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Neurocognition as a predictor of transition to psychotic disorder and functional outcomes in ultra-high risk participants: Findings from the NEURAPRO randomized clinical trial

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ABSTRACT

Background: Neurocognitive impairments experienced by individuals at ultra-high risk (UHR) for psychosis are potential predictors of outcome within this population, however there is inconsistency regarding the specific neurocognitive domains implicated. This study aimed to examine whether baseline neurocognition predicted transition to psychosis, or functional outcomes, at medium-term (mean = 3.4 years) follow-up, while controlling for other clinical/treatment variables associated with transition to psychosis.
Method: Analysis of data collected as part of a multi-centre RCT of omega-3 fatty acids and cognitive-behavioural case management (NEURAPRO) for UHR individuals was conducted on the 294 participants (134 males, 160 females) who completed neurocognitive assessment (Brief Assessment of Cognition for Schizophrenia) at baseline. Transition to psychosis was determined using the Comprehensive Assessment of At-Risk Mental States (CAARMS), and functioning was measured with the Global Functioning: Social and Role Scales.
Results: Mean baseline z-scores indicated that UHR participants performed a quarter to half a standard deviation below normative means in all domains (range mean $z = -0.24$ to -0.47), except for executive functioning (mean $z = 0.16$). After adjusting for covariates, poorer Executive ($p = .010$) and Motor ($p = .030$) functions were predictive of transition to psychosis. Processing Speed and Verbal Fluency were significant predictors of role functioning at 12 months ($p = .004$), and social functioning at medium-term follow-up ($p = .015$), respectively.

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Conclusions: Neurocognitive abilities are independent predictors of both transition to psychosis and functional outcomes within the UHR population. Further research is needed to determine the best combination of risk variables in UHR individuals for prediction of psychosis transition, functioning and other psychopathology outcomes.

1. Introduction

The ultra-high risk (UHR) for psychosis state (also referred to as high-risk, clinical high risk, or at-risk mental state) has received extensive research in an effort to identify individuals most at risk of developing full-threshold psychotic disorder (Yung et al., 2004), and to develop preventative interventions (Sommer et al., 2016). Criteria for UHR classification is divided into three groups: attenuated psychotic symptoms (APS), brief limited intermittent psychotic episodes (BLIPS), or trait vulnerability (schizotypal personality disorder, or a first-degree relative with a psychotic disorder) combined with a marked decline in psychosocial functioning, or chronic low functioning (Yung et al., 2005).

Past studies of UHR cohorts have reported variable transition rates, with percentages ranging from 8% to 40% over 12 months (Morrison et al., 2012; Yung et al., 2003), to 35% over 15-year follow-up (Nelson et al., 2013). Meta-analytical findings have demonstrated transition rates of 18% at 6-month, and 22%, 29% and 36% at 1-, 2-, and 3-year follow-up, respectively (Fusar-Poli et al., 2012a). Most existing UHR research has focussed on transition to psychosis as the primary outcome of interest, but evidence suggests that poor functional outcomes and disability are also highly prevalent within this group (Addington et al., 2011; Lin et al., 2011; Allen et al., 2015), and are reported as being the highest source of distress of UHR individuals (Rapado-Castro et al., 2015). Thus, functional outcomes should be a key outcome of interest within UHR research (Cotter et al., 2014).

Widespread compromised neurocognition is a well-established core feature of psychotic disorder, with impairments falling up to two standard deviations below healthy controls (Brewer et al., 2006; Mesholam-Gately et al., 2009). While the causes of these impairments remain unclear, a neurodevelopmental mechanism is supported by strong evidence of neurocognitive impairment emerging in early childhood in those who later develop psychosis (Cannon et al., 2002; Mollon et al., 2018). These deficits, and indeed, neurocognition in general, can be considered either globally (as a general factor; IQ), or domain-specifically (discrete, specific deficits; Reilly and Sweeney, 2014). Recent studies within UHR samples demonstrate impairments in the domains of attention, memory, and executive functioning (Giuliano et al., 2012; Mam-Lam-Fook et al., 2017), as well as in global neurocognitive ability (Seidman et al., 2010), typically falling half a standard deviation below healthy controls (Fusar-Poli et al., 2012b; Giuliano et al., 2012). Neurocognitive impairments tend to be more severe in UHR individuals who subsequently transition to full-threshold psychosis (Hauser et al., 2017), suggesting that neurocognition is a candidate marker for predicting transition to psychosis.

Deficits in verbal memory and processing speed have most consistently been implicated in holding predictive value, particularly within individualized psychosis risk calculators (Cannon et al., 2016; Carrión et al., 2016). Despite this apparent trend, and a general consensus that neurocognitive impairments are typically more profound in individuals who go on to transition to full-threshold psychosis (Seidman et al., 2010; de Paula et al., 2015), there remains heterogeneity within the literature (Mam-Lam-Fook et al., 2017). This is highlighted in the results of three meta-analyses, which collectively have implicated the domains of verbal and visual memory and learning, verbal fluency, processing speed, language, visual-spatial abilities, executive functioning, working memory, attention, as well as IQ, in predicting psychosis transition (Giuliano et al., 2012; Fusar-Poli et al., 2012b; Hauser et al., 2017).

