Metacognition strengthens the association between neurocognition and attenuated psychosis syndrome: Preliminary evidence from a pilot study among treatment-seeking versus healthy adolescents☆

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ARTICLE INFO

ABSTRACT

Background: In a pilot study, we assessed the potential value of deficits at the metacognitive versus the neurocognitive level of functioning for identifying adolescents with attenuated psychotic syndrome (APS).
Method: Twenty-two treatment-seeking adolescents with APS, 42 treatment-seeking comparisons, and 34 age-matched healthy comparisons were evaluated using the Prodromal Questionnaire, the Structured Interview for Prodromal Syndromes, and the Mood and Anxiety Symptom Questionnaire. Neurocognitive and metacognitive functioning were assessed in two non-social (verbal memory and executive functioning) and two social (facial emotion perception and theory of mind) cognitive domains. In addition to the standard neurocognitive administration of the tasks, subjects were asked to rate their confidence level on each answer and to choose whether they wanted it "counted" toward their overall task performance score on the task. Choices were rewarded.
Results: As hypothesized, APS among treatment-seeking adolescents was more strongly associated with impaired neurocognition than with impaired metacognition. Likewise, as hypothesized, impaired metacognition was shown to significantly improve the APS prediction beyond the contribution of impaired neurocognition alone, even after controlling for general intellectual ability, negative symptoms, social functioning, and depression.
Conclusions: These results suggest that metacognitive monitoring and control play a strengthening role in the association between neurocognition and APS. One possible explanation is that metacognition serves as an indicator of insight into the condition, accounting for differences in insight not explained by neurocognition alone. However, further research with larger samples that include non-treatment seeking individuals, established measures of insight, and follow-up data is required to assess this possibility.

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1. Background

1.1. Neurocognition and attenuated psychosis syndrome (APS): knowns and unknowns

It is well accepted that a majority of adolescents or young individuals who develop schizophrenia have a prodromal or high risk state in the period prior to psychosis (Fusar-Poli et al., 2013) analogous to the period of "mild cognitive impairment" that is identifiable in many older people who subsequently develop dementias such as Alzheimers disease (Petersen et al., 1999). This condition is variably described as "clinical high risk" (CHR), "ultra-high risk" (UHR), or "at-risk mental state" (ARMS) and denotes a "risk condition" that tends to evolve to a full psychotic disorder in about 30% of cases (Fusar-Poli et al., 2013). In order to distinguish the "high risk" status from a risk 'diagnosis', the descriptive term, "attenuated psychosis syndrome" (APS) has been adopted (Carpenter and van Os, 2011; Tsuang et al., 2013). A key determinant of attenuated psychosis that differentiates it from full-intensity psychosis is an openness to doubt regarding the "real" nature of the experience and maintenance of a relatively intact insight into its being a symptom (Miller et al., 2003).

Converging evidence from several cross-sectional and longitudinal studies (Bora and Murray, 2014; Fusar-Poli et al., 2012; Giuliano et al., 2012) suggests that impaired cognition is a key characteristic of clinical high-risk (CHR) for psychosis, as operationally defined by presence of

attenuated psychosis syndrome (APS) (Cannon et al., 2016; Seidman et al., 2016). However, this body of evidence leaves several important questions unanswered. First, because it does not include data about distressed individuals who might be at risk for other conditions, it leaves unresolved the degree to which these impairments are specific to APS. This issue is essential in light of a recent study which found that neurocognitive performance among treatment-seeking individuals at (CHR) for psychosis was similar to that of individuals at CHR for bipolar depression (Metzler et al., 2014). Second, although a remaining insight into one's unusual perceptual and cognitive experiences is a defining feature of APS (Fusar-Poli et al., 2012), the current body of data does not capture additional impairments that may be associated with the lack of insight and control over neurocognitive abilities (or deficits) in APS.

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The present study was motivated by the view metacognitive impairments are a particularly promising candidate as an influencing factor in the decline of insight. *Metacognition* is an umbrella concept for a variety of 'meta-level' abilities, such as those that can be described collectively as "knowing about knowing" (Metcalfe and Shimamura, 1994). It is a term used to distinguish what one knows about one's own cognitive abilities, states of knowledge, and actual performance using these cognitive abilities, from performance per se. It also includes the ability to use this 'meta-level' knowledge to regulate one's own performance. Hence, two important aspects of metacognitive functioning are *monitoring* (the subjective evaluation of one's own cognitive functioning) and *control* (the manner in which one's behavior is directed by this evaluation) (Nelson and Narens, 1990). Unlike other models of metacognition in schizophrenia that use the same term to refer to other abilities such as theory of mind (ToM), source monitoring, and executive functions (e.g., (Lysaker et al., 2011b), metacognition, as conceptualized here, is not examined with self-report questionnaires or "forced-response" tests that focus solely on input-bound performance (i.e., the percentage of input items that are answered correctly). Instead, its evaluation depends on incorporation of "free-response" tasks and output-bound measures into standard, base-level testing procedures (i.e., the percentage of answers that the participant believes to be correct). An important advantage of this approach, which is based on a paradigm developed in experimental psychology to study metamemory (Koriat and Goldsmith, 1996) is that it allows for isolation of the unique contribution of monitoring and control to one's overall performance. In addition, it enables an assessment of the extent to which performance improves (or deteriorates) when one is allowed to choose when to offer a response and when to withhold it. These capabilities are particularly important in the context of neurocognition in schizophrenia because of recent studies which show that metacognitive abilities can vary independently of neurocognitive skills per se, including ones, such as ToM, source monitoring, error detection and executive functions, that are sometimes referred to as "metacognition" (Koren et al., 2004, 2005). A more elaborated discussion of these points can be found in our previous conceptual paper on metacognition in schizophrenia (Koren et al., 2006).

