



Research Paper

Cognitive impairment and its improvement after six months in adolescents with schizophrenia

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ABSTRACT

Studies evaluating the cognitive impairment in schizophrenic adolescents reported a variable course following antipsychotic treatment, with improvement being associated to patients' demographic or clinical characteristics. **Objectives:** To examine the cognitive impairments of a Mexican sample of adolescents with schizophrenia using the MATRICS Consensus Cognitive Battery (MCCB) before and after six months of antipsychotic treatment and to determine which demographic or clinical characteristics could be associated to cognitive improvement.

Methods: A sample of 87 Mexican patients was evaluated with the MCCB. Domain scores for three age groups (12–13, 14–15 and 16–17 y.o.) were obtained at baseline, and after 3 and 6 months of treatment. The groups were compared for demographic and clinical variables (sex, school attendance, years of education, being on their first psychotic episode, duration of illness and mean dose of antipsychotic), and a logistic regression analysis was performed to determine which variables predicted larger improvement.

Results: The baseline performance showed scores below the standardized mean, with improvement in all domains except for social cognition; female adolescents showed a larger improvement in attention/vigilance and visual learning domains.

Conclusions: We observed cognitive impairments on schizophrenic adolescents, which improved after six months of treatment in almost all domains.

1. Introduction

Schizophrenia is a persistent mental illness characterized by disturbances in thought, perception and behavior (American Psychiatric Association, 2013) which are associated with a significant cognitive and functional disability (Green, 1996; Green et al., 2000; Peuskens et al., 2005). Up to 30% of patients have an illness onset before 18 years old (Krausz and Müller-Thomsen, 1993), this group shows greater impairment than adult-onset patients (Fleischhaker et al., 2005; Fraguas et al., 2014; Marshall et al., 2005).

Studies evaluating adolescents with schizophrenia reported deficits in a wide range of cognitive functions including memory, visual and verbal learning, attention, planning and psychomotor speed (Holmen et al., 2010; Kravariti et al., 2007; Puig et al., 2012; Rhinewine et al., 2005; Ueland et al., 2004). These cognitive impairments exhibit a variable course: while some studies did not find changes (De la Serna et al., 2011; Frangou et al., 2008), a 2 year follow up study in adolescents reported a significant increase for attention, learning and

memory, and global cognitive performance, with no significant changes for working memory and executive function (Mayoral et al., 2008). Recent investigations reported improvements following pharmacological treatment (e.g., aripiprazole was associated with fewer total errors and perseverative errors in the Wisconsin Card Sorting Test; Yeh et al., 2014) or cognitive remediation (particularly in verbal memory (Puig et al., 2014), working memory (Puig et al., 2014; Revell et al., 2015), learning (Revell et al., 2015), inhibition and reasoning (Urban et al., 2012)). Studies in adult samples have investigated demographics (sex, age, and education), duration of illness, antipsychotic dose, and symptoms as predictors of cognitive improvement (Farreny et al., 2016) and reported that improvement in the MATRICS Consensus Cognitive Battery (MCCB) domains was associated with younger age, higher education level, lower scores on the Positive and Negative Syndrome Scale (PANSS) (Lindenmayer et al., 2017) and low doses of antipsychotics (Vita et al., 2013). However, these factors have not been fully explored in adolescents; furthermore, the discrepancies in the results of studies with adolescent samples could also be explained by the

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use of different neuropsychological tests.

The MCCB is currently considered the gold standard for the assessment of patients with schizophrenia (Holmen et al., 2010; Nuechterlein et al., 2008; Silverstein et al., 2010) and has been used to compare schizophrenic adolescents with healthy controls (Holmen et al., 2010). Authors who standardized MCCB values using T scores (Nitzburg et al., 2014; Stone et al., 2016), reported important differences in age and sex and advised to consider these groups in further analysis. More recently, the scores of the tests that integrate all cognitive domains assessed by MCCB were compared in a multinational study comprising samples from Ireland, Norway, Sweden, and the USA (Smelror et al., 2018). Results included age effects for all tests and sex differences in scores related to reasoning and problem solving and speed of processing. Although site differences that would be expected to impact cognitive performance were not identified, the authors mentioned that it's unknown whether those findings could be related to the cognitive performance of youngsters from other countries (Smelror et al., 2018).

