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ORIGINAL PAPER

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Cognitive functioning in the early course of first-episode schizophrenia spectrum disorders

Timing and patterns

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Abstract *Objective* The aim of this study was to examine possible cognitive changes throughout the early course of schizophrenia spectrum disorders. *Method* Forty-two patients, aged 15–50 years, admitted to a first episode psychosis program (PAFIP) serving to the community of Cantabria (Spain) and 43 healthy volunteers completed a brief battery of five neurocognitive tests at four time-points over 3 months. The cognitive testing comprise five domains: attention, visuomotor speed, declarative memory, working memory and executive function. Baseline assessment occurred within 72 hour after the initiation of standard pharmacological treatment, and after then parallel forms of the tests were applied at week-2, week-6, and month-3. *Results* Patient scores showed a significant impairment compared to healthy volunteers in the five cognitive domains at baseline and week-2 assessments. After the first 3 months of antipsychotic treatment, the patient group performance reached healthy volunteers level on executive function (Stroop interference) and immediate verbal memory tests. In contrast, performance on working memory, sustained attention, visuomotor speed, and verbal memory delayed recall domains still remained below healthy volunteers, although visuomotor processing speed showed a significant improvement. *Conclusion* Schizophrenia spectrum patients show heterogeneous patterns and degrees of cognitive changes that contribute to stress the importance of when, what, and how neurocognitive functioning in the early phases of the illness is evaluated.

Key words cognitive functioning · first-episode psychosis · schizophrenia · stroop interference effect · neurocognitive assessments

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Introduction

Neurocognitive deficits have been considered as core features of schizophrenia, independent of other clinical symptoms (Binder et al., 1998; Heinrichs and Zazkanis, 1998; Mohs, 1999; Bilder et al., 2000). Previous research has established that cognitive deficits are present in first episode psychosis (FEP) (Gold et al., 1999; Mohamed et al., 1999; Saykin et al., 1994) and even earlier, in high-risk samples (Hawkins et al., 2004), suggesting that cognitive impairment might precede the onset of the first psychotic episode. FEP studies have shown that the profile of cognitive functioning is similar to that of chronic schizophrenia samples, although performing at intermediate levels with generalized impairment across the majority of cognitive domains and more selective deficits in memory and learning, executive functioning, attention and speed of information processing (Saykin et al., 1994; Hutton et al., 1998; Mohamed et al., 1999; Bilder et al., 2000; Riley et al., 2000).

The investigation on this topic has been limited by methodological issues such as (1) the absence of initial medication free baseline assessment to help to clarify disease effects on cognitive function; (2) being focused on chronic samples; (3) lack of control for the phase of the illness and, therefore, potential confounds related to mixed samples of chronic and first episode patients; (4) comparison of patients at just two points in time and few comparisons during the acute phase or with the exclusion of acute patients;

and (5) rarely including control groups followed in parallel (see Harvey and Keefe, 2001).

The evaluation of cognitive dysfunctions is particularly important because they may predict social and occupational functioning (Green, 1996; Harvey et al., 1998; Dickerson et al., 1999; Malla et al., 2002; Stirling et al., 2003), and have been also related to the ability to judge their own quality of life (Jensen et al., 2004). As a result, these deficits have been considered warning signs for the functional outcome of the disease (Moritz et al., 2000), which might generate the largest indirect costs of the illness (Sevy and Davidson, 1995). Cognitive impairment has also been seen as the expression of an underlying pathophysiological process (Waddington et al., 1998; Censits et al., 1997), which might act before the overt presentation of the clinical symptoms, lessening the social and occupational functioning in the "premorbid" or prodromal phases (Cornblatt et al., 1999).

Therefore, it seems to be crucial to explore when during early phases of the illness cognitive functioning should be validly assessed. The present study was designed to describe the cognitive function at the early phases of schizophrenia spectrum disorders, in order to find any specific patterns and timing of improvement. Patients were assessed within 72 h after the initiation of treatment. Three additional assessments were used with the aim of describing the evolution of cognitive functioning during the first 3 months of treatment. The testing domains comprise attention, visuomotor speed, declarative memory, working memory and executive function. Healthy volunteers served as comparison participants for the cognitive assessments.

Method

Study design

The study was performed in an integrated clinical and psychosocial program for intervention in non-affective psychotic disorders, the Cantabria intervention program of first-episode psychosis (PAFIP). The PAFIP was designed to provide a comprehensive and multidisciplinary mental health care serving a population of 555.000 in the catchment area of Cantabria, Spain. The PAFIP is embedded inside the outpatient service at the University Hospital Marques de Valdecilla and hospitalization for initial treatment and relapses is also available in the inpatient unit of the region, which is located at our hospital.

Referrals from primary care services, emergency services and mental health professionals between August 2003 and April 2004 were considered. Patients were eligible for the study if they were aged 15–50 years; met DSM-IV criteria of diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief reactive psychosis or psychosis not otherwise specified (NOS); lived in the catchment area; and provided written informed consent. Patients with a history of neurological disease, head injury, mental retardation (DSM-IV criteria) or drug dependence (DSM-IV criteria) were not included in the PAFIP.

