# Poor Premorbid Adjustment and Dysfunctional Executive Abilities Predict Theory of Mind Deficits in Stabilized Schizophrenic Outpatients

*Rosó Duñó [1], Esther Pousa [1], Monica Miguelez [1], Klaus Langohr [2,3], Diego Palao [1], Adolf Tobeña [4]*

## Abstract

Deficits in Theory of Mind (ToM) have been demonstrated in schizophrenia. The present study explored the relationship between ToM deficits, poor premorbid adjustment, and executive dysfunction in a sample of fifty-eight stabilized schizophrenic outpatients in contrast to a normative control group. Ordinal regression analysis revealed an association between deficits in both first- and second-order ToM tasks and poor social premorbid adjustment. In addition, deficits in first-order tasks showed an association with a low performance on the Trail Making Test B, while deficits in second-order tasks were related to male gender, a low performance on Block Design, and clozapine treatment. The R-square values amounted to 0.300 and 0.657, respectively. Years of illness evolution, the symptoms on the PANSS scale and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* diagnostic subtype were not significantly associated with first- or second-order ToM tasks. Results of this study define a homogeneous phenotypic subgroup of schizophrenia patients, characterized by poor prognostic outcome factors, together with deficits in ToM and dysfunctional executive capacities with a visuo-perceptual component. These deficits could explain social functioning impairment in patients' daily routine.

**Key Words:** Schizophrenia, Premorbid Adjustment, Theory of Mind, Executive Abilities

[1] *Psychiatry Department, Parc Taulí Hospital, Barcelona, Spain*
[2] *Pharmacology Research Unit, Institut Municipal d'Investigació Mèdica, Barcelona, Spain*
[3] *Department of Statistics and Operations Research, Technical University of Catalonia, Barcelona, Spain*
[4] *Department of Psychiatry and Forensic Medicine, Institute of Neurosciences, Autonomous University of Barcelona, Spain*

*Address for correspondence: Rosó Duñó, Psychiatry Department, Parc Taulí Hospital, Parc Taulí S/N, 08208 Sabadell, Barcelona, Spain*
*Phone: 003493 7231010, x22018; Fax: 003493 7237181;*
*E-mail: rduno@tauli.cat*

*Submitted: September 18, 2007; Revised: March 13, 2008; Accepted: April 25, 2008*

## Introduction

Patients with schizophrenia show striking deficits in many areas of social functioning, which may derive from anomalies in social cognition (1). Social cognition has been defined as the ability to construct representations of the relation between oneself and others and to use those representations flexibly to guide social behavior (2). A series of recent studies with schizophrenic samples has shown that such patients present impaired performance in Theory of Mind (ToM) tasks (3-5), a particular attribute of social cognition. ToM, as defined by Premack and Woodruff (6), refers to the ability of attributing mental states (desires, intentions) to others in order to predict, anticipate and explain their be-

havior; attributions that include the possibility of holding false beliefs (7). ToM deficits in schizophrenia often appear in the most severely affected individuals (8) and are not restricted to the acute phase of the psychotic illness (9). ToM is usually explored by means of experimental false-belief tasks, the most common being first- and second-order ToM tasks or even more complex ones (10).

There is mounting evidence that a deficit in social cognition may reflect a core feature of schizophrenia-spectrum disorder. In this respect, Janssen et al. (11) reported a poor performance on ToM tasks in first-degree relatives of patients with schizophrenia. Similarly, Langdon and Coltheart (12) and Pickup (13) found ToM deficits in nonclinical adults scoring high in schizotypy. In the same way, Pilowsky et al. (14) found that ToM tasks were impaired in childhood-onset schizophrenia, and these findings have been also documented by Schenkel et al. (15) among inpatients with poor childhood premorbid adjustment. A recent meta-analysis concluded that schizophrenic patients in remission show impairment in ToM, favoring the notion that mentalizing represents a possible trait marker in the illness (16).

Schizophrenia patients exhibit widespread deficits in many domains that range from abnormalities in basic sensory registration and processing to impairments in higher cognitive operations, such as sustained attention, processing speed, executive functioning and social cues interpretation (17, 18). Current theories of schizophrenia emphasize that core aspects of the pathophysiology are due to deficits in different levels of organization of perceptual systems, from concurrent sensorial inputs to consequent impairment in the generation of coherent cognitive activity. Finally, these deficits could underlie disruption of real life functioning (19). Heterogeneities in these perceptual organization anomalies in schizophrenia have been related to the illness subtype. Thus, patients with poor premorbid social histories and poor prognosis show a defective performance in these measures (19). Recent evidence has linked perceptual organization abnormalities with social cognition impairment in schizophrenia patients. In this line, Schenkel et al. (15) reported that the degree of ToM impairment in schizophrenia patients was associated with poor performance on context-processing tasks. Similarly, Uhlhaas et al. (20) found that impaired performance on ToM tasks was associated with dysfunctional visual-context processing. However, few investigations have examined the relationship between ToM deficits and executive functioning anomalies in schizophrenia patients with poor premorbid adjustment.

