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# Neurocognitive Correlates of Response to Treatment in Formal Thought Disorder in Patients With First-Episode Schizophrenia

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**Objective:** To examine the independent contribution of executive versus semantic function to improvement in formal thought disorder after initial stabilization in a first-episode sample.

**Background:** Neurocognitive deficits have been suggested to predict treatment response in patients with first-episode schizophrenia. However, studies targeting putative neurocognitive mechanisms to explore improvement in positive psychotic symptoms and especially formal thought disorder are lacking.

**Method:** Formal thought disorder symptoms in 81 first-episode patients with schizophrenia or schizoaffective disorder either showed significant improvement (responders > 60% change) or not (nonresponders < 60%) 6 months after initial stabilization of symptoms. These two groups were compared on neuropsychologic ( $n = 16$ ), clinical ( $n = 15$ ), and volumetric measures of the frontal and temporal lobes ( $n = 5$ ) in univariate analyses. The variables that significantly differed between these two groups were used in a forward binary logistic regression analysis.

**Results:** As compared with nonresponders, responders were younger at time of testing, had higher verbal intelligence and reading achievement scores, higher scores on the arithmetic subtest of the Wechsler Adult Intelligence Scale-Revised, and lower number of perseverative responses on the Wisconsin Card Sort Test. Responders also had larger frontal lobe volumes than nonresponders. Only two measures (perseverative responses on the Wisconsin Card Sort Test and age at testing) entered the regression equation. Measures of semantic competency and volumetric measures of the temporal lobes were not associated with formal thought disorder improvement.

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**Conclusions:** Neurocognitive deficits are associated with treatment response in formal thought disorder in first-episode patients with schizophrenia. The improvement in formal thought disorder is more strongly linked to executive than semantic function in this sample, pointing to the salience of frontal systems in treatment response in positive psychotic symptoms. (NNBN 2002; 15:88–98)

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The study of patients with first-episode schizophrenia or schizoaffective disorder has been a major focus of our group since 1986. In previous communications (1–3), we presented findings on treatment response for patients who initially entered the Prospective Study of Psychobiology in First Episode Schizophrenia and Schizoaffective Disorder at Hillside Hospital. We recently published the findings on acute treatment response and potential predictors of response for the entire final study group of 118 patients from which the patients described here were selected (4). We also previously reported preliminary neuropsychologic (NP) findings in selected subgroups (5–8) and recently published a comprehensive characterization of the neurocognitive function for this entire group of patients (9). The current report investigated the relation between these two lines of study. We argue that neurocognitive dysfunction secondary to functional or structural cerebral pathology is associated with symptomatic response to acute treatment and outcome.

Results from our group (4,9,10) and the results of one other first-episode study (11) lend support to this argument: 1) attention at baseline, defined as the average of the z-transformed scores on NP tests that measure attention (Wechsler Adult Intelligence Scale-Revised [WAIS-R], Digit Span, Arithmetic, and Digit Symbol; Mesulam-Weintraub Cancellation test; Trail Making Test A), predicted positive symptom improvement in our 1999 study (4); 2) Wisconsin Card Sort Testing (WCST) perseverative errors predicted long-term social/vocational outcome in the 1992 report (10); 3) in general, NP deficits explained approximately 5%–25% of the variance in ratings of course and general social/vocational outcome after 2 years in

our 2000 study (9); and 4) nonresponders in the Scottish First Episode Schizophrenia Study had greater mean Progressive matrices/Mill Hill Vocabulary discrepancy (8 points versus 3 points) (11). In this latter study, the number of nonresponders was too small to produce statistically significant differences.

Support for this report's argument that NP measures can and should be used to study treatment response in patients with schizophrenia, also derives from three reviews of the literature that investigated the functional consequences/outcome of neurocognitive deficits in schizophrenia (12–14). These reviews agree that NP measures of specific functions such as verbal memory, attention and executive function, reaction time, coordination, and vigilance have a robust tendency for predicting measures of long-term outcome, such as rehabilitation success, utilization of hospital services, problem solving, and skill acquisition. However, three limitations of relevance to the current study have been noted. First, most of the studies reviewed have focused on patients with chronic schizophrenia, with acute exacerbation of illness. Second, prediction of shorter-term treatment response was less widely studied and, when examined, was less impressive and at times contradictory (for review [12]). And third, the range of NP measures used to predict subsequent treatment response or outcome has been limited (12). In particular, there has been little systematic attention to selection of NP measures that represent the neurocognitive mechanisms (e.g., semantic versus executive) underlying the potential associations with treatment response.