Forty-two patients (26 men, 16 women) were recruited into the study from consecutive admissions to PAFIP. Of 57 consecutive admissions who met criteria for enrolment and were able to provide written consent 26.3% (n = 15) declined participation. Of the 44 patients initially enrolled, only two were unable to complete the baseline assessment. All participants carried out at least baseline and two follow-up assessments, and 61.9% (n = 27) completed the four evaluations. Baseline cognitive assessment was carried out as soon as possible during the 72 h after the pharmacological treatment was initiated. Subsequent assessments were administered 2 weeks, 6 weeks and 3 months past baseline. Thus 42 patients were followed over the course of the study and were included in the data analysis. Patients were a mean of 26.3 years of age (SD = 7.6) at baseline, and had a mean of 11.1 years (SD = 2.6) of education. Initial diagnoses, confirmed by Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995) at 6 months after inclusion in the study by an independent psychiatrist attached to the study, were: schizophrenia (60%), schizoaffective disorder (5%), schizophreniform disorder (21%) or psychosis NOS (14%). Participants were allocated randomly to three different antipsychotic treatments: risperidone (n = 13), olanzapine (n = 14) or haloperidol (n = 15). A complete description of the study was given to all the patients (and their families) before the initial assessment. A naturalistic design was chosen and a flexible-dose was dispensed to each patient (mean doses ± SD): 13.6 ± 2.6 mg olanzapine, 3.5 ± 0.7 mg risperidone, and 4.9 ± 1.32 mg haloperidol). Dosage adjustment was made independent of research participation by the treating psychiatrist. Some patients received benzodiazepines (32.5%) or anticholinergics (35%). Only one patient changed their antipsychotic during the study. The cognitive assessor was blind to the medication status of each patient.

For comparison purposes, 43 healthy volunteers (26 men, 17 women) with no history of mental illness treatment and no Axis-I mental disorder were recruited from a nursery university college and from vocational training workshops. The delay between follow-up assessments for the control group was equivalent to patients' group. Comparison controls were a mean of 26.5 years of age (SD = 6) at baseline, and had a mean of 11.9 years (SD = 1.6) of education. A brief screening interview Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) was used by a clinical psychologist in order to check this. The patient and healthy comparison groups did not differ statistically in age, sex and educational level.

Cognitive testing

Participants were administered a brief battery of five neurocognitive tests. Every cognitive assessment took between 20–30 min and was carried out in a single appointment by a trained psychologist. The battery was designed with the intention of being used anywhere (emergency room, bedside...) not just in a formal assessment context (for this reason all were pen and paper tests, no extra devices were needed), and also was designed to be not too demanding for acutely psychotic patients. When available, parallel forms of the same test were used in the following re-testing. The tests encompassed selective and sustained attention, visuomotor speed, immediate and delayed verbal memory, working memory and executive function. All tests were scored and transformed into the minimum meaningful variables.

Ruff 2 & 7 Selective Attention Test (Lezak, 2004)

This task measures selective and sustained attention. The test consists of twenty 3–line blocks of alternating "automatic" and "controlled" visual search and cancelling of two digits "2" and "7". Each line of 50 characters contains ten 2's and 7's. The "automatic search" condition consists of randomly mixed capital letters with the target digits "2" and "7" between them. In the "controlled search" condition, digits "2" and "7" are randomly intermixed into lines with other digits that act as less obvious distractors. In this study we administered just half of the blocks, five for each condition. Every 15 sec the subject is asked to go on the next block. Two scores were obtained, one for the "automatic" (speed) and one for the "controlled" (accuracy) condition.

Rivermead Behavioural Memory Test story recall (Wilson et al., 1985)

This subtest is part of the Rivermead Behavioural Memory Test (RBMT), and is a naturalistic way of measuring declarative memory (story recall). The examiner reads a brief newspaper article (adapted to Spanish names), stopping after for an immediate free recall, and 20 min later the subject is asked again to recall as many details as possible from the same story. Each story contains 21 memory units. The test has four parallel forms. Separate scores for the immediate and delayed recall were obtained.

Colour Trails Test (CTT) (Spreen and Strauss, 1998)

The test is related to several cognitive functions: speed for attention, sequencing, mental flexibility, and visuomotor tracking. It is an attempt to create a "culture-fair" version of the Trial Mating Test (TMT) by alternating between colours instead of between letters and numbers. The CTT consists of two parts (1 and 2). Part 1, similar to trial making test (TMT) Part A (except that odd-numbered have a pink background, and even-numbered have a yellow background), requires the subject to connect series of numbered circles arrayed randomly on a sheet of paper using a pencil. Part 2 shows numbered circles from 1 to 25 twice, one with a pink background and the other with a yellow background. The examinee is asked to connect the numbers from 1 to 25 alternating between the two colours. Four parallel forms for both parts are provided. Time for completion was used as the primary score for each part.

Stroop Colour Word Test (Lezak, 2004)

This test measures selective attention and cognitive flexibility. The classical card version was used. The person completes three parts for a 45–sec period, each with five columns of 20 items. Part 1 involves reading the words "red", "green" and "blue" printed in black ink. In part 2 the subject must identify and name the colour in which each stimulus is printed (an array of X in red, green or blue ink). Part 3 involves identification and naming of the ink colour (red, green or blue) in which the words "red", "green" and "blue" are printed, the content of each word conflicts with the colour of the ink it is printed in. Therefore, in this part the subject has to suppress a habitual response (reading the words) in favour of an unusual one (naming the ink colour). The interference effect was used as the primary score.

