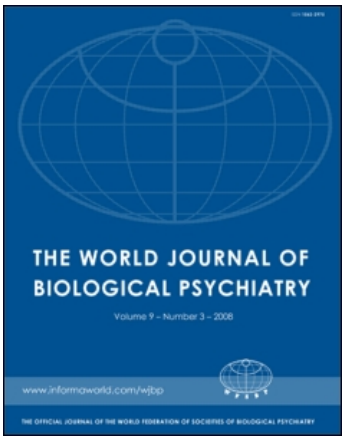

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ORIGINAL INVESTIGATION

Cognitive impairment of executive function as a core symptom of schizophrenia

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Abstract
Cognitive dysfunction is a common finding in schizophrenia. Nevertheless the specific pattern of neuropsychological impairment in schizophrenia compared to other severe mental illnesses has not been intensively studied. Twenty-four patients with schizophrenia belonging to different stages of the disease (11 first-episode patients, 13 patients with multiple episodes), 18 patients with bipolar disorder and 23 healthy control subjects underwent standardized neuropsychological assessment. Statistical analysis of covariance (ANCOVA) demonstrated that, compared to control subjects, patients with schizophrenia performed significantly worse in the trail-making test ($P=0.012$), verbal fluency (category letter, $P=0.004$), verbal learning/memory ($P=0.005$), and the Wisconsin Card Sorting Test (WCST) ($P=0.004$ for administered trials; $P=0.025$ for perseverative responses, T value) indicating significant deficits in attention and psychomotor performance, and in particular in verbal working memory and cognitive flexibility for schizophrenic patients. A significant difference between schizophrenic and bipolar patients was found only in the WCST. Schizophrenic patients made significantly more perseverative responses ($P=0.002$, ANCOVA), indicating a more pronounced and specific deficit in cognitive flexibility and frontally based executive function. In conclusion, these results may suggest a cognitive endophenotype in schizophrenia and underline the role of the prefrontal cortex in schizophrenic pathophysiology.

Key words: *Schizophrenia, bipolar disorder, cognitive dysfunction, endophenotype, first-episode psychosis*

Introduction

Schizophrenia is a complex illness with an estimated lifetime morbidity risk of 1% (Goldner et al. 2002). People suffering from schizophrenia experience abnormalities in many different kinds of mental activities, suggesting that more than one distinct brain region may be involved in pathophysiology. Cognitive dysfunction in schizophrenia has been documented in numerous studies in particular (e.g., Heinrich and Zakzanis 1998). Some studies have found rather widespread cognitive dysfunction (e.g., Bozikas et al. 2006), whereas others have provided evidence for more selective cognitive dysfunction (Saykin et al. 1991; Saykin et al. 1994). Cognitive domains especially of interest in schizophrenia are attention, memory, and executive functions. These domains are subserved by neural networks linking frontal and temporal-limbic regions of the brain (Aggleton and Brown 1999; Hopfinger et al. 2000; Gaffan, 2005), thus, the pattern of cognitive dysfunction specifically points to fronto-temporal networks being primarily affected (Hoff and Kremen 2002). In agreement with patterns of neuropsychological dysfunction, changes of brain morphology were observed particularly in these areas by volumetric magnetic resonance imaging (MRI) (e.g., Shenton et al. 2001; Wright et al. 2000). Brain energy metabolism has also been shown to be differently effected in gray and white matter of the fronto-temporal-striatal region in schizophrenic patients (Jensen et al. 2006).

Impairments in neuropsychological function have been demonstrated in patients with schizophrenia already at first presentation and even in their unaffected relatives (e.g., Heinrichs and Zakzanis 1998). Cognitive impairment is also found in patients with bipolar disorder (e.g., Quraishi and Frangou 2002). A study comparing schizophrenia

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patients with bipolar patients and controls found an impairment on seven out of eight cognitive domains (verbal, visual-spatial, abstraction-executive, verbal declarative memory, executive-motor, perceptual-motor, mental control, and sustained attention/vigilance) in schizophrenic patients, whereas bipolar patients were impaired on measures of verbal declarative memory. The pattern of deficits was similar for bipolar and schizophrenia patients, but schizophrenia patients were more significantly impaired than bipolar patients on abstraction, perceptual-motor, executive-motor, and vigilance measures (Seidman et al. 2002). A recent study compared neuropsychological disturbances in schizophrenia with bipolar patients, unaffected relatives of both diagnostic groups, and control participants (McIntosh et al. 2005). Current, verbal, and premorbid IQ were reduced in patients with schizophrenia and their close relatives, memory was impaired in all patient and relative groups, and psychomotor performance and performance IQ were impaired in both patient groups. In conclusion, there was no specific impairment in bipolar disorder, but a pattern of cognitive dysfunction related to genetic liability for schizophrenia.

