agree with the finding that disturbances in prefrontal and temporo-limbic systems and their interconnections are promising endophenotypes for schizophrenia and with the demonstrated familial aggregation of schizophrenia with deficits in neurocognitive tests sensitive to prefrontal and temporal damage (see Cannon et al., 2000; Myles-Worsley and Park, 2002; Seidman et al., 2002; Sitskoorn et al., 2000).

Our work must be interpreted in the context of its methodological limitations. As can be concluded from Table 2 most studies investigating cognitive functioning in relatives of patients focus on the domains of attention, memory and executive functioning. These are exactly those functions that are associated with frontal and temporal dysfunction. It is therefore not surprising that the largest deficiencies are found in these areas of functioning and that they are indicative for fronto-temporal involvement.

Functions studied less well bear potential but could not be included in the present meta-analysis due to lack of data. For example, previous research in patients (Zakzanis et al., 1999) and parents of patients (Appels et al., 2003) show that tests tapping
psycho-motor functioning like the Purdue Pegboard test might also be potential candidates for endophenotypic markers. Unfortunately, variables of psychomotor functioning were not reported by an adequate number of studies and could therefore not be evaluated.

It would be interesting to analyze studies with siblings and offspring separately, as their risk for developing schizophrenia is higher than in the parent group (approximately 10% vs. 4.4%) (Gottesman, 1991), and hence the genetic effect will be stronger in these groups. Unfortunately, the number of studies was too small to allow moderator analyses in order to investigate whether the degree of genetic loading would influence effect sizes.

Despite these limitations, our results suggest that cognitive deficiencies in relatives of schizophrenic patients parallel the deficits found in patients. This finding is consistent with the idea that certain cognitive deficiencies in relatives are caused by familial predisposition to schizophrenia and that these deficiencies might be putative endophenotypes for schizophrenia. However, our results do not address genetic causes directly. Further work is needed to determine whether certain cognitive traits are familial and whether there is co-inheritance of these traits with schizophrenia.

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