The lack of consensus as to which neurocognitive domains best predict transition to full-threshold psychosis may be attributable to methodological limitations within the existing literature, such as small sample sizes, differing measures, variability in reporting of sample characteristics, and time to follow-up (Seidman et al., 2016). Furthermore, many past studies have failed to control for important factors such as psychotic symptom severity and social functioning, as well as treatment, all which have been associated with transition to psychosis (Bousman et al., 2013; Amminger et al., 2015). It is essential that we endeavour to better understand the predictive value of neurocognition, and to identify the specific domains which may be involved in underlying transition to full-threshold psychosis. Furthermore, there is a need for well-powered studies which control for the effects of covariates shown to be associated with transition to psychosis, such as symptom severity, level of functioning, and treatment, in order for us to examine the utility of neurocognitive predictors over and above other clinical and treatment variables.

Research on frank psychosis has also demonstrated a significant relationship between poorer neurocognition and poorer functional outcomes (Fett et al., 2011). However, only a small number of studies have examined this relationship in UHR participants. Findings from recent longitudinal studies have implicated impairments in verbal learning and memory, verbal fluency, processing speed, and attention as being predictive of poorer functional outcome (Lin et al., 2011). Interestingly, participants who were classed as having either 'poor' or 'good' outcomes within this study (below-average vs average/above-average performance on functioning assessment batteries, respectively) did not display any significant differences with respect to overall IQ. This suggests that poorer functional outcomes may be associated with impairments in specific neurocognitive domains, rather than global neurocognitive ability (Lin et al., 2011; Carrión et al., 2013). Other studies have found spatial and working memory (Goghari et al., 2014), executive functioning (Eslami et al., 2011; Sawada et al., 2017), and global neurocognitive ability (Meyer et al., 2014) to be associated with functioning in UHR, again highlighting heterogeneity within the literature. Given this lack of consensus, and the fact that UHR individuals often experience pronounced impairments in functioning (Glenthøj et al., 2016), there is a need for further investigation.

The present study sought to examine the value of neurocognition (considered both generally and domain-specifically) in predicting psychosis and functional outcomes in UHR individuals, while controlling for the effects of other relevant clinical or treatment variables shown to be associated with transition to psychosis. The aims of the current study were to examine neurocognition as a predictor of i) transition to full-threshold psychosis, and ii) functional outcomes, in UHR participants at follow-up. Based on the most recent findings by Cannon et al. (2016) and Hauser et al. (2017), we hypothesized that baseline performance in processing speed, verbal memory, and overall IQ would be predictive of psychosis transition, while specific poorer baseline neurocognitive abilities would predict poorer functional outcomes.

2. Methods

2.1. Design, procedure, and participants

This study involved hypothesis-driven secondary analysis of baseline and follow-up data from a large international multi-site randomized controlled trial (RCT; 'NEURAPRO'; trial registration: anzctr.org.au, identifier: 12608000475347) involving 304 people at UHR for psychosis (see McGorry et al., 2017). In the NEURAPRO RCT, participants were allocated to the experimental or control condition, using double-blind randomisation. Those in the experimental condition were treated with long-chain omega-3 polyunsaturated fatty acids (ω-3 PUFAs), in combination with cognitive behavioural case management (CBCM), while the control group received a placebo and CBCM. All participants provided informed written consent. Ethics approval for the original RCT was received from the Melbourne Health Human Research Ethics Committee (HREC NO:2008.628), and for the current study by the Human Ethics Sub-Committee, College of Science, Health and Engineering, La Trobe University. Assessments were conducted at baseline, 6 months, 12 months, and medium-term follow-up (mean = 3.4 years) (Nelson et al., 2018). With respect to the primary outcome of the RCT (transition to psychosis), as well as the secondary functioning outcomes, no significant differences between the experimental and control conditions were found (McGorry et al., 2017). Treatment groups were therefore combined for the current study, without further examination of group differences.

Participants were recruited from ten early psychosis treatment centres across Australia (Melbourne, Sydney), Germany (Jena), Switzerland (Basel, Zurich), Austria (Vienna), Denmark (Copenhagen), The Netherlands (Amsterdam), Singapore, and Hong Kong (Pokfulam). For complete details of the study methodology including the inclusion/exclusion criteria, refer to Markulev et al. (2015) and McGorry et al. (2017). For the current study, an additional inclusion criterion was that participants needed to have completed the baseline neurocognitive battery.

2.2. Measures

2.2.1. Demographics

Key demographic information was collected at baseline including age, gender, race, current accommodation, highest educational achievement, employment status, and citizenship.