Given phenomenological similarities between schizophrenia and frontal dysfunction syndromes, executive functions have been suggested to be especially affected in schizophrenics. This assumption has been corroborated by behavioral (e.g., Chan et al. 2006), functional imaging (e.g., Holmes et al. 2005) and psychophysiological (e.g., Weisbrod et al. 2000) research. Executive functions encompass a number of abilities, including but not limited to the ability to initiate, plan, and sequence behaviors, the ability to abstract a principle or problem-solving strategy, and the ability to be cognitively flexible (i.e. switch cognitive sets). Although executive functions are largely subserved by the frontal cortex, they are also related to other parts of the brain that have strong connections to the frontal cortex such as the temporal-limbic complex (Gruber and Goschke 2004). Schizophrenia patients had been noted to have a loss of abstract attitude and to exhibit concrete thinking deficits as early as the 1950s. A recent meta-analysis of 71 studies demonstrated an overall effect size of -1.45 for schizophrenia patients relative to controls on measures of executive functioning. This is a substantial effect, suggesting that patients with schizophrenia are significantly impaired on these measures as compared with other psychiatric patients (effect size -0.40).

With regard to the cited literature there is some aspect of specificity in the degree and type of cognitive dysfunction of schizophrenia patients. To explore the specificity issue further, we administered a battery of neuropsychological tests to patients with schizophrenia, bipolar disorder, and healthy controls. Tests were organized into cognitive domains, assessing a wide spectrum of cognitive functions, including those reported in the literature to be sensitive to schizophrenia. That is, the potential functional consequences of the described disturbed communication between frontotemporal and frontothalamic structures – deficits in verbal fluency, attention, memory, and executive functioning in particular – were assessed. These deficits may be more related to structural and functional neuroimaging findings than psychopathological symptoms, which may result in part from these cognitive disturbances.

Method

Patients and control subjects

The present analysis includes the data of 65 persons recruited from the Department of Psychiatry and Psychotherapy, Saarland University, between 2003 and 2005. Diagnostically, the sample consisted of 24 patients with schizophrenia (ICD-10: F20, 11 patients with first-episode schizophrenia, 13 schizophrenic patients with multiple episodes), 18 euthymic patients with bipolar disorder (ICD-10: F31) and 23 healthy control subjects. All schizophrenic and bipolar patients were treated with psychotropic drugs. Subjects suffering from dementia, neurological illnesses, severe brain injuries, or brain tumours at the time of examination were excluded from the sample. Demographic statistics by diagnostic group are given in Table I.

This study, which is in accordance with the Declaration of Helsinki, was approved by the local ethic committee of the Saarland. After a complete description of the study, written informed consent was obtained from each participating subject.

Diagnostic procedures

The following standardized examinations were performed on each subject: a detailed biographic interview and a consensus diagnosis based on SCID I and II interviews (Wittchen et al. 1991) of two independent psychiatrists. The status of healthy controls was confirmed using SCID I and II.

Neuropsychological assessment

For neuropsychological assessment, we used tests in paper-pencil form and computerized versions (e.g., the Wiener Test System, WTS, and the CANTAB, Cambridge Neuropsychological Test Automated Battery). Premorbid intellectual function was

Table I. Sociodemographic characteristics in diagnostic groups.

	SZ-FE ($N=11$)	SZ-Chron ($N=13$)	Bipolar ($N=18$)	Controls ($N=23$)	F	P
Age in years, mean (SD)	29.8 (7.4)	34.8 (10.4)	42.1 (12.2)	30.13 (8.7)	7.91[a]	0.001
Gender; male/female (N)	8/3	10/3	7/11	10/13	5.90[b]	0.052
Education in years, $<9/10$–$12/13/>13$ (N)	0/6/5/0	2/7/4/0	2/10/3/3	1/7/11/4	9.45 [b]	0.15

N, number of subjects; SZ, schizophrenia; FE, first-episode; Chron, chronic disease; Bipolar, patients with bipolar disorder; *P*, probability; SD, standard deviation; *F*, F statistic.
[a]One-way analysis of variance.
[b]χ^2-test.

