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Prediction of functional outcome in young patients with a recent-onset psychiatric disorder: Beyond the traditional diagnostic classification system☆

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ABSTRACT

A critical research goal is to identify modifiable risk factors leading to functional disabilities in young psychiatric patients. The authors developed a multidimensional trans-diagnostic predictive model of functional outcome in patients with the recent-onset of a psychiatric illness.

Baseline clinical, psychosis-risk status, cognitive, neurological-soft-signs measures, and dopamine-related-gene polymorphisms (DRD1-rs4532, COMT-rs165599, and DRD4-rs1800955) were collected in 138 young non-psychotic outpatients.

116 individuals underwent follow-up (mean = 2.2 years, SD = 0.9) examination. A binary logistic model was used to predict low-functioning status at follow-up as defined by a score lower than 65 in the social occupational functioning assessment scale.

A total of 54% of patients experiences low functioning at follow-up. Attention, Avolition, and Motor-Coordination subscale were significant predictors of low-functioning with an accuracy of 79.7%. A non-significant trend was found for a dopamine-related-gene polymorphism (DRD1-rs4532). The model was independent of psychotic-risk status, DSM-diagnosis, and psychotic conversion.

A trans-diagnostic approach taking into account specific neurocognitive, clinical, and neurological information has the potential to identify those individuals with low-functioning independent of DSM diagnosis or the level of psychosis-risk.

Specific early interventions targeting modifiable risk factors and emphasize functional recovery in young psychiatric samples, independent of DSM-diagnosis and psychosis-risk, are essential.

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1. Introduction

Functional disabilities are common among mental disorders (Kessler et al., 2009). Even though psychotic spectrum disorders (PSDs) (Lee et al., 2015) are traditionally associated with greater functional disability than affective and anxiety disorders (Plaisier et al., 2010), a 2009 update from the World Mental Health Survey shows that severe functional impairments are not unique to the psychosis-spectrum (Kessler et al., 2009). A critical research goal is therefore to identify and intervene to target modifiable risk factors leading to long-term disability not only in PSDs, but in the whole spectrum of psychiatric disorders (Lee et al., 2015).

Studies of adults with chronic mental illness show that multiple factors are linked to functional decline across traditional diagnostic boundaries (Iosifescu, 2012). Baseline impairments in functioning (Carrión et al., 2013), cognition and theory of mind (Lee et al., 2015), as well as neurological, neurophysiological and brain structural abnormalities

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(Dazzan and Murray, 2002), have been associated with future poor functional outcomes in schizophrenia (Chan et al., 2015), mood , anxiety and personality disorders (Plaisier et al., 2010; Dazzan and Murray, 2002).

Findings in adult populations are often tempered by chronic illness and prolonged treatment (Allott et al., 2011). Research efforts targeting functional recovery should thus be focused on the earlier phases of psychiatric disorders, when individuals are less impaired and more amenable to therapeutic interventions (Fusar-Poli et al., 2014).

So far, most studies investigating functional outcome in early-onset psychiatric syndromes pertain to individuals with an "At-Risk Mental State" (ARMS) for psychosis (Carrión et al., 2013). Approximately 1/3 of ARMS individuals develops a psychotic episode (Fusar-Poli et al., 2014). However, many of them remain functionally impaired independently of psychosis transition, highlighting the need for a broad, trans-diagnostic approach to functional outcome, cutting across the psychotic spectrum (Carrión et al., 2013).

Given the relevance of functional outcome in psychiatry, and the evidence that disability is not unique to psychotic disorders (Kessler et al., 2009; Lee et al., 2015), research on early predictors of functional decline should target the full range of recent-onset psychiatric syndromes.

Specifically: negative and disorganized symptoms, neurological soft signs, theory of mind, neurocognition, and baseline functioning abnormalities have been consistently detected in young psychiatric outpatients and related to future outcomes independent of DSM diagnosis and psychosis-risk status (Lee et al., 2015; Plaisier et al., 2010; Iosifescu, 2012; Francesconi et al., 2016; Minichino et al., 2016a). These domains may represent optimal trans-categorical predictors of functioning and thus new promising therapeutic targets.

Some of these domains, such as neurocognitive and theory of mind impairments, seem to be linked to functional disability regardless of the expression of symptoms (Francesconi et al., 2016; Lee et al., 2015), as they are also expressed in the unaffected relatives of patients with mental illness (Tsang et al., 2015). These findings suggest that genetic factors could contribute to future outcome (Tsang et al., 2015) possibly as a mediating variable. Several susceptibility genes are associated with cellular mechanisms linked to cognitive processing domains that are predictors of functional outcome in ARMS studies (Plaisier et al., 2010). In particular, dopamine-related gene polymorphisms associated with dopaminergic function in prefrontal cortex, such as the Dopamine Receptor D1 (DRD1) rs4532, the Catechol-O-Methyltransferase (COMT) rs165599, and the Dopamine Receptor D4 (DRD4) rs1800955, have been linked to specific cognitive impairments (e.g. verbal fluency and working memory), in both relatives and patients across different diagnostic groups (Tsang et al., 2015).

The present study aimed to identify trans-diagnostic baseline predictors of low functional outcome, consistent with the trans-diagnostic approach of the Research Domain Criteria (RDoC) initiative from the National Institute of Mental Health (Cuthbert and Insel, 2013), in a large, prospective, longitudinal sample of help-seeking adolescents and young adults treated in secondary mental health services.

We addressed the following questions: (A) What are the functional trajectories of young patients with a recent-onset psychiatric disorder with 2 to 3 years of follow-up? (B) How are baseline functioning, cognition, theory of mind, genetic and neurological variables associated with long term functioning in these individuals? (C) Is prediction of functional outcome independent of (i) ARMS status; (ii) psychosis transition; and (iii) psychiatric diagnosis?

2. Methods

The institutional review board of Sapienza, University of Rome approved the study. Written informed consent (with assent from participants <18) was obtained from all participants.

