Neuropsychological impairment in deficit vs. non-deficit schizophrenia

Nicola G. Cascella a,*, S. Marc Testa a, Stephen M. Meyer a, Vani A. Rao a, Catherine M. Diaz-Asper a,c, Godfrey D. Pearlson a,d,e, David J. Schretlen a,b

a Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Meyer 144, Baltimore, MD 21287, United States
b Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Meyer 144, Baltimore, MD 21287, United States
c National Institute on Mental Health, National Institutes of Health, Bethesda, MD, United States
d Olin Neuropsychiatric Research Center, Hartford Hospital Institute of Living, Hartford, CT, United States
e Yale University School of Medicine, New Haven, CT, United States

Received 16 May 2007; received in revised form 20 September 2007; accepted 6 October 2007

Abstract

This study aimed to assess the severity and specificity of cognitive impairments that affect individuals with deficit versus non-deficit schizophrenia. We compared 26 patients with the deficit subtype of schizophrenia (SZ-D) and 79 with non-deficit schizophrenia (SZ-ND) to 316 healthy adults (NC). All study participants completed a battery with 19 individual cognitive measures. After adjusting their test performance for age, sex, race, education and estimated premorbid IQ, we derived regression-based T-scores for each measure and the six derived cognitive domains including attention, psychomotor speed, executive function, verbal fluency, visual memory, and verbal memory.

Multivariate analyses of variance revealed significant group effects for every individual measure and domain of cognitive functioning (all \( p < 0.001 \)). Post hoc comparisons revealed that patients with SZ-D performed significantly worse than NCs in every cognitive domain. They also produced lower scores than the SZ-ND group in every domain, but only the difference for verbal fluency reached statistical significance. The correlations of the effect sizes shown by the SZ-D and SZ-ND patients were of intermediate magnitude for the individual tests (\( r = 0.56, p < 0.01 \)) and higher, but not statistically significant for the cognitive domains (\( r = 0.79, p = 0.06 \)).

Patients with SZ-D demonstrate cognitive deficits that are both common and distinct from those shown by patients with SZ-ND. Their impairment of verbal fluency is consistent with the observation that poverty of speech is a clinically significant feature of patients with SZ-D.

© 2007 Elsevier Ltd. All rights reserved.

Keywords: Schizophrenia; Deficit syndrome; Cognitive testing; Neuropsychology

1. Introduction

The deficit syndrome of schizophrenia (SZ-D) has been proposed as an important biological subtype defined by severe primary negative symptoms that endure as trait-like features even during periods of clinical stability (Carpenter et al., 1988). By definition, primary negative symptoms are not attributable to secondary causes such as depression, medication side-effects, mental retardation or social deprivation. Patients with SZ-D differ from patients with the non-deficit form of schizophrenia (SZ-ND) in terms of risk factors (Messias et al., 2004), neurobiological correlates (Lahti et al., 2001; Quarantelli et al., 2002), treatment response (Kirkpatrick et al., 2001), and long-term clinical outcome (Tek et al., 2001). Patients with SZ-D also demonstrate cognitive deficits relative to healthy adults and,
possibly, to patients with SZ-ND (Wagman et al., 1987). While some investigators have found greater impairment of executive functions than other cognitive abilities (Bryson et al., 2001; Buchanan et al., 1994), others have not (Horan and Blanchard, 2003), and one group found greater impairment of focused attention than executive functions (Galderisi et al., 2002). However, it remains unclear whether patients with SZ-D suffer from cognitive deficits that are qualitatively distinct or simply more severe than patients with SZ-ND. Determining this could help clarify whether SZ-D represents a distinct syndrome or simply a more severe form of schizophrenia than SZ-ND.