2.2.2. Neurocognition

Baseline neurocognitive ability was assessed in two ways. The Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004) examined the specific neurocognitive domains of verbal memory and learning (Verbal Memory task), working memory (Digit Sequencing task), motor function (Token Motor task), verbal fluency (Semantic Fluency and Letter Fluency tasks, collectively referred to hereafter as the 'Verbal Fluency' task), speed of processing (Symbol Coding task), and executive function (Tower of London task). *Z*-scores derived from the BACS normative sample were used in analyses. A two-subtest short-form (Vocabulary and Matrix Reasoning subtests) of the Wechsler Adult Intelligence Scale–3rd Edition (WAIS-III; Wechsler, 1997) was administered to examine overall/global neurocognitive ability (estimated Full-Scale IQ; FSIQ).

2.2.3. Outcome and control measures

Transition to psychosis was assessed with the Comprehensive Assessment of the At-Risk Mental State (CAARMS; Yung et al., 2005). The Global Functioning: Social (GF:S) and Role (GF:R) Scales (Cornblatt et al., 2007) were used as outcome measures to assess social and role functioning. Potentially confounding variables were measured using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982) to assess negative symptom severity, Social and Occupational Functioning Assessment Scale (SOFAS, Goldman et al., 1992) to assess functioning, and the Brief Psychiatric Rating Scale – Psychotic scale (BPRS-P; Overall and Gorham, 1962), to assess positive psychotic symptom severity.

2.3. Statistical analyses

Statistical analyses were conducted using IBM® SPSS® Statistics Version 24.0.0. Prior to hypothesis-testing, the dataset was examined to check for missing data and outliers. Any value more than four standard deviations above or below the mean was checked against the original research file, and corrected if needed. The data were also assessed to ensure that results did not violate the assumptions of normality, linearity, homoscedascity, or multicollinearity (Hair Jr et al., 1995; Tabachnick and Fidell, 2013). Hierarchical Cox proportional hazards regression was used to examine neurocognitive predictors of transition to psychosis, with analyses occurring over two stages. First, the seven neurocognitive variables (FSIQ and BACS subscales) were entered simultaneously into the regression model, to examine their relative contributions. Second, the hierarchical regression examined whether significant neurocognitive predictors ($p < .05$) retained significance after adjusting for covariates. Covariates that were controlled for were baseline level of functioning (SOFAS), baseline negative and positive psychotic symptom severity (step 1), and number of cognitive-behavioural case management (CBCM) sessions (step 2), given that these have been previously reported in the literature as being associated with transition to psychosis (Bousman et al., 2013; Amminger et al., 2015). Neurocognitive variables were entered at step 3. Exploratory independent samples *t*-tests were also used to examine group differences in neurocognition at baseline, which are of clinical interest. Hierarchical linear regressions were used to identify neurocognitive predictors of functioning, and followed a similar methodology. Covariates controlled for were baseline level of functioning (step 1), transition to psychosis (step 2), baseline negative and positive psychotic symptom severity (step 3), followed by neurocognitive variables (step 4). For all analyses the alpha level (type I error) was set at 0.05. An a priori decision was made not to make a Bonferroni adjustment when interpreting significance to avoid increasing the risk of Type II error (Perneger, 1998; Armstrong, 2014).

3. Results

3.1. Participant screening and demographic information

Fig. 1 shows the flow of participants in the current study. Primary analyses in the current study were conducted on the 294 participants who had completed baseline neurocognitive assessments. The sample demographics are presented in Table 1.

3.2. Sample characteristics

Table 2 presents the baseline clinical and neurocognitive characteristics of the entire sample. Overall, IQ fell within the Average range (85–115; Lichtenberger and Kaufman, 2012), while performance across five of the six BACS domains fell a quarter to half a standard deviation below normative means, except for executive functioning (mean z = 0.016). Thirty eight (12.9%) participants made a transition to psychosis over the follow-up period. The average time to transition was 314 days ($SD = 326$; median = 229), ranging from 18 to 1573 days. Of those who transitioned, 42.1% had done so by 6-months, 73.7% by 12-months, and 89.5% by 24-months.

3.3. Does baseline neurocognition predict transition to psychosis?

Cox proportional hazards regression was used to examine whether neurocognitive variables predicted transition to psychosis. Preliminary regression analyses demonstrated that, when all seven neurocognitive predictors were entered simultaneously, performance on the Token Motor (motor function, $B = -0.309$, $p = .046$), and Tower of London (executive function, $B = -0.265$, $p = .046$) tasks were the only variables shown to make a unique, significant contribution to the model.