Letter-numbering Sequencing Test (LNS) (Wechsler, 1999)

This subtest of the WAIS-III is related to auditory working-memory and attention. In this task, subjects are told a string of intermixed numbers and letters, and are required to repeat back the numbers and letters separately in ascending order. Each item has an increased difficulty, by adding numbers and letters to the arrays. Letter-numbering sequencing test was administered according to the WAIS-III norms. A single score was obtained.

Statistical analysis

To compare demographic characteristics of the patient and control groups, independent sample *t*-test (for age and years of education) and χ^2–test (for sex) were applied. To analyse the evolution of patient group data were standardized to *z*-scores (with an average of 0 and a standard deviation of 1) using the healthy control group as reference point for each time-point assessment, so practice effects could be excluded. Repeated Measures analysis of variance (ANOVA) was used to explore differences among groups (significance level, $P \leq 0.05$) and the patients' sample performance across the four time points. The alpha level was adjusted for multiple testing by Bonferroni correction. When appropriate, Greenhouse–Geisser corrections for sphericity violations were applied and corrected degrees of freedom and *P*-values are reported. When a single assessment was missing, with the exception of baseline assessment, data imputation was applied by calculating the mean of nearby points.

Results

Within-group differences (patients across time)

Figure 1 shows longitudinal data of the patient group. We examined performance patterns for each cognitive domain and time-point in level and shape by calculating *z*-scores. To facilitate the results interpretation qualitative descriptors are provided. After the first 3 months of antipsychotic treatment, the patient group performance significantly improved towards a normalization of the cognitive response in three neurocognitive measures compare to baseline assessments (see Table 1). Bonferroni post hoc analysis revealed significant differences between baseline and end-point assessment on Stroop test ($F = 5.077$; df = 2.399; $P = 0.005$), CTT-1 ($F = 5.559$; df = 1.671; $P = 0.009$); and a statistically significant improvement was observed between week-6 and 3 months on RBMT immediate recall ($F = 3.301$; df = 2.297; $P = 0.035$). No other test improved significantly.

Between-group differences (patients-controls)

Performance of patient and healthy control groups in the cognitive tests at all time-point assessments is summarised in Table 1. At baseline and week-2 assessments the patient group scored below the healthy volunteers on all neurocognitive measures ($P > 0.05$ to $P > 0.001$). By week-6 only the Stroop test for patients did not reveal a significant difference in relation to the control group (Bonferroni post hoc: $F = 3.400$; df = 1; p = 0.180). At the endpoint data, the Stroop test ($F = 3.400$; df = 1; $P = 0.894$) and RBMT immediate story recall ($F = 9.462$; df = 1; $P = 0.132$), but not delayed form, have improved to an optimal level compared to healthy participants. However, other cognitive measures were still impaired to a greater or lesser extent. Differences observed ranged from 0.5 to 3 points in *z*-scores at initial assessment and 0 to 2 points on measures at 3 months. In a more descriptive way, variation can be observed from a slightly below average outcome (0.5) to a marked deterioration (more than 2 SD) throughout the study. The CTT and Ruff test, both measures related partly to visual scanning and psychomotor speed, showed throughout all assessments of the study the greater degree of underperformance in relation to healthy volunteers (1.5–3 points).

Discussion

We found a significant underperformance of first-episode schizophrenia patients compared to healthy

