ASSESSMENT OF PSYCHOSIS IN SCHIZOPHRENIA: NEUROPSYCHOLOGICAL PROFILE OF CHRONIC SCHIZOPHRENIA

Elena Ermoli, Simona Anselmetti, Margherita Bechi, Federica Cocchi, Enrico Smeraldi, Roberto Cavallaro

Summary

Object: This study aimed to describe the neuropsychological performance profile associated with clinically stabilized chronic schizophrenia responder to typical and atypical antipsychotics and to test the hypothesis that the heterogeneous neuropsychological impairments might follow individual patterns of association.

Method: We tested 94 patients with chronic schizophrenia, and a control group of 71 healthy subjects, matched for age and education with a neuropsychological battery including tests for the assessment of the cognitive domains usually compromised in schizophrenia.

Results: All performances evaluated were, in mean, significantly worse among the patients as a group than among healthy subjects in all tests administered. Among these clinically stabilized patients responders to haloperidol, risperidone and clozapine showed similar neuropsychological performances except for verbal memory, significantly worse in patients responder to clozapine in comparison to patients responder to risperidone. Individual profiles of performance showed that performances impaired in each of the seven neuropsychological domains tested were heterogeneously combined in different patients in half of the sample, while the remaining half showed a massive impairment of all or almost all performances. Good clinical response to different antipsychotics was associated to a 'ceiling' effect in neuropsychological performances, reached similarly with each pharmacological treatment.

Conclusions: Data on this clinically and pharmacologically homogeneous sample suggest that the neuropsychological profile of chronic schizophrenia responder to treatment is heterogeneous in a significant proportion of patients, and that individually includes also preserved performances. The residual impairments would be worth of other clinical interventions of neuropsychological performance gain like cognitive exercise strategies.

Key Words: Cognitive functions – Heterogeneity – Schizophrenia

Declaration of interest: none

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Introduction

Cognitive impairments across a number of domains in schizophrenia have been well documented. Patients with chronic schizophrenia show impairments that range between one and half to two standard deviations below healthy controls on several key dimensions of cognition, especially working memory, attention (Cornblatt and Keilp 1994), executive functions (Heinrichs 1990) and verbal fluency (Blanchard and Neale 1994), motor and tactile dexterity (Goldstein and Zubin 1990), spatial abilities (Green and Walker 1985), language functions (Crawford et al. 1993) and memory (Paulsen et al. 1995). Such neuropsychological impairments have an impact on functional outcome in schizophrenia, as they have been correlated with poor functional abilities (Green et al. 1996, 2000). However, still in recent years some of these studies lead to discordant conclusions. In fact, even though there is a broad agreement that schizophrenia produces impairments on a variety of neuropsychological tasks (Blanchard and Neale 1994), a number of studies did not confirm this homogeneity in patterns of individual performances (Weickert et al. 2000, Silverstein et al. 2003). A possible source of heterogeneous results is sampling: available studies include patients at different stages of their illness (acute vs chronic), or affected either by schizophrenia or schizophrenia and schizoaffective disorder, and, last, but not least, treated with a number of different drugs and doses, with wide range of qualitative and quantitative responses to treatment.

This study aimed to describe the neuropsychologi-

Received January 2005, accepted June 2005

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cal characteristics of a large sample of patients with chronic schizophrenia with a high homogeneity of clinical status and pharmacological response status, to test the hypothesis that cognitive deficits of schizophrenia, despite a general pattern of impairment, show heterogeneity in individual manifestations.

Method

Subjects

This study was carried out on 94 patients (38 females and 56 males) who were regularly attending the outpatient unit of the Department of Neuropsychiatric Sciences of San Raffaele Hospital in Milan. Inclusion criteria were DSM-IV-R criteria for schizophrenia, antipsychotic monotherapy for at least 6 months with demonstrated clinical response. A control sample of 71 healthy subjects (38 females and 33 males), matched for age, sex and education was also assessed. Both patients and controls age had to range from 18 to 65 years and both had no history of alcohol or drug abuse/dependence, major neurological diseases, head injuries or mental retardation. Personal and family history, was assessed and recorded through a clinical interview.

