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Cognition in Young Schizophrenia Outpatients: Comparison of First-Episode With Multiepisode Patients

Yoram Braw[2], Yuval Bloch[2,3], Shlomo Mendelovich[2,3], Gideon Ratzoni[2,3], Gilad Gal[4], Hagai Harari[2,3], Asaf Tripto[2], and Yechiel Levkovitz[1–3]

[2]Shalvata Mental Health Center, Hod-Hasharon 45100, Israel; [3]Tel-Aviv University Tel-Aviv, Israel; [4]The Academic College of Tel-Aviv-Yafo, Tel-Aviv, Israel

Cognitive impairments are recognized as a central feature of schizophrenia (SZ), largely independent of other symptoms, and a major cause of poor functioning. Studies indicate cognitive deterioration in the first years after the onset of SZ. These studies, however, have been criticized for using a small sample size, for having limited monitoring of confounding variables, and for the inclusion of cohorts of different ages. The current study compared the cognitive profile of first-episode schizophrenia patients, multiepisode schizophrenia patients and healthy controls ($n = 44$, $n = 39$, and $n = 44$; respectively). The study focused on the early stages of the disorder, recruiting only young patients. All subjects underwent an extensively validated computerized cognitive assessment (Cambridge Neuropsychological Test Automated Battery). The results revealed widespread cognitive impairments in SZ patients, compared with healthy control subjects. The multiepisode SZ patients were significantly more impaired than the first-episode ones, with deficits mainly related to psychomotor speed, pattern memory, and executive functioning. The functioning in other cognitive domains (ie, attention and spatial memory) was deficient even at an early stage of the disorder. These findings can help clarify the course of cognitive decline in young-aged SZ patients and aid in the development of phase-appropriate interventions.

Key words: cognition/CANTAB/attention/memory/executive functions

Introduction

Cognitive impairments are considered a central feature of schizophrenia (SZ) and a major determinant of poor psychosocial functioning.[1,2] There is still an ongoing debate, however, about the course of cognitive functioning in these patients.[3,4] Several lines of investigation using cross-sectional and longitudinal methods have suggested a relative stability of cognitive functioning.[5–7] Other studies suggested a process of cognitive deterioration mainly within the first 5–10 years after onset (see review[8]). These inconsistencies may be related to the confounding effect of including different aged cohorts within the studies. In line with this possibility, it is worth noting that specific subgroups of SZ patients exhibit distinct neurocognitive trajectories, especially in late life.[1,9,10] Previous studies were also criticized for insufficient monitoring of confounding variables.[3] For example, studies were done on patients treated with typical neuroleptics or included patients in psychotic states, factors that have differential effects on cognitive performance.[1,11,12]

The current study explored the cognitive functioning of first-episode (FE) and multiepisode (ME) SZ patients and focused specifically on the initial stages of the disorder. It also was selective in recruiting only young patients, an age group that received a limited attention in past research.[1] By isolating young patients from the overall SZ population, we aimed to identify cognitive changes at the initial stages of the disorder and clarify earlier findings that were confounded by heterogenous populations in terms of age. One secondary objective was to assist in the development of phase-appropriate rehabilitation interventions. To achieve all these aims, the study employed a cross-sectional approach. This approach, however, has methodological limitations, such as the possibility of incomplete sample matching. For example, FE patients with a better response to medication may drop out from mental health care follow-up. These limitations led to the recognition that cross-sectional studies could only provide an *indirect*, confirmatory approach to address the issue of neurocognitive changes in the course of SZ and that only a longitudinal approach would be able to *directly* provide more concrete infomation.[3,5] Longitudinal studies are also not without limitations, one of which is that the time interval between initial

[1]To whom correspondence should be addressed; Emotion-Cognition Research Center, Shalvata Mental Health Center, Hod-Hasharon, 45100 Israel; tel: +972-9-7478644, fax: +972-9-7478643, e-mail: ylevk@clalit.org.il.

assessment and retesting is often very short so that slow cognitive decline over time may remain undetected. Moreover, practice effects, lower psychopathology scores at follow-up, dropout from follow-up, and changes in medication regimen are difficult to control for in longitudinal studies and may mask cognitive decline (see review[4]). It follows, then, that both approaches would appear to have shortcomings and that they should be regarded as complementary methods. With regard to the current study, the possibility of incomplete sample matching was also mitigated by the central supervision of referrals by the country's mandatory medical insurance, a policy that inherently limits the risk of biased sample selection. Finally, given the above-cited drawbacks of earlier studies, this study gave special emphasis to the monitoring of possible confounders as an essential step to drawing valid conclusions.

