The Relative Contribution of Cognition and Symptomatic Remission to Functional Outcome Following Treatment of a First Episode of Psychosis

Gerald Jordan, MA; Danyael Lutgens, MA; Ridha Joober, MD, PhD; Martin Lepage, PhD; Srividya N. Iyer, PhD; and Ashok Malla, MB, FRCPC

ABSTRACT

Objective: Functional recovery remains the primary goal following treatment of a psychotic disorder, especially after a first episode. Evidence regarding relative contributions of predictors of functional outcome, including symptoms and cognition, remains equivocal. The objective of the study was to determine the relative contribution of cognition, in particular verbal memory, and symptomatic remission to social and occupational functioning while controlling for established predictors of functioning in a large sample of patients presenting with a first episode of a schizophrenia spectrum or affective psychosis.

Method: Patients (aged 14–35 years) met *DSM-IV* criteria for a first episode of a schizophrenia spectrum or affective psychosis and had been admitted to the Prevention and Early Intervention Program for Psychoses, Montreal, Quebec, Canada, between 2003 and 2009 for treatment and follow-up for 2 years. Established predictors (duration of untreated psychosis, medication adherence, age at onset, substance use, premorbid adjustment), verbal memory, and length of positive and negative symptom remission were regressed on functioning (using the Strauss Carpenter Scale) at 1 (n = 208) and 2 (n = 159) years. Regressions were conducted with established predictors in the first step, followed by verbal memory and consecutive months of combined positive and negative symptom remission in the third step. Regressions were then repeated with length of positive and negative symptom remission, respectively.

Results: Length of combined positive and negative symptom remission explained the most variance in functioning at 1 (R^2 adjusted = 0.35, $F_{9,129} = 9.33$, $P < .001$) and 2 (R^2 adjusted = 0.38, $F_{9,97} = 8.21$, $P < .001$) years, and verbal memory contributed only slightly to such outcome. While length of remission of negative symptoms was a stronger predictor of functioning than remission of positive symptoms at 1 year, length of positive symptom remission also made a large contribution at 2 years.

Conclusions: These results highlight the importance of achieving and maintaining remission of both negative and positive symptoms for longer periods in patients with a first episode of a psychotic disorder and the need for effective interventions to do so.

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Corresponding author: *Ashok Malla, MBBS, DPM, Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute, 6875 Blvd Lasalle, Montreal, Quebec H4H 1R3, Canada (ashok.malla@mcgill.ca).*

Trajectories of academic, employment, and social functioning, often interrupted with the onset of psychosis,[1,2] are important for recovery.[3] Cognitive deficits, especially in verbal memory, are present in many patients during their first episode of a psychotic disorder (FEP), most often within the schizophrenia spectrum. Furthermore, following treatment, many patients do not meet criteria for a full remission of positive and negative symptoms. While a predominant role of cognition, in particular verbal memory, and a relatively limited role of symptom levels in determining social and community functioning among patients with a psychotic disorder have been promoted,[4,5] some have demonstrated a more significant role for symptoms,[6,7] especially following treatment of a first episode. The consensus definition of remission in schizophrenia[8] has promoted an interest in exploring the role of symptom remission in functional outcome. Studies investigating the relative contribution of symptoms and cognition on functioning among FEP patients have produced mixed results. Some found that negative symptoms and cognition are important[7,9]; one study revealed the primacy of negative symptoms[10] and another demonstrated cognition to be more important.[11] Studies exclusively examining the role of either symptoms[12] or cognition[13,14] have simply confirmed their respective importance.

Our primary objective was to determine the relative contribution of verbal memory and symptomatic remission to social and occupational functioning in patients treated for FEP, thus validating the practical utility of remission criteria.[8] As a secondary objective, we examined separately the relative contribution of positive and negative symptom remission to functioning.