The present study aimed to compare the nature and severity of cognitive deficits shown by adults with deficit and non-deficit forms of schizophrenia relative to those of healthy adults. Because the two schizophrenia subgroups differed demographically from the normal controls, we used multiple regressions to derive demographically-residualized T-scores for 19 cognitive test variables. As described earlier (Schretlen et al., 2007), each test variable was assigned to one of six cognitive domains that span the full range of abilities recommended for studies of schizophrenia (Nuechterlein et al., 2004). These demographically - residualized test and domain scores were used to compare the neurocognitive profiles produced by patients with SZ-D or SZ-ND. If the two groups suffer from different cognitive deficits, then the effect sizes of their cognitive deficits ought to be uncorrelated. Such a finding would indicate that SZ-D and SZ-ND represent neuropsychologically distinct subtypes of schizophrenia. If their cognitive deficits differ in severity but are qualitatively similar, then the correlation of their effect sizes ought to be positive and significant. This would support the alternative view that SZ-D and SZ-ND patients differ more in severity than nature. Finally, if the two groups suffer from both common and distinct cognitive deficits, then their effect sizes should be characterized by correlations of intermediate magnitude.

2. Method

2.1. Participants

One-hundred-five adults with schizophrenia, diagnosed according to criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV; American Psychiatric Association, 1994) participated in the study. Of these, 38 were recruited for a study of structural neuroimaging and cognition in psychosis (the Psychosis study), 21 were recruited for an investigation of apathy in schizophrenia and traumatic brain injury (the Apathy study), and 46 were recruited for a study on the relation between viral markers and brain structural features in schizophrenia (the Stanley study). Most participants in all the studies were recruited from the outpatient clinics of Sheppard and Enoch Pratt Health System and via newspaper and radio announcements. In addition, 316 healthy adult participants in a community study of normal aging, brain imaging, and cognition (the ABC study) contributed data for this analysis. Participants in the ABC study were recruited from the Baltimore metropolitan region primarily via random digit dialing, although a few were recruited via telephone calls to randomly selected listings from the Baltimore metropolitan area residential telephone directory. Potential subjects were excluded from the ABC study only if they were unable to give informed consent or complete a brain magnetic resonance imaging (MRI) scan. However, ABC study participants who reported any history of dementia, stroke, transient ischemic attack, traumatic brain injury with >1 h loss of consciousness, Parkinson’s disease, multiple sclerosis, severe heart disease, complicated diabetes, bipolar disorder, schizophrenia, current major depression, current alcohol/drug abuse or dependence were excluded from the present analysis. Further, the cohort of healthy controls was chosen to match the combined patient groups in terms of age, sex, race, and estimated premorbid IQ. All four studies (Psychosis, Apathy, Stanley, and ABC) were approved by the Johns Hopkins Medicine Institutional Review Board and all participants provided written informed consent. All of the participants reported in this paper also contributed data to another analysis in which we compared the cognitive performances of patients with schizophrenia to those with bipolar disorder (Schretlen et al., 2007).

2.2. Procedures

2.2.1. Diagnostic and clinical assessments

Diagnostic and clinical assessments of patients recruited for the Psychosis study included the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994) and Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS; Andreasen and Olsen, 1982), which were administered by a study psychiatrist or psychologist. Patients recruited for the Apathy study and the Stanley study underwent a Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-IV: First et al., 1997) rather than the DIGS, but they also received the SANS, SAPS, and SUMD. Prior to making a diagnosis, the study clinician also reviewed any available medical and psychiatric records. The designation of deficit syndrome schizophrenia was based on the Schedule for the Deficit Syndrome (SDS), a semi-structured interview with known reliability (Kirkpatrick et al., 1989) by one of two study psychiatrists (N.G.C. or V.R.). The inter-rater reliability, similar to that of Kirkpatrick et al. (1989), for the SDS (κ = 0.73) was established, for both raters, after a training at the Maryland Psychiatric Research Center. Additional information was obtained from knowledgeable informants.

In order to minimize the effects of illness acuity on both clinician ratings and cognitive test performance, most patients were recruited and tested as outpatients. However,
six patients were tested shortly before discharge from the hospital, after their attending physicians had determined that they were stable.