The study reported here combined the study of treatment outcome and the study of neurocogni-

tion thereby merging the traditionally segregated cultures of psychiatry and clinical neuropsychology (10), and targeted the limitations of the previous studies by asking *how* neurocognition relates to *short-term* treatment response in a *first-episode* cohort. Specifically, we were interested in further exploring our previous finding that attention predicts positive symptom improvement (4). In our previous study, response criteria were based on positive psychotic (delusions, hallucinations, formal thought disorder, bizarre behavior) symptom reduction and a measure of global clinical improvement sustained for 8 consecutive weeks (4). In the current study, we targeted response to treatment in symptoms of formal thought disorder (FTD).

We used mostly NP, but also clinical and magnetic resonance volumetric measures, to study improvement in FTD after initial stabilization of symptoms. Our choice of the NP measures was guided by the current NP explanations of FTD, which focus on executive dysfunction, implicating frontal cortical systems, or semantic dysfunction, implicating more posterior systems. Supporting the first explanation are findings that thought disorder correlates with performance on the WCST and Trail Making Test B (TMT B) (15–16). Supporting the second explanation is the finding that the difference between phonemic and semantic fluency (S-P) contributes significantly to FTD (17). Therefore, we compared two sets of NP variables, relevant to the specific putative mechanisms of action (i.e., executive,  $n = 6$ ; and semantic,  $n = 6$ ) as predictors of improvement in FTD. Measures of general intellectual function ( $n = 4$ ), selected patient variables ( $n = 15$ ), and volumetric measures of the frontal and temporal lobes ( $n = 5$ ) as determined on magnetic resonance imaging (MRI) (18) were used as possible moderator variables. Bilateral prefrontal and temporal volumes were examined, because these are the lobes that have traditionally been associated with clinical symptoms in schizophrenia and with executive versus semantic functioning, respectively. Left superior temporal gyrus volumes were also examined based on their reported association with thought-disorder (19), hallucinations (20), and delusions (21).

## MATERIALS AND METHODS

The study methodology has been described in detail previously (2,22). Subjects were participants in the Prospective Study of Psychobiology in First Episode Schizophrenia and Schizoaffective Disorder at Hillside Hospital. Patients were recruited from consecutive admissions to the inpatient service of the department of psychiatry if admitted for a first episode of psychotic illness and had previously received less than 12 weeks of cumulative lifetime neuroleptic treatment. All patients satisfied Research Diagnostic Criteria for schizophrenia or schizoaffective disorder. Assessments were based on structured interviews (Schedule for Affective Disorders and Schizophrenia Change Version with Psychosis and Disorganization Items rating scale [SADS-C + PDI] and Schedule for the Assessment of Negative Symptoms) and review of history. The Hillside Intervention Research Center provided a training program designed to establish and maintain high interrater reliability between the study raters. Weekly courses lasting 3–4 months provided intensive training in the use of these rating instruments. Regular “refresher” sessions for each instrument monitored rater drift. Intraclass correlation coefficients obtained from one of these sessions were: 0.83, impaired understandability; 0.89, derailment; 0.80, illogical thinking (four raters, nine cases).

Patients were treated according to a standard algorithm under open conditions, progressing from one phase of the algorithm to the next until they responded. The sequence of medication trials was published previously (23). Briefly, patients initially received fluphenazine for up to 10 weeks (dose doubled after 6 weeks), and those who did not respond were treated with haloperidol for up to 10 weeks (dose doubled after 6 weeks). Lithium was then added and followed by a trial of a third neuroleptic from a different biochemical class. Clozapine was then given to the patients who were still treatment resistant. Patients were excluded for current or past history of serious neurologic or endocrine disorder. After complete description of the study, written informed consent was obtained. Further details of ascertainment and treatment have been published elsewhere (2,4,22,23).