SZ patients were hypothesized to present with a cognitive profile marked by generalized impairments compared with healthy controls (in line with previous studies using varied-age cohorts[5]). Our ME patients were hypothesized to be impaired in psychomotor speed compared with our FE patients (in accordance with[13,14]). We also hypothesized that ME patients would exhibit poorer executive functioning compared with the FE patients, based on earlier studies that suggested a more accelerated decline in executive functioning in the early stages of the disorder.[15] Executive functioning was investigated by using a fractionated approach for measuring the theoretically derived functions of working memory, cognitive shifting, and cognitive planning.[16–18] Such an approach is compatible with critiques on the narrow definition of executive functions used in many studies.[19–21] Finally, we did not have a specific hypothesis regarding visuospatial memory because most earlier studies mainly focused on verbal memory (eg, Albus et al[13], Saykin et al[14], Addington and Addington[22]).

Methods

Participants

A total of 83 SZ patients and 44 healthy controls participated in the study which was conducted in the Shalvata Mental Health Center, affiliated with Tel-Aviv University. The center receives referrals from a predetermined geographic location with central supervision by the national mandatory medical insurance. The patients were recruited from new admissions to the Shalvata Outpatient Program between 2 and 3 weeks after achieving clinical remission and being assigned outpatient status.[23,24]

FE patients ($n = 44$) were, by definition, experiencing their first psychotic episode and had received less than 12 weeks of cumulative lifetime neuroleptic treatment in the past. ME patients ($n = 39$), by definition, had experienced more than one acute episode of psychosis and had been admitted more than once for an acute relapse and their first admission to hospital for a psychotic episode had taken place more than 3 years before study entry. An "acute episode" necessitating hospitalization was defined as a psychotic episode by a psychiatrist. The study inclusion criteria were (1) age range 18–35 years, (2) *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, (*DSM-IV*[25]) diagnosis of nonaffective psychotic disorder established by a "Structured Clinical Interview for *DSM-IV*" (SCID[26]), (3) clinical status allowing participation in an outpatient program (as determined by the senior treating psychiatrist), (4) positive symptom scale ≤ 20 in the "Positive and Negative Syndrome Scale (PANSS) for SZ" in order to eliminate patients in psychotic states,[27] and (5) stable medication intake during the preceding month (as verified by the clinical staff and/or a family member). The exclusion criteria were (1) any acute, unstable, significant, or untreated medical illness with special emphasis on neurological disorders, (2) mental retardation (based on medical records or cognitive assessments conducted prior to current study), (3) earlier assessment using the Cambridge Neuropsychological Test Automated Battery (CANTAB), and (4) current drug abuse or dependency problem. The patients were not reimbursed and were free to withdraw at any time without prejudice.

During the study period (2003–2005), 120 patients who fulfilled the inclusion criteria were approached: 24 refused to participate (80% compliance). The patients' diagnoses were reassessed at the 6-month follow-up, and 13 patients were found unsuitable and their data were discarded (8 patients were rediagnosed as having psychotic depression and 5 as having bipolar disorder). The only difference between these patients and the study participants was that they were significantly older ($t_{94} = 3.49$, $P < 0.001$). All 83 patients who comprised the final study cohort were receiving atypical antipsychotic medication, and some were receiving adjuvant typical antipsychotic medication (10 patients in the FE group and 12 in the ME group). Three patients were receiving the typical antipsychotic medication as main medication (2 in the FE group and 1 in the ME group). One patient in the ME group received a mood stabilizer as main medication. The average daily doses of main medications were converted into chlorpromazine dose equivalents by standard formulas.[28]

Apparently healthy volunteers were recruited by advertisements posted around the Shalvata Mental Health Center. In order to ensure that healthy subjects or their first-degree relatives had not experienced a lifetime axis-1 psychiatric disorder, the subjects were required to undergo an interview to screen for psychiatric/medical history which was conducted by a trained research assistant. The screening procedure included the non-Patient Edition of the SCID[29] and assessment of lifetime psychiatric disorders in first-degree

relatives (subjects were asked whether their relatives had a major psychiatric disorder with brief examples given of SZ, depression, and bipolar disorder). In addition, the control subjects filled in the Brief Symptom Inventory (BSI[30]) and signed an informed consent form. These volunteers were not reimbursed and were free to withdraw at any time.

