# Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: a longitudinal study

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## Abstract

The stability of neuropsychological performance in schizophrenia and its relationship to clinical change was contrasted between 60 patients with schizophrenia (30 first-episode, 30 previously treated) and 38 healthy controls using a comprehensive neuropsychological battery and clinical scales administered at intake and at a 19-month follow-up. Consistent with the neurodevelopmental model of schizophrenia, patients demonstrated deficits in cognitive performance at initial testing and did not show decline at follow-up. There were no differences in neuropsychological performance over time between first-episode and previously treated patients, nor between male and female patients or controls. As expected, patients improved clinically with treatment with respect to both positive and negative symptoms. First-episode patients improved more on the positive symptoms of hallucination and delusion; male and female patients showed equivalent clinical improvement. Clinical improvement correlated positively with neuropsychological change, with improved negative symptomatology accounting for most of the significant correlations.

## 1. Introduction

With increased evidence that schizophrenia is a brain disease, an issue of considerable current debate is whether it is predominantly a neurodevelopmental or neurodegenerative disorder. Neuropsychological data continues to help elucidate this issue by providing behavioral measures that can be linked to regional brain function. Evidence for impaired learning and memory (e.g., Calev et al., 1983; Saykin et al., 1991; Goldberg et al., 1993), attention (e.g., Nuechterlein and Dawson, 1984; Harvey et al., 1990; Nestor et al., 1992), and executive functions (e.g., Goldberg

et al., 1987; Morrison-Stewart et al., 1992) has supported a model of fronto-temporal dysfunction in schizophrenia. The presence of these deficits at first presentation (e.g., Bilder et al., 1992; Saykin et al., 1994), combined with the lack of correlation with measures of chronicity (e.g., Goldberg et al., 1993; Nopoulos et al., 1994) are consistent with the neurodevelopmental hypothesis that stresses the relative stability of cognitive functions after the onset of schizophrenia (e.g., Weinberger, 1987; Wyatt, 1996). The cross-sectional rather than longitudinal design used in the majority of studies, however, precludes a rigorous test of the degenerative hypothesis since cross-sectional paradigms do not compare the same individuals at different times within the course of their illness.

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Few longitudinal studies have been reported, and these were limited by small samples and/or lack of a longitudinal control group. In a sample of 28 first-episode patients, studied at 6 months after entry into the study and again at a 12-month follow-up, Bilder et al. (1991) found evidence of general neuropsychological stability with specific improvements in attention, motor, and generalized memory functions. This study however, did not test controls at both time periods, raising the possibility that patient improvements resulted from practice effects or other factors unrelated to course of illness. Sweeny et al. (1991) reported in a sample of 39 patients, measured between an acute episode of schizophrenia and at 12-month follow-up, improvements in attentional and executive domains as well as in motor functions. They also reported improvement on Judgment of Line Orientation and the Rey Auditory Verbal Learning Test. However, this study utilized test norms rather than a matched longitudinal control group, raising the same problems in interpreting 'test improvement' as the previous study.

Hoff et al. (1991) and Saykin et al. (submitted for publication) did utilize a follow-up control reference group. Hoff and colleagues compared a sample of 15 patients and 25 controls over a 24-month period and noted improved executive and concentration speed functions for 15 of the patients and global cognitive improvement for 12 of the patients. Saykin et al. (submitted for publication) examined the differences in neuropsychological performance of 21 patients and 28 controls followed over an average of 28 months. They reported equivalent improvement in both patients and control groups.

The relationship between neuropsychological change and clinical improvement has received less attention, and current findings are mixed. Cross-sectional studies suggest that negative symptoms correlate more with neuropsychological change than do positive symptoms (Bilder et al., 1985; Andreasen et al., 1990; Shtasel et al., 1992a). Longitudinally, Saykin et al. (submitted for publication) found correlations between improvement in negative symptoms and neuropsychological change. The longitudinal study by Hoff et al. (1991), however, found no correlations between

either positive or negative symptoms and neuropsychological change. In a study of shorter duration (average 4 months) Silverstein et al. (1994) found no relationship between changes in six neuropsychological summary scores and changes in Brief Psychiatric Rating Scale symptoms, although they did report that neuropsychological impairment predicted blunted affect/emotional withdrawal at discharge.

