RESEARCH LETTER

Cognitive Impairment in Never-Medicated Individuals on the Schizophrenia Spectrum

Cognitive impairment is a key feature of schizophrenia. While a 2019 study[1] suggested that individuals with psychosis experience a progressive decline in certain cognitive domains during the first 10 years of their illness, other clinical studies[2,3] and functional magnetic resonance imaging–based studies[4,5] have proposed that most cognitive deficits are present during the first episode and remain stable over time. To examine the temporal nature of cognitive deficits on the schizophrenia spectrum, we examined cognition in never-medicated individuals at different stages of the illness.

Methods | We recruited 3 groups of patients: (1) individuals at clinical high-risk (CHR) for psychosis, (2) individuals experiencing their first episode of a nonaffective psychosis (FEP; defined as a duration of untreated psychosis for less than 74 weeks[6]), and (3) individuals with chronic schizophrenia (defined as a duration of untreated psychosis for more than 74 weeks). All 3 groups were naive to antipsychotic medications. Patients with any comorbid disorders or current substance use disorders were excluded from this study. We also recruited matched healthy control participants. All participants were recruited at the Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico. The study was approved by the Ethics and Scientific Committees of the Instituto Nacional de Neurología y Neurocirugía. Adults provided written informed consent and minors provided assent with written informed consent provided by both parents. Cognition was assessed with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery. Differences between groups were analyzed using a repeated-measures analysis of variance with cognitive domain as the intraindividual factor and Bonferroni correction for post hoc pairwise comparisons. Statistical significance was set at a 1-sided *P* value less than .05. Analyses were conducted using SPSS Statistics version 21 (IBM).

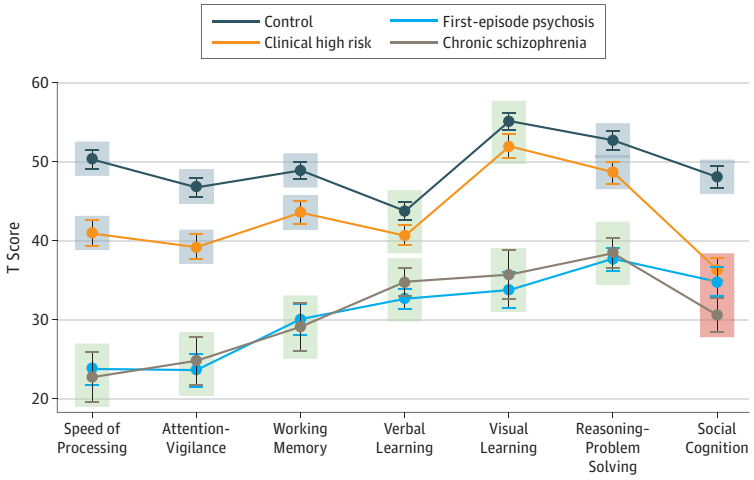
Results | The demographic and clinical characteristics of all participants are listed in the **Table**. Since age, sex, and parental

Table. Demographic and Clinical Characteristics of the Study Participants

Characteristic	Mean (SD)				Statistic	*P* Value
	Control (n = 102)	CHR (n = 87)	FEP (n = 64)	Chronic Schizophrenia (n = 40)		
Age, y	27.4 (11.1)	20 (4.6)	25.1 (7.7)	32.7 (11.3)	$F = 21.26$	<.001
Female, No. (%)	45 (44.1)	21 (24)	26 (41)	11 (28)	$\chi^2 = 10.09$	.02
Educational level, y	14.6 (3.6)	11.6 (2.7)	10.8 (2.9)	10.8 (3.4)	$F = 26.85$	<.001
Parental education, y	13.6 (5.5)	13 (3.9)	9.7 (4.2)	9.9 (5.7)	$F = 13.95$	<.001
SIPS subscale score						
Positive symptoms	NA	10.9 (4.7)	NA	NA	NA	NA
Negative symptoms	NA	14.3 (6.5)	NA	NA	NA	NA
Disorganization symptoms	NA	8 (4.1)	NA	NA	NA	NA
General symptoms	NA	9.2 (3.6)	NA	NA	NA	NA
Duration of untreated psychosis, mean (SD) [range], wk	NA	NA	14.4 (18.2) [1 to 67]	412.0 (399.6) [78 to 1352]	$t = -7.97$	<.001
PANSS subscale score						
Positive symptoms	NA	NA	26.8 (6.7)	27.3 (4.9)	$t = -0.37$	.71
Negative symptoms	NA	NA	24.1 (6.1)	25.3 (6.7)	$t = -0.97$	.33
General psychopathology	NA	NA	49.3 (9.1)	50.1 (8.5)	$t = -0.42$	.68
MCCB T scores						
Speed of processing	50.3 (8.7)	40.9 (12.4)	23.8 (14.0)	22.8 (17.4)	$F = 61.10$	<.001
Attention-vigilance	46.8 (9.5)	39.2 (10.7)	23.6 (12.5)	24.8 (16.0)	$F = 51.08$	
Working memory	48.9 (7.6)	43.6 (10.7)	30.1 (12.8)	29.1 (17.2)	$F = 37.84$	
Verbal learning	43.8 (7.4)	40.6 (8.2)	32.7 (7.5)	34.8 (8.9)	$F = 18.45$	
Visual learning	55.2 (8.4)	52.0 (10.7)	33.8 (15.1)	35.7 (17.2)	$F = 35.88$	
Reasoning-problem solving	52.7 (8.9)	48.7 (9.2)	37.7 (9.3)	38.5 (9.8)	$F = 30.69$	
Social cognition	48.1 (9.9)	36.3 (9.9)	34.8 (11.3)	30.6 (11.2)	$F = 29.07$	