Individuals recruited for the ABC study of normal aging also underwent diagnostic and clinical assessments by a study psychiatrist or psychologist. These included the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) interview (Wing et al., 1996), review of medical history, brief physical and neurological examinations, and laboratory blood studies. Finally, all patients and control subjects underwent anatomic brain magnetic resonance imaging. Analyses of the resulting data currently are underway and will be reported later.

2.2.2. Neuropsychological assessment

Neuropsychological assessment of the study participants included seven tests that were used in all three studies. By design, these tests assessed a broad range of cognitive abilities, required about two hours to administer, and yielded 19 individual measures. Following Heinrichs and Zakzanis (1998), each measure was assigned to one of six cognitive domains, as described previously (Schretlen et al., 2007). The neuropsychological tests, specific measures, and internal consistency (coefficients alpha) for each cognitive domain are shown in Table 1. All domains showed good to excellent internal consistency.

2.2.3. Data analyses

Data analyses began with the derivation of demographically-adjusted T-scores for all study participants. The general procedure for these adjustments has been described elsewhere (Heaton et al., 2004; Ivnik et al., 1992). Briefly, we first converted the NC group’s raw scores on all 19 cognitive measures to scaled scores (M = 10; SD = 3) using the cumulative frequency distribution of each measure. We then regressed these scaled scores on age, age-squared, sex, race (white vs. black), years of education, and estimated premorbid IQ based on the revised National Adult Reading Test (NART-R; Blair and Spreen, 1989). For these analyses we entered the predictor variables en bloc, saved the standardized residuals, and converted the latter to T-scores (M = 50; SD = 10). We next converted the SZ-D and SZ-ND patients’ raw test scores to scaled scores based on the NC distributions, and applied the multiple regression equations derived from the NC data to compute demographically-predicted scores for the patients. These predicted scores were subtracted from each patient’s actual scaled scores, and the differences were divided by the standard deviation of the NC group’s residuals for each measure. Finally, the resulting values were converted to T-scores for direct comparison with those produced by healthy controls. An advantage of these procedures is that they allow for the direct comparison of cognitive test performances produced by patient groups that differ from each other and from the healthy controls on any demographic characteristic. The reason is that the demographically-adjusted T-score distribution approximates a mean of 50 and standard deviation of 10 for every cognitive test in any NC subgroup selected on the basis of age, sex, race, years of education, or estimated premorbid IQ.¹ One concern with this approach is that “adjusting” test scores for years of education and estimated premorbid IQ might inadvertently minimize meaningful group differences in cognitive performance by over-correcting for these characteristics (Meehl, 1970). However, in a previous study of cognitive functioning, group differences among patients with schizophrenia or bipolar disorder and healthy controls using demographically-adjusted scores were as large or larger than reported by investigators using traditional matching techniques, covariate analyses, or no matching (Heinrichs and Zakzanis, 1998; Quraishi and Frangou, 2002).

Table 1

Neuropsychological test variables together with the cognitive domains they comprise and Cronbach’s alpha for each domain

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Neuropsychological tests and measures used</th>
<th>Cronbach’s alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor speed</td>
<td>Grooved Pegboard (GPT; dom. and non-dom. hands) (36); Trail Making (TMT; parts A and B, seconds) (37)</td>
<td>.84</td>
</tr>
<tr>
<td>Attention</td>
<td>Brief Test of Attention (BTA; total correct) (38); Conners’ Continuous Performance Test (CPT; hit RT, RT standard error, and d’) (39)</td>
<td>.69</td>
</tr>
<tr>
<td>Executive</td>
<td>Nelson Wisconsin Card Sorting Test (nWCST; categories completed, perseverative errors) (40)</td>
<td>.85</td>
</tr>
<tr>
<td>Ideational fluency</td>
<td>Letter word fluency (letters S and P); category word fluency (animals, supermarket items); design fluency</td>
<td>.71</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>Hopkins Verbal Learning Test-Revised (HVLT-R; words recalled on trials 1–3; delayed recall, recognition discrimination) (41)</td>
<td>.82</td>
</tr>
<tr>
<td>Visual memory</td>
<td>Brief Visuospatial Memory Test-Revised (BVMT-R; designs recalled on trials 1–3, delayed recall, recognition discrimination) (42)</td>
<td>.81</td>
</tr>
</tbody>
</table>