2.1. Participants and recruitment strategy

Subjects were recruited in three different clinics (Rome, Italy) that provide secondary general mental health care for adolescents and young adults. Patients who seek help in these clinical sites do not differ in terms of clinical and demographic characteristics. For 17 months (November 2011 to June 2013), the attending psychiatrists screened patients for the following exclusion criteria: current or past diagnosis of psychosis-spectrum or bipolar disorder; present or past diagnosis of a brief psychotic disorder with a duration equal to or >1 week; diagnosis of mental retardation or other cognitive disorders, psychiatric disorders due to a somatic factor or related to psychotropic substances; drug abuse within the last 3 months; central nervous system disorders; and history or current use of antipsychotic medications. After this first screening, patients aged 17–35 years old, were referred to a group of three trained interviewers. Referred individuals underwent the Structural Clinical Interview for DSM-IV Axis I (SCID-I) and II (SCID-II) disorders to certify exclusion criteria and diagnoses. Raters were experienced research clinicians who demonstrated adequate reliability at routine reliability checks.

2.2. Baseline assessment

Clinical information was obtained through the SCID-I and II and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The Comprehensive Assessment of At-Risk Mental States (CAARMS) interview was used to identify (Yung et al., 2005) ARMS + and ARMS − individuals. The CAARMS inter-rater reliability was assessed in 34 subjects (ICC = 0.93). NSS were assessed with the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989), which comprises the following subscales: "sensory-integration", "motor-coordination", "sequencing of complex motor acts", and "others". Items of the NES are scored on a three-point scale from 0 = no abnormality to 2 = marked impairment.

Neurocognition was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998). The RBANS comprises five index scores (Attention, Immediate and Delayed Memory, Language and Visuospatial indices) and a total score. Social cognitive ability was assessed using the following scales: the Reading the Mind in the Eye Test (Baron-Cohen et al., 1997), the Faux Pas (Stone et al., 1998) test and the Theory of Mind Assessment Scale (Bosco et al., 2009). Baseline Functioning was assessed using the Global Assessment of Functioning scale (GAF) (Hall, 1995), the Social and Occupational Functioning Assessment Scale (SOFAS) (Yung et al., 2005), and the Life Skills Profile-39 items (Rosen et al., 1989). The LSP-39 comprises 39 items grouped in 5 subscales: Self-Care, Responsibility, Communication, Non-Turbulence, and Social-contact. A total score can be obtained by summing the responses for all items with low scores reflecting high level of skills. The LSP-39 total score has been consistently used as a proxy of real-world living skills (Puig et al., 2013).

2.2.1. Genetic

Using salivary samples, the DRD1 rs4532 (−48A/G), the COMT rs165599 and the DRD4 rs1800955 (C-521T) polymorphisms were evaluated in a subgroup of participants ($n = 74$) (see eAppendix).

2.3. Follow-up procedure

Functional and clinical data were collected through a single follow-up face to face interview that took place at a mean time of 2.2 years from the baseline assessment. Transition to psychosis was defined according to previously operationalized criteria (Yung et al., 2005).

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2.4. Functional outcome

The primary outcome variable for this study was functional outcome at the follow-up visit as defined by the SOFAS.

This scale was used given its wide clinical and consistent use as primary measures of functional outcome in several studies and meta-analyses on ARMS individuals (Cotter et al., 2014; Fusar-Poli et al., 2015), thus potentially facilitating interpretation of findings and future replication studies.

The overall sample was divided in two groups: Low Functional (LF) and High functional (HF) outcome.

LF and HF were defined as a current score of 65 and higher (HF) or 64 and lower (LF) in the SOFAS during the follow-up examination.

The group split at SOFAS score of 65 was chosen according to previously published methods (Allen et al., 2015). The 60–70 range corresponds to the presence of "some difficulty in social or occupational functioning but [the subject] generally functions pretty well". SOFAS scores below 60 indicate "moderate to severe impairment", whilst sores above 70 correspond to "slight impairment to good function". Also, 65 was the median SOFAS value for the overall sample during the follow-up assessment.

The cut-off value was chosen following a consistent body of previous literature.

An additional measure of functional outcome, as defined by the LSP-39 total score was also collected at follow-up.

2.5. Statistical analysis

All analyses were conducted using SPSS version 21.0. Comparison of baseline characteristics was performed with ANOVAs for continuous variables and Pearson χ^2 tests for categorical variables (2-tailed, $P < 0.05$).

A binary logistic model was constructed to predict functional outcome according to the SOFAS-based definition of functioning at follow-up.

Based on previous evidence, predictor variables were generated within the following domains: demographic and clinical (Addington et al., 2015), neurocognitive (Meyer et al., 2014), theory of mind (Lee et al., 2014), NSS (Chan et al., 2009) and functioning at baseline (Carrión et al., 2013) (eTable1), and selected in several steps (Hosmer et al., 2013; Carrión et al., 2013) (eAppendix).

The final models were adjusted for the possible confounding effects of (i) psychosis transition at follow-up; (ii) ARMS status; (iii) DSM-IV diagnosis at baseline; (iv) PANSS general subscale score at baseline; (v) antipsychotic and psychotherapy intervention at baseline and follow-up; (vi) drug/alcohol abuse at follow-up; (vii) gender; (viii) SOFAS and LSP-39 total score at baseline.

3. Results

3.1. Participants

A total of 140 participants were referred to the study. Two individuals fulfilled SCID-I criteria for substance abuse, and were excluded. The remaining 138 individuals underwent CAARMS interview. A total of 67 ARMS + and 71 ARMS − were enrolled in the study.

Of the 138 subjects enrolled in the study, 22 (15.9%) were lost and 116 (84.1%) completed the follow-up clinical evaluation, (Fig. 1). Patients with follow-up information did not differ significantly from those lost to follow-up in any of the variables investigated.

Table 1 shows demographic, clinical, cognitive and NSS information of the HF and LF groups.