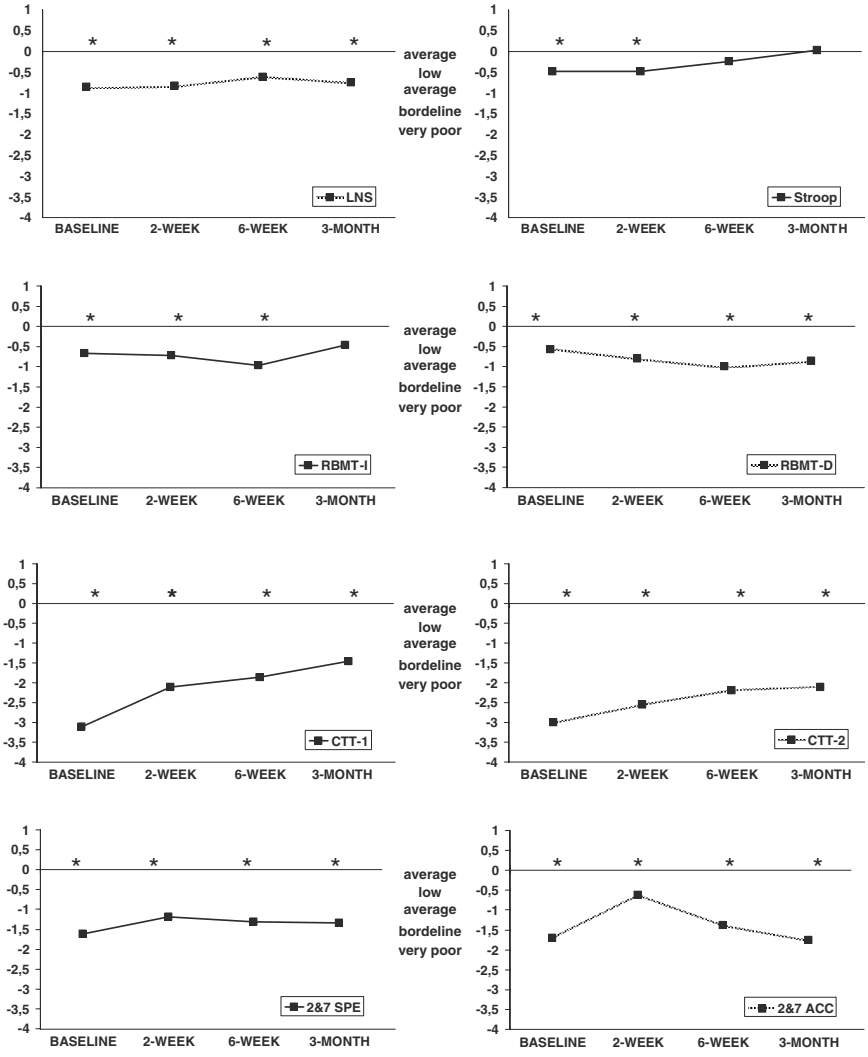

Fig. 1 Longitudinal mean z-scores for patients on each neurocognitive test relative to controls performance at each time-point using Bonferroni adjustment for multiple testing ($P^* \leq 0.05$)

volunteers in the five cognitive domains evaluated (i.e. attention, visuomotor speed, declarative memory, working memory and executive functioning) at baseline and week 2 assessments. However, executive functioning measured by Stroop Test (interference) reached a normative performance by week 6, and stayed at this optimal level thereafter; RBMT immediate story recall also improved to an adequate level by the end-point assessment. Attention, visuomotor speed, declarative memory delayed recall, working memory, and executive functioning (measured by CTT-2) still showed different degrees of neurocognitive impairments throughout the 3-month period. The patient group improved significantly in visuomotor speed tasks (CTT-1) once practice effects were ruled out. But the visuomotor domain, with the poorest degree of performance at baseline, was still 1.5 SD below healthy controls at the final assessment.

Our findings are overall consistent with prior investigations on cognitive functioning in first-episode schizophrenia spectrum disorders. Poor performance on measures of verbal memory, attention, speed processing, working memory and executive functions have been frequently reported (e.g. Gold et al., 1999; Mohamed et al., 1999; Saykin et al., 1994). Our data illustrate the presence of a cognitive deficit in multiple areas following illness onset and antipsychotic treatment. Moreover, the tasks used in this study for the assessment of attention, visuomotor speed, declarative memory, working memory and executive functioning comprised cognitive functions which are thought to be necessary for an adequate community functioning (Green, 1996).

Normalization of Stroop test and immediate story recall

The results obtained in the Stroop test and immediate memory recall are seemingly contradictory to previous reports on the same topic and need further explanation here. The Stroop test is one of the most widely used paradigms for the evaluation of selective attention. The need for active response inhibition

Table 1 Repeated Measures ANOVA of cognitive scores across 3 months period and difference between groups