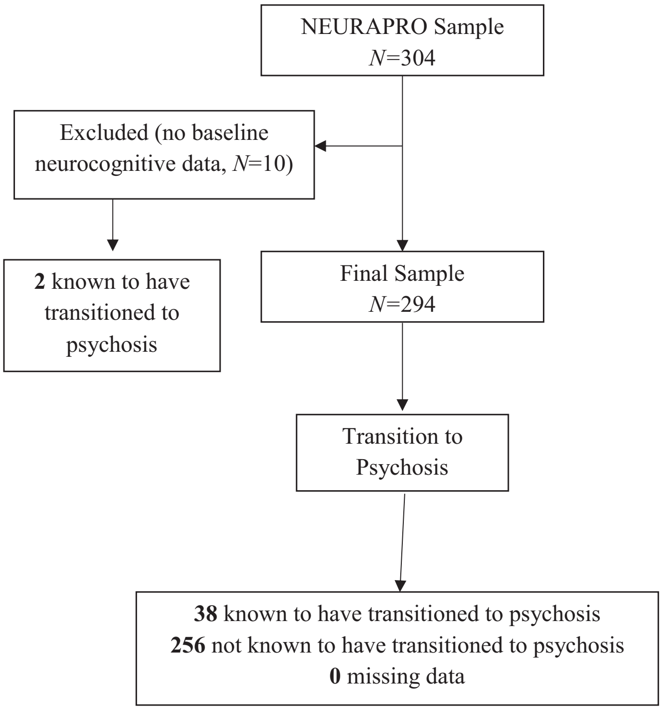

Fig. 1. Flow of participants in the current study.

Assumptions surrounding multicollinearity were closely assessed, and deemed not to have been violated, with the variance inflation factor (VIF) for each neurocognitive variable falling below 2, indicating inconsequential collinearity (Hair Jr et al., 1995). A hierarchical cox regression was then performed to examine the contribution of these neurocognitive domains after adjusting for covariates. Findings from this analysis are presented in Table 3.

Clinical variables (SOFAS, BPRS-P, and SANS) were entered in Step 1, and were statistically significant ($\chi^2(3) = 12.54$, $p = .006$). While the model retained significance after the inclusion of CBCM ($\chi^2(4) = 12.36$, $p = .015$), the inclusion of this variable alone did not make a significant improvement to the overall model ($\chi^2(1) = 0.08$, $p = .774$). At the conclusion of Step 3, the final model was statistically significant, $\chi^2(6) = 30.25$, $p < .001$, with the addition of the two neurocognitive variables making a statistically significant improvement to the model, $\chi^2(2) = 13.17$, $p = .001$, indicating that this set of variables significantly predicted the transition rate to psychosis. An examination of the individual contributions of each of the six variables in the complete model showed that motor function (Token Motor Task) and executive function (Tower of London) were the only variables to have a statistically unique effect on the rate of transition to psychosis, with a one-point increase on these domains decreasing the hazard by a factor of 0.701 and 0.743, respectively.

Independent samples *t*-tests were conducted to examine group differences between individuals known to have transitioned by medium-term follow-up ($N = 38$) and those who did not ($N = 256$), as such information is likely to be of clinical interest. As shown in Table 4, at baseline, those who transitioned to psychosis performed significantly worse than those who did not with regard to IQ ($p = .043$), working memory ($p = .033$), motor function ($p < .001$), processing speed ($p = .020$), and executive functioning ($p = .013$).

3.4. Does baseline neurocognition predict functional outcomes?

Multiple regression analyses (MRAs) were used to examine whether neurocognition could predict level of functioning, as assessed by the i) GF:S and ii) GF:R at the 12-month and medium-term assessment points. Six participants were excluded from these analyses due to Mahalanobis distance exceeding the critical $\chi 2$ for df = 7 (at $\alpha = 0.001$) of 24.32 (Tabachnick and Fidell, 2013).

Table 1
Demographic information of participants.

Characteristic	Total ($N = 294$)
	M (*SD*)
Age	19.13 (4.54)
Characteristic	Total ($N = 294$)
	% (*N*)
Gender	
Males	45.60 (134)
Females	54.40 (160)
Race	
Caucasian	81.30 (239)
Black or African American	2.40 (7)
Asian	12.20 (36)
Other	3.40 (10)
Nationality	
Native-born	90.50 (266)
Immigrant	8.80 (26)
Current accommodation	
Crisis accommodation	0.70 (2)
Rented flat/house	35.70 (105)
Own flat/house	5.80 (17)
Family home	47.30 (139)
Long stay psych hospital	1.70 (5)
Acute hospital	0.30 (1)
Supported residential service	1.00 (3)
Group home	2.70 (8)
Rooming house	0.30 (1)
Boarding house	0.30 (1)
Other	3.40 (10)
Employment status	
Unemployed	25.20 (74)
Full-time paid employment	5.10 (15)
Part-time/casual paid employment	6.80 (20)
Full-time student	52.00 (153)
Part-time student	2.70 (8)
Home duties/caregiver	0.70 (2)
Other	6.80 (20)
Highest completed level of education	
Primary school	37.10 (109)
Secondary school, discontinued prior to final year	18.40 (54)
Secondary school, completed final year	28.20 (83)
Trade or technical training	10.50 (31)
Undergraduate university course	4.80 (14)

N = Number of Participants; *M* = Mean; *SD* = Standard Deviation.