Preliminary support for this view comes from several recent studies, which found that metacognition assessed with either self-reports (Barbato et al., 2014; Brett et al., 2009), clinical ratings based on extensive interviews (Lysaker et al., 2010, 2011a), or behavioral measures (Eisenacher et al., 2015; Koren et al., 2004, 2005) is a critical determinant of clinical and functional outcome among APS, first-episode, and chronic schizophrenia patients that is not reducible to traditional neurocognitive functioning measures and can vary idependently of these skills (Koren et al., 2006) .

1.2. Goals and hypotheses

The overarching goal of this pilot study was to examine the relationship of neurocognition and metacognition with APS among treatment-seeking adolescents. More specifically, the study was designed to test three hypotheses: 1) neurocognitive and metacognitive deficits constitute distinct but moderately related impairment dimensions; 2) presence of APS is more strongly associated with neurocognition than with metacognition; but 3) APS prediction can be improved by considering both domains of impairment and the interaction between them.

The present study is novel in two important respects. First, unlike other models of metacognition in psychosis that use the same umbrella term to refer to primary abilities, such as theory of mind (ToM), source monitoring, and executive functions, metacognition, as conceptualized and measured here is a secondary process that is concerned with the output of primary abilities under free-choice (as opposed to forced-response) conditions. Second, while partially overlapping with our previous study (Scheyer et al., 2014), the present study is entirely novel and unique regarding the questions that it examined and the data that it used for this purpose. More specifically, it is the first to assess the relative degrees to which neurocognition and metacognition are impaired among individuals with and without APS as compared to the normal base, and to use metacognitive scores that are not affected by the number and difficulty level of the items in each task (see more below).

2. Method

2.1. Participants

The participants consisted of two groups. The first included 64 (27 females, 37 males) non-psychotic adolescents (age 13–18 years) seeking treatment in two youth mental health clinics in Israel (Rambam Medical Center in Haifa, and Schneider Children Hospital in Petach Tikva), and the second 34 (19 females, 15 males) non-treatment-seeking adolescents of the same ages and sociodemographic status recruited from the community.

Participants in the treatment-seeking group were included in the study if they met the following criteria: (1) age between 13 and 18 years, (2) fluency in Hebrew, (3) no past or present psychotic episodes as determined by a clinical psychiatric diagnostic assessment, (4) no organic causes for their symptoms, (5) no history of severe head injury or organic brain disorder, and (6) no intellectual disability as defined by an IQ estimate below 70, estimated using the WAIS-R Vocabulary and Block Design subtests. Although some patients had a first degree relative with a history of psychotic illness (see Table 1), this was not an inclusion criteria for this group. Of the 78 who met the inclusion criteria, 64 gave informed consent and completed the entire study protocol.

Participants in the healthy comparison group were recruited using an advertisement published on Facebook. To be included in this group, participants had to meet the inclusion criteria defined for the group of treatment-seeking participants, and also (1) had not sought help or received any treatment over the previous year, and (2) did not have a first-degree relative with a psychotic illness history. All adolescent participants' parents signed informed consent forms, which were reviewed and approved by the IRB committees of the two clinical institutions and the University of Haifa.

Twenty-two (36%) of the treatment-seeking group and none (0%) of the healthy comparisons (HC) met the diagnostic criteria for APS based on the Prodromal Questionnaire (PQ) and the Structured Interview for Prodromal Syndromes (SIPS) (for a detailed description of these measures see Section 2.2.2. below). Table 1 presents the demographic, clinical, and neurocognitive characteristics of the three groups in the study: youths with APS, treatment-seeking comparisons (TSC), and age-matched healthy comparisons (HC). As can be seen, the three groups were highly comparable on all demographic variables, including educational background and socioeconomic level. However, as one might expect, the two treatment-seeking groups were significantly more impaired than the HC group on IQ estimate, social and academic functioning, and all the clinical variables.

Table 1

Primary socio-demographic, educational, clinical, and neurocognitive characteristics of treatment-seeking adolescents with attenuated psychotic symptoms, treatment-seeking comparisons, and healthy comparisons.