The purpose of the present study was to establish in a large sample of patients with schizophrenia whether neuropsychological performance changes or remains stable relative to a group of healthy controls over a 1.5-year period. Both first-episode (FE) and previously treated (PT) individuals with schizophrenia were examined and any changes in neuropsychological performance were correlated with clinical change. Since symptoms and course of schizophrenia have been reported to be more severe in men (Goldstein, 1988; Angermeyer et al., 1990; Cowell et al., 1996), we also examined sex differences.

## 2. Methods

### 2.1. Subjects

Patients and controls were drawn from an on-going longitudinal investigation of brain function in schizophrenia, which is being conducted in the Schizophrenia Mental Health Clinical Research Center (MHCRC) at the University of Pennsylvania. Most of the patients in the MHCRC are referred from the inpatient service of the Hospital of the University of Pennsylvania, local community mental health centers and private practitioners. The remainder are referred from state hospitals. Healthy controls were recruited from paid advertisements in local community newspapers. After informed consent is obtained, participants undergo comprehensive screening and assessment, performed by the clinical research team (Shtasel et al., 1991). This includes the Structured Clinical Interview for Diagnostic and Statistical Manual Version III Revised (DSM-III-R), Patient Edition (SCID-P; Spitzer et al., 1986), detailed medical history, physical examina-

tion, and laboratory tests (SMA-20, CBC, RPR, ESR, ANA, thyroid functions and urine drug screen). Controls are screened with the non-Patient Edition of the SCID (SCID-NP; Spitzer et al., 1989). Entry criteria to the MHCRC for patients includes: (1) a diagnosis of schizophrenia or schizophreniform disorder by DSM-IIIR criteria (American Psychiatric Association, 1987); (2) no concomitant Axis I or II disorder including past or present substance abuse or dependence; (3) no history of a medical illness that might affect brain function (e.g., cardiac, renal, endocrine, pulmonary disease); and (4) no history of a neurological disorder (e.g., epilepsy, migraine, head trauma with loss of consciousness). Except for the diagnosis of schizophrenia, and the additional criterion of no first-degree relatives with a diagnosis of schizophrenia or affective illness, inclusion and exclusion criteria for controls were the same as for patients. Fifty-three of the 60 patients and all of the controls were judged to be right-handed based on a standardized behavioral and self-report inventory (Raczkowski et al., 1974).

The longitudinal sample consisted of 60 patients with schizophrenia and 38 healthy controls. Patients and controls were studied at intake, and again approximately 19 months after enrolment (range 6.2–32.2 months). Table 1 details the demographic and clinical characteristics of these two groups at intake. Patients are stratified in the table according to prior medication history.

Of the 60 patients, 30 were in their first-episode of illness (FE), and of these, 28 were neuroleptic-naive at the time of intake. For most of these cases, admission to the MHCRC represented the first occasion that psychiatric treatment was being sought. The two FE patients with previous neuroleptic exposure had been neuroleptic-free for a minimum of 2 weeks at the time of enrolment. The remaining 30 previously treated patients (PT) had prior treatment histories of varying lengths. All PT patients had not received medications for a minimum of 2 weeks prior to baseline assessment for this study. Neither patient group was washed off medication at 19-month follow-up. Onset of illness for both FE and PT patients was defined as the first time psychotic symptoms were noticed by the patient, family, or others in the context of

Table 1
Demographic and clinical characteristics of patient and control samples at intake. Mean(± SD)

|  | First-episode (FE) | Previously treated (PT) | Healthy controls (CNT) |
|---|---|---|---|
| N | 30 | 30 | 38 |
| Male | 17 | 21 | 25 |
| Female | 13 | 9 | 13 |
| African-American | 21 | 14 | 11 |
| Caucasian | 9 | 16 | 25 |
| Other | 0 | 0 | 2 |
| Age (years) | 30.3 (6.1) | 27.1 (5.5) | 31.0 (7.2) |
| Age at onset (years) | 23.7 (7.8) | 20.8 (4.9) | N/A |
| Duration of illness (years) | 3.3 (4.1) | 9.4 (4.7) | N/A |
| Number of hospitalizations | 0.12 (0.4) | 3 (4.7) | N/A |
| Parental education (years) | 12.2 (2.9) | 12.3 (3.4) | 13.2 (3.5) |