Table 2
Clinical and neurocognitive characteristics of the sample at baseline.

Variable	*M* (*SD*)
Clinical variables	
Social and occupational functioning (SOFAS)	53.42 (11.92)
Global functioning – social scale (GF:S)	6.48 (1.24)
Global functioning – role scale (GF:R)	5.96 (1.52)
Positive symptoms (BPRS-psychotic)	8.23 (2.65)
Negative symptoms (SANS)	18.28 (13.04)
Cognitive variables	
WAIS-III FSIQ estimate	102.74 (14.71)
BACS items	
Verbal memory (verbal memory and learning)	−0.28 (1.70)
Digit sequencing (working memory)	−0.41 (1.11)
Token motor task (motor function)	−0.44 (1.10)
Verbal fluency (verbal fluency)	−0.47 (1.20)
Symbol coding (processing speed)	−0.28 (1.24)
Tower of London (executive function)	0.16 (1.21)

SOFAS = Social and Occupational Functioning Assessment Scale; GF:S = Global Functioning – Social Scale; GF:R = Global Functioning – Role Scale; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; WAIS-III = Wechsler Adult Intelligence Scale – 3rd Edition; BACS = Broad Assessment of Cognition in Schizophrenia; *N* = Number of Participants; *M* = Mean; *SD* = Standard Deviation.

Table 3
Hierarchical Cox proportional hazards regression analysis of motor function (Token motor task) and executive function (Tower of London) as predictors of transition to psychosis after controlling for covariates.

Variables	*B*	*SE (B)*	Wald	*df*	*p*	Hazard ratio	95% C.I. Hazard ratio	
							Lower	Upper
Step 1								
SOFAS	0.007	0.020	0.122	1	0.727	1.007	0.969	1.046
BPRS-P	0.193*	0.077	6.297	1	0.012	1.212	1.043	1.409
SANS	0.026	0.015	2.952	1	0.086	1.026	0.996	1.057
Step 2								
SOFAS	0.007	0.020	0.127	1	0.721	1.007	0.969	1.046
BPRS-P	0.193*	0.077	6.324	1	0.012	1.213	1.043	1.409
SANS	0.027	0.015	3.025	1	0.082	1.027	0.997	1.058
CBCM	0.009	0.033	0.084	1	0.772	1.010	0.947	1.077
Step 3								
SOFAS	0.010	0.020	0.234	1	0.629	1.010	0.971	1.051
BPRS-P	0.130	0.074	3.042	1	0.081	1.138	0.984	1.317
SANS	0.023	0.016	2.063	1	0.151	1.023	0.992	1.056
CBCM	0.012	0.034	0.127	1	0.721	1.012	0.948	1.081
Token motor task	−0.356*	0.162	4.827	1	0.028	0.701	0.510	0.962
Tower of London	−0.297*	0.119	6.243	1	0.012	0.743	0.589	0.938

B = Unstandardized regression coefficient; *SE (B)* = Standard Error; Wald = Wald Statistic; *df* = Degrees of Freedom; SOFAS = Social and Occupational Functioning Assessment Scale; BPRS = Brief Psychiatric Rating Scale-Psychotic; SANS = Scale for the Assessment of Negative Symptoms; CBCM = Cognitive Behavioural Case Management.
* $p < .05$.

3.4.1. Does baseline neurocognition predict functional outcomes at the 12-month assessment point?

Initial analyses demonstrated that while neurocognitive variables failed to predict performance on the GF:S at 12 months, superior performance on the GF:R was predicted by performance on the Symbol Coding task, $B = 0.263$, $p = .028$, $sr^2 = 0.024$. A hierarchical MRA was subsequently performed to examine whether this neurocognitive predictor retained significance after adjusting for covariates (Table 5).

Baseline level of functioning, as assessed by the GF:R, was entered in Step 1 of the regression, and explained 4.3% of the variance in GF:R performance at 12-months. The inclusion of 'Transition to Psychosis (Y/N)' in Step 2, and clinical variables (BPRS-P) and SANS) in Step 3, explained an additional 11.7% ($p < .001$) and 0.4% ($p = .65$) of the variability in this outcome, respectively, with the model as a whole accounting for 16.4% of the variance, $F(4,198) = 9.72$, $p < .001$. After the inclusion of baseline processing speed (Symbol Coding Task), the final model explained 19.8% of the variance in GF:R performance at 12-months, $F(5,197) = 9.72$, $p < .001$. Performance on the Symbol Coding Task made a statistically significant contribution to the overall model, R^2 change = 0.034, $p = .004$, suggesting that processing speed at baseline uniquely explains 3.4% of the variability in role functioning at 12-months.