	1. Healthy controls (HC) N = 34	2. Treatment-seeking comparisons (TSC) N = 42	3. Treatment-seeking Attenuated Psychotic Symptom (APS) N = 22	Significance test	Post-hoc Tukey test
Mean (SD) age (years)	15.8 (1.0)	15.9 (1.5)	15.9 (1.4)	$F_{(2,93)} = 0.1$, p = .94	
Gender (% male)	44.2	57.1	59.1	$\chi^2_{(2)} = 2.1$, p = .35	
Socioeconomic level (% low/average/high)	9.1/84.8/6.1	3.3/90.0/6.7	12.5/75.0/12.5	$\chi^2_{(4)} = 2.2$, p = .69	
Mean (SD) Mother's years of education	14.0 (2.1)	14.8 (2.8)	13.6 (2.9)	$F_{(2,80)} = 1.6$, p = .21	
Mean (SD) Father's years of education	14.3 (2.2)	14.1 (2.8)	14.7 (3.2)	$F_{(2,74)} = 0.3$, p = .77	
Repeated grades (N), yes/no	0/34	1/41	2/20	$\chi^2_{(2)} = 4.1$, p = .13	
Diagnosed with depression and/or anxiety (N), yes/no	0/34	13/29	3/19	$\chi^2_{(2)} = 13.3$, p = .00	1 < 2 = 3
Diagnosed with ADHD (N), yes/no	0/34	7/35	1/21	$\chi^2_{(2)} = 7.5$, p = .02	1 < 2 = 3
Diagnosed with OCD (N), yes/no	0/34	7/35	2/20	$\chi^2_{(2)} = 6.3$, p = .04	1 < 2 = 3
Other axis I diagnoses* (N), yes/no	0/34	6/36	7/15	$\chi^2_{(2)} = 11.8$, p = .00	1 < 2 = 3
Took medication in the past (N), yes/no	0/34	16/26	6/16	$\chi^2_{(2)} = 16.0$, p = .00	1 < 2 = 3
Family history of schizophrenia (N), yes/no	0/34	6/36	4/18	$\chi^2_{(2)} = 6.2$, p = .04	1 > 2 = 3
Mean (SD) PQ positive symptoms	8.4 (6.2)	8.1 (7.8)	20.3 (4.6)	$F_{(2,91)} = 27.8$, p = .00	1 = 2 < 3
Mean (SD) PQ Negative symptoms	2.6 (2.2)	4.7 (4.1)	9.2 (3.9)	$F_{(2,91)} = 23.0$, p = .00	1 < 2 < 3
Mean (SD) PQ disorganized symptoms	2.2 (1.9)	2.9 (2.7)	5.7 (2.8)	$F_{(2,91)} = 14.3$, p = .00	1 = 2 < 3
Mean (SD) MASQ total score	28.9 (5.5)	30.2 (10.4)	37.8 (9.2)	$F_{(2,91)} = 7.3$, p = .00	1 = 2 < 3
Mean (SD) IQ estimate score	109.3 (12.7)	101.4 (12.3)	98.2 (9.8)	$F_{(2,93)} = 6.7$, p = .00	1 > 2 = 3
Mean (SD) GF:S scale	9.36 (0.72)	8.59 (1.52)	7.33 (2.12)	$F_{(2,73)} = 11.4$, p < .0001	1 = 2 > 3
Mean (SD) GF:R scale	8.43 (0.90)	8.00 (1.67)	7.13 (2.26)	$F_{(2,73)} = 3.5$, p = .04	1 = 2 > 3
WCST Total number of correct sorts§	50.5 (5.7)	45.2 (9.4)	41.4 (9.6)	$F_{(2,94)} = 9.3$, p = .00	1 > 2 = 3
RAVLT Free recall trials I-V§	54.2 (7.2)	54.8 (9.9)	50.0 (11.3)	$F_{(2,94)} = 1.8$, p = .17	
RAVLT Recognition§	39.4 (4.0)	39.4 (5.1)	38.5 (4.4)	$F_{(2,94)} = 0.4$, p = .60	
FEIT+FEDT Total correct responses†	38.9 (3.3)	37.0 (7.3)	38.1 (4.8)	$F_{(2,94)} = 1.0$, p = .36	
ToM total number of correct stories†	8.4 (1.4)	8.3 (1.4)	8.0 (1.6)	$F_{(2,94)} = 0.6$, p = .55	
ToM total points for unaided answers†	17.9 (1.4)	17.8 (2.2)	17.3 (2.2)	$F_{(2,94)} = 0.9$, p = .42	

Note: ADHD = Attention Deficit and Hyperactivity Disorder, GF:S = Global Functioning: Social, GF:R = Global Functioning: Role, MASQ = Mood and Anxiety Symptoms Questionnaire, OCD = Obsessive-Compulsive Disorder, WCST = Wisconsin Card Sorting Test, RAVLT = Rey Auditory Verbal Learning Test, FEIT = Face Emotion Identification Task, FEDT = Face Emotion Discrimination Task, ToM = Theory of Mind.