¹ To verify this, we divided the NC sample into five pairs of subgroups based on median splits for age, education, and estimated premorbid IQ, and by sex (male vs. female) and race (white vs. black). We then compared the demographically-adjusted T-scores produced by each subgroup. All 190 means (19 tests × 5 demographic characteristics × 2 subgroups for each characteristic) ranged from 48.0 to 50.7, and none of the 95 Student t-tests reached statistical significance (p < 0.05). Indeed, all but one of the obtained p values exceeded 0.12.

Please cite this article in press as: Cascella NG et al., Neuropsychological impairment in deficit vs. non-deficit schizophrenia, Journal of Psychiatric Research (2007), doi:10.1016/j.jpsychires.2007.10.002
prised each, served as the dependent variables. Planned contrasts compared each patient group to the healthy controls, and post hoc comparisons with Scheffe corrections were used to compare differences between the two patient groups on the 19 individual tests and six cognitive domains. Finally, in order to compare the patterns of cognitive deficits shown by SZ patients, we conducted two analyses. The first of these was a profile analysis (Stevens, 2002) in which we compared the mean cognitive domain demographically-residualized T-scores produced by the two patient groups. For the second analysis we computed Cohen’s d effect sizes (Cohen, 1988) of the differences between each patient group’s mean scores (across cognitive domains and individual tests) compared to healthy controls, and correlated these in order to assess the similarity of their cognitive profiles.

3. Results

As shown in Table 2, MANOVA and chi-square analysis revealed that the three groups differed significantly in age, years of education and NART-R estimated premorbid IQ. The three groups also differed significantly in sex ($\chi^2(1) = 20.0; p = 0.0001$), and race ($\chi^2(2) = 58.1; p = 0.0001$). Based on planned comparisons, both patient groups were significantly younger than healthy controls, completed fewer years of education and produced lower estimates of premorbid IQ. Scheffe-adjusted post hoc comparisons revealed that SZ-D and SZ-ND did not differ in age, education, or NART-R estimated premorbid IQ. Also as shown in Table 2, the patients with SZ-D and SZ-ND did not differ significantly in mean age at illness onset or number of psychiatric hospital admissions. Those with SZ-ND were ill longer than those with SZ-D at the time of study. As expected, SZ-D patients were rated as showing more severe negative symptoms (SANS) than SZ-ND patients. Conversely, the SZ-ND patients were rated as showing more severe positive symptoms (SAPS) than those with SZ-D. Finally, more SZ-ND than SZ-D patients was being treated with antidepressant medication.

Multivariate analyses of variance revealed significant overall differences among the three groups for the demographically-adjusted individual test (Hotelling’s trace = 1.14; $F_{(38,798)} = 12.0; p < 0.0001$; partial $\eta^2 = 0.363$) and cognitive domain (Hotelling’s trace = 0.94; $F_{(12,824)} = 32.2; p < 0.0001$; partial $\eta^2 = 0.319$) scores. As shown in Table 3, planned contrasts confirmed that the SZ groups performed significantly ($p < 0.0001$) worse than NCs on every cognitive measure and in every cognitive domain. Scheffe-adjusted post hoc comparisons showed that SZ-D patients performed significantly ($p < 0.05$) worse than SZ-ND patients on only one measure of semantic word fluency (Category Fluency) and one measure of visual learning (BVMT-R Learning). They also showed a trend ($p = 0.058$) toward worse performance on a measure of phonemic word fluency (Letter Fluency). Consistent with this, patients with SZ-D performed worse than those with SZ-ND in the domain of ideational fluency ($F_{(1,104)} = 6.94; p < 0.01$), but the two groups showed no significant differences on any other individual test or cognitive domain.