At baseline, the LF group had a higher prevalence of comorbid anxiety and mood disorders compared to the HF. Negative symptoms and functional impairments at baseline were significantly greater in the LF group, which was also characterized by a higher transition to psychosis

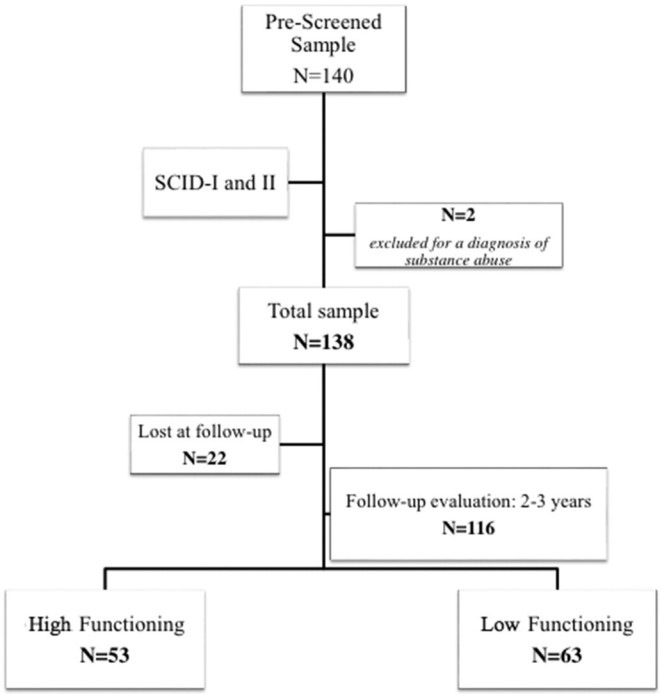

Fig. 1. Flow chart showing the different phases of the recruitment strategy and the follow-up at a mean time of 2.2 years. Abbreviation: SCID-I and II: structured clinical interview for DSM-IV Axis I and II disorders.

rate at follow-up (Table 1). Of note, the proportion of individuals who met ARMS criteria did not differ between the HF and LF groups.

During the follow-up period, there was a significant difference in the percentage of change in functioning between the two outcome groups. Patients in the HF group showed an improvement in SOFAS and LSP-39 total score (+12% and +7%, respectively), while the LF group showed a relevant functional decline (−21% and −17%).

At baseline, significantly lower scores on the RBANS Attention, Immediate Memory and Delayed Memory indices were found in LF individuals, as well as higher levels of motor- coordination signs (Table 1).

3.2. Correlation among measures of functional outcome at follow-up

Compared to the HF group, the LF group showed significantly lower scores in the follow-up LSP-39 total scores (Table 1).

At follow-up, SOFAS scores were significantly correlated with LSP-39 total scores ($r = -0.57$: $P \leq 0.001$).

3.3. Treatment

Table 1 reports baseline and follow-up medications of the HF and LF groups. At follow-up, the percentage of patients in the LF group receiving antipsychotics ($P < 0.01$), mood stabilizers ($P < 0.05$) anxiolytics ($P < 0.05$), and psychotherapy ($p < 0.01$) was significantly higher than at baseline. The HF group, as well, received more antipsychotics ($P < 0.01$) and psychotherapy ($P < 0.01$) compared to baseline. These data indicate active therapeutic interventions during the follow-up period in both LF and HF individuals. Finally, 13.8% of the sample developed a drug dependence/abuse diagnosis at follow-up ($P < 0.01$), but no differences were found between HF and LF.

3.4. Prediction of functional outcome

The RBANS Attention Index, the CAARMS Avolition item, and the NSS Motor-Coordination subscale were significant predictors of LF outcome (Table 2). The final multivariable model accounted for 35% of the

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Table 1
Demographic, clinical, genetic, cognitive and neurological soft signs variables in the two outcome groups (LF and HF).

Characteristic	LF ($n = 63$)	HF ($N = 53$)	P value
Demographic			
Age, mean (SD)	24.38 (3.78)	23.94 (3.47)	0.53
Education, years, mean (SD)	11.15 (3.05)	10.77 (2.78)	0.50
Male N, (%)	35 (57.4)	25 (48.1)	0.35
Clinical			
ARMS+, N, (%)	30 (47.6)	24 (45.3)	0.85
Transition to psychosis, N, (%)	16 (25.4)	5 (9.6)	**0.03**
CAARMS, mean (SD)			
Positive symptoms	7.68 (5.84)	7.11 (5.94)	0.61
Negative symptoms	5.79 (1.77)	4.55 (1.82)	<**0.001**
Emotional disturbances	4.73 (3.14)	4.66 (3.15)	0.90
Cognitive change	5.00 (1.73)	4.891 (1.61)	0.72
Behavioral change	11.05 (2.07)	10.66 (2.16)	0.33
PANSS, mean (SD)			
Positive symptoms	13.16 (3.87)	13.38 (2.77)	0.74
Negative symptoms	14.31 (3.03)	14.50 (3.37)	0.77
General symptoms	37.97 (6.18)	37.77 (7.52)	0.87
DSM-IV diagnosis, N, (%)			
Mood disorders [a]	24 (38.2)	25 (47.1)	0.32
Anxiety disorder [b]	4 (6.4)	8 (15.1)	0.12
Personality disorder [c]	10 (15.8)	10 (18.9)	0.67
Comorbidity of mood and anxiety disorders[d]	25 (39.6)	10 (18.9)	**0.02**
Duration of illness, years, mean (SD)	2.16 (0.88)	2.14 (0.89)	0.87
Baseline medications, N, (%)			
No medications	5 (8.2)	6 (11.5)	0.75
Antipsychotics	None	None	
Antidepressants	45 (73.8)	31 (59.6)	0.15
Anxiolytics	35 (55.5)	24 (45.2)	0.27
Mood stabilizers	16 (26.2)	10 (19.2)	0.50
Follow up medications, N, (%)			
No medications	None	11 (20.7)	<**0.001**
Antipsychotics	28 (44.4)	14 (26.4)	**0.04**
Antidepressants	41 (65.1)	25 (47.2)	0.06
Anxiolytics	48 (76.2)	13 (24.5)	<**0.001**
Mood stabilizers	33 (52.4)	11 (20.8)	<**0.001**
Psychotherapy (>5 sessions), N (%)			
Baseline	none	none	
Follow up	18 (28.5)	13 (24.5)	0.62
Baseline functioning			
Unemployed/not in education, N, (%)	30 (50.0)	23 (44.2)	0.57
GAF, mean (SD)	62.84 (9.48)	63.75 (8.49)	0.59
SOFAS Mean (SD)	64.60 (10.45)	65.00 (9.30)	0.83
LSP-39, mean (SD)			
Self-care	19.80 (5.98)	17.81 (4.21)	**0.04**
Non turbulence	24.00 (5.53)	22.77 (5.09)	0.22
Social contact	11.39 (3.36)	10.62 (2.39)	0.17
Communication	11.02 (2.89)	10.31 (2.49)	0.17
Responsibility	10.15 (2.18)	9.44 (1.75)	0.06
Total score	76.36 (13.91)	70.94 (9.02)	**0.02**
Follow up functioning			
SOFAS mean (SD)	50.03 (7.1)	70.94 (6.0)	<**0.001**
LSP-39 total score mean (SD)	86.84 (9.7)	74.91 (9.5)	<**0.001**
Genetics [N with analyzable data = 74]	**[$N = 41$]**	**[$N = 33$]**	
DRD1 rs4532 genotype, N (%)			