estimated by a test of verbal intelligence ('Wortschatztest', WST, Schmidt and Metzler 1992). For detecting deficits in attention, speed processing, and psychomotor performance, reaction times were measured using simple and associative perception tasks ('Reaktionstests', RT1 – single stimulus and RT3 – compound stimulus, subtests of the Wiener Test System, WTS, Schufried/Potsdam), and a divided attention task ('Geteilte Aufmerksamkeit', DA, a subtest of the test battery 'Aufmerksamkeitsprüfung', TAP, Zimmermann, Fimm/PSYTEST). For assessment of psychomotor performance and speed, we used the 'Zahlenverbindungstest' (ZVT; Oswald and Roth 1987), a test similar to the trail-making test (TMT, part A). Attention and working memory were appraised with a digit span task ('Zahlennachsprechen', a subtest of the HAWIE, Tewes 1991) and the working memory test 'Arbeitsgedächtnis' (subtest of the TAP), and visuospatial working memory was measured with the Corsi Block-Tapping Test (of WTS battery) and the test of Spatial Recognition Memory (CANTAB). Additionally, a verbal learning and memory test similar to the Auditory or California Verbal Learning Test ('Verbaler Lern- und Merkfähigkeitstest' VLMT; Helmstaedter et al. 2001) was administered, measuring the course of encoding capacity together with both direct and delayed recall and episodic recognition abilities. Nonverbal learning capacity was examined by the 'Nonverbaler Lerntest' (NVLT, subtest of WTS) (Sturm and Willmes 1999). Verbal fluency (VF) was measured by the 'Regensburger Wortflüssigkeits-Test' (RWT; Aschenbrenner et al. 2000). For the detection of deficits in concept formation, cognitive flexibility, and executive functions, the Wisconsin Card Sorting Test (WCST; Heaton et al. 1993), and the Tower of London test (TOL; Shallice 1982) were used. Additionally, a test tapping the controlled integration of information from different sensory channels, that is, intermodal comparison (IC, 'Intermodaler Vergleich', subtest of the Attention Test Battery, TAP) was conducted. Interference was tested by the 'Stroop' task (subtest of the WTS), including the word (Stroop-LI) and color (Stroop-BI) interference conditions.

Statistics

In order to reduce the large number of variables available, from each test a small number of variables was selected for further inspection, based on the literature, theoretical considerations and exploratory discriminant function analysis. This resulted in the selection of 20 variables potentially discriminating between groups. Statistical analyses were then performed with SPSS 10.0 for Windows (Norusis 2002). Domains of neuropsychological function (e.g., executive function and psychomotor performance) were compared between groups using analyses of covariance (ANCOVAs). Thus, analyses were controlled for age, gender, and education, including these potentially intervening variables as covariates. If the assumption of normal distribution was violated as indexed by Kolmogorov–Smirnov testing, non-parametric Kruskal–Wallis tests were performed. In the following, after reviewing demographic group differences, the results of the three group analysis (schizophrenic patients, bipolar patients, healthy control subjects) will be reported, followed by post-hoc group comparisons, applying the Bonferroni correction where applicable.

Results

For demographic variables, there was a significant difference in age between groups: patients with bipolar disorder were older than schizophrenic patients and control subjects (see Table I). In addition, the portion of males was not significantly higher in the group of schizophrenic patients, and control subjects tended to have higher education as compared to the other groups. In Table II, the results of the neuropsychological assessment, reporting means and standard deviations, are presented.

From the ANCOVA adjusted for gender, age and duration of education comparing controls, bipolar patients and schizophrenic patients, seven variables were capable of detecting significant across groups

Table II. Neurocognitive measures in diagnostic groups (mean, SD).