METHOD

Treatment Setting and Subjects

Participants included patients admitted (2003–2009) to the Prevention and Early Intervention Program for Psychoses (Montreal, Quebec, Canada) for treatment of a first episode of a schizophrenia spectrum or affective psychosis. This is the only specialized early intervention service providing care to an urban population of 400,000 in the catchment area of southwest Montreal. Admission criteria are as follows: diagnosis of a nonaffective or affective psychotic disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV)* criteria; aged 14–30 years; not having received antipsychotic medication for more than 1 month; intelligence quotient above 70; and absence of an organic brain condition. Patients with a secondary diagnosis of substance

Clinical Points

- Achieving and sustaining remission of both positive and negative symptoms of psychotic disorders is extremely important to achieve a good functional outcome (eg, employment and social relations) for patients, especially during the early years following onset.
- Achieving and maintaining remission of both positive and negative symptoms is likely to involve maintaining adherence to antipsychotic medication, engagement in other therapeutic interventions, and addressing other triggers of relapse such as substance abuse and interpersonal stress.
- Patients unable to achieve or sustain remission may need a more intensive specialized approach very early in the course of treatment.

abuse are included. Treatment mainly includes antipsychotic medication, case management, family interventions, and, where indicated, cognitive-behavioral therapy.[15] This study was approved by the Ethics Board of Douglas Mental Health University Institute (Montreal, Quebec, Canada), and informed consent was obtained from all study participants.

Materials

Patients presenting with the first episode of a schizophrenia spectrum disorder (schizophrenia, schizophreniform disorder, delusional disorder, or schizoaffective disorder) and affective psychotic disorder (bipolar or major depressive disorder with psychotic symptoms) were included. Diagnosis was established with the Structured Clinical Interview for *DSM-IV* (SCID)[16] and confirmed through consensus by 2 senior psychiatrists (R.J. and A.M.) at baseline and at 1-year follow-up (Table 1). In the rest of the article, all patients will be referred to as FEP for brevity and in agreement with vast literature published in the last 20 years.

Symptoms and remission. Symptoms were evaluated using the Scale for the Assessment of Positive Symptoms (SAPS)[17] and Scale for the Assessment of Negative Symptoms (SANS).[18] Interrater reliability coefficients revealed substantial agreement on the SAPS ($\kappa = 0.74$) and SANS ($\kappa = 0.71$). According to consensus remission criteria,[8] participants were considered in total remission if they scored ≤ 2 on all 4 SAPS global subscale items (hallucinations, delusions, bizarre behavior, thought disorder) and SANS global subscale items (affective flattening, alogia, apathy-avolition, asociality-anhedonia). Positive symptom remission was established when remission criteria for SAPS global items were met, while participants were considered in negative symptom remission when criteria for SANS global items were met.

Symptoms were assessed at baseline and at 8 subsequent times during the 2-year period of treatment and follow-up (months 1, 2, 3, 6, 9, 12, 18, and 24). When no assessments were conducted (eg, at months 4, 5, 7, 8 10, 11, 13–17, 19–23), positive symptom remission was established through clinical notes. The last observation carried forward (LOCF) technique was applied to SAPS data when sufficiently detailed notes were unavailable (eg, evaluations from month 3 were carried forward to month 6). For missing negative symptom remission data, we applied the LOCF technique because of doubts about the reliability of evaluating negative symptoms on the basis of clinical notes.

We examined the maximum number of continuous months in remission. If a participant was in remission for 5 consecutive months, followed by a period of no remission for 3 months, the maximum number of months in remission was recorded as 5. Previous research has demonstrated a 3-month time criterion for remission had equal predictive validity as a 6-month criterion in FEP.[12] Furthermore, using continuous variables may result in greater statistical accuracy and more face validity than categorical measures.[19] Comparison of remission status based on SAPS ratings with that obtained through the LOCF procedure, for participants for whom 12 complete months of data were available, showed that 82.87% of our LOCF estimates were correct.