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Table 1 (*continued*)

Characteristic	LF ($n = 63$)	HF ($N = 53$)	*P* value
AA	16 (39.1)	22 (66.7)	
AG	19 (46.3)	10 (30.3)	**0.04**
GG	6 (14.6)	1 (3.0)	
Presence of the G allele, N (%)			
AG or GG	25 (60.9)	11 (33.3)	**0.02**
DRD1 rs4532 allele frequency, N (%)			
A allele	51 (62.2)	54 (81.8)	<**0.001**
G allele	31 (37.8)	12 (18.2)	
DRD4 rs1800955 genotype N, (%)			
CC	15 (36.6)	15 (45.5)	0.29
CT	15 (36.6)	14 (42.4)	
TT	11 (26.8)	4 (12.1)	
Presence of the T allele N, (%)			
CT or TT	26 (63.4)	18 (54.5)	0.44
DRD4 rs1800955 allele frequency, N, (%)			
C Allele	45 (54.8)	44 (66.7)	0.14
T Allele	37 (45.2)	22 (33.3)	
COMT rs165599 genotype, N (%)			
AA	21 (51.2)	19 (57.6)	0.18
AG	16 (39.0)	14 (42.4)	
GG	4 (9.8)	0 (0.0)	
Presence of the G allele, N (%)			
AG or GG	20 (48.8)	14 (42.4)	0.58
COMT rs165599 alleles, N (%)			
A allele	58 (70.7)	52 (78.8)	0.26
G allele	24 (29.3)	14 (21.2)	
Neurocognition			
RBANS, mean (SD)			
Immediate memory index	92.70 (10.15)	97.19 (9.59)	**0.02**
Language index	89.79 (8.84)	89.77 (8.55)	0.99
Visuospatial index	91.41 (8.90)	92.62 (8.18)	0.45
Attention index	80.92 (8.32)	87.42 (7.87)	<**0.001**
Delayed memory index	89.14 (8.10)	93.49 (8.24)	<**0.001**
Total Score	81.98 (7.93)	86.30 (8.91)	<**0.001**
Theory of mind			
Faux Pas, mean (SD)			
Faux Pas questions	17.27 (1.81)	17.58 (1.43)	0.31
Faux Pas controls	38.78 (1.15)	38.74 (1.00)	0.84
RMET, mean (SD)	25.58 (3.08)	26.02 (2.80)	0.44
Th.o.m.as., mean (SD)			
Thomas A	33.47 (6.63)	35.18 (5.90)	0.15
Thomas B	28.71 (8.53)	29.08 (7.75)	0.81
Thomas C	25.77 (7.21)	28.02 (6.46)	0.08
Thomas D	28.32 (7.96)	28.24 (7.73)	0.95
Neurological soft signs			
NES, mean (SD)			
Motor coordination	1.97 (1.34)	1.09 (1.09)	<**0.001**
Sensory integration	1.54 (1.17)	1.26 (1.02)	0.18
Sequencing of complex motor acts	1.52 (1.45)	1.40 (1.23)	0.61
Others	1.83 (1.61)	1.45 (1.32)	0.18
Total score	6.86 (4.50)	5.21 (2.90)	**0.02**

Abbreviations: HF, High Functioning; LF, Low Functioning; ARMS+, Positive to At Risk Mental State; CAARMS, Comprehensive Assessment of At Risk Mental State ; PANSS, Positive And Negative Syndrome Scale; DSM- IV, Diagnostic and Statistical Manual of Mental Disorders 4th Edition; GAF, Global Assessment of Functioning; LSP-39, Life Skill Profile 39 items; SOFAS, Social and Occupational Functioning Assessment Scale; DRD1, Dopamine Receptor D1; DRD4, Dopamine receptor D4; COMT, Catechol-O-methyltransferase; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RMET, Reading the Mind Eyes in the Test; Th.o.m.a.s., Theory Of Mind Assessment Scale; NES, Neurological Evaluation Scale.

$p < 0.05$

[a] DSM-IV diagnoses: Major Depressive Disorder (MDD), Adjustment Disorder with Depressed Mood, Adjustment Disorder with Anxiety.

[b] DSM-IV diagnoses: Generalized Anxiety Disorder (GAD), Panic Disorder, Obsessive Compulsive Disorder.

[c] DSM-IV diagnoses: Borderline Personality Disorder.

[d] DSM-IV diagnoses: MDD and GAD, MDD and OCD, Adjustment Disorder with Depressed Mood and Anxiety.

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Table 2
Logistic regression model predicting functional outcome in the whole group of patients ($n = 116$).

Predictor variable	β	SE	Wald x^2	Hazard ratio	*P* value	AUC[a] (SE) [95% CI]	R^2_N	Sensitivity	Specificity
Attention (RBANS)	0.079	0.03	8.34	1.08	0.004				
Motor coordination (NES)	−0.547	0.21	6.79	0.57	0.009	0.797 (0.041) [0.717–0.878]	0.350	0.730	0.679
Avolition (CAARMS)	−0.744	0.26	8.02	0.47	0.005				

Abbreviations: RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; NES, Neurological Evaluation Scale; CAARMS, Comprehensive Assessment of At Risk Mental State; AUC, Area Under the Curve; R^2_N, Nagelkerke pseudo R^2 statistic; SE, Standard Error.
[a] The AUC values can range from 0.5 (indicates that an instrument can discriminate between groups no better than chance) to 1.0 (represents perfect discriminatory performance) and can be interpreted using the following categories: acceptable = 0.70, good = 0.80, and excellent = 0.90.

variance ($R^2_N = 0.350$) and showed a good discriminative ability, with an AUC of 79.7% (95% CI, 71.7–87.8; $P < 0.001$), a sensitivity of 73.0% and specificity of 67.9% (eFigure1).

Prediction of functional outcome in a subgroup of individuals ($n = 74$) with the analyzable genetics data.