### Formal Thought Disorder

The SADS-C + PDI was completed at baseline and every 2 weeks during acute treatment and every 4 weeks at other times. The 81 patients included in the current study are a subset of the 94 cases previously described (9), who completed this evaluation at baseline and again at time of NP testing. Improvement of FTD was calculated by subtracting NP exam date FTD from baseline FTD and then dividing the result by the latter: the higher the score the larger the improvement. Formal thought disorder was calculated as a composite score by taking the average of three SADS-C + PDI items (impaired understandability, derailment, and illogical thinking), which were rated on a scale from 0 to 6 (impaired understandability: 0 no information, 1 none, 2 slight, 3 mild, 4 moderate, 5 severe, 6 extreme; derailment: 0 no information, 1 not at all, 2 doubtful, 3 little impairment, 4 frequent, 5 very frequent, 6 impossible to understand; and illogical thinking: 0 no information, 1 not at all, 2 doubtful, 3 not grossly deviant, 4 definite defect, 5 marked defect, 6 completely illogical). These items have been previously used in our laboratory to define FTD and are consistent with other well-accepted components of FTD (4,24,25). The items had significant (all  $p < 0.0001$ ) nonparametric intercorrelations, ranging from 0.58 to 0.82 at baseline and 0.51 to 0.63 at NP testing. Coefficient alpha of the composite was 0.87 at baseline and 0.85 at NP testing (calculated over all nonmissing values). The distribution of the composite FTD score was negatively skewed ( $-0.97 \pm 0.27$ ) and, based on its inspection, we made an empirical decision to divide the subjects into two groups: responders ( $> 60\%$  improvement in FTD) versus nonresponders ( $< 60\%$  improvement).

### Neuropsychologic and Clinical Variables

Neuropsychologic tests were planned for 6 months after study entry if the patient had already achieved remission or a stable level of residual symptoms. We selected 6 months because pilot data showed there was no significant change in symptom remission after that point. Patients who did not satisfy the criteria for symptom remission or stable

residual symptoms at 6 months were tested as soon as possible after they satisfied the criteria. Remission was defined as a rating not greater than 3 (mild) on the positive psychotic symptoms items of the SADS-C + PDI psychosis and disorganization dimensions; a rating of 3 (mild) or less on the Clinical Global Impression severity items; a rating of 2 (much improved) or 1 (very much improved) on the Clinical Global Impression improvement items; and maintenance of this level of response for 8 weeks. Residual symptoms were defined stable if there were no changes greater than 1 point on the positive psychotic symptom items of the SADS-C + PDI psychosis and disorganization dimensions or on global ratings of the Schedule for the Assessment of Negative Symptoms for two consecutive biweekly rating periods.

The NP battery included 41 tests characterizing six neurocognitive domains represented by the following scales: language, memory, attention, executive, motor, and visuospatial. Premorbid intellectual ability was also evaluated based on the Wide Range Achievement Test-Revised reading subtest and the information and vocabulary subscales of the WAIS-R. Further details of the NP battery composition and administration procedures have been published elsewhere (9). For the current purposes, a total of 16 NP variables were selected. These included measures of semantic function (S-P, total number correct on animal fluency test: most productive 60 seconds, sentence repetition, token test, Boston Naming Test), executive function (total number correct on phonemic fluency, TMT B, TMT B minus TMT A, perseverative responses on WCST), other measures of working memory (WAIS-R digit span and arithmetic age corrected scaled scores), and overall intellectual functioning (scaled score on Wide Range Achievement Test-Revised reading, WAIS-R verbal, performance, and full-scale intelligence quotients). Using the coding system previously developed (26), one additional variable was derived from the semantic fluency task to target semantic processing. This measure, the Association Index (AI), is the cumulative number of shared attributes between all successive responses divided by the total number of words generated minus one (see [26]). This index provides a

measure of the organization or strength of association between all consecutive responses. The AI was used to explore semantic knowledge independent of the number of words produced, which can be reduced as a result of executive dysfunction or attention impairment. The validity of the AI to assess semantic processing has been demonstrated in a study showing that the AI, but not total words produced, distinguished cortical dementia from subcortical dementia patients (26). Similarly, we have recently demonstrated that the AI, but not total words produced, differentiated between patients with left temporal lobe epilepsy, a neurologically impaired group with semantic knowledge deficits, and a subset of the first-episode patients with schizophrenia included in the current study: the AI was significantly reduced in the former group relative to the latter and a healthy control group (27). The AI was available for 56 subjects.