The study received local and national Institutional Review Board committees' approval. The demographic and disorder-related data for the 2 patient groups and the control group are listed in table 1.

Procedure

SZ patients underwent the SCID by a trained clinician, who also filled in the PANSS, the "Scale for Assessment of Negative Symptoms (SANS),[31]" and the "Calgary Depression Scale for Schizophrenia.[32]" The healthy controls underwent the SCID-NP by a trained clinician and filled in the BSI. All subjects completed the CANTAB, a reliable and extensively validated computerized assessment battery.[33] CANTAB tasks were chosen in order to allow assessment of major cognitive functioning (ie, psychomotor speed, attention, and visuospatial memory domains) while comprehensively evaluating executive functions. The tasks have been used extensively in SZ research (eg, De Luca et al[34], Prouteau et al[35], Owen et al[36]). The analyzed measures were recommended by Cambridge Cognition Ltd (Eileen Marshall, personal communication, January 2006) and had been used in similar studies on patients with SZ (eg, Hutton et al[37], Pantelis et al[38], Iddon et al[39], and Wood et al[40]).

The following tasks were presented in a randomized fashion:

1. Psychomotor speed: Psychomotor speed was investigated in the motor task (MOT). The task is designed to accustom the subjects to the CANTAB interface[41] and to assess the subjects' psychomotor speed (response latency measured in milliseconds).
2. Attention: Attention was measured using the rapid visual processing (RVP) task, a Continuous Performance Test of sustained attention, highly sensitive to brain damage or dysfunction.[42] The selected measure was A' representing the subjects' ability to detect the target sequence, regardless of response tendency.
3. Memory: Pattern and spatial memory domains were investigated by the pattern recognition memory (PRM) and spatial recognition memory (SRM),[36] respectively. The selected measure was "percent of correct responses" for both tasks.
4. Executive functions, including the following domains:

a. Working memory—the spatial working memory (SWM) task assessed the ability to retain and manipulate information in SWM.[43] The selected measure in the task was the "number of errors" in 4-, 6-, and 8-box problems (with a corresponding increase in task difficulty).
b. Cognitive shifting and flexibility—the intra-extra dimensional (IED) shift task assessed the ability to shift between intradimensional and extradimensional sets as well as the capacity for reversal learning.[44] The task was scored by the number of errors and number of stages completed. The "number of errors" is a measure of the subject's ability, adjusted for the fact that subjects completing fewer levels also have fewer chances to make errors.
c. Cognitive planning—the Stockings of Cambridge (SOC) task assessed planning and organizing a goal-oriented sequence of actions.[45,46] The task was scored using a measure of the subjects' speed of movement before and after the first move had been made, averaging 2–5 move problems ("initial thinking time" and "subsequent thinking time"). An additional measure was "the number of problems solved in the minimum number of moves."

Data Analysis

Preliminary Analyses. The distribution of the parametric measures (demographic, disorder-related, and CANTAB measures) was evaluated using measures of skewness and kurtosis.[47] Two disorder-related measures showed deviations from normal distribution: (1) "time duration until first admission" (months) showing positive skewness and kurtosis and (2) "number of psychiatric hospitalizations" showing positive kurtosis. In addition, several of the CANTAB measures showed substantial positive skewness (response latency in the MOT, initial thinking time in the SOC, number of errors, and "stages completed" in the IED). All measures were log10 transformed with follow-up analyses confirming normal distribution (in accordance with Tabachnick and Fidell[47]).

Comparison in Demographic Measures. Demographic measures were compared for the 3 study groups (FE patients, ME patients, and healthy controls) by a chi-square analysis for nonparametric variables (gender distribution) or an analysis of variance (ANOVA) for parametric variables (age and educational level) with a between-subjects factor of "group" (FE patients/ME patients/healthy controls). Because the groups differed in education level (see the "Results" section), the variable used was a covariate in comparisons of cognitive functioning.