Cognition. Given the previously reported strong association of verbal memory with functional outcome[4,20] and early remission,[21] we tested the role of verbal memory (based on the Wechsler Memory Scale-III [WMS-III] logical memory immediate recall, delayed recall and recognition[22]) in predicting functional outcome. Based on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) recommendations,[23] we also examined the following additional cognitive domains: attention/vigilance (d2 Test of Attention[24]), working memory (digit span subtests of the Wechsler Adult Intelligence Scale, Third Edition-Revised [WAIS-III-R],[22] spatial span subtests of the WMS-III), visual learning and memory (WMS-III visual reproduction), reasoning and problem-solving (WAIS-III block design, Trail Making Test Part B[25]), and speed of processing (Trail Making Test Part A,[25] WAIS-III digit symbol coding). Tests were administered to participants when they were considered clinically stable, usually within the first 3 months after initiation of treatment. Clinical stability was based on the patient's ability to tolerate and participate in at least an hour of cognitive assessment and arrived at through consensus between clinicians and the senior author (A.M.). The same battery was administered to age- and gender-matched healthy controls (n = 73) recruited from the same catchment area.[20] To create domains, scores were z-transformed on the basis of mean and standard deviations from healthy controls and then averaged. Each domain was averaged and z-transformed to produce a global cognitive domain reflecting overall cognitive performance.

Established predictors of functioning. On the basis of their previously established influence on outcomes in FEP, we included age at onset,[26] premorbid adjustment,[27] duration of untreated psychosis,[28] gender,[29] medication adherence,[30] and substance use[31] as potential confounds. Premorbid Adjustment Scale (PAS)[27] scores were considered for childhood (up to age 11 years) and early adolescence (12–16 years) on educational and social domains. Ratings from late adolescence and early adulthood were omitted because of potential overlap with onset of prodromal and/

Table 1. Demographic and Clinical Characteristics: Comparisons of Study Participants Versus Nonparticipants[a]

	Year 1		Year 2	
Variable	Participants (n = 208)	Nonparticipants (n = 110)	Participants (n = 159)	Nonparticipants (n = 119)
Medication adherence, frequency (%)				
0%–74%	29 (14.3)	50 (50.5)**	12 (7.5)	47 (43.5)**
75%–100%	174 (85.7)	49 (49.5)	147 (92.5)	61 (56.5)
Age at entry, mean (SD), y	22.69 (4.01)	23.34 (4.09)	22.75 (4.01)	23.24 (4.03)
Age at onset, mean (SD), y	22.01 (3.77)	22.38 (3.85)	21.95 (4.03)	22.24 (3.99)
Gender, frequency (%)				
Male	144 (69.2)	70 (70.0)	108 (67.9)	82 (71.9)
Female	64 (30.8)	30 (30.0)	51 (32.1)	32 (28.1)
Substance abuse and dependence, frequency (%)				
No	81 (40.1)	41 (45.6)	68 (42.8)	47 (42.7)
Yes	121 (59.9)	49 (54.4)	56 (57.2)	60 (54.5)
Education, frequency (%)				
< High school	79 (38.5)	34 (36.2)	59 (37.6)	37 (33.6)
≥ High school	126 (61.5)	60 (63.8)	98 (62.4)	73 (66.4)
Marital status, frequency (%)				
Single	188 (90.4)	87 (88.8)	145 (91.2)	98 (86.7)
In a relationship	20 (9.6)	11 (11.2)	14 (8.8)	15 (13.3)
Socioeconomic status, frequency (%)				
Upper class	36 (18.0)	15 (15.8)	30 (19.6)	16 (14.3)
Upper middle	44 (22.0)	25 (26.3)	32 (20.9)	26 (23.2)
Middle	43 (21.5)	22 (23.2)	32 (20.9)	28 (25.0)
Lower middle	62 (31.0)	28 (29.5)	49 (32.1)	34 (30.4)
Lower	15 (7.5)	5 (5.3)	10 (6.5)	8 (7.1)
Diagnosis, frequency (%)				
Schizophrenia spectrum disorder	156 (74.86)	72 (73.50)	121 (76.10)	88 (78.60)*
Affective disorder	51 (24.50)	23 (23.50)	38 (23.90)	20 (17.90)
Duration of untreated psychosis (log), mean (SD)	1.25 (0.64)	1.32 (0.66)	1.23 (0.64)	1.35 (1.35)
Baseline Strauss Carpenter score, mean (SD)	4.11 (2.12)	4.53 (1.99)	4.2 (2.17)	4.12 (4.12)
Premorbid adjustment, mean (SD)	0.25 (0.14)	0.24 (0.13)	0.24 (0.14)	0.24 (0.24)