Table 1 shows the prevalence of the DRD1 rs4532, COMT rs165599 and DRD4 rs1800955 polymorphisms in the subgroup of patients with analyzable data ($n = 74$). There were no significant differences between LF and HF groups in terms of expression of COMT rs165599 and DRD4 rs1800955 polymorphisms. In contrast, the AG and GG genotypes of the DRD1 rs4532 were significantly more expressed in the LF than in the HF group ($P < 0.05$) (Table 1).

The "presence of the G allele (DRD1)" (i.e. expression of the AG or GG genotype) was thus added to the set of three variables previously identified, with the aim of evaluating whether genetic data could improve the final predictive model of functional outcome.

Given the smaller number of participants ($n = 74$) available for this analysis, we decided to report also non-significant statistical trend results ($P < 0.10$) for the final step of the regression.

We used this approach, even if limited by this liberal threshold, because it could represent a relevant hypothesis-generating finding. Indeed: 1) there is a lack of studies investigating the impact of clinical-genetic interactions on prognostic outcomes in psychiatry; and 2) given the young age and the relatively short duration of illness characterizing our sample, our findings may be useful for future studies investigating early modifiable risk factors of functional disabilities.

Using this approach, the Attention Index, Avolition and "presence of the G allele (DRD1)" predicted LF with an accuracy of 81.9% (Table 3) (95% CI, 72.6–91.3; $P < 0.001$; eFigure 2), a sensitivity of 75.6% and specificity of 72.7%. The "presence of the G allele (DRD1)" entered in the model with a significance level of 0.058.

The final model accounted for 39% of the variance ($R^2_N = 0.394$).

In both the multivariable models (with and without genetic findings), the identified predictive variables continued to predict functional outcome even after adjusting for potential confounding variables (eTable2), including ARMS status, ultimate conversion status, and DSM-IV diagnosis.

The Attention Index, Avolition and "presence of the G allele (DRD1)" were significant predictors of LF (Table 3). The final model accounted for 39% of the variance ($R^2_N = 0.394$). The overall predictive ability of this model was higher compared to the previous one, with an AUC of 81.9% (95% CI, 72.6–91.3; $P < 0.001$; **eFigure 2**), a sensitivity of 75.6% and specificity of 72.7%. In both the multivariable models, the identified predictive variables continued to predict functional outcome even after adjusting for potential confounding variables (eTable2), including ARMS status, ultimate conversion status, and DSM-IV diagnosis.

Similar results were obtained with an alternative multivariable model built using the LSP-39 total score as primary measure of functional outcome at follow-up (eModels).

4. Discussion

To the best of our knowledge, this is the first study using a broad trans-diagnostic approach, to identify predictors of functional outcome across recent onset psychiatric syndromes. Our sample was composed of individuals who came to a youth mental health clinic for treatment, did not meet criteria for a psychotic disorder and had different levels of risk for psychosis. In contrast to other ARMS samples, our participants were already diagnosed and treated for specific psychiatric disorders, with mean illness duration of 2.1 years, suggesting greater and more stable psychopathological severity. Our study yielded 4 relevant findings. First, 48% of the patients were ARMS +, however, low functional outcome was independent of ARMS classification and DSM-IV diagnosis. This confirms previous findings that baseline positive symptoms are not predictive of low functional outcome (Carrión et al., 2013), and suggests that categorizing patients based on traditional classification systems is not informative in regards to functional trajectories. Second, NSS, neurocognitive performance and negative symptoms at baseline were key predictors of LF during the early phases of different psychiatric syndromes. Third, a genetic marker improved the predictive model, suggesting that genetic markers may also have a relevant impact on functional outcome. Fourth, LF was not entirely dependent on the development of psychosis, further promoting the need for a broader trans-diagnostic approach in the field of functional recovery (Minichino et al., 2016a; Minichino et al., 2016b; Lee et al., 2015).

Patients in the LF group showed baseline impairments on the RBANS Attention, Immediate and Delayed indices, with Attention being a significant predictor of functional outcome. Previous evidence suggests that these indices assess similar constructs as more widely used neurocognitive batteries (Hobart et al., 1999). Poor performance on the RBANS Attention index has been shown to be associated with global functioning in cohorts of chronic psychiatric patients independent of the diagnosis (Carrión et al., 2013). The Attention index, composed of a Digit span and a Coding task (Hobart et al., 1999), is a combined

Table 3
Logistic Regression Model Predicting Functional Outcome in a subgroup of patients ($n = 74$) with genetic available data.

Predictor Variable	β	SE	Wald x^2	Hazard Ratio	*P* value	AUC[a] (SE) [95% CI]	R^2_N	Sensitivity	Specificity
Attention (RBANS)	0.078	0.03	5.11	1.08	0.024				
Presence of the G allele (DRD1)	−1.085	0.57	3.60	0.34	0.058	0.819 (0.048) [0.726–0.913]	0.394	0.756	0.727
Avolition (CAARMS)	−0.946	0.35	7.14	0.38	0.008				

Abbreviations: RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; DRD1, Dopamine Receptor D1; CAARMS, Comprehensive Assessment of At Risk Mental State. AUC, Area Under the Curve; R^2_N, Nagelkerke pseudo R^2 statistic; SE, Standard Error.
[a] The AUC values can range from 0.5 (indicates that an instrument can discriminate between groups no better than chance) to 1.0 (represents perfect discriminatory performance) and can be interpreted using the following categories: acceptable = 0.70, good = 0.80, and excellent = 0.90.

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measure of processing speed and working memory (Nuechterlein et al., 2004). In a real-world context, reduced reaction time and an impaired ability to maintain and process information might affect global functioning, for example reducing the ability to select and maintain conversational topics (Dickinson et al., 2007).

The LF group was also characterized by higher levels of negative symptoms, with Avolition being an independent predictor of functional outcome. Negative symptoms have traditionally been associated with schizophrenia spectrum disorders (Norman et al., 2015). However, a growing body of evidence suggests that they are expressed in association with LF across different psychiatric diagnoses (Minichino et al., 2016a). Thus, it is not surprising that Avolition may represent a predictor of functional outcome independent of the ARMS status and DSM-IV diagnosis.