Taking this in account, as well as the lack of reports of the use of MCCB in Latin American samples, the objectives of present study were (i) to examine the cognitive impairments of a Mexican sample of adolescents with schizophrenia using the MCCB before and after six months of antipsychotic treatment, (ii) to compare the MCCB scores according to age, and (iii) to determine if the patients demographic or clinical characteristics are associated with cognitive improvement.

2. Methods

The study was approved by the Institutional Ethics Committee and followed the guidelines of Declaration of Helsinki. Informed consent from the participants' parents/tutors was obtained before their inclusion in the study.

Study methods were described in detail in a previous publication (Ulloa et al., 2018). For the current report, the evaluation and follow up of cognitive functioning was performed as follows: participants were recruited at the inpatient and outpatient services of the Child Psychiatric Hospital in Mexico City. Inclusion criteria were male and female adolescents between 12 and 17 years, with a diagnosis of schizophrenia or schizophreniform disorder according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994). Participants were excluded if unstable medical conditions, a diagnosis change or substance related disorders were detected.

2.1. Instruments

- a) MINI International Neuropsychiatric Interview for children and adolescents (MINI KID)
The MINI KID is a structured diagnostic interview to evaluate psychopathology in children and adolescents (Sheehan et al., 2010). It examines the presence of 23 psychiatric disorders according to the DSM-IV and the International Classification of Diseases (ICD-10) criteria (World Health Organization, 1992).
- b) The Positive and Negative Syndrome Scale (PANSS)
Evaluates the severity of symptoms during an interview with the patients and their parents. Its psychometric properties were extensively studied (Kay et al., 1987) and has been used in studies with adolescent patients (Röpcke and Eggers, 2005; Savitz et al., 2015).
- c) MATRICS Consensus Cognitive Battery (MCCB)
Evaluates seven domains of cognitive functioning: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem-solving and social cognition. Speed of processing was tested by the Trail Making Test A (TMT), Symbol-Coding and Category Fluency; attention/vigilance was assessed with Continuous Performance Test-Identical Pairs (CPT-IP); working

memory was assessed with Spatial Span and Letter-Number Span; verbal learning was assessed with Hopkins Verbal Learning Test-Revised (HVLTR); visual learning was assessed with Brief Visuospatial Memory Test-Revised (BVMTR); the Mazes test was used to assess reasoning and problem-solving and the Mayer-Salovey-Caruso Emotional Intelligence Test, Managing Emotions (MSCEIT) was used to assess social cognition. The Spanish version of MCCB is available.

2.2. Data analysis

The analysis was performed with IBM SPSS Statistics (version 21) software. First, the MCCB test raw scores of the present sample were compared to the scores reported by Holmen et al. (2010) for healthy subjects using a one sample *t*-test. Then, the raw scores for the cognitive tests were converted to T-scores based on the guidelines of MCCB. Descriptive statistics were used for baseline clinical and demographic variables. Following the methodology of previous studies (Stone et al., 2016), the sample was divided into three age groups (12–13 y.o. $N = 18$, 14–15 y.o. $N = 35$, and 16–17 y.o., $N = 34$) and then compared using a repeated measures general linear model with age (age groups) and time (baseline, month 3 and month 6) as factors including schooling as a covariate to evaluate possible differences by group over time. To examine the degree of improvement, effect sizes on the change of each domain were calculated according to Cohen (1969), considering values of 0.2, 0.5 and 0.8 for low, moderate and high effect size, respectively.

The score changes in time for each individual was obtained by subtracting scores at month 6 to baseline scores (ΔS). Using the median value of these differences, participants were classified into two groups: those patients with a ΔS above the median value were considered to have a large improvement and those with a ΔS below the median value were considered to have a small improvement on each particular domain. Finally, a binary logistic regression analysis was performed to determine the variables which predicted the large improvement on each domain. The results were considered significant with a $p \leq 0.05$.