The following 15 patient and clinical variables were examined: sex, race, mean parental socioeconomic status on the Hollingshead scale in which 1 = highest and 5 = lowest (28), diagnosis subtype, handedness (Hand preference was assessed using a modified 20-item Edinburgh Inventory [29]). The total number of right- and left-hand items were scored, and a laterality quotient was computed as  $[(\text{total right} - \text{total left})/(\text{total right} + \text{total left})]$ , ranging from 1.00 to -1.00. Subjects with a laterality quotient  $> 0.70$  were classified as right-handed), education, age at testing, age at first treatment, weeks of psychotic and psychiatric symptoms, total duration of all outpatient psychiatric treatment, years of medication, chlorpromazine equivalent dose of antipsychotic medication, anti-parkinsonian treatment dose in benztropine equivalents, and cumulative antipsychotic dose from the beginning of treatment to the time of NP testing, in chlorpromazine equivalents.

### Imaging Procedures and Measurement of Brain Regions

Magnetic resonance brain scans were obtained during the index episode on a superconducting whole-body imaging system (Magnetom, Siemens, Erlangen, Germany), operating at a field

strength of 1.0 T (proton MRI frequency of 42.6 MHz). Coronal images were obtained by using a fast low-angle-shots, gradient-refocused, three-dimensional sequence with a 50 flip angle, repetition time of 40 milliseconds, and echo time of 15 milliseconds (30). The image obtained was  $T_1$ -weighted with a field of view of 300 mm and a matrix size of 256 by 256 (in-plane resolution = 1.17 x 1.17 mm). The slice thickness was 3.1 mm, and 63 contiguous coronal slices through the whole head were acquired in 11 minutes. A neuroradiologist and two of the investigators reviewed scan quality, and any scan showing substantial artifacts was repeated. Before the three-dimensional fast low-angle-shots scan, head position was adjusted by using laser markers on external landmarks (nasion, auditory meati), and a two-dimensional midsagittal fast low-angle-shots scan was used to position the subject so that the floor of the fourth ventricle was parallel to the y-axis of the scanner coordinate system (i.e., the inferior-superior anatomic plane). Patients routinely received 200–400 mg of amobarbital sodium orally 35 minutes before the procedure.

The measurement of regions of interests has been fully described (18). In brief, regional volumes were measured by using a semiautomated, computerized mensuration system (30). The regional volumes included cortical gray and hemispheric white matter but not subcortical structures. Landmarks for prefrontal and temporal identification and additional delineation criteria were from the section rostral to the rostrum of the corpus callosum to the frontal pole, for the former, and from the most caudal section through the splenium of the corpus callosum to the temporal pole, for the latter. The sylvian fissure separated the temporal region from frontal and parietal cortexes. The temporal stem was separated from the basal ganglia by a line from the most inferior part of the insular cisterns to the most lateral extent of the basal cisterns above the hippocampus. The superior temporal gyrus was delineated using the sylvian fissure and the superior temporal sulcus as the superior and inferior boundaries, respectively. The medial boundary was the circular sulcus of the insular cortex. The anterior

boundary was the most anterior coronal slice containing the temporal stem, determined separately for each hemisphere. The posterior boundary was the splenium of the corpus callosum. A single operator made all measurements. Interrater reliability for 10 scans was high (intraclass correlations between two operators in individual regions ranged from 0.96 to 0.99; the mean percent differences were 1% or less).

### Statistical Analyses

Part 1: The responders and nonresponders were compared on all selected clinical, NP, and volumetric variables. For dichotomous variables,  $\chi^2$  tests were used. For continuous variables, the clinical and NP effects could not be assessed using two separate MANOVAs because there were fewer than two nonsingular cell covariance matrices in both instances, and therefore, we examined group differences using *t* tests. *t* tests were also used to examine the differences in the volumetric measurements of the frontal and temporal lobes as this allowed for use of all nonmissing data for all variables.