	SZ (FE) ($N=11$)	SZ (chron) ($N=13$)	Bipolar ($N=18$)	Controls ($N=23$)
ZVT (*T* value)	39.27 (15.90)	34.73 (8.79)	43.94 (10.31)	52.36 (9.22)
Digit Span (value points)	10.18 (3.28)	11.45 (3.11)	11.43 (2.68)	12.14 (3.24)
RWT, prenames, (sum 1st and 2nd minute)	29.08 (6.65)	24.55 (8.34)	31.50 (11.78)	36.00 (7.81)
RWT, s-words (sum 1st and 2nd minute)	17.33 (6.31)	13.09 (4.46)	19.88 (8.25)	23.50 (5.57)
VLMT 1–5 (sum of trials 1–5)	51.55 (8.99)	41.50 (12.60)	50.07 (8.24)	60.05 (6.13)
VLMT-diff (difference between trial 5 and 7)	2.27 (2.24)	3.25 (1.54)	2.40 (2.53)	1.27 (1.42)
WST (*T* value)	53.55 (8.49)	47.69 (9.51)	52.06 (7.23)	58.78 (6.23)
NVLT (sum score, difference between right and false answers)	42.18 (13.27)	45.77 (12.81)	40.65 (7.09)	51.22 (10.00)
Corsi	5.55 (1.37)	5.46 (1.13)	5.29 (1.21)	6.00 (1.09)
Stroop-Reading (s)	0.23 (0.13)	0.26 (0.25)	0.24 (0.19)	0.17 (0.15)
Stroop-Naming (s)	0.21 (0.26)	0.15 (0.24)	0.27 (0.21)	0.09 (0.10)
RT1 (s)	54.45 (9.53)	50.83 (7.09)	54.39 (8.40)	59.17 (6.15)
RT3 (s)	47.91 (9.12)	46.50 (7.17)	43.00 (11.00)	51.43 (9.02)
WCST-ta (trials administered)	110.91 (18.56)	104.09 (18.42)	103.25 (20.92)	88.45 (16.77)
WCST-pr (% of perse-verative responses, *T* value)	52.82 (13.77)	52.55 (13.25)	63.69 (15.43)	62.00 (12.92)
TOL (sum score)	93.73 (11.36)	92.25 (9.36)	95.12 (9.92)	101.91 (8.43)
SRM (% of correct standard score)	−0.99 (1.71)	−1.37 (1.28)	−1.44 (1.15)	−0.56 (1.20)
TAP-WM (s)	724.5 (134.0)	856.3 (155.6)	739.9 (213.5)	625.0 (146.6)
TAP-DA (s)	777.5 (59.6)	758.4 (72.2)	784.7 (87.0)	695.4 (83.4)
TAP-IC (s)	545.7 (41.4)	576.8 (95.7)	549.8 (114.7)	437.5 (68.1)

SD, standard deviation; *N*, number of subjects; SZ, schizophrenia; FE, first-episode; Chron, chronic disease; Bipolar, patients with bipolar disorder; ZVT, Zahlenverbindungstest (similar to Trail Making Test A); RWT, Regensburger Wortflüssigkeitstest (Verbal Fluency); VLMT, Verbaler Lern- und Merkfähigkeitstest (similar to the Auditory Verbal Learning Test); WST, Wortschatztest (comparable to the Boston Naming Test); NVLT, Nonverbaler Lerntest (Nonverbal Learning Test); Corsi, Corsi Block Tapping; Stroop, Stroop Test; RT1, Reaction Test (of the Wiener Test System), single stimulus; RT3, Reaction Test (of the Wiener Test System), compound stimulus; WCST, Wisconsin Card Sorting Test; TOL, Tower of London Test; SRM, Spatial Recognition Memory; TAP, Testbatterie zur Aufmerksamkeitsprüfung (Attention Test Battery); WM, Working Memory; DA, Divided Attention; IC, Intermodal Comparison.

differences in cognitive function (see Table III for details): performance in the trail making test (ZVT) was significantly different across groups, pointing to differences in attention and speeded psychomotor processing. Significant group differences were also found in lexical word fluency (RWT 's'-words), verbal learning and immediate recall capacities (VLMT, sum of trials 1–5), verbal episodic recognition performance (VLMT, difference between trial 5 and 7), premorbid verbal intelligence (WST), executive function (WCST), and crossmodal binding (TAP-IC).

Schizophrenia patients versus controls

Compared to control subjects, patients with schizophrenia performed significantly worse in the trail-making test (ZVT), the verbal fluency test (RWT 's'-words) (see Figure 1), verbal learning and memory test (immediate list recall of VLMT), and the Wisconsin Card Sorting Test (sum of administered trials, and perseverative responses). This cognitive pattern indicates significant deficits in attention and psychomotor performance, and in particular in verbal working memory and cognitive flexibility for schizophrenic patients. Thus, high order cognitive functions were most affected in schizophrenics. Interestingly, there was evidence for significantly reduced premorbid intellectual function (lower WST score) only in chronic schizophrenic patients with multiple episodes, but not in first-episode patients, compared to control subjects. Nevertheless, first-episode patients performed worse in the WCST (sum of administered trials), suggesting cognitive dysfunction even at the beginning of the disease.

Schizophrenia versus bipolar patients

A significant difference between schizophrenic and bipolar patients was found only in the WCST. Schizophrenic patients made significantly more perseverative responses, indicating a more pronounced and specific deficit in cognitive flexibility and executive function (see Table III and Figure 2).

Correlations with other parameters

For sake of completeness, the influences of intervening demographic variables were tested by correlation analysis. Sex influenced performance as expected; females performed better in verbally based tests (RWT, VLMT, Stroop-LI) and the working memory test requiring cross-modal integration, whereas males fared better on the spatial Corsi test, corroborating a well-established pattern of

Table III. Diagnostic group comparisons.