3. Results

The study included 87 patients (69% males, mean age 14.9 ± 1.5 years), with 8.2 ± 1.6 school years, 42.9% attending school. Most of them (83.9%) were on their first psychotic episode, the mean duration of their illness was 13.6 ± 15.2 months. Their mean PANSS score was 93.3 ± 19.9 at baseline, 56.1 ± 20.3 at month 3 and 52.2 ± 20.1 at month 6. Their pharmacological treatment was mainly based on atypical antipsychotics (93%), with a mean dose of 219.8 ± 72.9 mg of chlorpromazine equivalents; none received cognitive remediation therapy.

Baseline cognitive evaluation showed that median T scores for all domains were well below 50, with speed of processing and attention/vigilance having the lowest median values (see Supplementary data). The MCCB test raw scores at baseline and month six were significantly lower than those reported on Holmen's et al. (2010) healthy sample of a similar age (Table 1). A significant time effect was observed in the T scores of almost all domains (Table 2); we observed medium effect sizes, with attention/vigilance and reasoning and problem solving exhibiting the largest values and working memory and speed of processing showing the highest percentage of subjects with large improvement (Table 3).

The binary logistic regression showed that female gender predicted a large improvement in attention/vigilance (OR = 7.93, 95% C.I. = 1.92–32.75) and visual learning (OR = 4.00, 95% C.I. = 1.14–13.98).

Table 1
MCCB test raw scores of patients with schizophrenia compared with normal control subjects.

MCCB test	Patients (14.8 ± 1.5 y.o.) ^a		Healthy subjects (16.0 ± 1.9 y.o.) ^g	Statistics Baseline	Statistics Month 6
	Baseline	Month 6			
TMT: part A	77.7 (56.6) ^a	53.4 (34.3) ^e	27.7 (10)	t = 8.054 df = 82 p = 0.000	t = 6.082 df = 65 p = 0.000
BACS symbol coding	33.9 (13.5) ^b	40.2 (12.1) ^e	61.9 (11.8)	t = -18.972 df = 83 p = 0.000	t = -14.460 df = 65 p = 0.000
HVLT-R	19.3 (6.7) ^b	22.8 (5.6) ^e	28.9 (3.5)	t = -12.834 df = 83 p = 0.000	t = -8.705 df = 65 p = 0.000
WMS-III spatial span	12.1 (4.5) ^b	14.6 (3.2) ^e	19.1 (2.9)	t = -13.918 df = 83 p = 0.000	t = -11.123 df = 65 p = 0.000
Letter-number span	8.5 (3.5) ^a	10.3 (3.3) ^e	16.1 (3)	t = -19.329 df = 82 p = 0.000	t = -14.054 df = 65 p = 0.000
NAB mazes	10.8 (5.7) ^a	14.9 (6.0) ^e	21.7 (4.2)	t = -17.045 df = 82 p = 0.000	t = -9.169 df = 65 p = 0.000
BVMT-R	17.2 (8.4) ^a	20.8 (7.3) ^e	28.6 (4.1)	t = -12.295 df = 82 p = 0.000	t = -8.650 df = 65 p = 0.000
Category fluency: animal naming	17.3 (6.1) ^a	18.9 (6.1) ^e	23.2 (4.8)	t = -8.659 df = 82 p = 0.000	t = -5.584 df = 65 p = 0.000
MSCEIT: Managing Emotions	79.5 (9.4) ^c	79.2 (9.7) ^f	87 (8.8)	t = -7.062 df = 78 p = 0.000	t = -6.423 df = 64 p = 0.000
CPT-IP DPrime	1.2 (0.6) ^d	1.6 (0.7) ^e	2.2 (0.7)	t = -13.071 df = 77 p = 0.000	t = -6.106 df = 65 p = 0.000

^a n vary by cognitive domain; actual n indicated by letter superscript: a = 83; b = 84; c = 79; d = 78; e = 66; f = 65, g = 67.

4. Discussion

4.1. Main findings

The aim of the present study was to examine the cognitive profile of adolescents with schizophrenia in a six-month follow-up. The results showed baseline deficits in all MCCB domains, which improved over time.

No age differences were found in the MCCB scores along the study. This result contrasts with the MCCB performance of healthy adolescents, where older subjects performed better in almost all domains (Smelror et al., 2018; Stone et al., 2016) and is in line with previous studies showing the disrupting effect of early onset psychosis on the patients' cognitive development (Bombin et al., 2013).