Psychopathology

Psychopathology was assessed by means of the Positive And Negative Symptoms Scale (PANSS, Kay et al. 1987). Using the 'composite index' (Kay et al. 1991) of the same scale patients were also classified into 'negative', 'mixed' and 'positive' psychopathological subtypes. The composite index is obtained by subtracting the PANSS negative symptoms subscale score from the positive symptoms subscale score. The classification into the three psychopathological subgroups was done using the original PANSS validation data. According to these, The 25th and 75th percentile limits (scores of –8 and +3) were used as cut-off levels for defining, respectively, the positive and negative subgroups. Patients with a composite index within the limits were classified as 'mixed'.

Neuropsychology

Neuropsychological performances were tested with a battery assessing the main domains known to be compromised in schizophrenia: executive functions, vigilance and sustained attention, verbal memory, working memory, verbal fluency, psychomotor function. We used a computerized version of the Wisconsin Card Sorting Test (Grant and Berg 1948), considering the percentage of perseveration errors as variable of interest to test executive functions. For sustained attention we used a computerized version of the Continuous Performance Test-AX, (Baddeley 1992) using as variable of interest the number of items missed. Verbal fluency, both semantic and phonological, was assessed using total number of words generated in 60 seconds, within a given category or letter(Novelli et al. 1986). For the other cognitive functions we used the following tasks belonging to a new pen-and-pencil neuropsychological battery (Brief Assessment of Cognition in Schizophrenia, Keefe et al. 2004) designed to assess patients suffering from schizophrenia: 'Words recall' measuring verbal memory (measure was the total number of words recalled), 'Digit Sequencing Task' assessing working memory (number of correct responses to a memory and reordering strings of numbers task), 'Token Motor Task' evaluating psychomotor functions (number of tokens placed in the container during the first 30 and 60 seconds).

Statistical Analysis

The descriptive analyses of the sample and the group comparison were carried out with non-parametric statistic tests (ANOVA Kruskal-Wallis, Spearman rank correlation, Mann-Whitney U-test for means comparison). Categorical variables were analysed by parametric tests (Chi square test). Bonferroni correction was used to adjust the level of significance in case of multiple comparison.

Results

Samples' demographic, clinical and neuropsychological variables

Table 1 shows in detail epidemiological characteristics of both groups and PANSS subscales and total score of the patients group. No epidemiological variable considered was significantly different between patients and controls, including age and education. According to the composite index 32 subjects were classified as 'negative' subtype, 53 subjects were classified as 'mixed subtype' and 8 subjects as 'positive subtype'. 20 patients were receiving haloperidol (mean dose=5.3 mg/day [SD=3.2]), 33 patients were receiving risperidone (mean dose=3.5 mg/day [SD=1.6]), 33 patients were receiving clozapine (mean dose=263.1 mg/day [SD=137.6]), 4 patients were receiving olanzapine (mean dose=10mg/day) and 3 patients were receiving thioridazine (mean dose=200mg/day).

Table 2 shows mean raw scores of neuropsychological performances for both groups studied: as expected schizophrenic patients performed, in mean, significantly worse than the healthy subjects in all the neuropsychological tasks administered.

Relationship between neuropsychological performances and clinical/treatment variables

We analysed whether epidemiological, clinical and pharmacological variables, including also PANSS-derived psychopathological subtype, presence/absence of the core positive symptomatology of schizophrenia (delusions, hallucinations and disorganization), antipsychotic treatment or presence of 1st grade familiarity for schizophrenia (these two last variables representing a way to possibly discriminate 'core' schizophrenia from other conditions diagnosed as schizophrenia, but with diminished biological load) influenced the single neu-

Table 1. *Demographic and clinical characteristics of patients and controls*

	Patients Controls Statistics M (sd) M (sd)
Age	33.61 (8.9) 33.94 (12.9) n.s.*
Education	12.16 (2.7) 12.80 (3.40) n.s.*
Sex (females/total)	38/94 38/71 n.s §
Onset	23.49 (5.7)
Duration of illness	10.13 (7.2)
PANSS subscales	
Positive	14.21 (6.40)
Negative	19.8 (8.14)
General	32.35 (12.86)
Composite index	-5.59 (6.87)