* Eating Disorder, Posttraumatic Stress Disorder, Adjustment Disorder, Somatoform Disorder, Tic Disorder.

§ Tasks operationalized as non-social.

† Tasks operationalized as social.

2.2. Measures

2.2.1. Neurocognition and metacognition

Metacognition was assessed using the metacognitive approach to neuropsychological testing developed by our group (Koren et al., 2006) in two social and two non-social cognitive domains (see Table 1 for definitions of variables). The non-social domains were verbal memory, assessed with the recognition task[2] of the Rey Auditory Verbal Learning Test (RAVLT: (Lezak, 2004), and executive functioning, which was measured using the Wisconsin Card Sorting Test (WCST: (Berg, 1948). These domains were selected because they have been found to be impaired in both patients and individuals at risk of developing schizophrenia (Morey et al., 2005). The two social domains were ToM, assessed with the Hinting Task paradigm (Corcoran et al., 1995), and social perception, measured using the Face Emotion Identification Task (FEIT) and the Face Emotion Discrimination Task (FEDT: (Kerr and Neale, 1993).

In accordance with our metacognitive approach, participants were also asked in all tasks 1) to rate their confidence level in the correctness of their response on a 0 ("just guessing") to 100 ("completely confident") scale, and 2) to decide whether they did or did not want to "venture" their response toward their overall test performance score. To motivate participants to improve their accuracy performance, they were offered a balanced incentive: each "ventured" response received a bonus of 0.2 NIS (approximately 5 cents) if correct, but an equal penalty if wrong. Thus, for each task, in addition to the standard "forced response" measure of cognitive performance, this procedure also yielded measures of "free response" performance that was dependent on the participant's metacognitive knowledge.

There were three metacognitive variables. 1) "Accuracy" score, defined as the percentage of correct responses out of the ventured responses. This measure taps the *dependability* of the answers and solutions to which the person *committed*, that is, the extent to which each freely volunteered response can be depended on to be correct. 2) "Monitoring resolution," defined as the extent to which the confidence judgments accurately discriminated between correct and incorrect responses, and calculated as the within-participant correlation across all responses between the level of confidence and the correctness of the answer. This measure adds important information about the participant's awareness of whether an answer is correct and therefore reflects the participants' subjective ability to evaluate their cognitive functioning. 3) "Control sensitivity," defined as the degree to which the decision to volunteer an answer was dependent on the confidence judgments. This was calculated as the within-participant correlation across all responses between the level of confidence and the decision to venture the response. This measure reflects the manner in which behavior is directed by the ability to evaluate one's cognitive functioning.

The monitoring and control measures were calculated using Goodman-Kruskal's gamma correlation. This correlation is widely used in this area because, unlike other correlations with the same range of possible values (e.g., Pearson r or Spearman rho), it does not consider paired ties (when two items receive identical confidence ratings or have the same venture/withhold status), which are unavoidable in metacognitive tasks (Nelson, 1984). Because some individual tasks were either too easy or too short (e.g., the ToM had only 10 items) to allow computation of metacognitive monitoring and control (i.e., there was no sufficient variance in the confidence ratings for the answers in that task or the decisions to volunteer or withhold them), we computed the metacognitive scores after combining the data from all four tasks. Although "mega" scores of this type involve the loss of potentially meaningful information, we used them because they offer a

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[2] The novel metacognitive approach was not applied to the immediate and delayed free-recall tasks because a different number of items were generated by each participant.

more robust and reliable performance measure that is not affected by the difficulty level and number of items in a given task. Moreover, they reduce the risk of Type 1 error inflation.

2.2.2. Attenuated psychosis

APS, the main outcome measure in the study, was assessed in two stages. First, we used a screening instrument, the *Prodromal Questionnaire* (PQ) (Loewy et al., 2005), a 92-item self-report questionnaire targeting positive, negative, disorganized, and general symptoms (Cronbach's alpha = 0.949) and then the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003) for participants who scored above the cut-off point for probable Prodromal Syndrome on the PQ (i.e., eight or more positive prodromal symptoms). The SIPS was administered by two interviewers, whose agreement with two gold-standard SIPS diagnoses during the training was in the high range (kappa>0.75).

2.2.3. Mood symptoms

Presence and severity of depressive and anxiety symptoms were assessed with the *Mood and Anxiety Symptom Questionnaire* (MASQ) (Watson and Clark, 1991), a 61-item self-report questionnaire covering general distress anxiety, general distress depression, anxious arousal, and anhedonic depression (Cronbach's alpha = 0.93).

2.2.4. Social and role functioning

Social and role (academic/work) functioning was assessed with the *Global Functioning: Social (GF:S) and the Global Functioning: Role (GF:R) Scales* (Cornblatt et al., 2007). These two clinician-rated scales were developed to assess *social* and *role* functioning among individuals at high risk for schizophrenia. The two scales were rated by the same clinicians that administered and scored the EASE and SIPS (NR and MA).