The first aim of the present study was to evaluate whether first- and second-order ToM deficits in stabilized schizophrenic outpatients were associated with poor premorbid adjustment across different age epochs. A second aim consisted of exploring the relationships between ToM performance and several basic to more complex neurocognitive abilities. Finally, we attempted to establish the relative weight of several variables at predicting ToM deficits including poor premorbid functioning, demographic and clinical data, response to antipsychotic treatment, as well as neurocognitive abilities. In line with the evidence reviewed above, it was hypothesized that an impaired ToM would significantly contribute to difficulties in social functioning together with neurocognitive and poor clinical prognostic factors.

## Method

Fifty-eight schizophrenic patients according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* (21) criteria were recruited for the study in a consecutive fashion during the years 2001–2005. The sample included forty-one males and seventeen females, with a mean age of 31.4 years (standard deviation [SD]=8.1). Sociodemographic and clinical characteristics are described in Table 1. Symptom severity (positive symptoms, negative symptoms and general psychopathology) was assessed with the Positive and Negative Syndrome Scale (PANSS) (22). Extrapyramidal symptoms were scored with a subscale of neurological effects of the Scale of Extrapyramidal Symptoms (23). Clozapine treatment was prescribed only to patients who met the criteria for antipsychotic treatment resistance (24).

Subjects who did not give their consent to participate, and those patients with a physical disability (visual or auditory) limiting the application of the tests, a neurological disease, or another chronic or acute condition that could interfere with cognitive performance, were not considered for recruitment. Nor were patients with an additional *DSM-IV* (21) diagnosis on Axis I/II. Participants showing an IQ below 70 were excluded from the study (25). All subjects were on clinical remission at five months of discharge from the Day Hospital of the Department of Psychiatry of the Parc Taulí Hospital. This facility manages a population of 400,000 inhabitants of the semi-urban area of Sabadell (Barcelona) and is part of a University General Hospital with five hundred beds.

The schizophrenic group was compared to a control group of forty-eight patients with no psychiatric diagnosis who had been admitted to the Orthopedics and Surgery Department of the same hospital. The control subjects were recruited at the same time as the group with schizophrenia and were matched by sex, age and educational level. The exclusion criteria for this control group included a history of psychiatric disorders, the presence of psychopathology and distress at the time of the evaluation according to the three global indices of the Symptom Checklist-90-Revised scale (SCL-90-R) (Positive Symptom Total, Global Severity Index, Positive Symptom Distress Index) (26), the medical pre-

scription of psychoactive drugs and an IQ score below 70. Sociodemographic factors and medical diagnosis according to the *International Classification of Diseases (ICD-10)* classification (27) of this group are described in Table 1.

## Assessment

### Premorbid Adjustment Evaluation

The Premorbid Adjustment Scale (PAS) (28) is a 14-item rating scale that assesses sociability and withdrawal, peer relationship, adaptation to school and scholastic performance for three life stages (childhood, up to age 11; early adolescence, 12–15 years of age; late adolescence, 16–18 years of age), as well as social-sexual aspects of life after age 11. The adulthood stage (up to age 19) was excluded from our analysis in order to avoid spurious high scores due to prodromal symptoms (29). The fifth PAS nonspecific section (premorbid educational, occupational and social functioning, as well as energy level) was not considered for analysis in the present study. This information was gathered in retrospect through interviews with close relatives who had lived with the patients up to their adulthood. Final scores were completed on the basis of all available data from the clinical records. The PAS (28) was applied by the expert staff psychiatrist of the Day Hospital (R.D.) blind to ToM and neuropsychological tasks and trained at PAS administration.

### Theory of Mind Tasks

A total of four Theory of Mind false belief tasks were used for ToM assessment: two first-order tasks (The Cigarettes [30] and Sally and Anne [31]), and two second-order tasks (The Burglar [32] and The Ice-Cream Van [33]). First-order tasks measure the recognition of a story character's false belief about the world, whereas second-order tasks investigate the understanding of the beliefs of a story character about another story character's thoughts (8). Stories were read aloud by the examiner and subjects were asked to listen and subsequently answer two questions. The first question had to be answered on the basis of the mental state of one of the characters (ToM question) and concerned that character's false belief within the situation. The second question (control question) reflected the subject's comprehension of the story. These tasks were rated according to the following schema:

- Correct ToM (task score=1): correct answer in both ToM and control questions.
- ToM deficit (task score=0): failure in ToM question and correct answer in control question.
- Comprehension error: correct answer in ToM question and failure in control question, or failure in both questions. Tasks in this category were omitted from the analysis.

Patients were excluded from the study if they showed comprehension errors in more than two ToM tasks. If the comprehension error was in a second-order ToM task, none of the second-order ToM tasks were considered for analysis, while first-order ones were. This was the same when comprehension errors appeared in first-order ToM tasks.

Subsequently, three categorical subgroups of ToM performance were established for both first- and second-order tasks by adding up scores previously obtained as follows: 0=two tasks with scores of 0 (severe ToM deficit); 1=one task scoring 1 and the other scoring 0 (low ToM performance); 2=score of 1 in both tasks (good ToM performance).