Part 2: We performed a binary logistic regression analysis to determine the contribution of the measures that were significant at the previous step to predicting improvement in FTD. This procedure was chosen over discriminant analysis because it is a robust procedure that makes few statistical assumptions (e.g., no assumption of homogeneity of variance or homogeneity of regression across groups). We were not concerned about Type I error in Part 1 that served as a screening tool for the more robust regression analysis in Part 2.

## RESULTS

Of the 81 subjects included in this study, 47 were men, 33 white, 30 black, 11 Hispanic, 5 Asian, and 59 were right handed. Mean education was 13 (2.3) years and age at testing was 25.7 (6.2) years. The patients satisfied criteria for schizophrenia ( $n = 61$ ; subtypes included: paranoid, 50; disorganized, 4; undifferentiated, 7) or schizoaffective disorder ( $n = 20$ ; subtypes included: mainly schizophrenic, 14; mainly affective, 4; other, 2). Severity of illness (Clinical Global Impression) was

extreme for 11%, severe for 39.5%, marked for 27.2%, and moderate for 14.8%. Severity of delusions at baseline had significant impact for 45.7% and major impact for 29.6%. Severity of hallucinations at baseline had significant effect for 32% and major impact for 19.8%. Baseline FTD ranged from none to marked and was evenly distributed between the severity levels. Age at first psychiatric symptoms was 21 (6.2) years, and age at first psychotic symptoms was 23 (6.3) years. Number of weeks of psychiatric symptoms to study entry was 153 (196.4), and number of weeks of psychotic symptoms to study entry was 79 (149.54). Mean age at first treatment of any psychiatric illness was 23 (6.5) years, total duration of all outpatient psychiatric treatment in weeks was 8.8 (26.8), and number of years on medications was 0.81 (0.6).

Table 1 includes all variables that were significant ( $p < 0.05$ ) in differentiating between the responders and nonresponders. From the 15 clinical variables inspected, only one (age at testing) was significant. Although the responders differed from the nonresponders in racial composition (50% versus 30% white, respectively) and age at first treatment ( $21.8 \pm 5.5$  versus  $24.5 \pm 7.3$  years, respectively), these variables did not reach statistical significance. The responders and nonresponders were well matched (all  $p > 0.1$ ) on gender (64% versus 51% men, respectively), handedness (73% right handed), diagnosis subtype (70% versus 81% schizophrenic), and parental socioeconomic status (32% versus 28% upper; 41% versus 36% lower). Among the 16 NP variables, only four variables significantly differed between the groups, and among the five volumetric measures, only the frontal lobe volumes significantly differed between the responders and nonresponders.

All variables in Table 1 were submitted to a forward logistic regression analysis. This model was appropriate for the data at both steps 1 (age at NP testing;  $\chi^2 = 9.6$ ,  $df = 1$ ,  $p = 0.0019$ , 64% of subjects classified correctly) and step 2 (age at NP testing + WCST perseverative responses;  $\chi^2 = 16.4$ ,  $df = 2$ ,  $p = 0.0003$ , 70% of subjects classified correctly) (Table 2). Controlling for whole brain volume did not change these results.

**TABLE 1.** Significant differences between responders (> 60% improvement in formal thought disorder) and nonresponders (< 60% improvement)

	Responders (N = 44)		Nonresponders (N = 37)		t	df	p
	Mean	SD	Mean	SD			
Clinical variables							
Age at testing	24.0	4.8	27.7	7	-2.8	62.2§	0.008
Neuropsychologic measures							
WAIS-R Arithmetic	8.9	2.7	7.3	2.6	2.6	79	0.010
WCST*	27.6	21.6	47	38.9	-2.5	45.7§	0.015
WAIS-R Verbal IQ	93.6	13.8	87.4	13.1	2.1	79	0.041
WRAT-R†	96.4	13.8	90	13.3	2.0	71	0.047
Volumetric measures‡							
Left frontal	71.2	14.8	61.7	11.6	2.6	56	0.013
Right frontal	71	14.2	63.4	11.6	2.1	56	0.038

\*Data missing for 8 subjects (3 responders, 5 nonresponders).

†Data missing for 8 subjects (4 responders, 4 nonresponders).

‡Data missing for 23 subjects (8 responders, 15 nonresponders).