N/A, not applicable.

a decline in functioning. Consequently, while all of the FE cases were in their first-episode of psychosis, there was a range of illness duration prior to intake examination. As can be seen in Table 1, compared to PT patients, FE patients had a later age at onset, a briefer duration of illness and fewer prior hospitalizations. There were no significant differences between controls (CNT) and FE and PT patients in age, gender or parental education. However, the racial distribution was not equivalent between controls and the two patient groups. Therefore, ethnicity was covaried during the statistical analysis (see below).

### 2.1.1. Medications

Treatment decisions (type and dosage of medication, route of administration) were made clinically by the treating physician (a member of the MHCRC or a community physician). A medication report was completed for each patient summarizing the duration and dosage of psychotropic medication prior to study entry and during the 19-month follow-up epoch after entry to the study. For intake and follow-up the average daily dose of neuroleptic medication per kilogram of body weight was quantified in chlorpromazine-equivalent (CPZ) units (Kaplan and Sadock, 1992; per-

sonal communications with Janssen and Sandoz Pharmaceuticals, 1996).

Previously treated patients were receiving a mean($\pm$SD) daily dose of $631 \pm 60$ CPZ units at intake prior to wash-out, and were receiving $601 \pm 47$ CPZ units at follow-up. Clozapine was the only atypical antipsychotic drug used and was administered at a dose of $320 \pm 25$ CPZ units in three patients. By definition, FE patients had not received medication prior to or at the time of intake, but were receiving $260 \pm 47$ CPZ units at follow-up.

### 2.1.2. Assessment scales

Clinical symptomatology was assessed with the Scale for Assessment of Negative Symptoms (SANS, Andreasen, 1983), and the Scale for Assessment of Positive Symptoms (SAPS, Andreasen, 1984) by investigators trained to a criterion reliability of 0.90 intraclass correlation (Shtasel et al., 1992b). These scales were administered both at intake and at repeated 6-month intervals in longitudinal follow-up, one of which corresponded with the 19-month follow-up analyzed for the current study. From these scales eight clinical outcome measures were utilized. Outcome measures on the SANS included Affect, Alogia, Avolition, and Anhedonia ratings, and outcome measures on the SAPS included ratings of Hallucinations, Delusions, Bizarre Behavior, and Positive Formal Thought Disorder (Gur et al., 1991).

### 2.1.3. Neuropsychological assessment

A comprehensive neuropsychological test battery was administered to the patients and controls by trained examiners at intake and again at follow-up testing. A second examiner independently re-scored test data to eliminate errors and permit assessment of interrater reliability. The test battery is listed in Table 2, including references for administration and scoring procedures. Patient and control raw test scores at intake and follow-up were standardized (z-scores), using the means and SDs of the MHCRC standard normative sample of 160 subjects. Test variables were grouped into eight summary measures by combining each subject's z-scores on tests assessing the same functional

domain, as in previous studies (Saykin et al., 1991, 1994; Cannon et al., 1994). Summary measures were calculated for the following domains: abstraction (ABF), attention (ATT), verbal memory, (VMEM), spatial memory (SMEM), language abilities (LAN), spatial abilities (SPA), sensory functions (SEN), and motor functions (MOT). This organization represents a minor modification of our previously published profile (Cannon et al., 1994) in that sensory and motor functions were separated into two individual factors, SEN, and MOT. The variables comprising these functions are presented in Table 2.

### 2.1.4. Statistical analysis

Data analysis proceeded in three stages. (1) The effect of time and diagnostic grouping on neuropsychological performance was examined using repeated measures multivariate analysis of covariance, with ethnicity (African-American, Caucasian, Other) as a covariate (MANCOVA; proc GLM procedure; SAS Institute Inc., 1987). (2) The effect of time on patient clinical status was analyzed with repeated measures MANCOVA. (3) The relationship between neuropsychological and clinical change for patients was examined by correlating neuropsychological and clinical change scores.