	ANCOVA[a] Factor diagnostic group			SZ (total) vs. Controls	SZ (total) vs. Bipolar	SZ-FE vs. Controls	SZ-Chron vs. Controls
	df	*F*	*P*	*P*	*P*	*P*	*P*
ZVT (*T* value)	2, 51	3.84	**0.028**	**0.012**	0.17	**0.041**	**<0.0005**
Digit span (value points)	2, 50	1.00	0.38				
RWT, prenames (sum 1st and 2nd minute)	2, 51	0.42	0.66				
RWT, s-words (sum 1st and 2nd minute)	2, 51	3.84	**0.028**	**0.004**	0.12	**0.035**	**<0.0005**
VLMT 1–5 (sum of trials 1–5)	2, 52	5.81	**0.005**	**0.005**	0.12	**0.013**	**<0.0005**
VLMT-diff (difference between trial 5 and 7)	2, 52	1.80	0.18				
WST (*T* value)	2, 56	3.45	**0.039**	**0.047**	0.92	0.31	**0.003**
NVLT (sum score, difference between right and false answers)	2, 56	2.70	0.076				
Corsi (total)	2, 56	0.97	0.39				
Stroop-Reading (s)	2, 56	0.69	0.50				
Stroop-Naming (s)*	2*	2.32	0.31				
RT1 (s)	2, 56	2.87	0.065				
RT3 (s)	2, 56	1.62	0.21				
WCST-ta (administered trials)	2, 52	3.51	**0.037**	**0.004**	0.44	**0.015**	**0.038**
WCST-pr (% of perseverative responses; *T* value)	2, 52	5.31	**0.008**	**0.026**	**0.002**	0.069	0.13
TOL (sum score)	2, 55	2.07	0.14				
SRM (% of correct standard score)	2, 48	1.83	0.17				
TAP-WM (s)	2, 50	1.99	0.15				
TAP-DA (s)	2, 48	2.85	0.067				
TAP-IC (s)	2, 47	5.66	**0.006**	**0.002**	0.54	**<0.0005**	**0.001**

[a]ANCOVA (factors diagnosis, gender; covariates age, education).

*Values were not normal distributed. In consequence non-parametric Kruskal–Wallis Test was performed, and $?^2$ instead of *F* are shown in the table.

N, number of subjects; SZ, schizophrenia; FE, first-episode; Chron, chronic disease; Bipolar, patients with bipolar disorder; df, degrees of freedom; *F*, *F* statistic; *P*, probability; ZVT, Zahlenverbindungstest (similar to Trail Making Test A); RWT, Regensburger Wortflüssigkeitstest (Verbal Fluency); VLMT, Verbaler Lern- und Merkfähigkeitstest (similar to the Auditory Verbal Learning Test); WST, Wortschatztest (comparable to the Boston Naming Test); NVLT, Nonverbaler Lerntest (Nonverbal Learning Test); Corsi, Corsi Block Tapping; Stroop, Stroop Test; RT1, Reaction Test (of the Wiener Test System), single stimulus; RT3, Reaction Test (of the Wiener Test System), compound stimulus; WCST, Wisconsin Card Sorting Test; TOL, Tower of London Test; SRM, Spatial Recognition Memory; TAP, Testbatterie zur Aufmerksamkeitsprüfung (Attention Test Battery); WM, Working Memory; DA, Divided Attention; IC, Intermodal Comparison.

cognitive sex differences. The influence of age was also as expected. Looking only at the directions of correlations, age correlated negatively with performance in every single index (correlation in the Stroop-LI test being the only exception), although of course many of these correlations were non-significant. Significant coherence, however, was found for memory measures in particular, including immediate recall and episodic recognition of VLMT, nonverbal learning performance (NVLT), and spatial and basic working memory (Corsi, TAP-WM), but also in tests tapping capacities to divide attention (TAP-DA) and react to compound stimuli (RT3). Although these results seemingly contradict findings of more specific age-related deficits especially with regard to memory (e.g., Cabeza 2006), age was already confounded with diagnostic group (i.e., older subjects were more likely to suffer from bipolar disorder). Finally, education had a large influence on many tests, as well, including but not limited to measures of verbal and nonverbal learning (VLMT, NVLT), working memory (ZNS, Corsi), and intelligence (WST). Most importantly for present concerns, there was no influence of these demographic variables on the WCST index selectively impaired in the schizophrenic group of patients.