Comparison in Disorder-Related Measures. Disorder-related measures (relevant only for the 2 SZ patient groups) were compared using a chi-square analysis for nonparametric variables or independent samples *t* tests

Table 1. Demographic and Disorder-Related Measures for First-Episode (FE) Patients, Multiepisode (ME) Patients, and Healthy Controls

Parametric Measures	FE, Mean ± SD (*n*)	ME, Mean ± SD (*n*)	Healthy, Mean ± SD (*n*)	Overall (*P*)	FE-Healthy (*P*)	FE-ME (*P*)	ME-Healthy (*P*)
Age (y)	24.01 ± 3.49 (44)	25.72 ± 3.91 (39)	25.55 ± 3.59 (44)	***	NS	NS	NS
Education level (y)	11.93 ± 1.17 (44)	12.28 ± 1.07 (39)	13.78 ± 1.56 (44)		***	***	***
Age at onset (y)[a]	22.00 ± 3.94 (44)	20.19 ± 3.97 (38)	—	—	NS	NS	NS
Age at first hospitalization (y)[a]	23.40 ± 3.47 (44)	21.75 ± 3.89 (38)	—	—	NS	NS	NS
Time duration until first admission[a] (mo)	18.37 ± 28.21 (38)	18.53 ± 31.73 (36)	—	—	NS	NS	NS
Illness duration from onset (mo)[a]	24.27 ± 27.57 (44)	64.02 ± 32.51 (38)	—	—	NS	***	NS
Illness duration from first hospitalization (mo)[a]	4.93 ± 7.28 (44)	54.66 ± 30.05 (38)	—	—	NS	***	NS
No. of psychiatric hospitalizations[a]	1 (criterion) (44)	2.55 ± 1.25 (39)	—	—	NS	***	NS
Range of psychiatric hospitalizations	0–1	2–9	—	—	—	—	—
Frequency of psychiatric hospitalizations	0 (n = 5), 1 (n = 39)	2 (n = 26), 3 (n = 9), 4 (n = 3), 9 (n = 1)	—	—	—	—	—
Duration of last hospitalization (d)[a]	147.85 ± 150.40 (42)	116.15 ± 131.80 (34)	—	—	NS	NS	NS
Chlorpromazine dose equivalents[a]	244.76 ± 171.78 (44)	281.90 ± 142.66 (39)	—	—	NS	NS	NS
PANSS-positive symptoms	13.64 ± 4.61 (44)	15.27 ± 4.44 (39)	—	NS	NS	NS	NS
PANSS-negative symptoms	21.97 ± 6.73 (44)	23.06 ± 5.62 (39)	—	NS	NS	NS	NS
PANSS-general psychopathology	44.04 ± 7.74 (44)	44.18 ± 8.44 (39)	—	NS	NS	NS	NS
SANS-total score	41.56 ± 19.34 (44)	42.15 ± 18.36 (39)	—	NS	NS	NS	NS
Calgary Depression Scale-total score	5.27 ± 3.89 (44)	5.28 ± 4.02 (39)	—	NS	NS	NS	NS
Nonparametric Measures	N/Group N	N/Group N	N/Group N				*P*
Gender (female)	10/44	15/39	17/44	NS	NS	NS	NS
Patients with a comorbid physical illness	8/41	4/38	—	NS	NS	NS	NS
Patients with mental disorders in first-degree relatives	23/41	19/37	—	NS	NS	NS	NS

Table 1. Continued

Parametric Measures	FE, Mean ± SD (*n*)	ME, Mean ± SD (*n*)	Healthy, Mean ± SD (*n*)	Overall (*P*)	FE-Healthy (*P*)	FE-ME (*P*)	ME-Healthy (*P*)
Patients with a past suicide attempt	5/43	4/38	—	NS	NS	NS	NS
Patients receiving atypical antipsychotics as main medication	42/44	37/39	—	NS	NS	NS	NS
Patients receiving typical antipsychotics as main medication	2/44	1/44[b]	—	NS	NS	NS	NS

Note: PANSS, Positive and Negative Syndrome Scale; SANS, Scale for Assessment of Negative Symptoms.
[a]Compared using a Bonferroni-corrected $\alpha = .00625$.
[b]One patient received mood stabilizer as main medication.
***$P < .001$.