Abbreviations: CHR, clinical high-risk; FEP, first-episode psychosis; MCCB, Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; SIPS, Structured Interview for Psychosis-Risk Syndromes.

Figure. Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery T Scores for Each Cognitive Domain and Group



Significance was set at a Bonferroni-corrected $P < .01$ adjusted by parental education and sex. Blue shading indicates significant differences with all 3 groups outside the shading. Green shading indicates no significant differences between the 2 groups within the shading but significant differences with the 2 groups outside the shading. Pink shading indicates no significant differences between the 3 groups within the shading but significant differences with the group outside the shading. Error bars indicate SEMs.

education were significantly different between the groups, they were included as covariates in the repeated-measures analysis of variance. In this revised model, there was no main effect of age ($F_{1,286} = 0.16$; $P = .69$; partial $\eta^2 = 0.001$) nor any interaction between age and any cognitive domain. Therefore, age was removed from the final model.

We observed a significant main effect of group ($F_{3,287} = 84.79$; $P < .001$; partial $\eta^2 = 0.49$). Pairwise comparisons revealed that while all patient groups were significantly impaired compared with the control group (CHR vs control: mean difference, 6.12; $P < .001$; FEP vs control: mean difference, 16.46; $P < .001$; chronic schizophrenia vs control: mean difference, 16.37; $P < .001$), individuals with both FEP and chronic schizophrenia had significantly more cognitive impairment than the CHR group (FEP vs CHR: mean difference, 10.34; $P < .001$; chronic schizophrenia vs CHR: mean difference, 10.25; $P < .001$). No significant differences were observed between the FEP and chronic schizophrenia groups (mean difference, 0.09; $P > .99$).

We also found a significant group × cognitive domain interaction ($F_{14.6,1307.9} = 8.72$; $P < .001$; partial $\eta^2 = 0.09$). The results for each cognitive domain are summarized in the **Figure**. Namely, all patient groups were cognitively impaired compared with the control group, except in the verbal and visual learning domains in which there were no significant differences between the control and CHR groups. No significant differences were found between the FEP and chronic schizophrenia groups in any domain. Moreover, the CHR group was not significantly different from the other clinical groups in the social cognition domain. Within the FEP and chronic schizophrenia groups, no significant associations were observed between duration of untreated psychosis and any cognitive domain.

Discussion | We observed significant cognitive deficits at all stages of the schizophrenia spectrum, including the CHR period. Patients with FEP were as impaired as those with chronic schizophrenia, while cognitive functioning observed in individuals at CHR was intermediate between controls and patients with syndromal psychosis. The main limitation of this study is the cross-sectional design. Nevertheless, these results emphasize the importance of presyndromal detection and prediction of burgeoning psychotic illness. Future research on strategies to mitigate the decline in cognitive function between presyndromal and FEP is warranted.

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CORRECTION

Updates to Conflict of Interest Disclosures and Additional Contributions: In the Original Investigation titled "Outcomes of Online Mindfulness-Based Cognitive Therapy for Patients With Residual Depressive Symptoms: A Randomized Clinical Trial,"[1] published online January 29, 2020, in the Conflict of Interest Disclosures, Dr Segal and Dr Dimidjian added that they are cofounders of Mindful Noggin, Inc. In the Additional Contributions, the NogginLabs team was added as helping with the design of Mindful Mood Balance, and affiliations were added for those acknowledged. This article has been corrected online.

1. Segal ZV, Dimidjian S, Beck A, et al. Outcomes of online mindfulness-based cognitive therapy for patients with residual depressive symptoms: a randomized clinical trial [published online January 29, 2020]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2019.4693