2.3. Data analyses

To examine the degree to which the three groups (APS, TSC, and HCs) were compatible on the primary demographic, clinical, and neurocognitive variables, a set of one-way analyses of variance (ANOVA) and chi-square tests were used for continuous and categorical variables, respectively.

The first hypothesis, regarding a small-to-medium association between neurocognition and metacognitive monitoring and control, will be tested with a series of equivalence tests that use the two one-sided tests (TOST) procedure (Walker and Nowacki, 2011). The TOST procedure was performed using an alpha level of 0.025 (hence, 95% confidence intervals) and against equivalence bounds of $\rho_L = -0.5$ and $\rho_U = 0.5$. These bounds were selected based on Cohen's conventions for small ($\rho_L = 0.1$), medium ($\rho_L = 0.3$), and large effects ($\rho_L = 0.5$) (Cohen, 1992). The second hypotheses, proposing a weaker association between impaired metacognition and APS, was tested using a two-way MANOVA (mixed design), with Group (APS vs. TSC vs. HC) as the between-groups factor, and Type of neurocognitive vs. metacognitive functioning (Quantity, Accuracy, Monitoring, and Control) as the within-groups factors. The standardized deviation test scores were formed using the HC mean and the pooled standard deviation within the three groups involved in the study (i.e., RMSE). As we were specifically interested in the differences in neurocognitive and metacognitive functioning between treatment-seeking adolescents with and without APS, we used preplanned contrasts to compare the mean scores of the APS group and the HC and TSC groups. To eliminate possible confounding effects of general cognitive ability and lack of effort, we repeated the above analyses with IQ estimates and negative and mood symptoms (as proxies of "effort") as covariates. The third hypothesis regarding the added value of metacognition for prediction of APS classification was evaluated by comparing the area under the curve (AUC) in two series of sequential logistic regression analyses for nested models with cognitive and metacognitive measures and the interaction between them as the independent variables and APS classification as the dependent variable. In the first series, the dependent variable was dichotomized as APS classification versus HC, and in the second, as APS classification versus TSC.

3. Results

3.1. Association between neurocognitive and metacognitive performance

Table 2 presents the correlations between the neurocognitive and metacognitive scores, both within each task and across tasks. Consistent with our first hypothesis that neurocognitive and metacognitive deficits constitute distinct but moderately related impairment dimensions, equivalence tests on the effect sizes of the associations of neurocognition with metacognitive monitoring (r = 0.26, SE = 0.10, 95% CI = 0.07 to 0.44) and control (r = 0.18, SE = 0.10, 95% CI = −0.02 to 0.37) showed that these effect sizes are statistically small-to-medium. Stated differently, they showed that the alternative hypothesis, according to which the true effects are smaller than $\rho = -0.5$ or larger than $\rho = 0.5$, can be rejected at the 0.025 significance level (because the 95% confidence intervals were included in the preselected equivalence bounds).

3.2. Association of APS with metacognition and neurocognition

Fig. 1 presents the means and standard errors of the deviation scores from the normal control base for neurocognition and metacognition in the APS and TSC groups. The deviation scores were formed using the HC mean and the pooled standard deviation (i.e., root mean square error) within the three groups. As can be seen, consistent with our second hypothesis, the level of impairment among APS was larger in the domain of neurocognition than in metacognition. In line with the visual picture, the two-way MANOVA revealed that the main effects of Group (APS vs. TSC vs. HC) ($F_{(2,93)} = 12.22$, p < .0001) and Domain of Functioning (Quantity, Accuracy, Monitoring, and Control) (Wilks' Lambda = 0.90, $F_{(2,92)} = 3.30$, p = .02) were statistically significant, but not their interaction effect (Wilks' Lambda = 0.91, $F_{(6,182)} = 1.50$, p = .18). The above results were not attenuated after gender, estimated IQ, social and academic functioning, and negative and mood symptoms, were used as covariates.

A preplanned APS vs. HC contrast revealed a significant Group ($F_{(1,93)} = 15.02$, p = .0002) but not a Group by Domain of functioning interaction effect (Wilks' Lambda = 0.96, $F_{(3,91)} = 126$, p = .29). A series of post-hoc Tukey tests revealed a significant difference between the two groups on all the measures except Metacognitive Monitoring. A preplanned APS versus TSC contrast failed to detect either significant Group ($F_{(1,93)} = 0.01$, p = .91) or Group by Domain of Functioning effects (Wilks' Lambda = 0.96, $F_{(3,91)} = 1.14$, p = .33). A series of post-hoc Tukey tests did not yield a significant difference between the two groups on any neurocognitive or metacognitive measures.