Greater motor-coordination abnormalities also made a significant independent contribution to the prediction of functional outcome. These results are consistent with a recent study by Mittal and colleagues (Mittal et al., 2014), which provides evidence for a role of NSS in predicting poor outcomes in ARMS individuals independent of psychosis transition. The authors also showed that NSS predicted a longitudinal decrease in the white matter integrity of the cerebello-thalamic tract that was associated with higher levels of negative symptoms. Consistent with the trans-diagnostic approach used in the current study, high levels of NSS have been associated with specific neural network abnormalities, cognitive dysfunction, negative symptoms and low functioning in both psychotic and non-psychotic individuals (Minichino et al., 2016a; Dazzan and Murray, 2002).

The expression of motor coordination dysfunctions, neurocognitive deficits, and negative symptoms can be related to overlapping brain structural and functional connectivity changes (Mittal et al., 2014), such as fronto-parietal (Chan et al., 2009) and cerebello-thalamo-prefrontal dysfunctions (Dazzan and Murray, 2002; Zhao et al., 2014; Minichino et al., 2014). Consistently, the LF group showed a higher prevalence of the G allele, which also showed a non-significant trend in prediction of functional outcome in a subgroup of patients.

The −48A/G polymorphism is associated with a reduced binding ability of DRD1 in the prefrontal cortex (PFC) (Beaulieu and Gainetdinov, 2011), and with a reduced PFC activation during cognitive tasks (Williams and Goldman-Rakic, 1995). Dysfunctions of DRD1 signaling in the PFC have been proposed as a potential cause of NSS (Russell et al., 2005), negative symptoms (Lynch, 1992) and neurocognitive deficits (Tsang et al., 2015) in both schizophrenia (Goldman-Rakic et al., 2004) and non-schizophrenia spectrum disorders (Tsang et al., 2015). Furthermore, evidence suggests that the DRD1 polymorphism may lead to antipsychotic resistance independent of the psychiatric diagnosis (Ota et al., 2012). It is possible that LF at follow-up could be associated with the expression of the G allele and thus with treatment resistance. This finding highlights the need for more targeted pro-cognitive intervention in patients with low functional trajectories.

The reduced binding ability of the DRD1 in the PFC may trigger a cascade of events leading to (i) NSS abnormalities; (ii) neurocognitive impairments; (iii) greater levels of negative symptoms; and (iv) antipsychotics resistance, defining the common thread that characterizes those individuals with low functional outcome across diagnostic categories. As previously highlighted, motor-coordination signs, processing speed and working memory deficits, as well as severity of negative symptoms, have been related to shared neural vulnerabilities, mainly involving the cerebello-thalamo-prefrontal network (Mittal et al., 2014; Zhao et al., 2014), which is rich in DRD1 receptors. Young patients expressing these characteristics may benefit from specific interventions based on plasticity-based trainings or non-invasive brain modulation techniques targeting this network (Minichino et al., 2015). These non-pharmacological strategies may be particularly helpful in patients expressing the DRD1-rs4532 polymorphism, given its association with antipsychotics resistance.

Finally, as mentioned in the Introduction, the approach used in the current study (i.e., examining markers across different categories of recent-onset psychiatric disorders) is consistent with the RDoC initiative. However, it has to be noted that there currently aren't some domains of interest in the specific RDoC matrix, for instance the construct representing motor or neurological dysfunction in psychiatric disorders. Our findings might represent a good evidence for a broader array of domains to be included in RDoC.

In conclusion, greater attention should be given to functional outcomes in patients with a recent onset psychiatric disorder even if they are not considered at risk for transition to psychosis. In secondary mental health services, a trans-diagnostic approach that takes into account specific neurocognitive, clinical and neurological dimensions, has the potential to identify those patients with a common functional trajectory, despite the clinical heterogeneity. While future studies with larger sample sizes are needed in order to draw definitive conclusions, our results provide useful information on a young psychiatric sample, in which specific therapeutic interventions have the potential to significantly limit functional disability.

4.1. Strengths and limitations

Developing site-specific predictor profiles, as proposed here, has a number of limitations, the need for cross-validation being a primary one. Second, norms for the RBANS in children and adolescents are not yet available. Hence, consistent with previous evidence (Holzer et al., 2007), the raw scores in this study were scaled using the norms for 20–39 year olds also for all participants aged 17–19. Given the short administration time and its reliability, the RBANS represents an interesting screening tool compared to more time-consuming cognitive assessment batteries. Third, our ARMS + detection rate is higher compared to those reported by previous studies (Rietdijk et al., 2012). However, it is still consistent with evidence suggesting that: (i) a consecutive screening in a secondary mental health facility detects more ARMS + than a referral at suspicion strategy (54) and (ii) greater and more stable general psychopathology is associated with a reduction in ARMS false positives and a higher detection rate (Rietdijk et al., 2012). Similarly, the rate of psychotic conversion in the identified ARMS sample (25.4%) is consistent with previously published rates of conversion over a 1–2.5 year time period (Cornblatt et al., 2003). Fourth, the choice of using a dichotomic outcome (LF vs HF) instead of a continuous one (SOFAS scores) could represent an additional limitation of the study. However, given the growing body of literature investigating functional outcomes in recent-onset psychiatric disorders, we decided to report a result that could be potentially more easily replicable and comparable across different research groups. Furthermore, it should be noted that from a clinical perspective it is the change in SOFAS over time, more than its absolute value at follow-up, to be considered more relevant. As highlighted in Section 3.1, patients in the LF group experienced a significant drop in functioning over time, in contrast to what observed in the HF group. This suggests that the variables identified in our final predictive models might help to identify not only those patients who experienced LF at follow-up, but also those who developed a functional decline. However, since functional decline was not our primary outcome measure, this consideration is speculative and only future studies may address this issue.

Finally, we did not take into account in our analyses some relevant treatment-related factors, such as acceptance and compliance with treatment, and other psychosocial factors (e.g. stress, relationship with families), which could have a significant impact on future outcome in psychiatric disorders. Future studies should address this issue.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional

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committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2016.12.019.

References

Addington, J., Liu, L., Buchy, L., Cadenhead, K.S., Cannon, T.B., Cannon, T.D., Cornblatt, P.D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., Woods, S.W., Bearden, C.E., Mathalon, D.E., McGlashan, T.H., 2015. North American Prodrome longitudinal study (NAPLS 2): the prodromal symptoms. J. Nerv. Ment. Dis. 203 (2), 328–335.