*ANOVA; § χ^2

Table 2. *Neuropsychological testing results in patients and controls, statistics (Kruskal Wallis ANOVA comparing patients and control mean values) and cut-off values used to classify performances on neuropsychological tests as 'good' or 'bad'*

	Patients	Healthy Subjects	Statistics	Cut-off value good performance
Test (measure of interest analysed)	Mean (sd)	Mean (sd)		
Wisconsin Card Sorting Test (% of perseveration errors)	15.9 (11.5)	5.7 (6.1)	H=38.2 p=.001	<8.4
Continuous Performance Test (n of items missed)	36.8 (34.9)	5.08 (9.4)	H=70.5p=.001	<6
Phonological Fluency (n of words generated)	26.9 (11.8)	44.9 (12.3)	H=64.4p=.001	>37
Semantic Fluency (n of words generated)	15.1 (5.5)	24 (44.8)	H=72.6p=.001	>21
Token test (tokens in the first 30 seconds)	33 (9.2)	45.9 (7)	H=64.1p=.001	>42
Verbal Memory (n of items recalled)	34.4 (11.9)	51.6 (14.6)	H=54.2p=.001	>44
Digit Sequencing (n of correct responses)	17.07 (4.9)	23.6 (4)	H=57.9p=.001	>21

ropsychological performances, comparing the mean values obtained by these different subgroups. None of these variables resulted to influence any neuropsychological performance, except for the neuroleptic treatment for the single performance of verbal memory. In this analysis about drug treatment effects we included only patients taking haloperidol, risperidone and clozapine, which numerosity was sufficient for statistical analysis. Patients who were receiving clozapine performed significantly worse in the verbal memory test compared to patients who were receiving risperidone (Kruskal Wallis ANOVA p<.01, Mann Whitney U-Test for post-hoc analyses p<.005). The results on neuropsychological performances comparisons were confirmed also by a parametrical ANOVA carried out on standardized z scores with the Bonferroni correction applied. No other neuropsychological performance differed between the three treatment groups at both statistical approaches.

General cognitive ability index

In order to calculate an index of general cognitive ability, besides a mean quantitative comparison of schizophrenic patients performance with that of healthy subjects, we decided to set a cut-off level to describe qualitatively (good/bad performance) each of the performances in each patient and then to generate a score deriving from the sum of the 'good performances' found. We decided to consider as 'good performances' at each test those that fell within the 75th percentile (or