3.3. Added value of metacognition beyond neurocognition for the prediction of APS

Fig. 2 presents the receiver operating characteristic (ROC) curves from four series of sequential logistic regressions for nested models in which APS classification (versus HC and TSC) regressed, namely, conventional neurocognitive measures alone, novel metacognitive measures alone, neurocognitive by metacognitive interaction terms, and all main and interaction terms together. Consistent with our second hypothesis, the goodness-of-fit measures and the areas under the ROC curve (AUC) were statistically significant for all four models used to predict APS classification versus HC status (Likelihood Ratio χ2 = 15.09, p < .0001, AUC = 0.80 for the neurocognition-alone model, Likelihood Ratio χ2 = 25.46, p < .0001, AUC = 0.86 for the metacognition-alone model, Likelihood Ratio χ2 = 17.96, p = .0004, AUC = 0.79 for the neurocognition by metacognition model, and Likelihood Ratio χ2 =

Table 2
Pearson correlations in the entire sample between the cognitive and metacognitive measures within each task and in all tasks combined.

Novel metacognitive scores	Conventional neurocognitive measure (quantity)				
	WCST	RAVLT	FEIT/FEDT	ToM	All tasks combined
	r, p,	r, p,	r, p,	r, p,	r, p,
	[95% CI]	[95% CI]	[95% CI]	[95% CI]	[95% CI]
Accuracy	0.78, 0.0001	0.82, 0.0001	0.81, 0.0001	0.91, 0.0001	0.78, 0.0001
	[0.69, 0.85]	[0.75, 0.88]	[0.73, 0.87]	[0.85, 0.93]	[0.67, 0.84]
Monitoring resolutions	0.03, 0.80	0.23, 0.02	−0.09, 0.42	−0.27, 0.001	0.26, 0.01
	[−0.18, 0.22]	[0.04, 0.42]	[−0.28, 0.12]	[−0.4, −0.07]	[0.07, 0.44]
Control sensitivity	−0.06, 0.53	0.17, 0.09	−0.12, 0.23	−0.23, 0.02	0.18, 0.08
	[−0.27, 0.13]	[−0.03, 0.36]	[−0.32, 0.08]	[−0.41, −0.04]	[−0.02, 0.37]

Note: WCST = Wisconsin Card Sorting Test; RAVLT = Rey Auditory Verbal Learning Test; FEIT = Face Emotion Identification Task; FEDT = Face Emotion Discrimination Task; ToM = Theory of Mind. 95% CI = 95% confidence interval.

30.55, p < .0001, AUC = 0.90 for the saturated model). Moreover, consistent with our third hypothesis, the difference between the AUC of the saturated model (i.e., that containing all the measures and their interactions together) and the nested, neurocognition-only model was statistically significant (AUC difference = 0.09, SE = 0.05, 95% CI = 0.005–0.18, $\chi2$ = 4.31, p = .04).

Consistent with the negative results of the second preplanned contrast, none of the models used to predict APS classification versus TSC status was statistically significant (Likelihood Ratio $\chi2$ = 3.34, p = .07, AUC = 0.65 for the neurocognition-alone model, Likelihood Ratio $\chi2$ = 1.75, p = .63, AUC = 0.61 for the metacognition-alone model, Likelihood Ratio $\chi2$ = 1.39, p = .71, AUC = 0.59 for the neurocognition by metacognition model, and Likelihood Ratio $\chi2$ = 13.05, p = .07, AUC = 0.78 for the saturated model). However, consistent with our third hypothesis, the difference between the AUC of the saturated model and the nested, neurocognition-only model was statistically significant (Likelihood Ratio difference $\chi2$ = 9.71, p = .08; AUC difference = 0.13, SE = 0.06, 95% CI = 0.01–0.26, $\chi2$ = 4.60, p = .03).

4. Discussion

4.1. Prevalence of APS

Although the PPV level yielded by the two-step screening and interview procedure that was used in the study is similar to those reported in previous studies that used the PQ among help-seeking adolescents and young adults(Ising et al., 2012; Lindgren et al., 2010; Loewy et al., 2012; Rietdijk et al., 2012; van der Gaag et al., 2012), the estimated prevalence of APS cases in this study (36%) was higher than that (4–5%) found among previous samples of unselected treatment-seeking adolescents

Fig. 1. Mean standardized deficits neurocognitive and metacognitive scores for treatment-seeking adolescents with attenuated psychosis syndrome (APS) and treatment-seeking comparisons (TSC) relative to the healthy comparison (HC) group.

and young adults(Ising et al., 2012; Jarrett et al., 2012; Lindgren et al., 2010; Rietdijk et al., 2012; van der Gaag et al., 2012; Zhang et al., 2014). However, it was quite comparable to the prevalence (33–51%) found among treatment-seeking adolescents referred for specialized psychosis evaluations(Grano et al., 2011; Kline et al., 2012; Loewy et al., 2005; Mossaheb et al., 2012; Niessen et al., 2010). These similarities suggest that these findings can be generalized to other populations of treatment-seeking adolescents or young adults referred for psychosis risk evaluation.