Allen, P., Chaddock, C.A., Egerton, A., Howes, O.D., Barker, G., Bonoldi, I., Fusar-Poli, P., Murray, R., McGuire, P., 2015. Functional outcome in people at high risk for psychosis predicted by thalamic glutamate levels and prefronto-striatal activation. Schizophr. Bull. 41 (2), 429–439.

Allott, K., Liu, P., Proffitt, T.-M., Killackey, E., 2011. Cognition at illness onset as a predictor of later functional outcome in early psychosis: systematic review and methodological critique. Schizophr. Res. 125 (2–3), 221–235.

Baron-Cohen, S., Jolliffe, T., Mortimore, C., Robertson, M., 1997. Another advanced test of theory of mind: evidence from very high functioning adults with autism or asperger syndrome. J. Child Psychol. Psychiatry 38 (2), 813–822.

Beaulieu, J.-M., Gainetdinov, R.R., 2011. The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol. Rev. 63 (1), 182–217.

Bosco, F.M., Colle, L., Fazio, S.D., Bono, A., Ruberti, S., Tirassa, M., 2009. Th.O.M.A.S.: an exploratory assessment of theory of mind in schizophrenic subjects. Conscious. Cogn. 18 (1), 306–319.

Buchanan, R.W., Heinrichs, D.W., 1989. The neurological evaluation scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res. 27 (3), 335–350.

Carrión, R.E., McLaughlin, D., Goldberg, T.E., Auther, A.M., Olsen, R.H., Olvet, D.M., Correll, C.U., Cornblatt, B.A., 2013. Prediction of functional outcome in individuals at clinical high risk for psychosis. JAMA Psychiatry 70 (3), 1133–1142.

Chan, R.C., Dai, S., Lui, S.S., Ho, K.K., Hung, K.S., Wang, Y., Geng, F., Li, Z., Cheung, E.F., 2015. Re-visiting the nature and relationships between neurological signs and neurocognitive functions in first-episode schizophrenia: an invariance model across time. Sci. Rep. 5, 11850.

Chan, R.C., Wang, Y., Wang, L., Chen, E.Y., Manschreck, T.C., Li, Z.J., Yu, X., Gong, Q.Y., 2009. Neurological soft signs and their relationships to neurocognitive functions: a re-visit with the structural equation modeling design. PLoS One 4, e8469.

Cornblatt, B.A., Lencz, T., Smith, C.W., Correll, C.U., Auther, A.M., Nakayama, E., 2003. The schizophrenia prodrome revisited: a neurodevelopmental perspective. Schizophr. Bull. 29 (4), 633–651.

Cotter, J., Drake, R.J., Bucci, S., Firth, J., Edge, D., Yung, A.R., 2014. What drives poor functioning in the at-risk mental state? A systematic review. Schizophr. Res. 159 (2–3), 267–277.

Cuthbert, B.N., Insel, T.R., 2013. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 11, 126.

Dazzan, P., Murray, R.M., 2002. Neurological soft signs in first-episode psychosis: a systematic review. Br. J. Psychiatry 181, 50–57.

Dickinson, D., Ramsey, M.E., Gold, J.M., 2007. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch. Gen. Psychiatry 64 (5), 532–542.

Francesconi, M., Minichino, A., Carrión, R.E., Chiaie, R.D., Bevilacqua, A., Parisi, M., Rullo, S., Bersani, F.S., Biondi, M., Cadenhead, K., 2016. Theory of mind as a mediator variable between neurocognition and functioning in young individuals in treatment with secondary services for non-psychotic disorders. Psychiatry Res. 246, 415–420.

Fusar-Poli, P., Nelson, B., Valmaggia, L., Yung, A.R., McGuire, P.K., 2014. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. Schizophr. Bull. 40, 120–131.

Fusar-Poli, P., Rocchetti, M., Sardella, A., Avila, A., Brandizzi, M., Caverzasi, E., Politi, P., Ruhrmann, S., McGuire, P., 2015. Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis. Br. J. Psychiatry 207 (3), 198–206.

Goldman-Rakic, P.S., Castner, S.A., Svensson, T.H., Siever, L.J., Williams, G.V., 2004. Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction. Psychopharmacology 174 (1), 3–16.

Hall, R.C., 1995. Global assessment of functioning. A modified scale. Psychosomatics 36 (3), 267–275.

Hobart, M.P., Goldberg, R., Bartko, J.J., Gold, J.M., 1999. Repeatable battery for the assessment of neuropsychological status as a screening test in schizophrenia, II: convergent/discriminant validity and diagnostic group comparisons. Am. J. Psychiatry 156 (12), 1951–1957.

Holzer, L., Chinet, L., Jaugey, L., Plancherel, B., Sofia, C., Halfon, O., Randolph, C., 2007. Detection of cognitive impairment with the repeatable battery for the assessment of neuropsychological status (RBANS) in adolescents with psychotic symptomatology. Schizophr. Res. 95 (1–3), 48–53.

Hosmer Jr., D.W., Lemeshow, S., Sturdivant, R.X., 2013. Applied Logistic Regression. John Wiley & Sons, Inc., Hoboken, NJ, USA.

Iosifescu, D.V., 2012. The relation between mood, cognition and psychosocial functioning in psychiatric disorders. Eur. Neuropsychopharmacol. 22 (3), S499–S504.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (1), 261–276.

Kessler, R.C., Aguilar-Gaxiola, S., Alonso, J., Chatterji, S., Ormel, J., Ustün, T.B., Wang, P.S., 2009. The global burden of mental disorders: an update from the WHO world mental health (WMH) surveys. Epidemiol. Psichiatr. Soc. 18, 23–33.

Lee, R.S.C., Hermens, D.F., Naismith, S.L., Lagopoulous, J., Jones, A., Scott, J., Chitty, K.M., White, D., Robillard, R., Scott, E.M., Hickie, I.B., 2015. Neuropsychological and functional outcomes in recent-onset major depression, bipolar disorder and schizophrenia-spectrum disorders: a longitudinal cohort study. Transl. Psychiatry 5, e555.

Lee, T.Y., Hong, S.B., Shin, N.Y., Kwon, J.S., 2014. Social cognitive functioning in prodromal psychosis: a meta-analysis. Schizophr. Res. 164 (1–3), 28–34.