### Neurocognitive Evaluation

In order to efficiently analyze the cognitive functioning tests, variables were grouped into cognitive domains, from basic to high level of cognitive processes according to Nuechterlein et al. (34). These domains were: Attention (Digit Span Forward) (35), Speed Processing (Trail Making Test A [TMT-A]) (36), Working Memory (Digit Span Backward) (35), Executive Functions (Stroop Color-Word [37], Trail Making Test B [TMT-B] [36], Block Design [35]) and Verbal Learning and Memory (California Verbal Learning Test) (38).

The Intelligence Quotient was examined through the abbreviated form of the Wechsler Adult Intelligence Scale (WAIS-III), which included the following four subtests of the complete WAIS-III: information, block design, arithmetic, and digit symbol (24).

All study subjects were administered experimental ToM tasks and a comprehensive neuropsychological assessment by a psychometrist trained in standardized assessment and scoring procedures (E.P.).

### Statistical Analysis

Sociodemographic characteristics of schizophrenia patients and subjects of the control group were compared by means of either the $\chi^2$-test (for categorical variables) or the t-test (for age). Among the schizophrenia patients, the relationship between premorbid adjustment during childhood and both early and late adolescence, on one hand, and the performance on both first- and second-order ToM tasks, on the other hand, was examined. For this purpose, the median values of premorbid adjustment of patients of category 2 ToM performance were compared separately with those of categories 1 and 0 using the nonparametric Wilcoxon test. The same test was applied to compare the neuropsychological test scores among the study subjects. For this analysis, schizophrenia patients of category 2 ToM performance were compared separately with those of categories 0 and 1, as well as with control subjects.

Moreover, ordinal regression models were employed to

**Table 1 Sociodemographic and Clinical Characteristics of Study Cohort**

| | Schizophrenia Group (N=58) | Control Group (N=48) | p-Value |
|---|---|---|---|
| **Sociodemographic Characteristics** | | | |
| **Males** | 41 (70.7%) | 36 (75.0%) | $\chi 2=0.246$; p=0.620 |
| **Age (SD)** | 31.4 (8.1) | 33.9 (8.6) | t= -1.518; p=0.132 |
| **Years of education:** | | | $\chi 2=0.302$; p=0.583 |
| ≤8 years | 42 (72.4%) | 37 (77.1%) | |
| >8 years | 16 (27.6%) | 11 (22.9%) | |
| **Marital status:** | | | **$\chi 2=33.331$; p<0.001** |
| Single | 47 (81.0%) | 14 (29.2%) | |
| Couple | 5 (8.6%) | 27 (56.3%) | |
| Separated | 6 (10.3%) | 6 (12.5%) | |
| Widow | 0 | 1 (2.1%) | |
| **Living with own family** | 15 (25.9%) | 35 (72.9%) | **$\chi 2=23.336$; p<0.001** |
| **Children** | 8 (13.8%) | 26 (54.2%) | **$\chi 2=19.650$; p<0.001** |
| **Employed** | 12 (20.7%) | 41 (85.4%) | **$\chi 2=44.014$; p<0.001** |
| **Clinical Measures** | | | |
| **Age of illness onset (SD)** | 21.6 (4.9) | | |
| **Psychiatric diagnosis *(DSM-IV)*:** | | | |
| Paranoid schizophrenia | 39 (67.2%) | | |
| Disorganized schizophrenia | 5 (8.6%) | | |
| Undifferentiated schizophrenia | 2 (3.4%) | | |
| Residual schizophrenia | 1 (1.7%) | | |
| Schizophreniform disorder | 6 (10.3%) | | |
| Schizoaffective disorder | 5 (8.6%) | | |
| **Global activity *(DSM-IV)* (SD)** | 61.6 (11.7) | | |
| **SCL-90-R*:** | | | |
| Positive Symptom Total (SD) | | 24.9 (11.2) | |
| Global Severity Index (SD) | | 0.27 (0.12) | |
| Positive Symptom Distress Index (SD) | | 1.19 (0.20) | |
| **PANSS:** | | | |
| Positive (SD) | 11.7 (4.2) | | |
| Negative (SD) | 17.3 (9.6) | | |
| General (SD) | 31.7 (9.4) | | |
| Total (SD) | 60.9 (19.1) | | |