For the first stage of analysis, a 2 (patient vs. control group) $\times$ 2 (time 1 vs. time 2) $\times$ 8 (neuropsychological function) MANCOVA with repeated measures for the second and third factors was performed with the $\alpha$ level set at 0.05. This was done to test for a main effect of diagnostic group and time, as well as any interactions between group and time, or group $\times$ time $\times$ neuropsychological function. If a main effect of diagnostic group was found, this MANCOVA was followed by post-hoc between-group univariate repeated-measures ANCOVAs for each neuropsychological function to determine if there was a time $\times$ group interaction within each cognitive domain. In addition, the effect of sex or patient group (first-episode vs. previously treated) on neuropsychological performance was examined using between-group repeated measures ANCOVAs with one between group (i.e., sex or patient group), and two repeated measures factors

Table 2
Neuropsychological test battery by functional domain

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**Abstraction:** Categories and preservative responses, Wisconsin Card-Sorting Test (Heaton, 1981)
**Attention:** Stroop Color and Word (Golden, 1978); Trail-Making Test (Reitan and Woltson, 1985); Digit Span and Digit Symbol WAIS-R (Wechsler, 1981); Vigilance and Distractibility, Continuous Performance Test (Gordan, 1986)
**Verbal memory:** Logical Memory Passages (immediate and 30-min delay) WMS (Wechsler, 1945); Learning trails 1 through 5, California Verbal Learning Test (Delis et al., 1983)
**Spatial memory:** Design Reproduction (immediate and 30-min delay) WMS
**Language abilities:** Controlled Oral Word Association (letters C, F, and L) MAE (Benton and Hamsher, 1976); Animal Naming and Boston Naming Tests BDAE (Goodglass and Kaplan, 1983); Reading Recognition, WRAT-R (Jastak and Wilkinson, 1984); Token Test MAE
**Spatial abilities:** Benton Line Orientation Test (Benton et al., 1975); Block Design WAIS-R (Wechsler, 1981); Rosen Drawing Test (Kareken et al., 1995)
**Sensory abilities:** Reitan-Klove Sensory-Perceptual Exam HRB
**Motor abilities:** Thumb Finger Sequential Touch (right and left hands) LNNB (Golden et al., 1980); Finger Tapping (right and left hands) HRB

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WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS, Wechsler Memory Scale; MAE, Multilingual Aphasia Examination; BDAE, Boston Diagnostic Aphasia Examination; WRAT-R, Wide Range Achievement Test-Revised; HRB indicates Halstead-Reitan Battery; and LNNB, Luria Nebraska Neuropsychological Battery.

(within group time and neuropsychological function).

The clinical analysis (stage two), mirrored the neuropsychological analysis: a repeated-measures MANCOVA was used to test the effect of time across the eight clinical functions. This was followed by separate ANCOVAs examining time effects for each individual clinical variable. The effect of sex and patient status was also examined using individual ANCOVAs.

In stage three, neuropsychological and clinical change were related using simple change scores that were calculated by subtracting each clinical and neuropsychological outcome measure at intake from their respective follow-up values. Because subtraction scores can be influenced by initial values, the eight clinical and eight neuropsychological change scores were also corrected for initial values using linear regression (Yudkin and Stratton, 1996). Because of the opposite polarity of the clinical and neuropsychological change scores, positive values reflecting greater severity in the former and better performance in the latter, the clinical change scores were multiplied by $-1$ to facilitate interpretation of correlational results (i.e., positive correlations will reflect improvement in both clinical and neuropsychological domains). These change scores were used to calculate correlation coefficients between the eight neuropsycho-

logical and eight clinical functions in order to examine the relationship of change in neuropsychological performance with change in clinical status. Pearson product moment correlation coefficients were used if the distribution of the change scores was normally distributed, otherwise Spearman Rho coefficients were used.