We computed Cohen’s (1988) $d$ effect size estimates of the performance difference between each patient group and the healthy controls for all 19 cognitive test variables and the six domain scores. This involved subtracting the mean score for each measure/domain from the NC group’s mean score for the corresponding measure/domain, and dividing the difference by the pooled standard deviations (Rosnow and Rosenthal, 1996) for each patient group. For SZ-D patients, the effect sizes ranged from $d = 0.83$ to 1.63 across the 19 individual measures and from 1.25

### Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Deficit SZ (n = 26)</th>
<th>Non-deficit SZ (n = 79)</th>
<th>NC (n = 316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.1 ± 12.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41.5 ± 10.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54.4 ± 18.6&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sex (M:F%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>77:23&lt;sup&gt;a&lt;/sup&gt;</td>
<td>66:34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44:56&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Race (W:B:O %)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>27:62:11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>43:53:4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80:18:2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.7 ± 2.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.1 ± 2.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14.3 ± 3.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Est. premorbid IQ</td>
<td>93.2 ± 7.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>97.3 ± 10.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>105.2 ± 10.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age at onset</td>
<td>22.3 ± 7.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23.0 ± 7.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td># Hospitalizations</td>
<td>4.7 ± 8.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.3 ± 4.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>11.9 ± 8.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19.1 ± 10.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>SANS (sum)</td>
<td>16.3 ± 3.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.2 ± 3.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>SAPS (sum)</td>
<td>3.3 ± 3.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.2 ± 3.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Typical neuroleptics (%)</td>
<td>37.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Atypical neuroleptics (%)</td>
<td>75.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>74.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Any antidepressant (%)</td>
<td>8.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Lithium (%)</td>
<td>0.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Any anticonvulsant (%)</td>
<td>4.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> For sex, M = male, F = female.

<sup>b</sup> For race, W = white, B = black, O = “other.”

<sup>a,b,c</sup> Subscripts denote statistically significant ($p < .05$) group differences (see text for explanation). SZ = schizophrenia; NC = normal control. Estimated premorbid IQ based on the NART-R (Blair and Spreen, 1989) (43).

Please cite this article in press as: Cascella NG et al., Neuropsychological impairment in deficit vs. non-deficit schizophrenia, Journal of Psychiatric Research (2007), doi:10.1016/j.jpsychires.2007.10.002
Psychomotor speed  
50.0 ± 7.5a  35.2 ± 7.9b  36.9 ± 8.4b

See Table 1 for descriptions of neuropsychological test measures that comprised each cognitive domain. Post hoc comparisons with Scheffe correction were used to evaluate pairwise group differences (denoted by superscripts).

Table 1. ES pooled root mean square by domain.

- PM Speed = psychomotor speed; Atten = divided and sustained attention; Executive Function = card sorting; Fluency = word and design fluency; Verbal Memory = verbal learning/memory; Visual Memory = visual learning/memory.

The Pearson r of the effect sizes produced by each group on the 19 individual test scores was 0.56 (p < 0.01). The correlation of the two groups’ cognitive domain effect sizes was 0.79 (p = 0.06). The qualitative similarity of demographically-adjusted cognitive domain scores produced by SZ-D and SZ-ND patients can be seen in Fig. 1.
4. Discussion

In this study, patients with the deficit and non-deficit subtypes of schizophrenia showed basically similar patterns of neuropsychological functioning with subtle differences in both the nature and severity of their cognitive deficits. In fact, the most notable exception was that patients with the deficit form of schizophrenia showed more impoverished ideational fluency than those without. This was most apparent on a test of semantic word fluency, but it also was seen on a test of letter word fluency.