3.4.2. Does baseline neurocognition predict functional outcomes at the medium-term assessment point?

Initial MRAs showed that a model containing all seven neurocognitive variables did not predict GF:S performance at medium-term follow-up, $R^2 = 0.090$, adjusted $R^2 = 0.044$, $F(7,136) = 1.93$, $p = .069$. However, performance on the verbal fluency task made a unique contribution to the overall model, $B = 0.215$, $p = .047$, $sr^2 = 0.027$, suggesting that superior verbal fluency abilities were associated with superior social skills. No significant neurocognitive predictors of GF:R performance at this time-point were found. Based on these findings, a hierarchical MRA was performed to examine whether performance on the verbal fluency task retained its significance as a predictor of GF:S performance, after adjusting for covariates (Table 6).

Baseline level of social functioning (GF:S), was entered in Step 1 of the regression, and explained 11% of the variance in GF:S performance at medium-term follow-up. The inclusion of 'Transition to Psychosis (Y/N)' in Step 2, and clinical variables (BPRS-P and SANS) in Step 3, explained an additional 3.2% ($p = .022$) and 1.4% ($p = .311$) of the variability in this outcome, respectively, with the model as a whole accounting for 15.6% of the variance, $F(4,140) = 6.48$, $p < .001$. After the inclusion of baseline verbal fluency abilities (Verbal Fluency Task), the final model explained 19.2% of the variance in GF:S performance at follow-up, $F(5,139) = 6.60$, $p < .001$. Performance on the Verbal Fluency Task made a unique, statistically significant contribution to the overall model, R^2 change = 0.036, $p = .015$, suggesting that verbal fluency at baseline uniquely explains 3.6% of the variability in social functioning at medium-term follow-up.

Table 4
Independent samples *t*-test examining differences between neurocognitive performance of known transition cases (UHR-P) and non-transition cases (UHR-NP) at baseline.

Variable	Transition to psychosis				*t*	*df*	*p*
	UHR-P (*N* = 38)		UHR-NP (*N* = 256)				
	M	*SD*	*M*	*SD*			
WAIS-III FSIQ estimate	98.263	12.631	103.446	14.911	−2.031	278	0.043*
Verbal memory	−0.692	1.861	−0.212	1.666	−1.630	285	0.104
Digit sequencing	−0.764	1.224	−0.352	1.087	−2.142	285	0.033*
Token motor task	−1.023	1.043	−0.350	1.078	−3.598	283	<0.001*
Verbal fluency	−0.723	1.349	−0.433	1.177	−1.386	285	0.167
Symbol coding	−0.712	1.442	−0.213	1.192	−2.333	285	0.020*
Tower of London	−0.414	1.515	0.252	1.128	−2.603	43.489	0.013*

N = Number of Participants; *M* = Mean; *SD* = Standard Deviation; *df* = Degrees of Freedom; WAIS-III = Wechsler Adult Intelligence Scale (3rd Ed.)
* $p < .05$.

4. Discussion

The current study sought to identify whether neurocognitive performance (examined both globally and domain-specifically) could predict transition to psychosis, and/or functional outcomes, within a UHR cohort at follow-up after accounting for relevant clinical or treatment variables. While many previous studies have suggested that neurocognition is an important factor in predicting transition to psychosis, there is significant heterogeneity regarding the specific domains implicated (Mam-Lam-Fook et al., 2017). By further examining the interplay between neurocognitive ability and outcomes within this large cohort we sought to shed further light on this issue.

Inconsistent with our hypothesis, executive function and motor function were the only neurocognitive domains to emerge as significant predictors of transition to full-threshold psychosis, after adjusting for covariates. Participants who transitioned to psychosis displayed more pronounced deficits in these domains at baseline compared to those who did not (Table 4), approaching the level of impairment associated with first-episode psychosis (Mesholam-Gately et al., 2009). The finding that deficits in executive function are predictive of psychosis is consistent with previous research (Giuliano et al., 2012; Fusar-Poli et al., 2012b). In the current study, the executive functioning measure (Tower of London) was the only task where the mean group performance at baseline did not fall below the norm, with the collective sample performing, on average, a quarter to half a standard deviation below normative means in the remaining five domains assessed by the BACS (Table 2). This might indicate that impaired executive functioning may be an especially sensitive indicator of transition risk. The Tower of London task specifically taps problem-solving and cognitive flexibility aspects of executive function (Keefe et al., 2008), which theoretically may be necessary for adequate reality-testing. It may be that a breakdown in these abilities may increase the risk of transitioning to

Table 5
Hierarchical multiple regression analysis of processing speed (Symbol coding task) as a predictor of functional outcomes (GF:R Performance) at 12-months after controlling for covariates.