**—continued**

**Table 1 Sociodemographic and Clinical Characteristics of Study Cohort**

| | Schizophrenia Group (N=58) | Control Group (N=48) | p-Value |
|---|---|---|---|
| **Clinical Measures (continued)** | | | |
| **Years of illness evolution (SD)** | 9.6 (7.7) | | |
| **Drugs:** | | | |
| Mean dose haloperidol (mg/day) (SD) | 8.7 (7.3) | | |
| Conventional antipsychotic | 14 (24.1%) | | |
| Atypical antipsychotic | 35 (60.3%) | | |
| Mixed antipsychotic | 6 (10.3%) | | |
| Clozapine† | 17 (29.3%) | | |
| Anticholinergic | 8 (13.8%) | | |
| Antidepressant | 15 (25.9%) | | |
| **UKU scale:** | | | |
| 0 | 24 (41.4%) | | |
| 1 | 20 (34.5%) | | |
| 2 | 6 (10.3%) | | |
| 3 | 6 (10.3%) | | |
| 4 | 1 (1.7%) | | |
| 8 | 1 (1.7%) | | |
| **Medical diagnosis *(ICD-10)*** | | | |
| **Surgery department:** | | **24** | |
| Pneumothorax | | 6 (25.0%) | |
| Appendicitis | | 5 (20.8%) | |
| Diverticular disease | | 9 (37.5%) | |
| Cholelithiasis | | 4 (16.7%) | |
| **Orthopedic surgery department:** | | **24** | |
| Degenerative disc disease | | 10 (41.7%) | |
| Fracture of rotula | | 3 (12.5%) | |
| Complicated fracture of radius/cubita | | 2 (8.3%) | |
| Complicated rupture of knee ligament | | 4 (16.7%) | |
| Fracture-dislocation of maleolar | | 2 (8.3%) | |
| Dislocation temporomandibular | | 3 (12.5%) | |

Results are presented as mean (standard deviation [SD]) in case of continuous variables and as frequency (%) in case of categorical variables.
*Mean normative values: Positive Symptom Total, 25.32 (SD: 14.3); Global Severity Index, 0.51 (SD: 0.36); Positive Symptom Distress Index, 1.75 (SD: 0.48)
†Percentage of patients on clozapine from the total on atypical antipsychotics
*DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;*
SDL-90-R=Symptom Checklist-90-Revised; PANSS=Positive and Negative Syndrome Scale;
*ICD-10=International Classification of Diseases*

analyze the association between the results of first-order and second-order ToM tasks with sociodemographic variables, premorbid adjustment and neuropsychological test scores. Starting with regression models including gender and the PAS for social isolation, further explanatory variables included in the model were those that significantly improved the model fit and yielded maximum R-square values. Several link functions for ordinal regression models were considered and those that yielded maximum R-square values were chosen. Finally, it was proved that the models for first- and second-order ToM tasks held the model assumption of parallel lines (39). Statistical analysis was performed with the statistical software packages R, v. 2.4.0 "exact RankTest" (40) and SPSS, version 14.0 (SPSS Inc., Chicago, IL). P-values below 0.05 were considered statistically significant. In case of multiple comparisons, the Bonferroni correction was considered.

## Results

### ToM and Premorbid Adjustment

Retrospective median scores of the premorbid adjustment across age epochs and their relation with the performance on first- and second-order ToM tasks in the schizophrenia group are presented in Table 2. In general, ToM performance was worse than the more impaired premorbid adjustment. The median scores of premorbid adjustment increased over the years in all three categories (for both first- and second-order tasks). Concerning first-order ToM tasks, significant differences were found between ToM performance categories 2 and 0. Regarding second-order ToM tasks, differences were found between category 2 and both categories 1 and 0 (see Figure1).

### ToM and Neurocognition

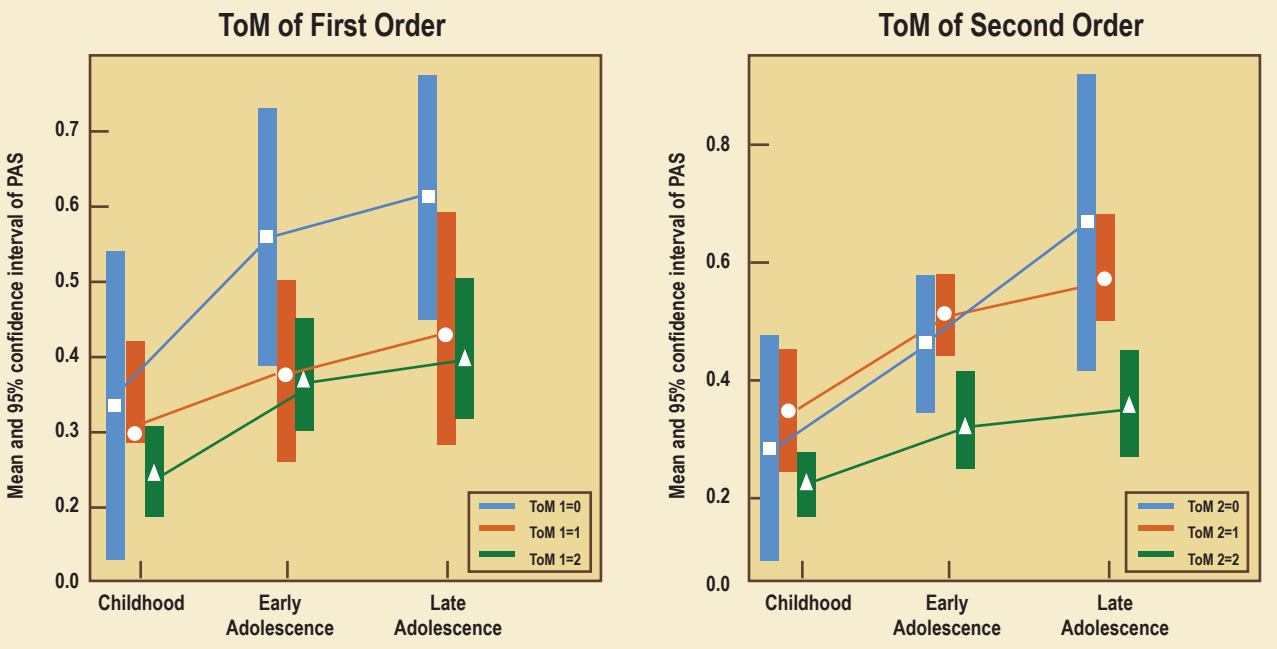
Median scores of the neurocognitive tests among schizophrenic patients and controls and their relation with first- and second-order ToM tasks are shown in Tables 3A and 3B, respectively. In both first- and second-order tasks a significant difference was revealed between category 2 schizophrenic patients and controls with regards to TMT-A. Concerning the schizophrenia groups for first-order ToM tasks, the median scores of categories 2 and 1 were higher than category 0. Using p-values of 0.017 as critical values for statistical significance, subjects of category 2 obtained higher scores only than those of category 0 with respect to TMT-A, Stroop Color-Word and TMT-B. Regarding second-order ToM tasks, the median scores of category 2 patients were better than categories 1 and 0. Category 2 patients showed a significantly better performance than those of category 1 with respect to TMT-A, Block Design and Free Immediate Recall. Furthermore, category 2 patients obtained higher