[a]Numbers may not add up to 208 and 159 for all variables due to missing data or rounding.
*$P < .05$. **$P < .01$.

or psychotic symptoms. Duration of untreated psychosis was defined as the period between the onset of psychotic symptoms until treatment with antipsychotic medication for 30 days[32] using the Circumstances of Onset and Relapse Schedule.[33] Medication adherence was assessed through a previously validated method[12] using multiple sources (patients, families, case managers, and clinical notes), and patients were rated as being adherent (75%–100% of the time) or nonadherent (0%–74%). Presence or absence of a comorbid SCID diagnosis of substance abuse/dependence at baseline was considered in the analyses.

Functional outcome. Functional outcome was measured using the Strauss Carpenter Scale (SCS[34,35]) at months 12 and 24 during face-to-face interviews. The SCS is a widely used and validated composite index of functioning.[36] Only the social adjustment (eg, number of times friends are seen per month) and occupational functioning (eg, amount of time employed during the past year) subscales were used, as the other 2 subscales (eg, rehospitalization, psychiatric symptoms) overlap with the concept of being in remission. Participation in educational courses replaced the employment variable where appropriate.

Data analyses. To evaluate the primary objective, the established predictors of functioning (eg, duration of untreated psychosis, medication compliance, gender, age at onset, substance abuse, premorbid adjustment) were entered in the first step followed by verbal memory in the second step. Step 3 contained the maximum number of consecutive months in total (combined positive and negative) symptom remission. To evaluate the secondary objective, we again entered the established predictors in step 1, verbal memory in step 2, the maximum number of consecutive months of positive symptom remission in step 3, and, lastly, negative symptom remission in step 4. To determine if overall cognitive performance was as important for functioning as verbal memory, we also repeated each regression by substituting verbal memory with the global cognitive domain. All analyses were regressed on SCS scores at 1 and 2 years.

RESULTS

Preliminary Analysis

Among the participants included in the evaluation of functional outcome at 1 year (n = 318), 66 dropped out prior to completing 1 year of treatment, 38 refused to complete symptom assessments, and 6 were reassessed as not having a psychotic disorder, yielding a final sample of 208. Among the participants included in the evaluation of functional outcome at 2 years (n = 278), 92 participants had dropped out of treatment and 27 were excluded from analyses due to incomplete assessments, yielding a final sample of 159. Dropouts were not different on demographic, cognitive, or clinical characteristics compared to those who were included in treatment (Table 1).

Duration of untreated psychosis (weeks) was positively skewed and was corrected with a logarithmic transformation. No multicolinearity among known predictors was detected.

Figure 1: Differences Between Healthy Controls (n = 73) and Participants Who Completed 2 Years of Treatment (n = 159) on Neurocognitive Domains

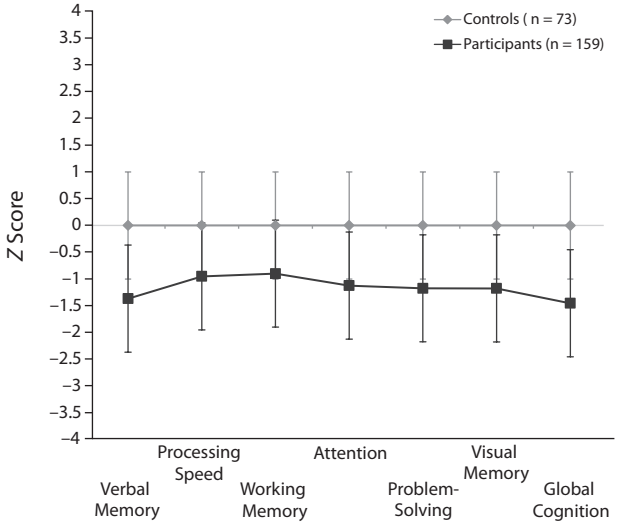

Table 2. Bonferroni Corrected Pearson Correlations Between Remission, Cognitive Domains, and Functioning at 1 and 2 Years