Although mean T scores did not surpass the normal value of 50, scores of verbal learning, visual learning, speed of processing, working memory, reasoning and problem solving, and attention/vigilance exhibited improvements at month six, with effect sizes ranging from medium to large. Considering that the current design was not addressing the comparison between drug effects or treatment effects, there are several ways in which to interpret such improvements: the first one is to attribute them to the learning processes related to performing the MCCB tasks more than once and the second one is to attribute them to cognitive improvements observed in development. While learning effects almost surely took place, these are almost impossible to disentangle from treatment itself. However, learning effects are reduced by the MCCB design which includes small variations in several tests. Additionally, effect sizes observed far surpassed those reported on a blinded review of 12 trials including 813 patients with schizophrenia, which found a mean change in the MCCB during receipt of placebo of < 0.2 SDs (Keefe et al., 2017). Thus, we are inclined to attribute the observed improvement mainly to the effects of treatment, which are in line with the findings of longitudinal studies performed in adolescent

patients (Crespo-Facorro et al., 2009; Cuesta et al., 2009) and in adults on their first psychotic episode (Davidson et al., 2009).

Previous studies on adults have shown that several factors could be associated with cognitive improvement, such as treatment with low doses of antipsychotics or the severity of symptoms such as conceptual disorganization or preoccupation (Knowles et al., 2010; Vita et al., 2013). In addition, sex differences in the cognitive improvement after antipsychotic treatment were reported in adult patients (Rubin et al., 2008). Present results only found female gender as a predictor of large improvement in attention/vigilance and visual learning. To the best of our knowledge, there is no information regarding the association between sex and cognitive improvement in other samples of adolescents with schizophrenia, and this information could be useful in cognitive remediation programs for adolescents.

Speed of processing and social cognition were among the most affected cognitive domains, having low baseline values and a small effect size improvement. The score of speed of processing is based on 3 different tests including the Symbol Coding Test, where the performance of psychotic patients is frequently poor. Low speed of processing has been mentioned as the core characteristic of cognitive impairment in these patients (Dickinson et al., 2007) and was reported in previous studies with adolescents with psychosis (Kelleher et al., 2013), high risk subjects (Cannon et al., 2006; Carrión et al., 2011) and a meta-analysis of studies with adult samples (Dickinson et al., 2007). The poor results on the social cognition domain could be explained by the MSCEIT lack of validity, given that it describes social situations which are foreign to adolescents' experiences (Holmen et al., 2010) and has lead studies to not include this domain (Smelror et al., 2018). This work, along previous references, highlight the importance of developing a proper measure of social cognition, as it is one of the cognitive functions that mainly impacts the daily life of patients (Schmidt et al., 2011; Sergi et al., 2006; Vaskinn et al., 2008).

Table 2
Group means and group comparisons for MCCB domains in adolescent patients.