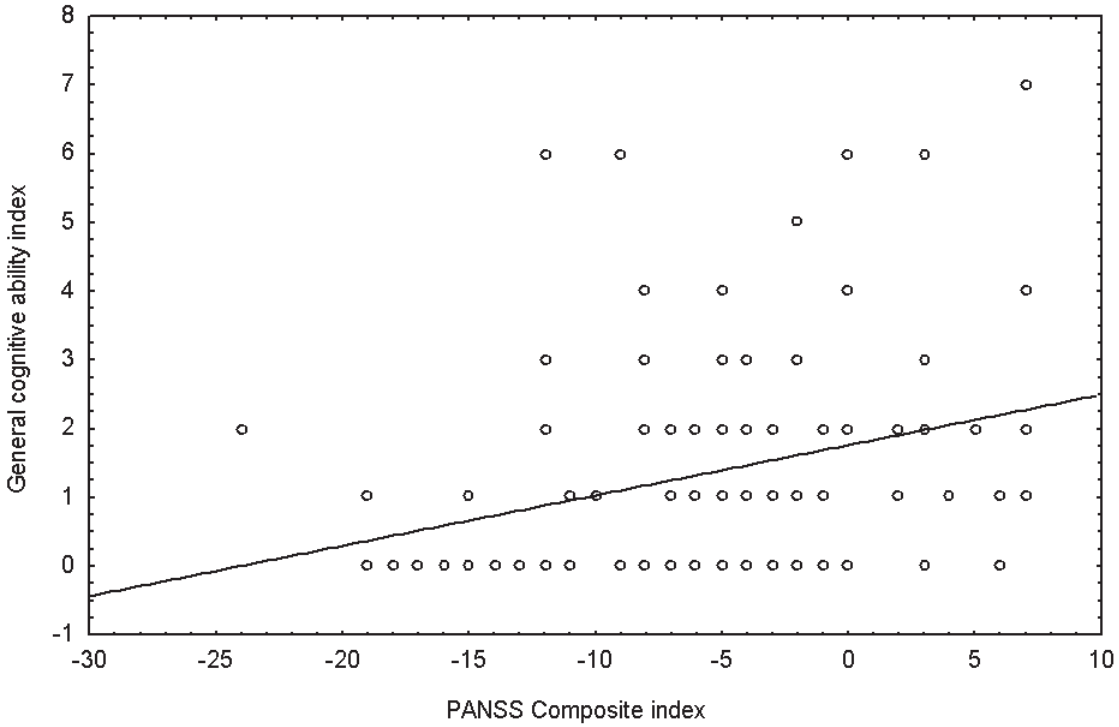


Figure 1. *Correlation between PANSS 'composite index' and the 'general cognitive ability' index'. Spearman Rank Correlation r =.29748 p<.001*

the 25th percentile, depending from the measure used in each test) of the healthy subjects performance distribution and to define as 'bad performances' those performances that fell out of these limits. Table 2 shows the cut-off values that were found for each test. This procedure has been successfully used in other studies (Cavallaro et al. 2003).

According to this classification the frequency of 'bad performances' among the patients was 69.9% on the executive functions test, 81.7% on the sustained attention test, 82.2% on the phonological fluency test, 84.9% on the semantic fluency test, 80.6% in the working memory test, 84.9% on the psychomotor skills task and 75.2% on the verbal memory test (Figure 1).

We created then the 'general cognitive ability index' (GCAI) consisting in the sum of 'good performances' for each patient, so that the score '0' corresponded to all 'bad' performances and the score '7' to all 'good' performances. At this parameter 40.9% (38 patients) scored 0, 22.6% (21 patients) scored 1, 17,2% (16 patients) scored 2, 8.6% (8 patients) scored 3, 4.3% (4 patients) scored 4, 1.07% (1 patient) scored 5, 4.3% (4 subjects) scored 6 and 1.07% (1 patient) scored 7 (Figure 2).

GCAI distribution was then studied in relation to epidemiological/clinical (1st grade familiarity for schizophrenia, age, age of onset, education, illness duration) and psychopathological (PANSS Positive, Negative and General subscale scores; PANSS-derived and psychopathological subtype; presence of the core positive symptoms of schizophrenia). None of these variables was significantly related to GCAI, except for a linear relationship with the PANSS Negative subscale score (Spearman R=-0.27 p<.01) and the PANSS 'composite index' (Spearman R=.34 p<.001). (Figure 3). That is the lower the CGAI, the higher the negative-deficitary psychopathology

Finally, in order to describe qualitatively and in a multifaceted way our sample's set of performances we assessed the possible different assortments of single neuropsychological 'bad' performances occurring in single patients. According to the previously described classification we considered each neuropsychological function compromised when the performance was 'bad' according to the above criteria.

In this way, we found 36 possible assortments of single neuropsychological 'bad' performances: 33.3% of the patients was characterized by a 'bad performance' in all tests administered, 13.9% of the patients performed badly in all tests except for the verbal memory test and 5.3% had a 'bad performance' in all the neuropsychological domains evaluated except for the executive functioning. The remaining part of our clinical sample (47.5%) exhibited a less extended, but highly heterogeneous profile of neuropsychological bad performances (Figure 4).