TESTS	FEP patients $n = 42$ Mean (SD)	Healthy volunteers $n = 43$ Mean (SD)	Time effect (patient group z-scores)	Between group effect	Between Group effect. Bonferroni post hoc *P*-value
LNS			$F = 1.711$; df = 2.096;	$F = 11.958$; df = 1;	
Baseline	7.39 (3.69)	10.09 (3.01)	$P = 0.186$	$P = 0.001$***	0.001
Week 2	8.43 (3.16)	11.23 (2.79)			0.002
Week 6	9.19 (2.79)	10.85 (2.46)			0.019
Month 3	9.59 (2.51)	10.97 (2.16)			0.005
Stroop			$F = 5.077$; df = 2.399;	$F = 3.400$; df = 1;	
Baseline	−4.42 (6.51)	−0.39 (7.57)	$P = 0.005$**	$P = 0.05$*	0.034
Week 2	−0.96 (8.02)	2.80 (8.11)			0.045
Week 6	−1.11 (7.15)	2.84 (16.40)			0.180
Month 3	4.22 (7.17)	3.27 (8.52)			0.894
RBMT (immediate)			$F = 3.301$; df = 2.297;	$F = 9.462$; df = 1;	
Baseline	5.00 (2.86)	7.33 (2.91)	$P = 0.035$*	$P = 0.003$**	0.005
Week 2	6.43 (3.19)	8.89 (3.53)			0.002
Week 6	6.41 (3.92)	8.91 (2.49)			0.003
Month 3	8.52 (3.79)	8.87 (2.76)			0.132
RBMT (delayed)			$F = 1.267$; df = 2.271;	$F = 13.156$; df = 1;	
Baseline	4.00 (2.90)	6.05 (2.83)	$P = 0.289$	$P = 0.001$***	0.016
Week 2	5.27 (3.25)	8.12 (3.61)			0.001
Week 6	5.34 (3.60)	8.18 (2.73)			0.001
Month 3	7.52 (4.50)	9.00 (2.92)			0.006
CTT−1			$F = 5.559$; df = 1.671;	$F = 30.392$; df = 1;	
Baseline	72.35 (47.11)	35.74 (10.70)	$P = 0.009$**	$P < 0.001$***	<0.001
Week 2	59.57 (28.10)	31.64 (10.93)			<0.001
Week 6	53.97 (23.67)	31.24 (11.46)			<0.001
Month 3	47.53 (21.50)	31.70 (12.15)			<0.001
CTT−2			$F = 2.568$; df = 2.538;	$F = 28.307$; df = 1;	
Baseline	150.25 (85.28)	77.88 (21.33)	$P = 0.069$	$P < 0.001$***	<0.001
Week 2	136.51 (59.97)	73.05 (23.33)			<0.001
Week 6	122.86 (74.30)	70.29 (23.55)			<0.001
Month 3	107.88 (42.82)	74.63 (21.15)			<0.001
2&7SAT (speed)			$F = 3.714$; df = 1.687;	$F = 39.337$; df = 1;	
Baseline	89.93 (31.39)	129.50 (24.03)	$P = 0.062$	$P < 0.001$***	<0.001
Week 2	104.81 (26.66)	147.49 (31.31)			<0.001
Week 6	109.30 (25.83)	150.68 (30.45)			<0.001
Month 3	114.66 (24.35)	151.93 (28.99)			<0.001
2&7SAT (accuracy)			$F = 2.171$; df = 1.777;	$F = 9.895$; df = 1;	
Baseline	180.92 (23.52)	191.86 (5.74)	$P = 0.128$	$P = 0.002$**	0.022
Week 2	187.35 (10.20)	193.13 (5.03)			0.032
Week 6	189.57 (12.40)	194.99 (3.89)			0.017
Month 3	191.36 (7.59)	195.89 (3.53)			0.004

*$P < .05$; **$P < .01$; ***$P \leq 001$

LNS- Letter-numbering sequencing; **Stroop**- Stroop Colour Word Test (interference score); **CTT**- Colors Trails Test; **RBMT**- Rivermead Behavioural Memory Test (Story recall); **2&7SAT**- Ruff 2 & 7 Selective Attention Test

(selective attention) is the reason for this task to be considered a measure of executive functioning. Some studies with this paradigm have suggested that the card version produces increased interference in both with chronic and first-episode schizophrenia patients (Albus et al., 1996; Henik and Salo, 2004). However computerized single trial version studies show interference comparable to normal controls (Henik and Salo, 2004), also samples of first-episode psychosis (Chen et al., 2001). Barch et al. (2004) have argued that a lack of increased reaction time (RT) interference among patients with schizophrenia might reflect the increase in errors that patients demonstrate in the incongruent condition. In healthy individuals, it is commonly assumed that responses are slowed in the incongruent condition because the influence of the word interferes with the processing of the colour. However, among patients with schizophrenia, selective-attention deficits appear to be severe enough to lead to more than just a slowing in the incongruent condition, with patients actually responding to the word and not to the colour (i.e. increased errors). In our study, with the card version, subjects were required to give a correct answer before moving on to the next stimulus, so errors were penalized with the time to correct the response. But this may still be considered a spurious way of ruling-out error rates from RT, as the examiner might miss errors in this kind of speeded task. The normalization observed of the Stroop interference effect does not mean remediation of selective-attention domain. The other measure of our study accounting for selective-attention (2 & 7 SAT) reflects a sustained underperformance across assessments. We hypothesised that

Stroop interference may also slow down the execution of healthy subjects, and, in the same way, this could lessen the sensitivity of the task. On the other hand, recent research on selective attention reveals that distractor processing depends on the level and type of load involved in the processing of goal-relevant information (Lavie, 2005). Paradoxically, Lavie (1995) suggests that more difficult tasks (i.e. those with high load) can be performed better, show less interference. These two tasks (Stroop and Ruff tests) are different in nature; our results suggest that both tasks address diverse aspects of selective attention.

The other normalised test scores by the endpoint assessment is the RBMT immediate story recall. It must be noted that in many ways story recall tests most resemble everyday memory demands for the meaningful discourse found in conversation, radio and television, and written material (Lezak, 2004). In contrast, the majority of literature reveals a stable and wide ranging association between schizophrenia and memory impairments (Saykin et al., 1991; Saykin et al., 1994; Aleman et al., 1999; Goldman et al., 1999; Bilder et al., 2000; Muller et al., 2005). However, some aspects of memory may be affected to a greater extent than others, as not all cognitive process are equally affected (Lussier and Stip, 2001). Previous research has suggested that explicit recall is disturbed when memory is tested for recently presented material (Stip and Lussier, 1996), but performance is usually unaffected for recognition or implicit tasks (Danion et al., 2001). In this sense, story recall used in our study may be a less cognitively demanding method than word lists. On the other hand, results for delayed recall subtest show a stable underperformance which is consistent with previous reports. Brebion et al. (2000) have observed that the early phase of storage and the retrieval function seem unaffected in schizophrenia. Dissimilar patterns between immediate and delayed recall found in our study may support the hypothesis that memory performance is related to the depth of encoding (Brebion et al., 2000).