## 3. Results

### 3.1. Neuropsychological change

As can be seen in Fig. 1 there was a main effect of diagnostic grouping (patient vs. control; $F(1,65)=51.71$, $p=0.0001$), with patients performing worse at intake and follow-up on all neuropsychological functions relative to controls at intake and follow-up. A main effect of neuropsychological function ($F(7,59)=4.38$, $p=0.0006$) was also found, indicating that the performance profile for both groups was non-flat. There was no main effect of time, or any time × group interaction, indicating that performance was stable for patients and controls. An interaction was found between neuropsychological function and diagnostic group ($F(7,59)=5.79$, $p=0.0001$), indicating that the degree of patient impairment was more pronounced for some neuropsychological functions. The only other interaction was between
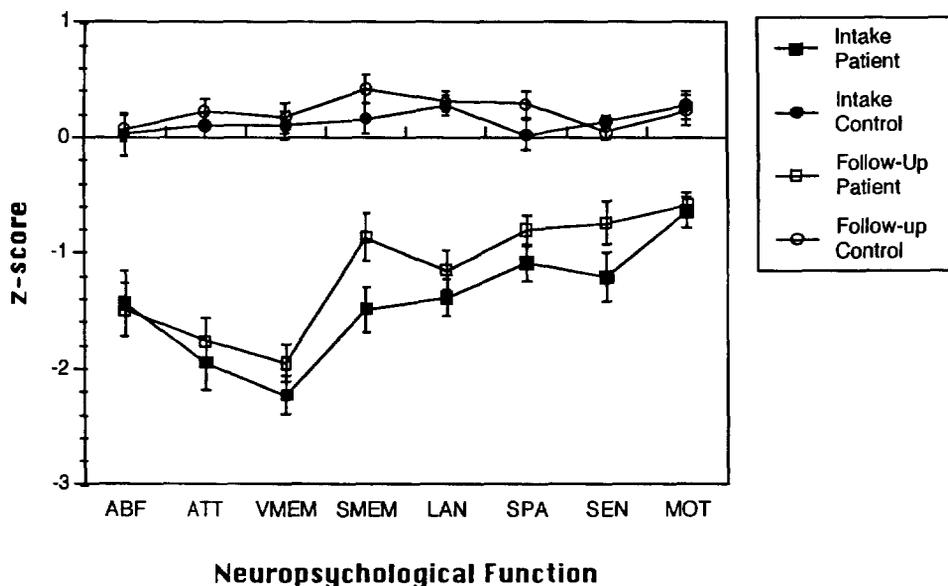
Fig. 1. Neuropsychological profiles (mean($\pm$SEM)): $z$-scores of patients and controls tested at intake and at follow-up. Variables are abbreviated as follows: abstraction (ABF), attention (ATT), verbal memory (VMEM), spatial memory (SMEM), language ability (LAN), spatial ability (SPA) and motor function (MOT).

neuropsychological function and ethnicity ($F(7,59) = 3.96$, $p = 0.0013$), indicating that the performance on some neuropsychological functions differed between racial groups across diagnosis. As in previous studies (Saykin et al., 1994; Cannon et al., 1994), patients showed generalized impairment (i.e., >1SD below normative values) on all functions except motor, and the greatest level of impairment (i.e., >2SD) on verbal memory function. The profile shape was similar for both intake and follow-up evaluations.

Because of the interactions between diagnostic and racial groups with neuropsychological function, post-hoc ANCOVAs were performed separately for each of the eight functions. These analyses again showed that there were no interactions between time and diagnostic or racial group for any of the neuropsychological functions. Main effects of ethnicity were observed across diagnostic groups on the neuropsychological functions of abstraction ($F(1,72) = 6.07$, $p = 0.02$), attention ($F(1,91) = 6.66$, $p = 0.01$), verbal memory ($F(1,93) = 4.17$, $p = 0.04$), spatial memory ($F(1,91) = 4.95$, $p = 0.03$), language ($F(1,90) = 9.99$, $p = 0.0021$), and spatial factors ($F(1,88) = 20.79$, $p = 0.0001$). Performance was consistent for all six functions within each ethnic group, with the Caucasian group's scores ($n = 50$) ranking above the African-American group's scores ($n = 46$). Group 'Other' was ignored in this ranking since it contained only controls and only two subjects.