4.2. The association between neurocognitive and metacognitive performance

The study's first set of results replicate previous findings, suggesting that metacognitive monitoring and control can vary independently of neurocognitive skills per se (including cognitive functions sometimes referred to as "metacognition," such as executive functions and ToM), and are not measuring the same construct (Koren et al., 2006). These findings suggest that impaired metacognition and impaired neurocognition constitute two distinct but related aspects of neurocognitive performance not only after the onset of schizophrenia-spectrum illnesses but also in their pre-onset phase. As such, they can potentially contribute uniquely to the risk prediction for psychosis over and beyond each other.

4.3. Association of neurocognition and metacognition with APS

Consistent with previous reviews and meta-analyses (Addington and Heinssen, 2012; Fusar-Poli et al., 2012; Giuliano et al., 2012; Pukrop and Klosterkotter, 2010; Seidman et al., 2010), the present findings provide further support for the notion that APS is associated with mild-to-moderate impairments in neurocognitive performance when compared to that of matched healthy individuals. Furthermore and as expected, based on the fact that residual insight is a defining feature of APS, the findings show that metacognitive monitoring and control are less impaired in APS than is neurocognitive quantity.

However, inconsistent with earlier studies, the present study failed to detect significant differences between treatment-seeking adolescents with and without APS on both neurocognitive and metacognitive functioning. This lack of significant differences suggests that impaired neurocognition and metacognition may not be specific to sub-clinical psychosis. This finding is consistent with a recent study that found similar levels of neurocognitive functioning among help-seeking individuals at CHR for psychosis and CHR for bipolar depression (Metzler et al., 2014). However, this conclusion should be considered very cautiously. First, some effect sizes of the differences between the two groups, especially that in neurocognitive quantity, were in the medium range and the study was underpowered to detect effect sizes of this magnitude (see more below). Second, APS differs from actual psychosis,
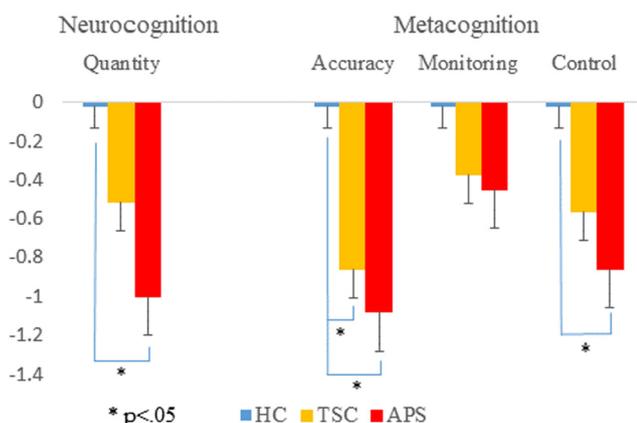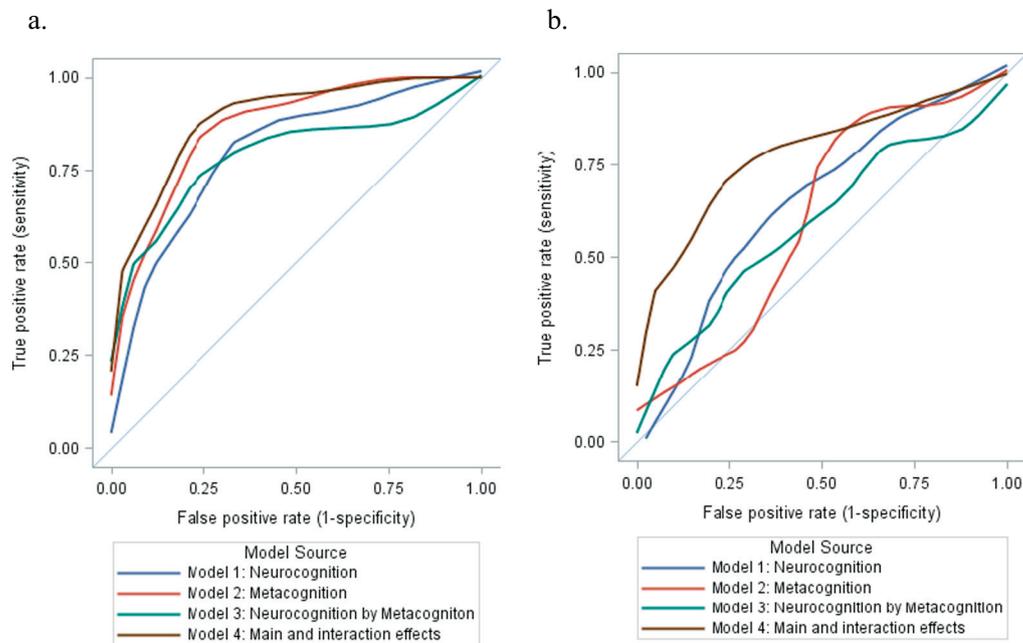
a.

b.

Fig. 2. Receiver operating curves: Neurocognitive and metacognitive scores predicting attenuated psychosis syndrome (APS) classification vs. healthy comparison (a) and APS classification vs. treatment-seeking comparisons classification (b).

and this study did not include information about the latter (for more details see the Limitations subsection).