	Functional Outcome at Year 1		Functional Outcome at Year 2	
Variable	r^a	*P*	r^a	*P*
Remission				
Months in total symptom remission	0.553	<.001*	0.507	<.001*
Months in negative symptom remission	0.610	<.001*	0.530	<.001*
Months in positive symptom remission	0.283	<.001*	0.329	<.001*
Cognition				
Verbal memory	0.191	.014	0.191	.041
Processing speed	0.055	.481	0.129	.173
Working memory	0.131	.088	0.177	.056
Attention	0.071	.378	0.168	.081
Problem-solving	0.101	.191	0.070	.453
Visual memory	0.153	.059	0.092	.343
Global cognition	0.165	.032	0.177	.056

[a]Pearson correlation coefficient.
*P < .005.

Sixty-two participants (30%) were in total remission at month 12 for a mean of 2.4 (SD = 3.25) months, while 141 (67.8%) and 69 (33.2%) were in positive or negative symptom remission for a mean of 7 (SD = 4.17) and 2.9 (SD = 3.55) months, respectively. Likewise, 66 (41.5%) were in total remission by month 24 (mean = 5.7 months, SD = 6.57), with 110 (69.2%) and 77 (48.4%) in positive and negative symptom remission for a mean of 13.9 (SD = 7.91) and 6.79 (SD = 7.31) months, respectively. Cognitive profiles of participants and healthy controls were significantly different (P < .001) (Figure 1), with patients performing poorly on most dimensions.

Correlations Between Cognitive Domains, Symptom Remission, and Functional Outcomes

Correlations between positive and negative symptom remission were observed over 1 (r_{207} = 0.327, P < .001) and 2 (r_{158} = 0.369, P < .001) years. Furthermore, an extremely modest correlation between global cognition and negative symptom remission was found at 1 year (r_{207} = 0.149, P = .043), which did not persist at 2 years (r_{144} = 0.005, P = .96). SCS scores at 1 and 2 years and length of remission (eg, total, positive, and negative symptom remission) were strongly correlated. Functional outcome, as assessed by SCS score, was not correlated with any cognitive domain (Table 2).

Table 3. Symptom Remission, Cognition, and Other Predictors of Functional Outcome: Regression Analysis

	Year 1		Year 2	
Block	SE β	β	SE β	β
Block 1				
Duration of untreated psychosis	0.271	−0.073	0.369	0.008
Medication compliance	0.516	0.066	0.807	0.018
Age at onset	0.045	−0.110	0.052	−0.001
Gender	0.384	0.152†	0.472	−0.029
Substance abuse	0.366	−0.054	0.029	−0.212*
Premorbid adjustment	1.252	−0.199*	1.566	−0.308**
Block 1 R^2 change	0.072		0.128	
Block 2				
Duration of untreated psychosis	0.266	−0.033	0.372	0.034
Medication compliance	0.504	0.101	0.801	0.021
Age at onset	0.044	−0.089	0.051	0.000
Gender	0.378	0.200*	0.490	−0.075
Substance abuse	0.360	−0.003	0.029	−0.196*
Premorbid adjustment	1.231	−0.153†	1.600	−0.272**
Verbal memory	0.133	0.277**	0.183	0.162
Block 2 R^2 change	0.065		0.021	
Block 3				
Duration of untreated psychosis	0.235	0.030	0.328	0.058
Medication compliance	0.451	0.003	0.712	0.082
Age at onset	0.039	−0.138†	0.045	0.006
Gender	0.340	0.089	0.432	−0.060
Substance abuse	0.316	−0.021	0.025	−0.153†
Premorbid adjustment	1.083	−0.108	1.436	−0.179*
Verbal memory	0.121	0.138†	0.162	0.104
Months in total remission	0.048	0.498**	0.028	0.468**
Block 3 R^2 change	0.206		0.198	
Block 3 R^2 adjusted	0.302		0.294	

†P < .1. *P < .05; **P < .01.