A “qualitative” and not a quantitative difference between deficit and non-deficit patients was proposed by an early study (Wagman et al., 1987) using a principal component analysis to address putative differences on neuropsychological performance between the two groups. The authors found that deficit patients differed on what they called a “general performance factor”, a mixture of poor performance on the Halstead-Reitan Category test and the Tactual Performance task. Nonetheless, in that study no differences between deficit and non-deficit patients were found when the data were analyzed with univariate t tests possibly because of lack of power. Subsequent studies (Buchanan et al., 1994; Putnam and Harvey, 2000) also found “qualitative” differences in the abnormal neuropsychological functioning of deficit patients compared to non-deficit patients with schizophrenia.

We have re-analyzed data from Buchanan et al. (1994) by computing the mean of z-transformed scores for each of the tests the authors used in their study and rank ordering the mean effects sizes. These results are similar to ours in that the two groups share a similar pattern of neuropsychological impairment with no qualitative differences. Indeed, a recent study (Cohen et al., 2007) failed to confirm earlier findings (Buchanan et al., 1994) of a selective impairment of cognitive functions subserved by frontoparietal circuits in deficit schizophrenia, confirming the findings of a meta-analysis reported in the same article. These investigators suggested that defining a unique cognitive profile in deficit schizophrenia will require a more sophisticated and rigorous examination of neuropsychological function in the deficit syndrome. A similar view was expressed in the “Consensus Statement on Negative Symptoms” issued by the NIMH-MATRICS study group (Kirkpatrick et al., 2006). In the present study, we failed to find a neuropsychological signature of the deficit syndrome despite comparing cognitive functioning across different domains using measures that quantify test performance in a common metric that controlled simultaneously for multiple demographic characteristics and premorbid IQ. The failure to find a neuropsychological signature of SZ-D does not rule out a categorical distinction between SZ-D and SZ-ND because various test categories are correlated and may relate to an underlying structure (Dickinson et al., 2004). In this case we could have distinctly different causes resulting in similar profiles of impairment. A severity difference, like our data suggest, between SZ-D and SZ-ND would mean a severity difference in cognition, not that the two groups are “necessarily” on a severity continuum of the same disease. This paradigm would be similar to considering various dementias as the same disease because of similarities in their cognitive profile when in fact various dementias are related to different etiological risk factors and pathologic attribute that makes them into separate category of diseases. Indeed, there is evidence, as already stated in our introduction to this report, from the study of variables other than cognitive performance, of categorical differences between SZ-D and SZ-ND (Kirkpatrick et al., 2001).

Our results differ from those of Buchanan et al. (1994) as far as the verbal fluency is concerned but confirm the data by Brazo et al. (2002) who found deficit patients to be less fluent than their non-deficit controls.

The literature on verbal fluency and negative symptoms of schizophrenia, with one single exception (Morrison-Stewart et al., 1992), is overall consistent with the notion that verbal fluency, though not in a unique fashion, is associated with negative symptoms of schizophrenia. Stolar et al. (1994) found that alogia but not flat affect were associated with poor performance on verbal fluency test. Breier et al. (1991) in their longitudinal study on schizophrenia found that results of neuropsychological tests of frontal cortical function, including verbal fluency, were significantly related to outcome negative symptoms and social functioning but not to positive symptoms. Liddle and Morris (1991) reported that psychomotor poverty correlated with poor performance on verbal fluency test.

In agreement with previous studies (Bryson et al., 2001; Buchanan et al., 1994), our data did not support a relationship between deficit syndrome and WCST performance.

The results may indicate that verbal fluency and not WCST performance is more strongly related to the presence of those frontal lesions that are thought to underlie the pathophysiology of the deficit subtype. Recent literature seems indeed to suggest that phonemic fluency is more strongly and specifically related to the presence of frontal lesions than the WCST scores (Henry and Crawford, 2004). Brain imaging studies using functional magnetic resonance imaging (fMRI) have significantly associated the activation of the inferior frontal gyrus to verbal fluency tasks (Costafreda et al., 2006). Our findings confirm the role played by frontal brain structures in mediating the negative symptoms of schizophrenia.