for parametric measures. A Bonferroni correction[48] was employed in *t* test comparisons in order to keep the total chance of erroneously reporting a difference below .05α (corrected α was set to .00625 for the 8 comparisons: comparisons are presented in table 2). The psychiatric rating scales were analyzed using a multivariate analysis of covariance (MANCOVA) for PANSS, SANS, and Calgary total scores, with "group" as a between-subjects factor. A similar MANCOVA was performed for the 3 PANSS factors, ie, positive, negative, and general psychopathology symptoms. Detailed parametric and nonparametric measures assessed in the study are listed in table 1.

Comparison of Cognitive Functioning. Cognitive measures in CANTAB tasks were compared using an ANCOVA or MANCOVA (for cognitive domains assessed by several measures, ie, memory and executive functions) with a between-subjects factor of "group." Analysis of the "number of errors" in the SWM task was conducted by a repeated-measures ANCOVA with a between-subjects factor of "group" and a within-subjects factor of "task difficulty" (4-, 6-, and 8-box problems). In all analyses, significant group differences were followed by Scheffe post hoc tests in order to identify the source of significant effects. Additional analyses were conducted in order to assess the contribution of illness duration and number of hospitalizations (as a measure of psychiatric episodes): (1) analyses were performed using either of the measures as covariate and (2) the 2 measures were included in a stepwise regression that included demographic and illness-related measures (for all SZ patients). This analysis was conducted in order to ascertain the predicative power of demographic and illness-related measures on cognitive functioning (table 1).

Results

Comparison of Demographic Measures Between FE Patients, ME Patients, and Healthy Controls

The groups were similar in gender distribution (NS; chi-square analysis) and in age ($F_{2,124} = 2.82$, NS). They did, however, differ in education levels ($F_{2,124} = 25.18$, $P < .001$; $r = 0.52$): the healthy controls had more years of education compared with both patient groups ($P < .001$ for both comparisons). Therefore, education level was used a covariate in ANOVA/multivariate ANOVA analyses (table 1).

Comparison in Disorder-Related Measures (Patient Groups)

No significant differences between the 2 SZ patient groups (FE and ME) were found for nonparametric disorder-related measures: existence of a comorbid physical illness, existence of mental disorders in first-degree

Table 2. Cognitive Functioning of the 3 Study Groups (First-Episode [FE] Patients, Multiepisode [ME] Patients, and Healthy Controls)

Cognitive Domain	Measure	FE, Mean ± SD (*n*)	ME, Mean ± SD (*n*)	Healthy, Mean ± SD (*n*)	Overall (*P*)	Covariate Analysis[a]	Effect Size (*r*)	FE-Healthy (*P*)	FE-ME (*P*)	ME-Healthy (*P*)
Psychomotor speed (MOT)	Response latency (msec)	818.32 ± 32.07 (44)	1011.74 ± 57.89 (39)	707.38 ± 13.75 (44)	***	*/NS	0.44	=	**	***
Attention (RVP)	*A*' (%)	88.21 ± 1.02 (43)	86.75 ± 0.93 (37)	92.65 ± 0.69 (42)	**	NS/NS	0.30	**	=	***
Pattern memory (PRM)	% correct	85.27 ± 1.69 (43)	77.96 ± 2.42 (37)	92.42 ± 1.15 (44)	***	NS/NS	0.38	*	*	***
Spatial memory (SRM)	% correct	76.47 ± 1.96 (43)	77.53 ± 1.64 (37)	86.50 ± 1.29 (44)	**	NS/NS	0.30	***	=	**
Executive function (working memory; SWM)	4-box errors (*n*)	1.88 ± 0.45 (44)	2.60 ± 0.54 (35)	0.44 ± 0.13 (43)	*	NS/NS	0.24	*	=	**
	6-box errors (*n*)	9.45 ± 1.37 (44)	13.74 ± 1.48 (35)	3.00 ± 0.52 (43)	***	NS/NS	0.42	***	*	***
	8-box errors (*n*)	19.54 ± 2.08 (44)	26.88 ± 2.33 (35)	10.06 ± 1.20 (43)	***	*/NS	0.40	**	*	***
Executive function (flexibility; IED)	Errors (*n*)	5.99 ± 0.66 (43)	8.50 ± 0.75 (38)	4.74 ± 0.57 (44)	***	*/*	0.29	=	*	*
	Stages completed (*n*)	8.45 ± 0.12 (43)	7.86 ± 0.16 (38)	8.45 ± 0.16 (44)	*	*/NS	0.25	=	*	***
Executive function (planning; SOC)	Initial thinking time (msec.)	668.83 ± 54.09 (44)	858.21 ± 75.37 (38)	555.26 ± 42.73 (44)	**	NS/NS	0.32	=	=	**
	Subsequent thinking time (msec.)	790.45 ± 97.82 (44)	1618.78 ± 144.91 (38)	484.82 ± 58.75 (44)	***	***/**	0.55	=	***	***
	Problems solved in minimum moves (*n*)	7.65 ± 0.36 (44)	7.11 ± 0.31 (38)	8.62 ± 0.26 (44)	*	NS/NS	0.22	=	=	**