No differences between men or women were found when sex was entered as an additional classification variable in the overall MANCOVA. There were also no differences between first-episode and previously treated patients on any of the neuropsychological functions at either time. The lack of differences between the two patient groups in neuropsychological performance argues that medication did not have a deleterious effect. However, to confirm this we also examined the correlations between neuroleptic dose and neuropsychological performance on the eight functions. This was done both for intake and follow-up medication and neuropsychological values. None of these correlations were significant.

### 3.2. Clinical change

There was general improvement in the eight clinical variables between intake and follow-up

$(F(1,58) = 43.29, \ p = 0.0001)$. There was also a main effect of clinical factor $(F(7,52) = 25.0, \ p = 0.0001)$, and an interaction between time and clinical factor $(F(7,52) = 2.49, p = 0.03)$, indicating that degree of improvement was different for one or more of the clinical variables. There were no effects of ethnicity on clinical change. The patient sample was, therefore, collapsed across ethnicity for subsequent post-hoc analyses. To understand the time × clinical factor interaction, post-hoc ANCOVAs were performed. As can be seen in Table 3, patients improved clinically on every measure except the Anhedonia index of the SANS.

As in the analysis of neuropsychological change, there were no sex differences when clinical change was examined. When first-episode and previously treated patients were contrasted, there was no main effect of patient type, or interaction between patient type and time. However, there was a significant time × clinical factor × patient type interaction $(F(7,51) = 3.02, p = 0.01)$. Again, there was no effect of ethnicity and the combined patient sample was used for additional analyses. Separate ANCOVAs for each clinical factor revealed that the three-way interaction was due to time × patient type interactions for hallucination $(F(1,58) = 28.62, p = 0.0001)$, and delusion factors $(F(1,58) = 31.02, \ p = 0.0001)$, on the SAPS. First-episode patients improved significantly more than did previously treated patients on these two factors.

### 3.3. Relationship between clinical and neuropsychological change

The change scores for the eight neuropsychological and eight clinical factors are presented in Table 3.

As can be seen in Fig. 2, all the significant correlations were positive, indicating that clinical improvement was generally associated with cognitive improvement. Ten of the 15 significant correlations were with negative symptom factors. Of the negative symptoms, Anhedonia showed the most consistent correlations, being associated with abstraction, attention, spatial memory, and language and spatial ability neuropsychological functions. Although the most consistent correlations were with negative symptoms, the largest correlation coefficient was obtained between bizarre ideation on the SAPS and language functioning.

## 4. Discussion

The results do not support a neurodegenerative model of schizophrenia. Patients' neuropsychological performance was equally impaired for first-episode and previously treated patients, and both groups showed the same test profile. The lack of difference in patient groups is consistent with cross-sectional findings of equal impairment in first-

Table 3
SANS and SAPS factor scores (mean ± SD) at intake and follow-up

| Variable | Intake mean | Follow-up mean | Simple change score | Corrected change score | $F$ | $p$ |
|---|---|---|---|---|---|---|
| SANSTOT | 50.85 (22.66) | 37.15 (22.63) | −13.70 (24.33) | 13.66 (20.89) | 27.92 | 0.0001 |
| SAPSTOT | 49.72 (20.99) | 24.12 (21.94) | −25.60 (26.94) | 25.52 (21.57) | 28.61 | 0.0001 |
| N_AFF | 2.60 (1.22) | 1.77 (1.32) | −0.83 (1.47) | 0.83 (1.25) | 18.87 | 0.0001 |
| N_ALO | 2.27 (1.41) | 1.55 (1.44) | −0.72 (1.45) | 0.71 (1.28) | 14.41 | 0.0004 |
| N_AVO | 2.65 (1.31) | 2.07 (1.57) | −0.58 (1.79) | 0.57 (1.53) | 27.92 | 0.0001 |
| N_ANH | 3.13 (1.26) | 2.97 (1.39) | −0.17 (1.61) | 0.16 (1.34) | 0.63 | ns |
| P_HAL | 2.73 (1.61) | 1.38 (1.64) | −1.35 (2.06) | 1.35 (1.64) | 28.61 | 0.0001 |
| P_DEL | 3.23 (1.03) | 2.03 (1.62) | −1.20 (1.77) | 1.19 (1.68) | 31.02 | 0.0001 |
| P_BIZ | 1.50 (1.21) | 0.63 (1.15) | −0.87 (1.48) | 0.88 (1.136) | 20.92 | 0.0001 |
| P_THD | 2.30 (1.37) | 1.15 (1.33) | −1.15 (1.39) | 1.12 (1.186) | 40.55 | 0.0001 |