**Table 2** **Premorbid Adjustment Scale (PAS) Scores for Each Epoch by Category Grouping on the ToM Tasks**

| | First-Order ToM Task | | | Pairwise Comparisons* | |
|---|---|---|---|---|---|
| | **0 (N=6)** | **1 (N=6)** | **2 (N=39)** | **0 vs. 2** | **1 vs. 2** |
| **Childhood** | 0.36 (0.12–0.62) | 0.33 (0.17–0.42) | 0.27 (0.00–0.58) | W=144.5<br>p=0.308 | W=139.5<br>p=0.396 |
| **Early adolescence** | 0.52 (0.37–0.83) | 0.40 (0.20–0.50) | 0.40 (0.00–0.87) | W=172.5<br>p=0.029 | W=111.5<br>p=0.993 |
| **Late adolescence** | 0.57 (0.47–0.90) | 0.43 (0.26–0.55) | 0.40 (0.06–1.00) | **W=169**<br>**p=0.015*** | W=103.5<br>p=0.531 |
| | **Second-Order ToM Task** | | | **Pairwise Comparisons*** | |
| | **0 (N=6)** | **1 (N=14)** | **2 (N=32)** | **0 vs. 2** | **1 vs. 2** |
| **Childhood** | 0.27 (0.12–0.50) | 0.40 (0.04–0.58) | 0.21 (0.00–0.58) | W=105<br>p=0.636 | **W=314.5**<br>**p=0.016*** |
| **Early adolescence** | 0.47 (0.33–0.60) | 0.52 (0.37–0.83) | 0.32 (0.00–0.87) | W=136<br>p=0.050 | **W=343**<br>**p<0.001*** |
| **Late adolescence** | 0.68 (0.30–1.00) | 0.55 (0.43–0.90) | 0.33 (0.06–0.86) | **W=142.5**<br>**p=0.006*** | **W=323**<br>**p<0.001*** |

PAS scores are presented as medians (range). Higher scores indicate worse premorbid adjustment.
*Bonferroni correction for two simultaneous tests per epoch: p-values <0.05/2=0.025 are considered statistically significant.

**Figure 1** First-and Second-Order ToM Task Scores by Subgroups by Life Stages




scores than category 0 on Block Design, almost reaching statistical significance.

## Ordinal Regression Model for ToM

Tables 4 and 5 show the variables included in the ordinal regression models for first- and second-order ToM tasks, respectively. The negative sign of the regression coefficients corresponding to premorbid adjustment (PAS Social Isolation) in both models indicates a negative relationship between that variable and the outcome. That is, ToM deficits were associated with poor premorbid adjustment. Concerning first-order ToM tasks, deficits also were related to a poor performance on the TMT-B. In contrast, the test that showed the highest significant association with second-order ToM tasks was the Block Design. In addition, significant gender differences and an effect of clozapine treatment were found. Specifically, male patients, as well as those taking clozapine, had higher probabilities of presenting ToM deficits. Regarding the goodness-of-fit of both regression models, the relatively high percentages of correct classification by the models (83.7% and 84.3%, respectively) indicate a satisfying model fit in both cases. Moreover, Nagelkerke's R-square amounted to 0.300 and 0.657, respectively, implying that deficits shown by the second-order task can be predicted more accurately by the variables considered in this study. Years of illness evolution, symptoms of the PANSS, and diagnostic subtype according to *DSM-IV* were not significantly associated with first- or second-order ToM tasks.