Differences in magnitude of cognitive impairment

In regard to the magnitude of cognitive impairment, notably, visuomotor speed tasks, as CTT and Ruff Selective Attention test, showed a poorer outcome than any other task, at the baseline and at the 3 months assessment, highlighting the relevance of slowness in visuomotor performance during the acute phase of a psychotic illness. Differences of 1.5 SD or greater as shown in our study are large enough to be considered clinically meaningful. Other domains, such as verbal memory, executive functioning and working memory display a performance slightly below average (<1 SD). Although this data might be clinically interpreted as if these cognitive functions remain unaffected, we may hypothesize that on more complex tasks in natural environments (such as university studies or competitive work) impairment on these domains can be functionally appreciated. McGurk and Mueser (2003) found that job complexity was correlated with impaired executive functions among clients working independently, but not in supported employment. They suggested that supported employment programmes may help schizophrenia patients to compensate cognitive impairments and, to a lesser extent, by creating environments in which these deficits do not impede their ability to perform the job demands.

In this early course, an improvement in processing speed was also observed. This cognitive function showed marked disturbance at baseline, but at the same time was the one with greater gains: about 1–1.5 SD. The subtest more related to visuomotor processing speed (CTT-1) improved significantly. Statistical analysis showed a trend to significance in other subtests also related to visuomotor speed but with a higher load on executive functioning, such as CTT-2 and Ruff test (for speed subtest, not for accuracy). This finding is consistent with previous investigations (Braff, 1993; Tollefson, 1996; Townsend et al., 2001; Hong et al., 2002). It has been suggested that other cognitive deficits may be related to the slowness in speed processing (Brébion et al., 1998). Indirect evidence against this is cognitive response in tasks less affected by speed processing, which remain stable despite the improvement shown in speeded tests.

It is noteworthy that performance on the Stroop test improves to the healthy volunteers' level, whereas CTT-2 does not. This leads to the idea that these group of tasks although typically related to executive functions and frontal cortex functioning (Lezak, 2004) may be reflecting the existence of different kinds of processing within the frontal lobe that dissociate in the case of schizophrenia patients. Previous investigations support the notion that TMT-B (a task similar to CTT-2) is related to dorsolateral prefrontal cortex (Stuss et al., 2001) whereas Stroop task has been related to orbitofrontal cortex functioning (Ruff et al., 2001; Purdon, 1998). Our recent research (Rodriguez-Sanchez et al., 2005) suggests that functions related to dorsolateral prefrontal cortex measured with TMT show deficit, whilst orbitofrontal related functions measured by the Iowa Gambling Task remain preserved, and this may be in concordance with our current findings. At the same time, working memory showed no improvement during our study. Stable and poor results near one standard deviation below comparison sample are obtained across all assessments. This finding supports the hypothesis that working memory is a core deficit in schizophrenia spectrum disorders and schizophrenia proneness (Goldman-Rakic, 1994; Goldman-Rakic, 1999; Mitropoulou et al., 2005).

When to assess cognitive functioning?

Taken all together, our data may help to address a critical issue: when it is appropriate to carry-out a baseline cognitive assessment in first-episode schizophrenia spectrum disorders. Some authors have applied stabilization criteria, whereas others have fixed an arbitrary time, or a combination of both. Testing during the first weeks of treatment is possible for the majority of patients (about 95% of our sample), but extrapolations of cognitive functioning in schizophrenia spectrum disorders should be cautious. The early course of cognitive response of this patients recruited from a treatment programme suggests that baseline assessments undertaken as the pharmacological treatment is initiated might reflect confusing results. Measures that show impairment at baseline and week 2 can be normalised by week 6. We may suggest, based on our findings that some point between week 6 and month 3 seems more appropriate to carry out an initial assessment for neurocognitive longitudinal studies.

Strengths and limitations

The strengths of the study are (1) it was a relatively large sample representative sample of patients, as they were recruited from a community programme that deals with all new first-episode psychosis cases detected by public services of our region; (2) study subjects were assessed several times during a short time-period of prospective follow-up; and (3) we use controls performance in each time-point to eliminate potentially confounding practice effects. On the other hand, certain limitations need also to be taken into account. First, few test were used in the neurocognitive assessment of this study. This may restrict the validity of the results; however, the tests selected are representative tasks of key cognitive domains in schizophrenia related disorders: sustained attention, executive functioning, verbal memory, and working memory (Green, 1996). Secondly, the duration of this study was relatively short and may not detect further development of benefits or deterioration (Hoff et al., 1999). Nevertheless our purpose was to describe the short-term cognitive course after the initiation of standard pharmacological treatment. Longer follow-ups are also limited in several ways by potential confounds such as effects of other medications or psychosocial treatments. Finally, we have not controlled for response of clinical symptoms. Beyond cognitive response to antipsychotics or the relation of symptoms to cognition, our main interest was to describe differences in timing and patterns of key cognitive domains during this early phase.

This study adds new evidence to understand the complex profile of cognitive functioning in the early course of schizophrenia spectrum disorders. Moreover, heterogeneous patterns and degrees of cognitive dysfunction shown in this study contribute to stress the importance of when, what, and how we evaluate in this challenging and controversial issue.