Discussion

Many studies confirmed that neuropsychological deficit is a core, stable characteristic of schizophrenia,

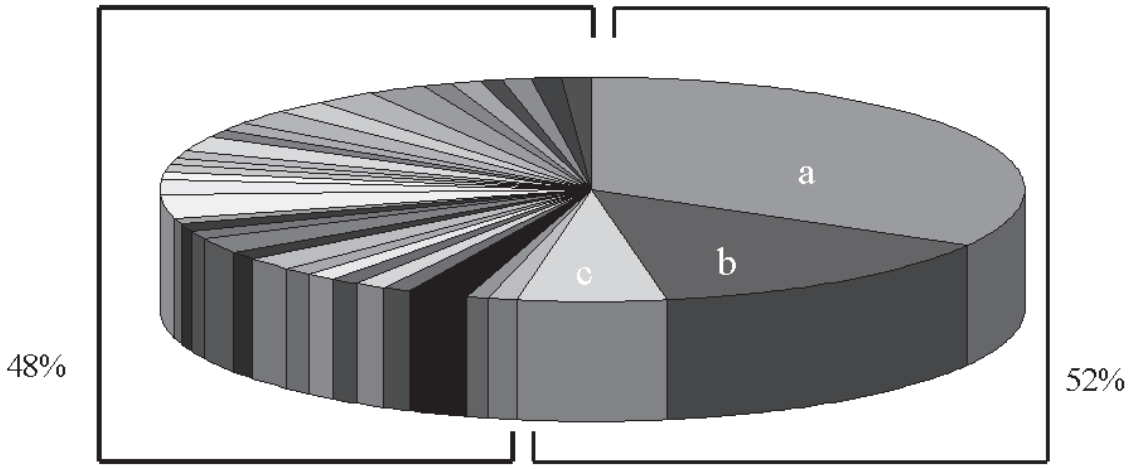


Figure 2. *Frequency of deficitary neuropsychological performances combinations. Segment a= all performances deficitarian; segment b= all performances deficitarian except for Verbal Memory test; segment c= all performances deficitarian except for the WCST. Each of the remaining segments represent a different combination of good/bad performances in the set of tests administered, with two or more preserved performances*

widely represented among patients affected by this illness (Goldberg and Weinberger 1988), presenting since the clinical onset (Mohamed et al. 1999) and after acute phase remission (Nuechterlein et al. 1992). Nonetheless, clinical variables, such as illness stage and duration, qualitative and quantitative response to pharmacologic treatment, may influence residual neuropsychological performances and their assessment. This may lead to controversial results, showing different cognitive performances, in different populations among which such variables are heterogeneously represented (i.e acute vs chronic schizophrenia, responders to treatment vs non responders etc). This study was designed to limit these sampling biases: subjects were all clinically stable since at least 6 months after assessed response to the antipsychotic treatment.

Findings confirmed the general pattern of neuropsychological characteristics of schizophrenic patients, reported in previous studies (Goldberg and Weinberger 1998, Shelton and Weinberger 1986, Staal et al. 2000). As expected, neuropsychological deficits were common among schizophrenic patients, and involved cognitive domains mainly related to frontal cortex activity, such as attention, memory, language, and executive functions, confirming previous evidence (Saykin et al. 1991, Gold et al. 1997, Frith 1993, Goldberg and Weinberger 1988). The stable clinical and pharmacological response status allowed also the evaluation of the possible influences of chronic psychopathology, residual after acute phase stable remission, on neurocognitive characteristics. Our data confirm the lack of any correlation between schizophrenia core positive symptoms, in particular hallucinations and delusions, and neuropsychological deficits severity (Cornblatt et al. 1985, Green and Walker 1997, Nuechterlein et al. 1986, Green et al. 1992, Strauss 1993).