## Discussion

The present study confirmed that one of the most important characteristics of schizophrenia, poor social functioning, is related to deficits in social cognition abilities (1, 41, 42). Furthermore, the study identified a subgroup of patients with poor prognostic clinical features who presented different degrees of deficit severity in social cognition and in executive capacities with a visuo-perceptual component.

Cohering with mainstream findings in schizophrenia, the present sample of stabilized outpatients exhibited difficulties across diverse interpersonal functions in contrast to normative controls: they were mainly single, with no children, living with their parents, and either unemployed or disabled (43). When the interdependence between ToM tasks and premorbid adjustment was explored, lower scores on first- and second-order ToM tasks were associated with a general tendency to show a worse premorbid functioning from infancy through adolescence. Declining premorbid adjustment across age epochs in which full-blown schizophrenia symptoms appear has been found in other studies (44, 45). Schenkel et al. (15) reported an association between poor premorbid adjustment, measured as quality of peer relationships during childhood, and ToM deficits in a sample of schizophrenic inpatients. These data suggest that problems in social cognition and interpersonal functioning may start during infancy in subjects who will develop schizophrenia later on. In our patients, second-order ToM tasks were more discriminative than first-order ones in re-

**Table 3A** **Neuropsychological Test Scores among Schizophrenia Patients and Controls and Relation with First-Order ToM Tasks**

| | ToM of First Order | | | Controls (N=48) | Pairwise Comparisons* | | |
|---|---|---|---|---|---|---|---|
| | 0 (N=6) | 1 (N=6) | 2 (N=39) | | 0 vs. 2 | 1 vs. 2 | 2 vs. Controls |
| **General Abilities:** | | | | | | | |
| **Intelligence Quotient** | 94.9 (77–103) | 89.4 (73–143) | 93.5 (69–158) | 102.0 (72–154) | W=101.5 p=0.618 | W=106.5 p=0.738 | W=723.5 p=0.070 |
| **Attention:** | | | | | | | |
| **Digit Span Forward** | 8.0 (6–9) | 8.5 (6–10) | 8.0 (4–13) | 9.0 (6–13) | W=110.5 p=0.841 | W=128 p=0.731 | W=679 p=0.026 |
| **Speed of Processing:** | | | | | | | |
| **Trail Making Test A** | 50.0 (36–57) | 45.0 (36–109) | 36.0 (17–82) | 28.5 (14–60) | **W=196 p=0.006*** | W=150.5 p=0.049 | **W=1327.5 p=0.001*** |
| **Working Memory:** | | | | | | | |
| **Digit Span Backward** | 4.5 (2–7) | 6.0 (4–9) | 6.0 (2–11) | 5.0 (2–9) | W=69.5 p=0.112 | W=125 p=0.808 | W=1026 p=0.439 |
| **Executive Function:** | | | | | | | |
| **Stroop Color-Word** | 24.0 (16–41) | 42.0 (8–57) | 35.0 (22–64) | 42.0 (10–76) | **W=43.5 p=0.013*** | W=145.5 p=0.293 | W=609 p=0.012 |
| **Trail Making Test B** | 151.5 (104–210) | 78.0 (71–252) | 85.0 (41–266) | 81.0 (43–157) | **W=211.5 p=0.001*** | W=101.5 p=0.893 | W=1074 p=0.241 |
| **Block Design** | 38.0 (19–56) | 43.5 (22–52) | 41.0 (12–64) | 46.0 (24–64) | W=91 p=0.399 | W=101.5 p=0.619 | W=837.5 p=0.403 |
| **Verbal Learning and Memory:** | | | | | | | |
| **Total Recall A1–A5** | 33.5 (22–49) | 47.0 (29–61) | 43.0 (14–72) | 44.0 (22–64) | W=58.5 p=0.050 | W=116 p=0.980 | W=887 p=0.679 |
| **Free Immediate Recall** | 6.0 (5–12) | 10.5 (3–15) | 10.0 (3–15) | 10.0 (3–15) | W=68 p=0.102 | W=131 p=0.651 | W=822 p=0.331 |

Results are presented as median scores (range). Pairwise comparisons of median scores were carried out with the Wilcoxon test.
*Bonferroni correction for three simultaneous tests per test score: p-values <0.05/3=0.017 are considered statistically significant.

lation with poor premorbid adjustment across the different age epochs, thus indicating that these tasks could be more suited to assess mentalistic abilities in schizophrenia. First-order ToM tasks were originally designed for children, though afterwards more complex versions were created for schizophrenic adults (46). Despite the higher sensitivity of second-order ToM tasks, a schizophrenic subgroup with low performance in first-order ToM tasks, in parallel with a poor premorbid adjustment, also was found in our study. Such a subgroup may be formed by a particular profile of autistic-like patients characterized by a severe deficit in social cognition and extreme disruption of social functioning from early life periods. This agrees with Pickup and Frith's (47) data indicating the existence of a developmental course subtype of schizophrenia presenting severe deficits in social cognition in a premorbid stage. In general, we suggest that ToM deficits shown by the profile of patients identified in the present study may be trait-like, taking into account that in other subgroups of patients mentalizing impairments may be found only in relation to particular symptoms (48).