Discussion

In our study, overall, psychiatric patients exhibited poorer performance on many variables of neurocognitive assessment, although it should be highlighted that about half of the variables did not vary significantly with subjects' status. Although variables were selected in order to mirror group effects, many cognitive functions seem to be rather unimpaired in schizophrenia (and bipolar disorder). For example, patients performed quite well in pure working memory tasks (digit span, Corsi, TAP-WM) and did not show dramatically increased susceptibility to basic interference (Stroop). Differences in ZVT (trail making) might also be due to differences in

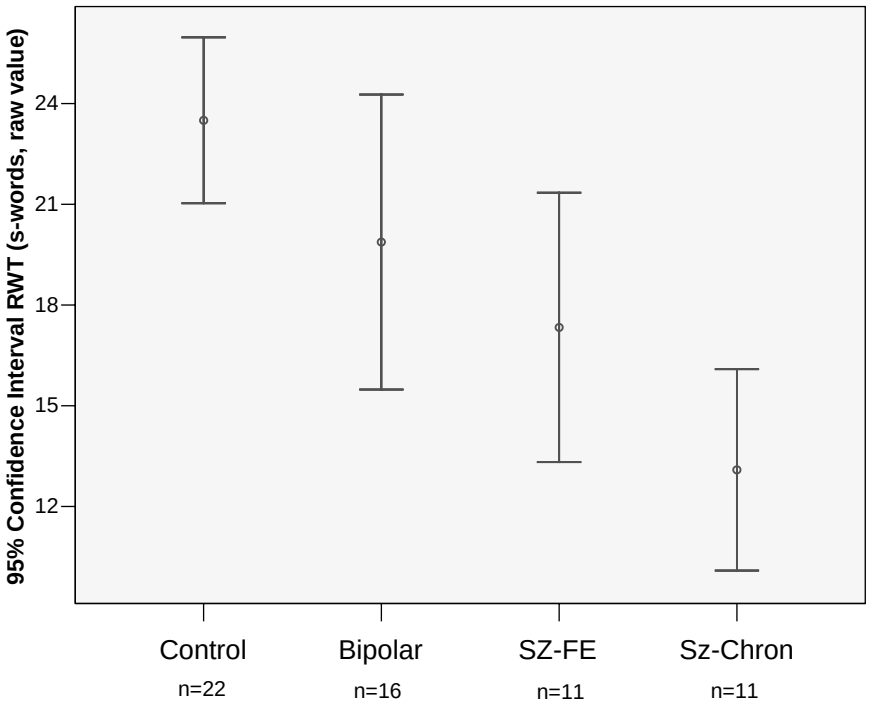

Figure 1. Verbal fluency (RWT, s-words) in diagnostic groups. Comparison of the performance in the verbal fluency task (RWT), letter category, words beginning with the letter 's' (s-words), sum of raw values in first and second minute. ANCOVA (factors diagnosis, gender; covariates age, education), $F=3.84$; df $=2,51$; $P=0.028$, for factor diagnosis. Analysis of diagnostic subgroup: SZ-FE vs. Controls: $P=0.035$; SZ-Chron vs. Controls: $P<0.0005$. RWT, Regensburger Wortflüssigkeits-Test; ANCOVA, analysis of covariance; df, degree of freedom; *P*, probability; SZ, schizophrenia; FE, first-episode; Chron, chronic disease; Controls, healthy controls; Bipolar, bipolar patients.