There are several methodological issues that require comment. First, the group difference in verbal fluency and lack of group differences in other domains could reflect differential sensitivity of the tests used rather than true differences in cognitive ability. Test sensitivity depends on both task difficulty (patients and controls might perform equally on an easy test, but not on a more difficult test) and reliability (less reliable tests yield “noisier” results that can obscure group differences). However, if our results were due to differences in test sensitivity, then we would not expect patients to perform most poorly on tests of...
motor speed because these are the “easiest” tests in the battery. In addition, as shown in Fig. 1, verbal fluency showed the second largest effect size for patients with SZ-D and the second smallest effect size for patients with SZ-ND. It is difficult to reconcile this finding with the idea that verbal fluency distinguished the two groups because it is either easier or more difficult than other tests included in the battery.

Second, although deficit and non-deficit patients were similar on multiple clinical and demographic variables, the non deficit patients had a significantly higher level of positive symptoms at the time of neuropsychological testing than the deficit patients. Although it is unlikely that differences in the level of psychotic symptoms underlie the deficit–non-deficit differences on neuropsychological testing, we entered the SAPS global score for hallucinations and delusions as a covariate and the results did not change ($F_{2,199} = 6.99; p < 0.01$) for verbal fluency. Third, the non-deficit patients were more chronically ill than the deficit patients at the time of the assessment. We also entered duration of illness as a covariate without any change on the differences of neuropsychological testing between the two groups of patients. Finally, the premorbid IQ, as assessed by NART-R, was lower in the deficit group though the value did not reach statistical significance. Previous studies have found similar results (Bryson et al., 2001; Buchanan et al., 1994). Buchanan et al. argued that differences in intelligence/general abilities between deficit and non-deficit groups may not represent just a “nuisance” to control for but aspects of a more complex relationship between intelligence and the deficit syndrome. We elected to use the premorbid IQ as a covariate in the data analysis because of the uncertainty that still surrounds this issue.

A note of interest is the finding that only 8% of the deficit patients as compared to 28% of the non-deficit group were on antidepressant medications at the time of testing. The finding seems to indicate that deficit patients are less prone to develop clinical depression as previously suggested (Kirkpatrick et al., 1994).

Several possible explanatory models of the relationship between negative symptoms and cognitive impairment in schizophrenia have been proposed (Harvey et al., 2006). Altogether, the results of this study indicate that patients with primary, enduring negative symptoms are similar to non-deficit patients in their qualitative performance on cognitive tests but exhibit impoverished verbal fluency that is consistent with the poverty of speech observed clinically in patients with SZ-D. The results could be construed as consistent with a model in which cognitive deficits and negative symptoms have separable but related etiologies as described by Harvey et al. (2006). Alternatively, the obtained results could also be consistent with a model in which cognitive deficits and negative symptoms share correlations with distal features but are etiologically distinct (Harvey et al., 2006). Because the present results do not clearly favor one model over the other, further research is needed.

Conflict of interest

Nicola G. Cascella has received honoraria from Pfizer, Lilly, Bristol-Meyers, Astra-Zeneca for his speaker activity. David J. Schretlen receives royalties for the Brief Test of Attention. All other authors declare that they have no conflicts of interest.

Contributors

Nicola G. Cascella, Vani Rao, David J Schretlen and Godfrey Pearlson designed the study and wrote the protocol.

David J. Schretlen and Marc Testa undertook statistical analysis. Catherine Diaz-Asper and Stephen Meyer administered the testing. Nicola G. Cascella wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Role of funding sources

Funding for this study was provided by NARSAD Young Investigator Award to NGC, NARSAD award to DJS, Stanley Foundation to NGC and NIH (MH60504 and MH43775) to GDP and DJS.

NARSAD, NIMH, and Stanley Foundation had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References


Please cite this article in press as: Cascella NG et al., Neuropsychological impairment in deficit vs. non-deficit schizophrenia, Journal of Psychiatric Research (2007), doi:10.1016/j.jpsychires.2007.10.002