Note: MOT, motor task; RVP, rapid visual processing; PRM, pattern recognition memory; SRM, spatial recognition memory; SWM, spatial working memory; IED, intra-extra dimensional; SOC, Stockings of Cambridge; =, NS (no significant difference between the two groups).
*$P < .05$, **$P < .01$, ***$P < .001$.
[a]*P* when using covariates (illness duration/number of hospitalizations).

relatives, performance of a past suicide attempt, treatment with atypical antipsychotics as main medication, and treatment with typical antipsychotics as main medication. There were also no significant differences in several parametric disorder-related measures, including age at first episode, age at first hospitalization, interval between first episode and first admission, length of last hospital stay, and chlorpromazine dose equivalents for neuroleptic medication ($t_{80} = 1.56$, NS; $t_{80} = 0.69$, NS; $t_{72} = 0.67$, NS; $t_{74} = 0.96$, NS; $t_{81} = 1.06$, NS, respectively). No differences were found between FE and ME patients in PANSS, SANS, and Calgary total scores ($F_{3,78} = 0.04$, NS). Similarly, there were no group differences for the 3 PANSS factors, ie, positive/negative/general symptoms ($F_{3,78} = 1.42$, NS). As could be expected from the selection criteria, ME patients had significantly longer illness duration (from first episode and from first hospitalization) and more hospitalizations ($t_{80} = 5.31$, $P < .001$; $t_{80} = 10.63$, $P < .001$; $t_{81} = 18.34$, $P < .001$, respectively). These differences remained significant after applying a Bonferroni correction (table 1).

Comparison of Cognitive Functioning (All Participants)

The 3 groups were compared in the following cognitive domains (table 2):