§Degrees of freedom are corrected for unequal variances.

IQ, Intelligence Quotient; WAIS-R, Wechsler Adult Intelligence Scale—Revised; WCST, Wisconsin Card Sort Test perseverative responses; WRAT-R, Wide Range Achievement Test—Revised: Reading scaled score.

## DISCUSSION

Our goal in the current study was to examine the neurocognitive mechanisms that underlie treatment response in symptoms of FTD 6 months after initial stabilization in a first-episode patient cohort. Results revealed that of 16 NP variables examined, only one measure, perseverative responses on the WCST, significantly entered a binary logistic regression model and, together with age at testing, correctly classified 70% of the subjects as either responders or nonresponders. Three other NP measures (one measure of working memory and two measures of general intellectual functioning and achievement) differentiated between the groups in univariate analyses but did not enter the regression model. Of note is the fact that the six NP measures

that specifically targeted semantic processing did not differentiate responders from nonresponders at a statistically significant level.

Our results thus suggest that executive and not semantic function processes are associated with improvement in FTD in first-episode patients with schizophrenia. The results of other studies provide support to our findings; commission errors on the continuous performance test predicted post-treatment (residual) FTD after the most recent psychotic episode in 41 schizophrenia patients (31). In a more recent study, improvement in performance on the TMT B was correlated ( $r = 0.4$ ) with improvement in psychotic symptoms in 54 patients with first-episode ( $n = 21$ ) or recent onset schizophrenia assessed at index hospitalization and

**TABLE 2.** Results of binary logistic regression analysis of variables significantly differentiating responders (> 60% improvement in formal thought disorder) and nonresponders (< 60% improvement) at 6 months follow-up in 53\* subjects with schizophrenia

Measure	B	SE	Wald	df	p	R
Step 1: Age at neuropsychologic testing	0.15	0.05	7.7	1	0.006	0.28
Step 2: Age at neuropsychologic testing	0.18	0.06	8.4	1	0.004	0.30
Perseverative responses on WCST	0.03	0.01	4.8	1	0.029	0.20

\*Analyses were conducted over all nonmissing values for all measures. Results were the same when the volumetric measures were excluded, increasing sample size to 69. All other variables in the model are listed in Table 1.

WCST, Wisconsin Card Sort Test.

again after 5 years (32). Our results are also consistent with a growing body of literature suggesting a significant role for the executive, attentional, and organizational functions in the expression of schizophrenic thought disorder measured as a stable disease characteristic (as compared with response of symptoms to treatment): associations were reported with performance on TMT B, number of categories on the WCST (16), proportion of errors produced on a verbal fluency task (33), and continuous performance or span of apprehension tests (31,34–38).

Interestingly, of the six variables selected to represent executive and working memory functions in this study, all psychometrically valid tests of executive functioning that are widely used in clinical and research settings, only WAIS-R arithmetic and number of perseverative responses on the WCST differed between responders and nonresponders, and only the latter variable entered the regression model. This result serves well to remind us that there is no unitary executive function (39,40). The possibility that some aspects of executive functioning (e.g., response to feedback) are more critical than others (e.g., divided attention) in underlying improvement in FTD cannot be overstated.

The fact that responders and nonresponders differed in frontal but not temporal lobe volume measures in the current study offers further evidence to support our suggestion that improvement in FTD symptoms after initial stabilization is associated more strongly with self-control and regulation functions than with the integrity of semantic knowledge. Consistent with our results, an inverse relation was reported between degree of response to treatment and prominence of prefrontal sulci as assessed by a rating scale applied to computed tomography images (41). Again, studies of positive symptoms measured as a stable disease characteristic offer further support to our findings. Thus, an inverse relationships between Thought, Language and Communication scale total scores and prefrontal volume was reported in a group of 19 young patients with schizophrenia (42), and milder severity of disorganization was associated with higher frontal lobe volume in 54 men with schizophrenia (43). As concerns left superior temporal gyrus vol-

umes, results have been inconsistent; several studies have shown no relation with positive symptoms (42,44,45), whereas others reported either positive (21) or negative (19,20,46,47) associations. Clearly, this area deserves further study, with confounding variables methodically addressed.