	Total simple	Age groups: mean (± SD)			Statistics (RMGLM)		
		12–13 years	14–15 years	16–17 years	Age effect	Time effect	Time * age effect
Speed of processing							
Baseline	22.3 (15.6)	26.4 (13.5)	22.5 (12.7)	20.5 (15.5)	F = 0.05	F = 24.23	F = 1.83
Month 3	29.2 (12.9)	28.6 (11.4)	29.4 (11.5)	30.1 (11.9)	df = 2, 56	df = 2,99	df = 4,99
Month 6	30.7 (14.5)	30.7 (15.8)	33.7 (14.3)	31.9 (12.0)	p = 0.94	p = 0.000	p = 0.13
Attention/vigilance							
Baseline	23.6 (9.4)	18.6 (8.1)	21.1 (8.7)	24.7 (8.1)	F = 1.74	F = 45.34	F = 1.09
Month 3	28.6 (10.4)	26.9 (9.6)	27.2 (8.3)	30.4 (10.7)	df = 2,52	df = 2, 104	df = 4, 104
Month 6	30.1 (10.7)	32.0 (7.8)	28.9 (9.2)	34.5 (10.1)	p = 0.18	p = 0.000	p = 0.36
Working memory							
Baseline	28.9 (13.0)	26.9 (11.9)	29.3 (12.2)	30.1 (12.4)	F = 1.03	F = 27.99	F = 0.90
Month 3	34.0 (11.6)	31.2 (12.8)	35.1 (8.5)	35.4 (9.0)	df = 2,56	df = 2,91	df = 3,91
Month 6	36.5 (10.6)	32.9 (12.4)	36.5 (9.7)	40.1 (9.2)	p = 0.36	p = 0.000	p = 0.44
Verbal learning							
Baseline	34.8 (10.1)	34.2 (6.8)	34.0 (9.7)	36.5 (9.7)	F = 0.43	F = 15.10	F = 0.94
Month 3	38.6 (10.3)	38.1 (8.7)	37.5 (11.2)	40.3 (8.5)	df = 2,56	df = 2,99	df = 4,99
Month 6	40.0 (9.5)	38.3 (9.4)	41.8 (10.0)	41.3 (9.1)	p = 0.65	p = 0.000	p = 0.43
Visual learning							
Baseline	37.0 (13.2)	33.8 (15.9)	33.4 (12.3)	38.5 (10.4)	F = 0.92	F = 25.98	F = 0.71
Month 3	41.4 (13.3)	39.7 (16.0)	40.8 (11.7)	43.8 (9.3)	df = 2,56	df = 2,90	df = 3,90
Month 6	42.6 (11.4)	40.3 (13.0)	43.9 (10.3)	45.2 (9.8)	p = 0.40	p = 0.000	p = 0.55
Reasoning and problem solving							
Baseline	37.3 (6.2)	37.2 (5.3)	36.5 (5.8)	37.5 (6.9)	F = 0.15	F = 25.35	F = 0.12
Month 3	39.4 (6.0)	39.7 (5.0)	39.1 (7.2)	39.5 (5.2)	df = 2,56	df = 2112	df = 4, 112
Month 6	42.3 (8.1)	42.6 (7.7)	42.2 (8.4)	43.7 (8.8)	p = 0.86	p = 0.000	p = 0.97
Social cognition							
Baseline	30.1 (10.7)	30.3 (11.1)	31.2 (11.5)	29.0 (7.3)	F = 1.04	F = 1.18	F = 0.31
Month 3	29.2 (10.6)	26.4 (10.1)	31.0 (12.8)	26.8 (9.3)	df = 2,53	df = 2106	df = 4106
Month 6	29.8 (11.1)	28.7 (10.3)	32.7 (10.1)	28.1 (12.2)	p = 0.36	p = 0.31	p = 0.86
Overall composite score							
Baseline	20.4 (13.0)	19.7 (10.0)	20.1 (10.8)	20.1 (11.9)	F = 0.07	F = 50.37	F = 0.31
Month 3	25.5 (12.7)	25.3 (10.7)	25.8 (11.7)	26.7 (10.4)	df = 2,50	df = 2,83	df = 3,83
Month 6	28.0 (11.8)	28.1 (10.6)	30.7 (12.1)	30.4 (10.2)	p = 0.93	p = 0.000	p = 0.83

RMGLM: repeated measures general linear model.

4.2. Limitations

Present results should be examined considering the lack of a control group, the relatively short follow up period and sample size, the unavailability of premorbid IQ, in addition to the inclusion of patients with first psychotic episode and patients with chronic illness. On the other hand, reporting the cognitive assessment of a Latin American sample of adolescents with schizophrenia could be seen as a strength.

4.3. Conclusions

Adolescents with schizophrenia show deficits in several cognitive domains, particularly in speed of processing and social cognition. These deficits improve after treatment, with women showing a better outcome in some domains.

Supplementary data to this article can be found online at [https://](https://doi.org/10.1016/j.scog.2019.100135)

Table 3
Changes in the score of each MCCB domain from baseline to month 6.

	Mean difference	Median	Effect size	Percentage of subjects showing large improvement
Speed of processing	9.50	9	0.60	57.1
Attention/vigilance	9.03	9	0.96	50.8
Working memory	8.42	7	0.64	58.7
Verbal learning	5.90	5	0.58	54
Visual learning	8	8	0.60	51.6
Reasoning and problem solving	5.69	5.5	0.91	50
Social cognition	-0.11	0	-0.01	43.3
Overall composite score	9.74	8.5	0.74	50

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REU and RA designed the study, GV, MFR and REU carried out the analysis and wrote the draft manuscript. All authors revised and approved the final version of the manuscript.

Conflict of interest

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