4.4. Added value of metacognition beyond neurocognition for the prediction of APS

Consistent with our third hypothesis, the study findings show that metacognition and the interaction between neurocognition and metacognition significantly improves the prediction of APS classification versus TSC beyond neurocognition alone. Because the contribution of metacognition alone to the prediction of APS classification is relatively small and not significant (i.e., it is not a sound predictor itself), these findings suggest that metacognitive monitoring and control play a strengthening role in the association between neurocognition and APS.

One likely way in which this strengthening role can take place is by accounting for differences in insight within APS that are not captured by neurocognition alone. According to this explanation, APS patients with good insight into their condition are more likely to correctly monitor and control their level of neurocognitive performance than do patients with poor insight into their condition. According to this view, the initial correlation between neurocognition and APS was spuriously low, because it was based only on treatment-seeking adolescents whose level of insight into their condition is relatively high. This possibility is supported by previous studies (Gilleen et al., 2016; Koren et al., 2004) that found an association between metacognitive monitoring and control and insight into schizophrenia symptoms. However, it should be considered tentative until tested in future research with non-treatment seeking adolescents and validated measures of insight into APS.

4.5. Possible confounding factors

A noteworthy final issue is the degree to which the findings were affected by confounding factors such as general cognitive ability (i.e., IQ), social and academic functioning, and lack of effort. This is raised because there were significant differences between the two treatment-seeking groups and the HC group on IQ estimate, social and academic functioning, and negative and mood symptoms. The overall pattern of results was slightly attenuated but remained significant after statistically

adjusting for these factors. This finding suggests a minimal, if any, effect of general cognitive ability and low effort on metacognition. Further provisional support for the latter can be found in the perfect rate of task completion and zero number of requests for early discontinuation. However, this conclusion should be drawn cautiously because negative and mood symptoms are not direct measures of the level of effort.

4.6. Strengths and limitations

A major strength of this study lies in its novel approach to the assessment of cognitive and metacognitive performance as part of one, unified process. To the best of our knowledge, this is the first study to apply this approach to APS. Another significant strength of the study is the "non-enriched" nature of its sample (i.e., the selection of participants for this study was not guided by their initial level of future psychosis risk). Consequently, it allows secure extrapolation of the findings to replicable samples of treatment-seeking adolescents.

However, the study also has several significant limitations. First, and most importantly, it does not include a comparison group of non-help seeking adolescents. Subsequently, it leaves unanswered the degree to which the present findings are generalizable to the entire population of adolescents with APS. This limitation is vital in light of recent studies, which suggest that there is a substantial number of youth in the general population who meet UHR criteria but do not seek help (Addington et al., 2008; Mills et al., 2017; Poulton et al., 2000).

Second, the study lacks follow-up data on the clinical and functional outcome of the participants over time. Because only a subset of patients with APS is likely to develop psychosis whereas the majority is not, this limits the ability to conclude the validity of metacognitive functioning as a potential marker of risk for future clinical or sub-clinical schizophrenia-spectrum symptoms.

Third, the study sample size was relatively small, and thus its statistical power is quite limited. In light of recent studies, which show that the neurocognitive differences between CHR-converters and non-converters are rather modest (Fusar-Poli et al., 2012; Giuliano et al., 2012; Seidman et al., 2010, 2016), this may explain the nonsignificant differences between APS and TSC found in this study. Future studies using larger sample sizes and additional neurocognitive tests, both laboratory based ones and more daily life oriented tasks (e.g. shopping

list), are needed to compare APS and TSC. Fourth, the range of domains that were assessed was somewhat limited and did not adequately represent those shown in prior studies to be associated with transition to psychosis (e.g., sustained attention, processing speed).

4.7. Conclusions, implications, and future directions

Despite the limitations above, the results of this pilot study provide the first preliminary support for the notion that impaired metacognition may play a strengthening role in the association between neurocognition and APS. In addition to the theoretical implications of this suggestion, the present findings provide pilot support for the promising potential of surpassing standard cognitive measures to isolate and understand the possible role that neurocognition plays in identifying risk or protective (e.g., insight) factors for schizophrenia-related psychosis. Finally, the study highlights the importance of future prospective investigations with larger samples of treatment- and non-treatment-seeking individuals and broader task batteries that will further clarify the potentially distinct roles that the various aspects of metacognition play in APS, and the unique contribution of each of its aspects to the risk prediction for schizophrenia-spectrum conditions.

Data availability

All the material and data used in the study will be available upon request from the corresponding author.

Conflicts of interest

The authors declare no competing financial or non-financial interests.

Role of funding

CRediT authorship contribution statement

Danny Koren: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing - original draft, Writing - review & editing. **Ravit Scheyer:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration. **Yonatan Stern:** Formal analysis, Validation, Writing - review & editing. **Merav Adres:** Data curation, Investigation. **Noa Reznik:** Data curation, Investigation. **Alan Apter:** Conceptualization, Data curation, Resources, Supervision. **Larry J. Seidman:** Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Writing - original draft.

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