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References

1. Albus M, Hubmann W, Ehrenberg C, Forcht U, Mohr F, Sobizack N, et al. (1996) Neuropsychological impairment in first episode and chronic schizophrenic patients. Eur Arch Psychiatry Clin Neurosci 246:249–255
2. Aleman A, Hijman R, de Haan EH, Kahn RS (1999) Memory impairment in schizophrenia: a meta-analysis. Am J Psychiatry 156(9):1358–1366
3. Andreasen NC, Flaum M, Arndt S, (1992) The Comprehensive Assessment of Symptoms, History (CASH) An instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 49(8):615–23
4. Barch DM, Carter CS, Cohen JD (2004) Factors influencing Stroop performance in schizophrenia. Neuropsychology 18:477–484
5. Bilder RM (1997) Neurocognitive impairment in schizophrenia and how it affects treatment options. Can J Psychiatry 42:255–264
6. Bilder RM, Goldman RS, Volavka J, et al. (2002) Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 159:1018–1028
7. Bilder RM, Goldman RS, Robinson D, et al. (2000) Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. Am J Psychiatry 157:549–559
8. Binder J, Albus M, Hubmann W, Scherer J, Sobizack N, Franz U, Mohr F, Hecht S (1998) Neuropsychological impairment and psychopathology in first-episode schizophrenic patients related to the early course of illness. Eur Arch Psychiatry Clin Neurosci 248(2):70–77
9. Braff DL (1993) Information processing and attention dysfunction in schizophrenia. Schizophr Bull 19:233–259
10. Brébion G, Amador X, Smith MJ, Gorman JM (1997) Mechanisms underlying memory impairment in schizophrenia. Psychol Med 27(2):383–93
11. Brébion G, Amador X, Smith MJ, et al. (1998) Memory impairment and schizophrenia: the role of processing speed. Schizophr Res 30:31–39
12. Censits DM, Ragland JD, Gur, RC, et al. (1997) Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: a longitudinal study. Schizophr Res 24:289–298
13. Chen EY, Wong AW, Chen RY, Au JW (2001) Stroop interference and facilitation effects in first-episode schizophrenic patients. Schizophr Res 48(1):29–44
14. Cornblatt B, Obuchowski M, Roberts S, et al. (1999) Cognitive and behavioral precursors of schizophrenia. Dev Psychopathol 11:487–508
15. Danion JM, Meulemans T, Kauffmann-Muller F, Vermaat H (2001) Intact implicit learning in schizophrenia. Am J Psychiatry 158(6):944–8
16. Dickerson F, Boronow JJ, Ringel N, et al. (1999) Social functioning and neurocognitive deficits in outpatients with schizophrenia: a 2-year follow-up. Schizophr Res 37(4):13–20