1. Psychomotor speed: There was a group main-effect for response latencies in the MOT ($F_{2,123} = 15.79$, $P < .001$); Scheffe post hoc tests indicated that healthy controls had similar response latencies to those of FE patients and shorter ones than ME patients. FE patients had shorter response latencies compared with ME patients.
2. Sustained attention: There was a group difference in A' (probability to detect a target) in the RVP task ($F_{2,118} = 5.88$, $P < .01$): the healthy controls gave more correct responses compared with both patient groups (with no significant differences between the 2 patient groups).
3. Memory: There was a "group" main-effect for the "% correct responses" in the MANCOVA for memory performance ($F_{4,238} = 7.37$, $P < .001$, $r = 0.33$) with significant effects for both PRM and SRM tasks ($F_{2,120} = 11.09$, $P < .001$; $F_{2,120} = 6.10$, $P < .01$, respectively). In the PRM task, the healthy controls gave more correct responses than the patient groups and the FE patients gave more correct responses than the ME patients. In the SRM task, the healthy controls gave more correct responses than the patient groups but there was no significant difference between the 2 patient groups.
4. Executive functions:
   a. Working memory (SWM task)—There was a "group" and "task difficulty" main-effects in the "% errors" performed in this task ($F_{2,118} = 13.46$, $P < .001$, $r = 0.42$; $F_{2,236} = 11.11$, $P < .001$, $r = 0.28$, respectively]. The 2 main-effects were qualified by a "group" × "task difficulty" interaction ($F_{4,236} = 8.73$, $P < .001$, $r = 0.34$). Separate ANCOVAs for each task difficulty indicated an increasing differentiation between the study groups: (1) 4-box problems ($F_{2,118} = 3.85$, $P < .05$): healthy controls performed fewer errors compared with both FE and ME patients. There was no significant difference between the 2 patient groups. (2) 6-box and 8-box problems ($F_{2,118} = 13.09$, $P < .001$; $F_{2,118} = 11.58$, $P < .001$, respectively): a similar trend was evident in both tasks, with healthy controls conducting the fewest errors, followed by the FE patients, and then the ME patients.
   b. Cognitive shifting and flexibility (IED task)—there was a "group" main-effect in the MANCOVA for IED measures ($F_{4,240} = 3.10$, $P < .05$, $r = 0.2$) with differences found for both "number of errors" and "number of completed stages" ($F_{2,121} = 8.38$, $P < .001$; $F_{2,121} = 4.62$, $P < .05$, respectively); healthy controls completed a similar "number of stages" as the FE patients and fewer compared with the ME patients. A similar pattern was found for the "number of errors" performed in the IED task.
   c. Cognitive planning (SOC task)—there was a "group" main-effect in the MANCOVA for SOC measures ($F_{6,240} = 9.19$, $P < .001$, $r = 0.42$) with significant differences found for "initial thinking time," "subsequent thinking time," and the "number of problems solved in minimum moves" ($F_{2,122} = 7.11$, $P < .01$; $F_{2,122} = 27.27$, $P < .001$; $F_{2,122} = 3.35$, $P < .05$, respectively). The healthy controls had longer thinking time (initial and subsequent) and completed more stages in the least number of moves compared with the ME patients. There were no significant differences between the healthy controls and the FE patients in all tested measures. The FE patients had shorter subsequent thinking times compared with the ME patients.

Next, we focused on the SZ patients in order to explore the ability of patient variables to predict their cognitive functioning. Both "illness duration" and "number of hospitalizations" were strong predictors of cognitive functioning. Illness duration significantly predicted psychomotor speed (response latency; MOT), pattern memory (% correct responses; PRM), cognitive shifting (errors; IED), and cognitive planning (initial and subsequent thinking times; SOC). Number of hospitalizations had a lower predictive power (compared with illness duration), significantly predicting working memory (errors in 6- and 8-box problems; SWM) and cognitive flexibility

(number of completed stages; IED). The effect of illness duration and number of hospitalizations on cognitive functioning can also be evident in the fact that the use of the 2 as covariates led to a reduction in group differences (see table 1).

To summarize, SZ patients exhibited widespread cognitive impairments when compared with healthy control subjects. While no differences were found in SZ symptoms, the 2 patient groups showed a different profile of deficits. ME patients were significantly more impaired than the FE patients as indicated by slower psychomotor speed and poorer pattern memory and executive functioning.

Discussion

The current study assessed the cognitive functioning of FE and ME patients and compared the findings with those of healthy control subjects. Both patient groups showed impairments in major cognitive domains compared with controls as had been shown earlier by others.[3,49] The 2 patient groups, however, showed a distinctly different cognitive profile: the FE patients exhibited focused deficits in selected cognitive domains in contrast to the more generalized spread of cognitive deficits of the ME patients.

The ME patients had slower response latencies compared with the FE patients, indicating deficits in *psychomotor speed* (in agreement with Albus et al[13] and Saykin et al[14]). As for *visuospatial memory*, the ME group showed deficits only in pattern memory but not in spatial memory (compared with the FE patients). Earlier studies demonstrated poorer visual memory performances for ME patients.[13,14,22] The current study adds more data to these previous findings, suggesting a possible dissociation between pattern and spatial domains of visual memory. The emerging picture is that of a focused memory impairment among ME patients, concentrating on visual pattern memory, without accompanying verbal memory impairments.[5,22]