Primary Objective

The regression on functional outcome at 1 year (Table 3) showed an effect for premorbid adjustment, but the overall model at step 1 was not significant ($F_{6,132}$ = 1.700, P = .126, R^2 adjusted = 0.030). Adding verbal memory to the model in the second step was significant ($F_{7,131}$ = 2.97, P = .006) and explained 9% of the variance in functioning (R^2 adjusted = 0.091), with male gender and verbal memory as significant predictors. Adding consecutive months in total remission in the final model explained an additional 20% of variance and 30% of the total variance in functioning (R^2 adjusted = 0.302, $F_{8,130}$ = 8.48, P < .001). Only consecutive months in total remission significantly predicted functional outcome in this model.

The analysis of functional outcome at 2 years (Table 3) showed a significant effect for the first step, and absence of a substance use diagnosis and better premorbid adjustment were significant among established predictors ($F_{6,100}$ = 2.46, P = .029). This step explained 8% of variance in functioning

Table 4. Separating the Influence of Positive and Negative Symptom Remission on Functional Outcomes: Regression Analysis

	Year 1		Year 2	
Block	SE β	β	SE β	β
Block 1				
Duration of untreated psychosis	0.271	−0.073	0.369	0.008
Medication compliance	0.516	0.066	0.807	0.018
Age at onset	0.045	−0.110	0.052	−0.001
Gender	0.384	0.152†	0.472	−0.029
Substance abuse	0.366	−0.054	0.029	−0.212*
Premorbid adjustment	1.252	−0.199*	1.566	−0.308**
Block 1 R^2 change	0.072		0.128	
Block 2				
Duration of untreated psychosis	0.266	0.372	0.034	0.021
Age at onset	0.044	−0.089	0.051	0.000
Gender	0.378	0.200*	0.490	−0.075
Substance abuse	0.360	−0.003	0.029	−0.196*
Premorbid adjustment	1.231	−0.153†	1.600	−0.272**
Verbal memory	0.133	0.277**	0.183	0.162
Block 2 R^2 change	0.065		0.021	
Block 3				
Duration of untreated psychosis	0.258	−0.013	0.339	0.021
Medication compliance	0.498	0.048	0.730	0.000
Age at onset	0.043	−0.135	0.047	−0.038
Gender	0.366	0.185*	0.446	−0.089
Substance abuse	0.349	−0.018	0.026	−0.183*
Premorbid adjustment	1.191	−0.149†	1.456	−0.268**
Verbal memory	0.132	0.215*	0.169	0.080
Months in positive remission	0.040	0.263**	0.025	0.404**
Block 3 R^2 change	0.061		0.154	
Block 4				
Duration of untreated psychosis	0.226	0.033	0.309	.055
Medication compliance	0.437	0.002	0.706	0.134
Age at onset	0.038	−0.161*	0.043	−0.021
Gender	0.333	0.049	0.412	−0.013
Substance abuse	0.305	−0.041	0.024	−0.141†
Premorbid adjustment	1.050	−0.081	1.353	−0.183*
Verbal memory	0.119	0.089	0.154	0.065
Months in positive remission	0.036	0.124	0.027	0.189*
Months in negative remission	0.046	0.517**	0.029	0.453**
Block 4 R^2 change	0.196		0.129	
Block 4 R^2 adjusted	0.352		0.380	

†$P<.1$. *$P<.05$. **$P<.01$.