Concerning neurocognitive tests, when the schizophrenic subgroup with good performance on ToM tasks was compared with controls, only psychomotor speed measures distinguished between them. This indicates that neuropsychological functions were quite preserved in this subgroup. In addition, our data add weight to the idea that a reduction in psychomotor speed does not preclude good social inferences. This is further supported by Schenkel et al. (15), who found no significant associations between speed processing and second-order ToM tasks deficits in a schizophrenia sample.

**Table 3B** **Neuropsychological Test Scores among Schizophrenia Patients and Controls and Relation with Second-Order ToM Tasks**

| | ToM of Second Order | | | Controls (N=48) | Pairwise Comparisons* | | |
|---|---|---|---|---|---|---|---|
| | 0 (N=6) | 1 (N=14) | 2 (N=32) | | 0 vs. 2 | 1 vs. 2 | 2 vs. Controls |
| **General Abilities:** | | | | | | | |
| **Intelligence Quotient** | 84.3 (77–103) | 83.0 (70–143) | 100.4 (73–158) | 102.0 (72–154) | W=50.5 p=0.069 | W=132 p=0.027 | W=717 p=0.620 |
| **Attention:** | | | | | | | |
| **Digit Span Forward** | 8.0 (6–10) | 7.0 (5–13) | 8.0 (4–13) | 9.0 (6–13) | W=81 p=0.556 | W=180.5 p=0.298 | W=634.5 p=0.184 |
| **Speed of Processing:** | | | | | | | |
| **Trail Making Test A** | 49.0 (30–57) | 45.0 (30–109) | 36.0 (17–69) | 28.5 (14–60) | W=139.5 p=0.084 | **W=310.5 p=0.009*** | **W=1076 p=0.002*** |
| **Working Memory:** | | | | | | | |
| **Digit Span Backward** | 4.0 (3–6) | 5.0 (2–9) | 6.0 (3–11) | 5.0 (2–9) | W=42.5 p=0.029 | W=167.5 p=0.176 | W=920.5 p=0.130 |
| **Executive Function:** | | | | | | | |
| **Stroop Color-Word** | 32.5 (20–64) | 30.5 (8–60) | 39.0 (22–58) | 42.0 (10–76) | W=68.5 p=0.326 | W=175.5 p=0.315 | W=565.5 p=0.096 |
| **Trail Making Test B** | 98.5 (63–165) | 104.0 (70–269) | 78.5 (41–182) | 81.0 (43–157) | W=124 p=0.274 | W=300 p=0.020 | W=826.5 p=0.569 |
| **Block Design** | 34.5 (19–54) | 35.5 (22–49) | 49.5 (12–64) | 46.0 (24–64) | W=43 p=0.032 | **W=100.5 p=0.002*** | W=824 p=0.586 |
| **Verbal Learning and Memory:** | | | | | | | |
| **Total Recall A1–A5** | 43.5 (35–55) | 39.5 (22–51) | 46.0 (14–72) | 44.0 (22–64) | W=79 p=0.512 | W=136 p=0.035 | W=832 p=0.533 |
| **Free Immediate Recall** | 9.0 (5–14) | 8.0 (3–11) | 10.0 (3–15) | 10.0 (3–15) | W=73 p=0.367 | **W=109.5 p=0.005*** | W=813.5 p=0.657 |

Results are presented as median scores (range). Pairwise comparisons of median scores were carried out with the Wilcoxon test.
*Bonferroni correction for three simultaneous tests per test score: p-values <0.05/3=0.017 are considered statistically significant.

Subsequent regression analysis showed that a low performance on TMT-B and Block Design was predictive of ToM deficits on first- and second-order tasks, respectively, together with a poor social premorbid adjustment. Results indicated that, consistent with others (1, 49, 50), schizophrenic patients with deficits in social cognition performed poorly on executive tests. Furthermore, the present study found that executive tests with a visuo-perceptual component were associated with specific ToM deficits, with a gradation of dysfunction severity from milder (planning—Block Design, second-order ToM tasks) to more severe (mental flexibility—TMT-B, first-order ToM tasks) (35, 51) in patients with poor premorbid adjustment. In this line, several studies have suggested that deficits in perceptual organization (grouping, integrating objects, forms) or in the ability to modify perceptual selected demands are observed mainly when task-relevant processing requires top-down influences (52, 53). On this basis, it could be speculated that impairment severity, both on executive tasks with a visuo-perceptual component and on ToM tasks, could be due to integration or flexibility difficulties together with a dysfunction in top-down mechanisms that select relevant information in a dynamic fashion (15, 52).