Using a fractioned approach to executive functioning, the ME patients were found to be impaired in *working memory* performance compared with the FE patients (SWM task). These working memory deficits are likely to interfere with their capacity to carry out multistep activities, to complete mental manipulations, and to follow complex instructions. Moreover, group differences were mainly evident in more difficult tasks (ie, 6- and 8- box problems), indicating that the impairments of ME patients are likely to appear only in more demanding tasks (compared with the FE patients). The ME patients were also deficient in their *cognitive flexibility* (IED task), in their ability to look at situations from multiple vantage points and in their ability to produce a variety of behaviors. Finally, the ME patients had difficulties in "*cognitive planning and organization*" (SOC task), in setting a goal, and in determining the best way to reach that goal. Taken together, these findings draw a consistent picture of executive dysfunctions among ME patients compared with patients at earlier stages of the disorder. Such a profile is in agreement with most earlier studies (eg, Saykin et al[14], Fucetola et al[15], Addington and Addington[22]) and the prefrontal dysfunctions of SZ patients.[50] The reason that other studies failed to find FE-ME group differences in executive functions may be related to the inclusion of older patients (masking cognitive changes between the groups) (eg, Rubin et al[51]). These inconsistencies stress the need for future studies to focus on executive functions. The fact that executive functions are a major determinant of functional outcome underscores this need.[52] As such, it would be worthwhile to conceptualize executive functions as a number of different higher order cognitive processes (as we have done in the current study).

The findings of the current study indicate that ME patients do not differ from FE patients in their *sustained attention* and *spatial memory* capabilities. Functioning in other key cognitive domains was found to be deficient in ME patients when compared with FE patients, suggesting cognitive changes with illness progression. Several tentative lines of evidence indicate that 2 disorder-related variables (ie, illness duration and number of hospitalizations) are a major source of differences between the patient groups. First, group assignment in the current (and similar studies) is highly dependent on these 2 disorder-related variables. Second, entering these variables as covariates eliminated many of the significant effects. Finally, a regression analysis suggests that these 2 variables are strong predictors of the cognitive differences between the 2 groups. The regression analysis further suggests that illness duration is a stronger predictor of cognitive functioning. This may stem from the fact that the number of hospitalizations is only a "proxy" measure of the number of psychotic episodes (that are difficult to measure reliably), thereby lowering its predictive ability. Future studies should focus on these 2 variables and explore their specific effects of cognitive functioning. Moreover, the use of regression analysis and more direct measures of psychotic episodes (ie, number and intensity) are recommended. Such studies may extend the findings of the current study, which point toward the decisive effects of illness duration on cognitive functioning at the initial stages of SZ.

Before concluding the article, several methodological issues and limitations of the current study should be addressed. The use of a cross-sectional design raises the risk of biased sample selection. As elaborated in the "Introduction" section, this constitutes a limitation for the study and raises the need for complementary longitudinal research (assessing neurocognitive changes with illness progression). In addition, several earlier studies reported findings that are not in line with our current ones. For example, Saykin et al[14] and Albus et al[13] found poorer attention performance of more chronic patients.

These inconsistencies may be related to inadequate management of confounding variables, such as changes in neuroleptic medication.[3,5] This necessitates a careful monitoring of possible confounders and a careful detailing of patient characteristics (allowing the demonstration of a similarity between patient groups). Finally, the current study did not assess premorbid functioning of the patients. Cognitive deficits were already evident in individuals who eventually developed SZ and had been evaluated before the onset of the disorder.[53] Such a pattern was evident in patient populations of several additional studies,[54–56] as well as in persons at genetic high-risk for the development of SZ.[57] These findings stress the need to assess premorbid functioning and (if possible) to incorporate this in the study design and data analyses.

Overall, the current study points toward both stable and progressively deteriorating cognitive functioning during the initial stages of SZ. The fact that both trends are evident reflects the move away from earlier contrasting models of SZ, ie, the *neurodevelopmental and neurodegenerative theories of SZ*.[58–60] The neurodevelopmental theory generally supports an early deficit in cognitive functioning, while the neurodegenerative theory predicts a gradual cognitive decline in affected individuals. Later conceptualizations presented a synthesis of these earlier viewpoints (progressive neurodevelopmental model[59,61,62]). Such a synthesis is in line with findings indicating both stable and putatively declining cognitive functioning (eg, Fucetola et al[15]). The fact that memory and executive functions are highly related to community functioning[63–66] stresses the need to develop rehabilitation programs that focus on these cognitive domains. The first years after onset may represent a therapeutic window for rehabilitation efforts focusing on the specific needs of SZ patients. Without proper intervention, the growing cognitive impairments will inevitably complicate rehabilitation efforts and impact the patients' daily performance.

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