(R^2 adjusted = 0.076). The second model with the addition of verbal memory was also significant ($F_{7,99} = 2.48$, $P = .022$), explained only 2% unique variance in the model, and accounted for 9% of total variance in functioning (R^2 adjusted = 0.089). The third step with the addition of months in total remission was significant ($F_{8,98} = 6.51$, $P < .001$) and represented a 19% increase in variance. In this final model, number of months in total remission and better premorbid adjustment were significant predictors and explained a total of 29% of variance in functioning (R^2 adjusted = 0.294).

Secondary Objective

In the 1-year analysis (Table 4), gender, verbal memory, and months in *positive* symptom remission were significant at step 3 ($F_{8,130} = 4.01$, $P < .001$), explaining 15% of variance in functioning (R^2 adjusted = 0.148). In step 4, adding months in *negative* symptom remission added 20% unique variance to the model and was significant ($F_{9,129} = 9.33$, $P < .001$), explaining a total of 35% of variance in functioning (R^2 adjusted = 0.35). In this final model, younger age at onset and consecutive months in negative symptom remission were significant.

With respect to the analysis of 2-year outcome (Table 4), adding consecutive months in positive symptom remission in the third step was significant ($F_{8,98} = 5.33$, $P < .001$) and associated with 24% of variance in functioning (R^2 adjusted = 0.24). Better premorbid adjustment and the absence of a substance use diagnosis were also significant at this step. The addition of months in negative symptom remission in the final step added an additional 13% of variance. This final model explained 38% of variance in functioning (R^2 adjusted = 0.38, $F_{9,97} = 8.21$, $P < .001$) and consisted of premorbid adjustment and length of positive and negative symptom remission.

Post Hoc Tests

When the analyses were repeated with global cognition replacing verbal memory, a greater effect of global cognition was not found, suggesting that verbal memory may be a stronger predictor of functioning than overall cognitive performance. All analyses were also repeated without the known predictors of functioning in the first step, yielding similar results to the original analyses with respect to verbal memory as well as total, positive, and negative symptom remission.

DISCUSSION

Our objective was to determine the relative contribution of cognition, specifically verbal memory, and symptom remission (positive and negative) to functional outcome in the first 2 years of treatment of FEP, after controlling for other known predictors. Results showed that sustained remission of symptoms, especially of negative symptoms, made a larger contribution to functional outcome than verbal memory.

The relatively strong contribution of negative symptom remission for functional outcome was particularly evident at 1 year. At 2 years, length of total symptom remission explained the largest proportion of variance in outcome. The latter was largely contributed by the length of positive symptom remission. The unique contribution of negative symptom remission was lower than that observed at 1 year. Correlations between negative and positive symptom remission were stronger over 2 years than 1 year. Those who continued to not meet remission criteria may have had both residual positive and negative symptoms. Some patients who achieved remission of positive symptoms early on may have relapsed, not achieved full remission, and maintained persistent positive symptoms, especially in the second year.

Our finding of a modest contribution of verbal memory to functioning is somewhat consistent with previous studies showing that performance on verbal tasks is important for outcome.[23] It has been proposed[37] that cognition imparts the capacity to function, while negative symptoms determine the motivation and likelihood to perform these tasks. The role of poor motivation and apathy in functional outcome has been reported previously in a relatively small sample of more chronically ill schizophrenia patients.[38] This differential

nature of contribution of cognition and negative symptoms may explain our findings and may also correspond to the importance of premorbid functioning as was reflected in our models. Of importance is that the negative symptom dimension is relatively independent of cognition, and any overlap between these 2 domains cannot explain our findings.

It could be argued that there may be some overlap between the item content of some of the domains of negative symptoms (apathy and asociality) and items on the SCS. However, we examined correlations separately for the 2 relatively independent domains of negative symptoms (affective flattening-alogia and apathy-avolition)[39] with the SCS scores and found both to be equally correlated ($r = 0.496$ and 0.504, respectively) with the outcome variable (SCS scores). The role of amotivation in functional outcome, as assessed by an independent apathy scale, has previously been demonstrated in a sample of chronically ill patients.[38] Further, we have used a composite definition of remission, currently recommended through expert consensus,[8] which incorporates all domains of negative symptoms and has received support for its utility through validation with functional outcome.[12] Further, our results also show that, at 2 years, length of positive symptom remission makes a large contribution to functional outcome, suggesting the importance of achieving lengthy remissions of both positive and negative symptoms.