17. First MB, Spitzer RL, Gibbon M, Williams JBW (1995) Structured Clinical Interview for DSM-IV Axis I Disorders. New York, Biometrics Research Department, New York State Psychiatric Institute
18. Gold S, Arndt S, Nopoulos P, et al. (1999) Longitudinal study of cognitive function in first episode and recent-onset schizophrenia. Am J Psychiatry 156:1342–1348
19. Goldman RS, Bates JA, Bilder RM, et al. (1999) Severity and selectivity of memory dysfunction in first-episode schizophrenia. Schizophr Res 36:130
20. Goldman-Rakic PS (1994) Working memory dysfunction in schizophrenia. J Neuropsychiatry Clin Neurosci 6(4): 348–357
21. Goldman-Rakic PS (1999) The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. Biol Psychiatry 46(5):650–661
22. Green MF (1996) What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153:321–330
23. Harvey PD, Howanitz E, Parrella M, et al. (1998) Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. Am J Psychiatry 155:1080–1086
24. Harvey PD, Keefe RS (2001) Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am J Psychiatry 158:176–184
25. Hawkins KA, Addington J, Keefe RSE, et al. (2004) Neuropsychological status of subjects at high risk for a first episode of psychosis. Schizophr Res 67:115–122
26. Heinrichs RW, Zazkanis K (1998) Neurocognitive deficits in schizophrenia: a quantitative review of the evidence. Neuropsychology 12(3):426–445
27. Henik A, Salo R (2004) Schizophrenia and the stroop effect. Behav Cogn Neurosci Rev 3(1):42–59
28. Hill KS, Schuepbach D, Herbener ES, et al. (2004) Pretreatment and longitudinal studies of neuropsychological deficits in antipsychotic-naïve patients with schizophrenia. Schizophr Res 68:49–63
29. Hoff AL, Sakuma M, Wieneke M, et al. (1999) Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. Am J Psychiatry 156:1336–1341
30. Hong KS, Kim JG, Koh HJ, et al. (2002) Effects of risperidone on information processing and attention in first-episode schizophrenia. Schizophr Res 53:7–16
31. Hutton SB, Puri BK, Duncan LJ, et al. (1998) Executive function in first-episode schizophrenia. Psychol Med 28:463–473
32. Jensen J, Nilsson LL, Levander S (2004) Neurocognitive and psychopathological correlates of self-monitoring ability in schizophrenia. Eur Arch Psychiatry Clin Neurosci 254(5):312–7
33. Keefe RSE, Silva SG, Perkins DO, et al. (1999) The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. Schizophr Bull 25:201–222
34. Lavie N (1995) Perceptual load as a necessary condition for selective attention. J Exp Psychol Hum Percept Perform. 21(3):451–68
35. Lavie N (2005) Distracted and confused?: Selective attention under load. Trends Cogn Sci 9(2):75–82
36. Lezak MD (2004) Neuropsychological assessment (4th edn). Oxford University Press, New York
37. Lussier I, Stip E (2001) Memory and attention deficits in drug naive patients with schizophrenia. Schizophr Res 48(1):45–55
38. Malla AK, Norman RMG, Manchanda R, et al. (2002) Symptoms, cognition, treatment adherence and functional outcome in first-episode psychosis. Psychol Med 32:1109–1119
39. McGurk SR, Mueser KT (2003) Cognitive functioning and employment in severe mental illness. J Nerv Ment Dis 191(12): 789–98
40. Meltzer HY, McGurk SR (1999) The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr Bull 25:233–255
41. Mitropoulou V, Harvey PD, Zegarelli G, New AS, Silverman JM, Siever LJ (2005) Neuropsychological performance in schizotypal personality disorder: importance of working memory. Am J Psychiatry 162(10):1896–903
42. Mohamed S, Paulsen JS, O'leary D, et al. (1999). Generalized cognitive deficits in schizophrenia: a study of first-episode patients. Arch Gen Psychiatry 56:749–754
43. Mohs RC (1999) Cognition in Schizophrenia: Natural history, assessment, and clinical importance. Neuropsychopharmachology 21,(S6):203–210
44. Moritz S, Krausz M, Gottwalz E, et al. (2000) Cognitive Dysfunction at Baseline Predicts Symptomatic 1-Year Outcome in First-Episode Schizophrenics. Psychopathology 33:48–51
45. Muller U, Ullsperger M, Hammerstein E, Sachweh S, Becker T (2005) Directed forgetting in schizophrenia Prefrontal memory and inhibition deficits. Eur Arch Psychiatry Clin Neurosci 255(4):251–257
46. Purdon SE (1998) Olfactory identification and Stroop interference converge in schizophrenia. J Psychiatry Neurosci 23(3):163–171
47. Purdon SE, Jones BD, Stip E, et al. (2000) Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. Arch Gen Psychiatry 57:249–258
48. Riley EM, McGovern D, Mockler D, et al. (2000) Neuropsychological functioning in first-episode psychosis – evidence of specific deficits. Schizophr Res 43:47–55
49. Rodriguez-Sanchez JM, Crespo-Facorro B, Perez-Iglesias R, Gonzalez-Blanch C, Alvarez M, Llorca J, et al. (2005) Prefrontal cognitive functions in stabilized first-episode patients with schizophrenia spectrum disorders: A dissociation between dorsolateral and orbitofrontal functioning. Schizophr Res 77: 279-288
50. Ruff CC, Woodward TS, Laurens KR, Liddle PF (2001) The role of the anterior cingulate cortex in conflict processing: evidence from reverse Stroop interference. Neuroimage 14(5):1150–1158
51. Saykin AJ, Gur RC, Gur RE, et al. (1991) Neuropsychological function in schizophrenia: a selective impairment in memory and learning. Arch Gen Psychiatry 48:618–624
52. Saykin AJ, Shtasel DL, Gur RE, et al. (1994) Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Arch Gen Psychiatry 51:124–131
53. Sevy S, Dadvison M (1995) The cost of cognitive impairment in schizophrenia. Schizophr Res 17:123–129
54. Spreen O, Strauss E (1998) A Compendium of neuropsychological test: Administration, norms, and commentary (2nd edn). Oxford University Press, New York
55. Stip E, Lussier I (1996) The heterogeneity of memory dysfunction in schizophrenia. Can J Psychiatry 41(7 Suppl 1):S14–S20
56. Stirling J, White C, Lewis S, et al. (2003) Neurocognitive function and outcome in first-episode schizophrenia: a 10-year follow-up of an epidemiological cohort. Schizophr Res 65:75–86
57. Stuss DT, Bisschop SM, Alexander MP, Levine B, Katz D, Izukawa D (2001) The Trail Making Test: a study in focal lesion patients. Psychol Assess 13(2):230–239
58. Tollefson GD (1996) Cognitive function in schizophrenic patients. J Clin Psychiatry 57(11):31–39
59. Townsend LA, Malla AK, Norman MG (2001) Cognitive functioning in stabilised first-episode psychosis patients. Psychiatry Res 104:119–131
60. Waddington J, Buckley PF, Scully P, et al. (1998) Course of psychopathology, cognition and neurobiological abnormality in schizophrenia: developmental origins and amelioration by antipsychotics? J Psychiatric Res 32:179–189
61. Wechsler D (1999) Wechsler Adult Intelligence Scale-III. TEA ediciones, Madrid
62. Wilson B, Cockburn J, Baddeley A (1985) The rivermead behavioural memory test. Thames Valley Test Co., Bury St. Edmunds