These anomalies in cognitive/perceptual organization are heterogenically manifested in the schizophrenia spectrum since they do not appear in all illness subtypes. There is also evidence of an association between the aforementioned anomalies and factors of clinical severity, such as poor premorbid adjustment and poor prognosis (52). Results of the present study would be in line with this proposal. Other fac-

**Table 4A** Regression Coefficients of Ordinal Regression Model for First-Order ToM Tasks of First Order including Premorbid Adjustment (Social Isolation), Trail B and Gender as Explanatory Variables

| | Regression Coefficient | 95% Confidence Interval | p-Value |
|---|---|---|---|
| Threshold (ToM1=0) | -3.225 | (-4.700; -1.750) | <0.001 |
| Threshold (ToM1=0) | -2.667 | (-4.057; -1.278) | <0.001 |
| PAS: Social Isolation | -1.990 | (-3.754; -0.227) | 0.027 |
| Trail B | -0.009 | (-0.016; -0.001) | 0.026 |
| Males | -0.385 | (-1.357; 0.586) | 0.586 |

The link function applied was the probit link. Pseudo R-square values amounted to: 0.224 (Cox and Snell); 0.300 (Nagelkerke); and 0.184 (McFadden).

**Table 4B** Accuracy of the Ordinal Regression Model for First-Order ToM Tasks of First Order including Premorbid Adjustment (Social Isolation), Trail B and Gender as Explanatory Variables

| | | Predicted Response Category | | | Total |
|---|---|---|---|---|---|
| | | 0 | 1 | 2 | |
| Theory of Mind Tasks of First Order | 0 | 3<br>6.1% | 0 | 3<br>6.1% | **6**<br>**12.2%** |
| | 1 | 1<br>2.0% | 0 | 4<br>8.2% | **5**<br>**10.2%** |
| | 2 | 0 | 0 | 38<br>77.6% | **38**<br>**77.6%** |
| **Total** | | **4**<br>**8.2%** | **0** | **45**<br>**91.8%** | **49**<br>**100%** |

**Table 5A** Regression Coefficients of Ordinal Regression Model for Second-Order ToM Tasks including Premorbid Adjustment (Social Isolation), Block Design, Clozapine and Gender as Explanatory Variables

| | Regression Coefficient | 95% Confidence Interval | p-Value |
|---|---|---|---|
| Threshold (ToM2=0) | -5.975 | (-12.251; 0.300) | 0.062 |
| Threshold (ToM2=0) | -0.317 | (-4.673; 4.040) | 0.887 |
| PAS: Social Isolation | -14.003 | (-26.340; -1.666) | 0.026 |
| Block Design | 0.291 | (0.033; 0.549) | 0.027 |
| Clozapine | -3.379 | (-6.734; -0.025) | 0.048 |
| Males | -5.580 | (-10.775; -0.385) | 0.035 |

The link function applied was the Cauchy link. Pseudo R-square values amounted to: 0.551 (Cox and Snell); 0.657 (Nagelkerke); and 0.440 (McFadden).

**Table 5B** Accuracy of the Ordinal Regression Model for Second-Order ToM Tasks including Premorbid Adjustment (Social Isolation), Block Design, Clozapine and Gender as Explanatory Variables

| | | Predicted Response Category | | | Total |
|---|---|---|---|---|---|
| | | 0 | 1 | 2 | |
| Theory of Mind Tasks of Second Order | 0 | 3<br>5.9% | 1<br>2.0% | 2<br>3.9% | **6**<br>**11.8%** |
| | 1 | 0 | 11<br>21.6% | 3<br>5.9% | **14**<br>**27.5%** |
| | 2 | 0 | 2<br>3.9% | 29<br>56.9% | **31**<br>**60.8%** |
| **Total** | | **3**<br>**5.9%** | **14**<br>**27.5%** | **34**<br>**66.7%** | **51**<br>**100%** |

tors that predicted poor performance on second-order ToM tasks were male gender and clozapine treatment. In this line, a recent study by Caspi et al. (54), exploring antipsychotic treatment resistance and prognostic factors, partially supports our findings in the sense that refractory treatment response was associated with male gender and a low social premorbid functioning. In addition, associations between a poor premorbid adjustment and unfavorable prognostic factors have been widely reported in the literature, defining a characteristic phenotype or subgroup of schizophrenic patients (55). Perhaps future studies combining mentalizing and neurocognitive measures along the lines studied here, with targeted genetic profiling of this subpopulation, would uncover fruitful pathways toward the etiology of this phenotype. Furthermore, future definitions of schizophrenia in international classifications of mental disorders should consider the inclusion of social cognition deficits as core characteristics.

This study had obvious limitations. The ToM tasks employed, although widely used in the literature, have not been fully validated. Also, retrospective assessment of premorbid adjustment may have biased the results, although we cautioned against that through repeated testings with patient subsamples and their relatives. With this in mind, it may be summarized that stabilized schizophrenic outpatients with poor prognostic factors show deficits in ToM that go hand in hand with planning and flexibility dysfunctions, particularly those with a visuo-perceptual component. These factors help to understand social competence impairment shown by schizophrenic patients in their everyday lives.

## Acknowledgments

We gratefully acknowledge the financial support of the Parc Taulí Foundation. We would like to thank the Day Hospital team, Roser Prats, Elena Polo and Josep Romero for their continuous support throughout the study.

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