Nonetheless severity and predominance of negative symptomatology on positive one resulted to be related to the degree of extension of the neuropsycological dysfunction across the different domains, as measured by the general cognitive ability index. This result supports most of the previous studies (Censits et al. 1997, Nuechterlein et al. 1986) showing a strong association between negative symptoms and neuropsychological compromission, particularly for those tasks that require an active effort (Addington et al. 1991). The causal 'direction' of this relationship (do negative symptoms or cognitive impairments come first?) is still unclear, even though preliminary data suggest that neuropsychological deficit comes before the onset of negative symptoms (Cornblatt et al. 1992). In this view, at least part of the negative symptoms might derive from an avoidance behaviour reinforced by recurrent failures in social interactions, due to impaired cognitive abilities. Conversely another hypothesis is that negative symptoms reduce the possibility to exercise 'ecologically' in everyday's life the performances assessed. An answer may come by future longitudinal studies aiming to this topic.

Concerning pharmacological treatment effects, results were only partially unattended: the neurocognitive profile of drug responder patients looks very similar in the three subgroups receiving the antipsychotic drugs mainly represented (clozapine, risperidone and haloperidol). This result is apparently in contradiction with literature data suggesting that atypical antipsychotics improve neuropsychological functioning more than traditional treatments (Keefe et al. 1999, Kern et al. 1999, Meltzer and McGurk 1999). In particular, clozapine was found to improve performances of specific cognitive domains such as attention, psychomotor abilities and verbal fluency but to have negative effects on memory performances (Buchanan et al. 1994, Hagger et al. 1993, Lee et al. 1994) and risperidone was shown to improve psycho-

motor abilities, attention and vigilance (Kern et al. 1999, Gallhofer et al. 1999, Stip and Lussier 1996). Indeed, our results are only apparently in contrast with these data because we didn't compare pre-post drugs effects of different antipsychotics, but we purposely selected patients at their best treatment response. In fact patients entered a sequential design of treatment in which they received risperidone only if they were non responder to haloperidol, and they were treated with clozapine only if they were non responder to both haloperidol and risperidone (Cavallaro et al. 2001). In this way patients were highly homogeneous in terms of drug response and they better represented "stabilized schizophrenia". Another result, similarly related to this study design is that patients treated with different drugs were similar at PANSS total and partial scores. Results, both for psychopathology, and neuropsychological performances, suggest that the global clinical result at the best of the response, obtained sequentially with different drugs in each patient, suffer from a sort of 'ceiling effect', to improve which other pharmacological and non-pharmacological treatments (i.e. cognitive exercise) are necessary. At this stage, the only drug-related difference among the cognitive performances assessed was verbal memory, worse among clozapine responders. This is in line with literature data and it is fairly explained by the strongest anticholinergic profile of clozapine relative to risperidone, known to influence this kind of performance (Spohn and Strauss 1989).

Probably the most surprising result concerns the descriptive analysis of the performances categorized by means of the control population derived cut-off. In fact, even though the majority of our sample showed a general cognitive impairment, more than 47% of patients had a less extended and more heterogeneous pattern of neuropsychological impairment. This might be related to IQ differences, as shown in previous studies (Weickert et al. 2000), but the absence of a standardized intellectual evaluation, precluded in our sample the testing of this hypothesis. To solve this limit a specific research on this topic is currently ongoing. Another view is that the various performances assessed are, at least in part, functionally overlapping, since it's likely that different components of each performance could compensate or reinforce the others, as they all relate to frontal or fronto-temporal cortex activity. Our results are only descriptive and cannot be interpreted as explanatory, but it could be hypothesized that while the majority of patients suffering from schizophrenia are not able to remediate illness related deficits, another, consistent proportion is able to compensate some of the impairments with other preserved abilities. Larger samples, characterized by a high inter-individual cognitive performance variability, could be analyzed with linear and non-linear multiple correlations, to explain possible underlying interactions. In conclusion, our description of the wide variety of different neuropsychological profiles shows that even though we studied a sample with high clinical homogeneity, the neurocognitive functioning is still in part heterogeneous. This finding is worth of consideration in view of cognitive rehabilitation plans, that are usually illness specific, suggesting a more effective use of individual profiles. The priority of a personalized cognitive enhancement strategy to potentiate and strenghten other simultaneous or following clinical interventions, is also evidenced by literature data showing neuropsychological impairment as a key factor limiting 'traditional psychosocial rehabilitation' (Green et al. 2000).

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