Consecutive months in remission were predictive of functional outcome, suggesting that a fixed criterion of 6 months may not be necessary for examining associations between remission and functional outcome. Our results highlight the importance of persistent symptoms for their impact on functional outcome. More intensive treatment including the more targeted use of antipsychotic medication (eg, early use of clozapine), reducing substance abuse,[40] improving adherence to medication,[41] and intensive psychosocial interventions (eg, family intervention) may result in improved rates and longer sustenance of remission.

Findings concerning the role of comorbid substance abuse and premorbid adjustment[12,42] were consistent with previous studies, especially at 2 years. This result may suggest that premorbid adjustment is more of a trait variable and has a lasting effect on functioning[20] while substance abuse is more difficult to treat[43] and remains a significant predictor of relapse even in patients who are totally adherent to medication.[40] On the other hand, a significant impact of duration of untreated psychosis[44] and earlier age at onset[45] were not confirmed in our study. Younger age at onset was associated with better functioning at 1 year, consistent with another study,[26] perhaps due to the extra support received by younger patients from their families. The effect of duration of untreated psychosis on outcome may generally be overshadowed by other variables that come into play after the patient enters treatment as suggested by another study.[46] The absence of the effect of duration of untreated psychosis on functional outcome may also reflect a relatively short duration of untreated psychosis for the majority of patients in this program, achieved through many years of active early case identification interventions in the community.

Strengths and Limitations

Our study has several strengths. Use of a relatively large sample of well characterized patients, with minimal previous treatment, consecutively admitted to a specialized service for FEP in a defined catchment area with no alternative services is likely to make these results generalizable to FEP patients. Our data were derived from repeated prospective evaluations of symptoms and functioning at multiple time points and included a large number of variables known to influence functional outcome. This design is likely to reduce random variation of responses and increase confidence in interpreting the data. Further, we applied both a symptom and time criteria of remission, while others[47,48] have examined symptom severity only. Consecutive months of remission as a continuous measure may better reflect the influence of remission than a priori fixed criterion creating a dichotomous variable. Use of an operationalized definition of remission is likely to be of real clinical relevance and applicable in clinical practice as a goal of treatment.

Our choice of functional outcome (employment/education and social relations) is generally considered important from societal as well as personal perspectives. However, a recent study on recovery in psychotic disorders have suggested that patients' own perspectives on a variety of domains of recovery (illness-related, social-functional, and psychological) may also be of importance.[3] Our results have examined at least 2 of these dimensions: remission (illness-related) and social-functional. Another limitation worth noting is that we did not assess social cognition, which may be more likely to impact capacity for social interaction and overall functioning than verbal memory alone or global cognition.

Our results suggest that consecutive months in remission can be used reliably to predict functioning in FEP. Further, our findings support the validity of the Remission in Schizophrenia Working Group criteria[8] for remission in this population except for the 6-month criterion, as also suggested by an earlier study on an independent sample of FEP patients.[12] Clinically, our results highlight the importance of achieving and sustaining complete remission of symptoms as a meaningful treatment target in FEP. The difficulties associated with achieving complete remission underline the importance of searching for effective treatment of persistent positive and, especially, negative symptoms.

Drug names: clozapine (Clozaril, FazaClo, and others).

Author affiliations: Department of Psychiatry, McGill University, Prevention and Early Intervention Program for Psychoses, Douglas Mental Health University Institute, Montreal (Drs Joober, Lepage, Iyer, and Malla and Mr Jordan and Ms Lutgens); and Brain Imaging Group, Douglas Mental Health University Institute, Montreal (Dr Lepage), Quebec, Canada.

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