Variables	*B*	*SE(B)*	95% C.I. B		β	*p*	sr^2
			Lower	Upper			
Step 1							
Baseline functioning (GF:R)	0.222*	0.073	0.077	0.366	0.209	0.003	0.043
Step 2							
Baseline functioning (GF:R)	0.210*	0.069	0.074	0.345	0.197	0.003	0.039
Transition to psychosis (Y/N)	−1.653*	0.313	−2.271	−1.036	−0.342	<0.001	0.117
Step 3							
Baseline functioning (GF:R)	0.185*	0.075	0.037	0.333	0.174	0.015	0.026
Transition to psychosis (Y/N)	−1.625*	0.319	−2.255	−0.996	−0.336	<0.001	0.110
BPRS-P	0.016	0.042	−0.066	0.098	0.026	0.702	0.001
SANS	−0.008	0.009	−0.026	0.010	−0.068	0.356	0.004
Step 4							
Baseline functioning (GF:R)	0.168*	0.074	0.023	0.314	0.158	0.024	0.021
Transition to psychosis (Y/N)	−1.557*	0.315	−2.178	−0.937	−0.322	<0.001	0.100
BPRS-P	0.030	0.041	−0.051	0.111	0.049	0.469	0.002
SANS	−0.008	0.009	−0.026	0.010	−0.064	0.376	0.003
Symbol coding task	0.251*	0.087	0.079	0.422	0.187	0.004	0.034

GF:R = Global Functioning - Role Scale; *B* = Unstandardized regression coefficient; *SE (B)* = Standard Error; C.I. = Confidence Interval; β = Standardized regression coefficient; sr^2 = Squared semi-partial correlation coefficient; BPRS = Brief Psychiatric Rating Scale-Psychotic; SANS = Scale for the Assessment of Negative Symptoms.
* $p < .05$.

psychosis, which is characterized by an impaired view of reality (Seligman et al., 2001).

Previous studies have also supported the predictive value of impaired motor functions, over and above other neurocognitive domains, with Mittal and Walker (2007), Blanchard et al. (2010) and Rakhshan et al. (2016) all collectively finding that poorer performance on a measure of motor functioning was associated with subsequent transition to psychosis. In the current sub-group who transitioned, the largest impairment in cognitive performance at baseline was on the Token Motor task, with performance falling one standard deviation below the norm, potentially indicating generalized motor and cognitive slowing within this group. However, processing speed (Symbol Coding task) did not emerge as a significant predictor, suggesting that the 'motor' component is more important than the 'cognitive' processing in predicting transition. Given that past research has implicated motor dysfunction in early childhood as being predictive of transition to psychosis in later life (Erlenmeyer-Kimling et al., 2000; Cannon et al., 2006; Dickson et al., 2012), deficits in motor functioning may be an especially early risk marker for psychosis.

Taken together, these findings suggest that impaired executive and motor functions may be useful for identifying UHR individuals who are at highest risk of transitioning to psychosis. Despite adding to the overall heterogeneity in findings, the observation that impaired performance on the Token Motor and Tower of London tasks replicates findings which have shown the contribution of motor and executive functions, as assessed by the BACS, to psychosis transition (Fusar-Poli et al., 2012b; McDonald et al., 2018). Furthermore, the consideration of neurocognition both generally and domain-specifically addresses a common criticism within the UHR literature, with many past studies solely utilizing global test batteries (Mam-Lam-Fook et al., 2017), instilling greater confidence in the current findings. However, replication of these results and validation in independent samples is essential before these findings can be incorporated into psychosis risk models. Furthermore, ongoing consideration of the role of neurocognition in combination with other important risk factors such as symptoms and functioning is critical, as has been done by others in the field (Addington et al., 2017; Cornblatt et al., 2017). The findings were consistent with our hypothesis that poorer baseline neurocognitive abilities would be predictive of poorer functional outcomes. Specifically, impairments in processing speed were shown to be predictive of role functioning at 12-months, while poorer verbal fluency abilities were predictive of social functioning at medium-term, after controlling for covariates.

Table 6
Hierarchical Multiple Regression Analysis of Verbal Fluency (Verbal Fluency Task) as a Predictor of Functional Outcomes (GF:S Performance) at Medium-Term Follow-up after Controlling for Covariates.

Variables	*B*	*SE(B)*	95% C.I. B		β	*p*	sr^2
			Lower	Upper			
Step 1							
Baseline functioning (GF:S)	0.340*	0.081	0.180	0.500	0.331	<0.001	0.110
Step 2							
Baseline functioning (GF:S)	0.315*	0.081	0.156	0.474	0.307	<0.001	0.092
Transition to psychosis (Y/N)	−0.698*	0.301	−1.293	−0.102	−0.182	0.022	0.032
Step 3							
Baseline functioning (GF:S)	0.249*	0.093	0.066	0.432	0.243	0.008	0.043
Transition to psychosis (Y/N)	−0.667*	0.304	−1.267	−0.066	−0.174	0.030	0.029
BPRS-P	0.016	0.040	−0.062	0.095	0.033	0.685	0.001
SANS	−0.014	0.009	−0.032	0.004	−0.142	0.128	0.014
Step 4							
Baseline functioning (GF:S)	0.192*	0.094	0.006	0.378	0.187	0.043	0.024
Transition to psychosis (Y/N)	−0.631*	0.299	−1.222	−0.041	−0.164	0.036	0.026
BPRS-P	0.015	0.039	−0.063	0.092	0.030	0.710	0.001
SANS	−0.018*	0.009	−0.036	0.000	−0.187	0.046	0.024
Verbal fluency task	0.211*	0.085	0.042	0.380	0.196	0.015	0.036