Variables are abbreviated as follows: SANS total (SANSTOT); SAPS total (SAPSTOT); negative affect (N_AFF); alogia (N_ALO); avolition (N_AVO); anhedonia (N_ANH); hallucinations (P_HAL); delusions (P_DEL); bizarre idealization (P_BIZ); and thought disorder (P_THD). ns, not significant.
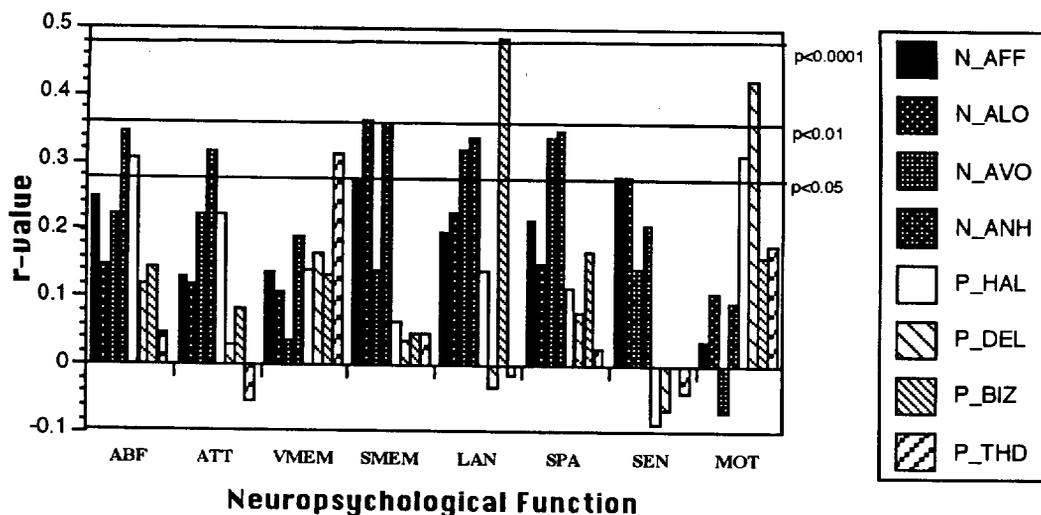
Fig. 2. Correlations between neuropsychological and clinical corrected change scores. Clinical variables abbreviated as in Table 3; functions abbreviated as in Fig. 1.

episode and previously treated patients (Saykin et al., 1994; Sweeny et al., 1991). In addition, these data show that longitudinally, no deterioration occurs over a 19-month period: patients did not show deterioration over time but remained stable in all domains.

The clinical results also do not support a neurodegenerative model: patients improved clinically on measures of both positive and negative symptomatology. Although improvement was seen in both types of symptoms, the most consistent correlations with cognitive change were seen with negative symptom improvement. This finding is consistent with previous reports in the literature supporting the generalization that negative symptoms account for more of the neuropsychological variance than positive symptoms (Bilder et al., 1985; Andreasen et al., 1990), and that they represent core-features of schizophrenia (Carpenter et al., 1988).

No sex differences were found for either neuropsychological or clinical change in this sample, although sex differences in the severity and course of schizophrenia have been documented (Shtasel et al., 1992a). This negative finding may reflect sample size. A larger sample size may also permit a more detailed examination of individual items on the clinical scales in relation to specific neuro-

psychological domains. Such an analysis could help identify possible mechanisms through which clinical and neuropsychological changes covary. Clinical phenomena and neuropsychological performance ultimately do both reflect behavioral manifestations of the same disease process.

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