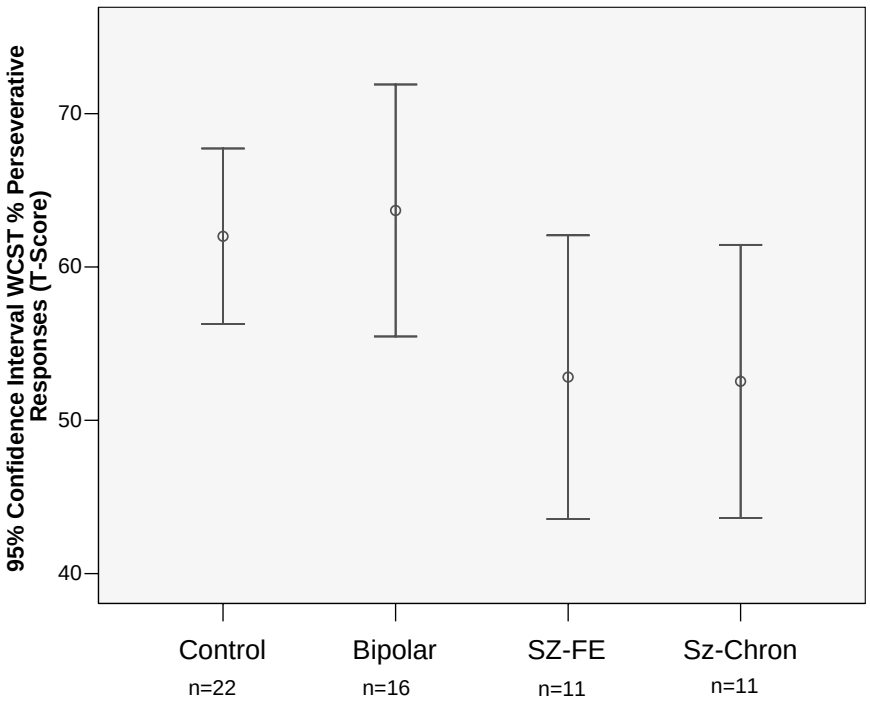

Figure 2. WCST (Perseverative Responses) in diagnostic groups. Comparison of the performance in the WCST, percent (%) of perseverative responses, *T* score, in diagnostic groups. ANCOVA (factors diagnosis, gender; covariates age, education), $F=5.31$; df $=2,52$; $P=0.008$, for factor diagnosis. Analysis of diagnostic subgroup: SZ (total) vs. Controls: $P=0.026$; SZ (total) vs. Bipolar: $P=0.002$. WCST, Wisconsin Card Sorting Test; ANCOVA, analysis of covariance; df, degrees of freedom; *P*, probability; SZ, schizophrenia; FE, first-episode; Chron, chronic disease; Controls, healthy controls; Bipolar, bipolar patients.

assessment-related arousal, as basic reaction time distributions did not differ across groups, speaking against a pure 'speed of processing' account of deficits. Overall results did not indicate a simplified 'task difficulty' account of deficits, as there were no significant group differences in the most challenging tasks (TOL, Stroop, TAP-WM), whereas easier tasks did show group differences (e.g., the VLMT recognition task, in which controls performed near ceiling, or the TAP-IC test).

Taken together, the results point to general higher-level cognitive functioning being primarily impaired in the patient groups. For instance, basic (pure) working memory tests were not sensitive to group differences (despite numerical tendencies); however, groups differed in the immediate recall of categorized word lists. Even though the latter also heavily relies on working memory processing (and working memory processing per se comprises control processes), performance in this task strongly benefits from additional strategic processing (clustering the groups, generating associations or images, and other strategies). A similar picture arises when comparing performance in the two word fluency tests. In the semantic version (i.e., list all first names you can think of), there is less need for generation of retrieval cues (letters of the alphabet are easily available cues) and strategy switches (subjects would typically follow the alphabet or go through their friend/family circle) as compared to the lexical version (i.e., list all words you can think of commencing with an 's'), requiring flexible generation of retrieval cues and strategy adjustments. Summarising our findings, schizophrenic patients showed deficits as compared to healthy controls in a number of tasks that seem to tap into higher-order cognitive processes, thus requiring multiple brain regions to act in concert to achieve high levels of performance.

The comparison with the bipolar group demonstrates, however, that these deficits might be of a rather general nature, not specific to schizophrenia. In contrast, they could be based on factors in common to both types of psychotic disorders (i.e. bipolar disorder and schizophrenia (Häfner et al. 2005)). Other related causes may be the intake of psychotropic drugs in both groups, a lower premorbid level of functioning, the influence of hospitalization, motivational factors, or an interaction of these and other conceivable factors.

More importantly, however, this study revealed a very specific deficit more peculiar to schizophrenia: schizophrenic patients (both first episode and chronic patients) produced significantly higher levels of perseverative responding in the Wisconsin Card Sorting Test (WCST), demonstrating inability to shift from an incorrect response set, compared to bipolar patients. Although the WCST has been subject to some criticism – mainly due to initial attempts to treat it as a 'pure' measure of frontal cortex function – it is not coincidentally one of the most administered neuropsychological tests worldwide, contributing uniquely to neuropsychological assessment (e.g., Greve et al. 1998). The present pattern points to a specific deficit in the ability of schizophrenic patients to flexibly adapt to the environment – a behaviour requiring high levels of action–effect monitoring and strategic control. This deficit is typically demonstrated by patients suffering from frontal lobe lesions. It indicates that frontally based executive functions are more disturbed in schizophrenia than in bipolar disorder. Yet, other functions also require a certain amount of frontal control, those subserving pure working memory tasks for example, and these were not strongly affected by group status in this study. Thus, the index of perseverative responses may be a rather pure measure of the psychological function needed to solve the task (strategy adjustment), but this function is most likely subserved by a distributed neural network rather than a single region. Apparently, this network is specifically disturbed in schizophrenia, and equally so across successive stages of the disease.