Lynch, M.R., 1992. Schizophrenia and the D1 receptor: focus on negative symptoms. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 16 (6), 797–832.

Meyer, E.C., Carrión, R.E., Cornblatt, B.A., Addington, J., Cadenhead, K.S., Cannon, T.D., McGlashan, T.H., Perkins, D.O., Tsuang, M.T., Walker, E.F., Woods, S.W., Heinssen, R., Seidman, L.J., 2014. The relationship of neurocognition and negative symptoms to social and role functioning over time in individuals at clinical high risk in the first phase of the north American Prodrome longitudinal study. Schizophr. Bull. 40 (6), 1452–1461.

Mittal, V.A., Dean, D.J., Bernard, J.A., Orr, J.M., Pelletier-Baldelli, A., Carol, E.E., Gupta, T., Turner, J., Leopold, D.R., Robustelli, B.L., Millman, Z.B., 2014. Neurological soft signs predict abnormal cerebellar-thalamic tract development and negative symptoms in adolescents at high risk for psychosis: a longitudinal perspective. Schizophr. Bull. 40 (6), 1204–1215.

Minichino, A., Francesconi, M., Carrión, R.E., Chiaie, R.D., Bevilacqua, A., Parisi, M., Rullo, S., Bersani, F.S., Biondi, M., Cadenhead, K., 2016a. From neurological soft signs to functional outcome in young individuals in treatment with secondary services for non-psychotic disorders: a path analysis. Psychol. Med. (Accepted, in press).

Minichino, A., Delle Chiaie, R., Cruccu, G., Piroso, S., Giulia, D.S., Francesconi, M., Bersani, F.S., Biondi, M., Truini, A., 2016b. Pain-processing abnormalities in bipolar I disorder, bipolar II disorder, and schizophrenia: a novel trait marker for psychosis proneness and functional outcome? Bipolar Disord. http://dx.doi.org/10.1111/bdi.12439.

Minichino, A., Bersani, F.S., Bernabei, L., Spagnoli, F., Vergnani, L., Corrado, A., Taddei, I., Biondi, M., Delle Chiaie, R., 2015. Prefronto-cerebellar transcranial direct current stimulation improves visuospatial memory, executive functions, and neurological soft signs in patients with euthymic bipolar disorder. Neuropsychiatr. Dis. Treat. 11, 2265–2270.

Minichino, A., Bersani, F.S., Trabucchi, G., Albano, G., Primavera, M., Delle Chiaie, R., Biondi, M., 2014. The role of cerebellum in unipolar and bipolar depression: a review of the main neurobiological findings. Riv. Psichiatr. 3, 124–231.

Norman, R.M.G., Manchanda, R., Harricharan, R., Northcott, S., 2015. The course of negative symptoms over the first five years of treatment: data from an early intervention program for psychosis. Schizophr. Res. 169, 412–417.

Nuechterlein, K.H., Barch, D.M., Gold, J.M., Goldberg, T.E., Green, M.F., Heaton, R.K., 2004. Identification of separable cognitive factors in schizophrenia. Schizophr. Res. 72 (1), 29–39.

Ota, V.K., Spíndola, L.N., Gadelha, A., dos Santos Filho, A.F., Santoro, M.L., Christofolini, D.M., Bellucco, F.T., Ribeiro-dos-Santos, A.K., Santos, S., Mari Jde, J., Melaragno, M.I., Bressan, R.A., Smith Mde, A., Belangero, S.I., 2012. DRD1 rs4532 polymorphism: a potential pharmacogenomic marker for treatment response to antipsychotic drugs. Schizophr. Res. 142 (1–3), 206–208.

Plaisier, I., Beekman, A.T.F., de Graaf, R., Smit, J.H., van Dyck, R., Penninx, B.W.J.H., 2010. Work functioning in persons with depressive and anxiety disorders: the role of specific psychopathological characteristics. J. Affect. Disord. 125 (1–3), 198–206.

Puig, O., Penadés, R., Baeza, I., De la Serna, E., Sànchez-gistau, V., Làzaro, L., Bernardo, M., Castro-Fornieles, J., 2013. Assessment of real-world daily-living skills in early-onset schizophrenia trough the life skills profile scale. Schizophr. Res. 145 (1–3), 95–100.

Randolph, C., Tierney, M.C., Mohr, E., Chase, T.N., 1998. The repeatable battery for the assessment of neuropsychological status (RBANS): preliminary clinical validity. J. Clin. Exp. Neuropsychol. 20, 310–319.

Rietdijk, J., Klaassen, R., Ising, H., Dragt, S., Nieman, D.H., van de Kamp, J., Cuijpers, P., Linszen, D., van der Gaag, M., 2012. Detection of people at risk of developing a first psychosis: comparison of two recruitment strategies. Acta Psychiatr. Scand. 126 (1), 21–30.

Rosen, A., Hadzi-pavlovic, D., Parker, G., 1989. The life skills profile: a measure assessing function and disability in schizophrenia. Schizophr. Bull. 15, 325–337.

Russell, V.A., Sagvolden, T., Johansen, E.B., 2005. Animal models of attention-deficit hyperactivity disorder. Behav. Brain Funct. 1 (1), 9.

Stone, V.E., Baron-Cohen, S., Knight, R.T., 1998. Frontal lobe contributions to theory of mind. J. Cogn. Neurosci. 10 (5), 640–656.

Tsang, J., Fullard, J.F., Giakoumaki, S.G., 2015. The relationship between dopamine receptor D1 and cognitive performance. npj Schizophr. 1, e14002.

Williams, G.V., Goldman-Rakic, P.S., 1995. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. Nature 376 (6541), 572–575.

Yung, A.R., Yuen, H.P., McGorry, P.D., Philips, L.J., Kelly, D., Dell'Olio, M., Francey, S.M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005. Mapping the onset of psychosis: the comprehensive assessment of At-risk mental states. Aust. N. Z. J. Psychiatry 39 (11), 964–971.

Zhao, Q., Li, Z., Huang, J., Yan, C., Dazzan, P., Pantelis, C., Cheung, E.F., Lui, S.S., Chan, R.C., 2014. Neurological soft signs are not "soft" in brain structure and functional networks: evidence from ALE meta-analysis. Schizophr. Bull. 40 (3), 626–641.

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