Our results point to an association between size of the frontal lobes and FTD treatment response, such that the larger the frontal volumes the better the response and the smaller the frontal volumes the worse the FTD response to treatment. These current results extend our previous results where, compared with normal brain morphology, definite or questionable brain pathology was associated with longer recovery time (2). The fact that the nonresponders, who had an average of 9% decrease of the bilateral frontal lobe volumes as compared with the responders, also demonstrated worse performance on the WCST, is consistent with the focus on the integrity of the frontal lobes, their function and connectivity in schizophrenia (e.g., [48,49]). It is possible that the neuroleptic treatment in the nonresponders did not have a significant neurobiologic effect (e.g., normalizing frontotemporal function), being associated with both medical unresponsiveness of FTD symptoms and cognitive dysfunction (increased perseveration).

To the authors' knowledge, only one other study used MRI scans to examine treatment response in a first-episode cohort (50). This study documented a significant correlation between cortical gray matter and improvement in positive symptoms 1 week after treatment initiation in 26 first-episode patients. However, this study did not examine the separate contribution of selected lobes to treatment response. Thus, although not the focus of the current study, our results contribute to this largely unresolved area of investigation (for review [51]) in that, using MRI to quantify selected brain cortical regions and targeting FTD response to treatment in a first-episode cohort, we documented the salience of the frontal lobes as compared with the temporal lobes in differentiating responders from nonresponders.

Another point to be made is that responders were of younger age at NP testing and also more



likely to be of younger age at onset than nonresponders. In contrast to our findings, earlier age at onset of schizophrenia has been associated with poor outcome (e.g., greater impairment at follow-up, poorer response to treatment, and higher risk of rehospitalization) in numerous studies (52–55). Several explanations for this difference seem plausible although sample characterization is the most evident. The sample included in this study was comprised of individuals with a more restricted range of age at onset than typically reported (e.g., 10–44 versus 5–55 years), with 52% of patients being at their third decade (20–30 years) at disease onset, one at the fifth decade, and none at the first decade. It is possible that the association between age and treatment response is age dependent. Indeed, in 322 patients with schizophrenia or schizoaffective disorder, a drop in the probability of being neuroleptic resistant was documented for the 22–24 years age group, subsequently followed by an increase for the 25–27 years age group (56). Had only these two groups been included, results of this study would have suggested, similarly to ours, that treatment resistance increases with an increasing age. Other variables, such as sex, race, subtype of schizophrenia, and duration of untreated symptoms, might have separately or in combination modified the association between age and response to treatment in our study and deserve further study.

Finally, our results are consistent with reports in patients with chronic schizophrenia that earlier age at onset and less prefrontal abnormality are factors associated with improvement in psychopathology (e.g., [57]). However, it is important to note that duration of illness, although not directly impacting drug response, may indirectly affect our results. First, in our cohort, the cumulative percentage of patients responding by 1 year was 87%, with a median time to response of 9 weeks, a much higher degree of response in comparison with the response rates for multi-episode patients (4). Second, it is not unexpected for a longer duration of illness to be associated with higher levels of clinical and functional impairment, possibly modifying the association between psychotic/psychiatric symptoms and their underlying neurocognitive mechanisms. Therefore, it is possible that early in the

course of schizophrenia, executive dysfunction is the primary contributor to FTD response to treatment while as illness progresses, semantic factors gain prominence (for example, [17]). Future research in large diverse samples is needed to determine the role of duration and severity of illness in FTD.

A limitation of our study includes the possibility that some of the results reported in Table 1 were spurious, reaching a statistically significant level because of the large number of comparisons we conducted. However, we did not want to set a conservative level of significance (such as 0.01) or to use the restrictive Bonferroni correction, as our sample size was small and, although guided by hypotheses, these analyses were also of exploratory nature. We protected against Type I error by submitting the results of the univariate tests in Part 1 to the robust logistic regression analysis in Part 2. Had the results in Part 1 been spurious, the results of the multivariate analysis would not have reached a statistically significant level. Yet, the results of this study should be validated in a larger cohort.

To summarize, our findings indicate that executive function is more critical a mechanism than semantic processing in underlying short-term improvement in disturbed thought processes in a sample of patients with first-episode schizophrenia.

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