There are several limitations of this study. We did not control for the possible influence of psychotropic drugs on cognitive dysfunction. In this study, all of the schizophrenic subjects patients were treated with antipsychotic agents, in nearly all cases with second-generation antipsychotics. Bipolar patients received mainly mood stabilizers and to some extent second generation antipsychotics. Both patient groups were not treated with anticholinergic agents (like biperiden), or benzodiazepines at the time of neuropsychological assessment.

However, the influence of antipsychotics on neuropsychological performance should not be overrated, because a recent study (Rémillard et al. 2005) suggests that antipsychotics (risperidone, haloperidol) do not substantially or differentially affect executive functioning as measured by the WCST. Although several methods were applied intending to reduce the number of dependent variables, there still remained the large number of 20 variables. This raises the question of false positive findings caused by multiple testing. However, findings for the different neuropsychological tests were consistent, therefore there is evidence that the results may be interpreted as outlined above.

Notably, our results confirm some findings in the literature. For instance, it was reported that schizophrenia patients perform worse than normal controls on the WCST, with patient siblings showing

intermediate performance (El Hamaoui et al. 2006). This is in line with our assumption that frontal lobe/executive dysfunction marks a cognitive endophenotype in schizophrenia. In a study including both schizophrenic and depressed patient groups, executive dysfunction was found specifically in schizophrenic patients, which was associated with abnormal right frontal cortex activity (Holmes et al. 2005). Another study reported similar results, also showing that executive function (WCST, number of categories) was significantly more impaired in schizophrenic than in bipolar patients (Martinez-Aran et al. 2002).

Other studies have reported more global differences between the two patient groups. For instance, a study with large patient samples revealed evidence for more severe global and specific neuropsychological deficits in schizophrenia compared to psychotic affective disorders (Mojtabai et al. 2000), and another trial demonstrated similar patterns of cognitive dysfunction across groups, but the deficits of schizophrenic patients were more severe (Dickerson et al. 2004).

Nevertheless our results stand in contrast to other studies comparing performance of schizophrenic patients and controls. In one study the greatest deficits of schizophrenics were reported in visuomotor and attentional functions, whereas only intermediate deficits in cognitive flexibility could be demonstrated (Albus et al. 1996). Our study suggests that the former deficit is probably not peculiar to schizophrenia, whereas the latter may in fact be. Also, other research groups comparing neuropsychological performance between the two clinical groups have reported other result patterns, for instance, comparable performance on WCST accompanied by a selective deficit in verbal fluency tests shown by schizophrenia patients (Frangou et al. 2006). Patients suffering from schizophrenia have been reported to show a significant decrease in memory test performance, compared with both normal controls and affectively disturbed patients (Landrø et al. 1993), and these deficits did not correlate with performance on the WCST. A comparison between unaffected siblings of these two patient groups suggested a common impairment in verbal recall and a more pronounced deficit of sensory-perceptual analysis and spatial working memory in the unaffected siblings of schizophrenic patients (Keri et al. 2001). Finally, a study comparing neuropsychological performance between schizophrenic and bipolar patients over a 3-year period found similar results in both groups and stability of cognitive dysfunction over time also in bipolar disorder (Balanza-Martinez et al. 2005).

We propose that a key factor in the resolution of this rather ambiguous state of affairs will be concerned with the ascertainment of more homogeneous clinical subgroups. Interestingly, when bipolar patients with manic or depressive features were compared with schizophrenic patients with disorganized or predominantly negative symptoms, it was observed that executive dysfunction was more related to the symptom profile than to the diagnosis itself (Kravariti et al. 2005). An investigation similar to our study demonstrated a more generalized cognitive impairment and greater degree of impairment in schizophrenia compared with euthymic bipolar subjects (Altshuler et al. 2004). Compared to healthy controls, subjects with bipolar disorder were impaired in two specific domains (verbal memory, measured by CVLT, and executive function, measured by WCST). In this study the bipolar group consisted of a subset with relatively normal executive functioning and a subset with significant impairment, indicating that this patient group is not homogenous.

Further research also including modern imaging methods is necessary in order to confirm the suggestion that impairment of executive function or frontal lobe dysfunction describes a cognitive endophenotype in schizophrenia. Although meta-analyses have concluded that WCST performance is not specifically affected in schizophrenia in general (Laws 1999), there is some evidence of impaired executive functioning as indexed by WCST in patients exhibiting predominantly negative symptoms (Nieuwenstein et al. 2001). Thus, applying multi-method approaches and taking individual pathology patterns into account (e.g., Donohoe et al. 2006; Kurtz and Wexler 2006; Zalla et al. 2006) seems to be the most promising agenda for future research.

Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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