GF:S = global functioning − social scale; *B* = Unstandardized regression coefficient; *SE (B)* = Standard Error; C.I. = Confidence Interval; β = Standardized regression coefficient; sr^2 = Squared semi-partial correlation coefficient; BPRS = Brief Psychiatric Rating Scale-Psychotic; SANS = Scale for the Assessment of Negative Symptoms.
* $p < .05$.

This is perhaps unsurprising, given that processing speed would likely be important for the day-to-day tasks of daily living indexed by the GF:R (Cornblatt et al., 2007). Furthermore, verbal fluency abilities would theoretically be required for conversational and relationship skills, which in turn would play a role in social functioning, as assessed by the GF:S (Cornblatt et al., 2007). The current results add to previous research which has implicated impairments in specific neurocognitive domains, rather than overall neurocognitive ability, as being predictive of poorer functional outcomes in UHR (Lin et al., 2011). However, given the relatively low associations between neurocognition and functional outcomes, it may be the case that these outcomes may be better predicted by alternative domains of cognition, such as social cognition, as previous studies have shown (Cotter et al., 2017; Niendam et al., 2009; Mancuso et al., 2011). Given that social cognition was not assessed in the current study, future research should seek to address this.

The current study has several notable strengths, the first of which is the large sample size. Furthermore, we carefully controlled for a number of other factors which have been shown to be associated with the transition to psychosis, such as negative and positive psychotic symptoms, and low psychosocial functioning (Amminger et al., 2015). This allowed for the assessment of the unique contribution of neurocognitive factors in predicting outcomes for UHR individuals over and above clinical and treatment factors.

A limitation which should be noted is that the low number of participants who transitioned to psychosis ($N = 38$) may have limited the power to detect significant predictors of transition. We have previously speculated that this low transition rate may have been attributable to a number of potential confounds, such as ongoing CBCM and high levels of antidepressant use amongst participants, or alternatively, that this may instead reflect the decreasing enrichment for psychosis risk that has been observed in UHR samples (McGorry et al., 2017; Yung et al., 2007). This shortcoming was further compounded in the current study, with an additional two participants who were found to have transitioned in the original study being excluded due to not having completed the baseline neurocognitive assessment. This meant that 5% of those who transitioned were excluded from analysis, which may have affected the results. Consequently, it is difficult to determine whether the current findings reflect the greater importance of the domains found to be significant, or whether this is instead attributable to sample confounds.

In conclusion, the findings from this study have demonstrated that neurocognitive domains predict mental health outcomes within UHR for psychosis individuals. Impairments in executive and motor functions were predictors of transition to psychosis, continuing to make a unique significant contribution over and above other clinical/treatment variables. Poorer processing speed and verbal fluency, were shown to be predictive of role functioning at 12 months, and social functioning at medium-term follow-up, respectively. Future research should continue to examine which neurocognitive domains best predict transition to psychosis, and expand on risk models of psychosis by including relevant clinical and functioning factors, as well as biomarkers to develop multimodal predication models. Similarly, studies should continue to explore how these domains can be used to predict other outcomes, such as functioning, within a UHR cohort.

Conflict of interest

All authors declare no conflict of interest.

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Luke K. Bolt: Conceptualization, Data curation, Formal analysis, Project administration, Writing - original draft. **G. Paul Amminger:** Conceptualization, Formal analysis, Writing - review & editing. **John Farhall:** Conceptualization, Formal analysis, Writing - review & editing. **Patrick D. McGorry:** . **Barnaby Nelson:** . **Connie Markulev:** . **Hok Pan Yuen:** Formal analysis, Writing - review & editing. **Miriam R. Schäfer:** . **Nilufar Mossaheb:** . **Monika Schlögelhofer:** . **Stefan Smesny:** . **Ian B. Hickie:** . **Gregor Emanuel Berger:** . **Eric Y.H. Chen:** . **Lieuwe de Haan:** . **Dorien H. Nieman:** . **Merete Nordentoft:** . **Anita Riecher-Rössler:** . **Swapna Verma:** . **Andrew Thompson:** . **Alison Ruth Yung:** . **Kelly A. Allott:** Conceptualization, Formal analysis, Writing - review & editing.

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