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A CROSS-SECTIONAL STUDY OF CLINICAL, NEUROCOGNITIVE, AND DEMOGRAPHIC FACTORS ASSOCIATED WITH FUNCTIONAL IMPAIRMENT IN THE BRAIN AND MIND YOUTH COHORT

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ABSTRACT

Objectives: To determine the unique and shared contributions of clinical, neurocognitive, and demographic factors to functional impairment in a large, transdiagnostic, clinical cohort of adolescents and young adults.

Design: Cross-sectional baseline data from a prospective, cohort study.

Setting: Help-seeking youth referred from outpatient services were recruited to the *Brain and Mind Youth Cohort* (2008-2016) in Sydney, Australia.

Participants: In total, 1003 outpatients were recruited, aged between 12 and 36 years (M = 20.4 years, 54% female), with baseline diagnoses of affective, psychotic, developmental or behavioural disorders.

Interventions: Treatment as usual by referring clinicians.

Primary outcome measures: Social and occupational functioning was used to index level of functional impairment. Structural equation modelling was employed to examine associations between neurocognition, core clinical symptoms, alcohol and substance use, sleep and circadian changes, and clinician- and researcher-rated functional impairment. Moderator analyses were conducted to determine the potential influence of demographic and clinical factors (e.g. medication exposure).

Results: Independent of diagnosis, we found that neurocognitive impairments, and depressive, anxiety and/or negative symptoms, were significantly associated with functioning. The association of neurocognition with social and occupational functioning remained significant even when age (younger) and diagnosis (affective disorder) were included in the model.

Conclusions: This study demonstrated that, in a clinically representative sample of youth, the key determinants of functioning may not be disorder specific. Further, evidence of

neurocognitive dysfunction suggests that interventions that target cognition and functioning should not necessarily be reserved only for older adults with established illness.

Keywords: Neurocognition; transdiagnostic; functional impairment; mental illness; symptom dimensions; alcohol use.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This was one of the largest studies to date (N > 1,000) to examine the associations between a broad range of illness characteristics and functional impairment in an adolescent and young adult clinical sample.
- Given the transdiagnostic approach, this study was equipped to disentangle the shared and unique associations between core illness phenotypes and functional impairment across a range of common mental disorders.
- The use of latent-variable, structural equation modelling controlled for aspects of measurement imprecision.
- The main limitation of this study was that it was cross-sectional and, as such, the direction of effects remains unclear.

INTRODUCTION

In recent decades, early intervention services for youth with emerging mental disorders have extended their targets beyond those at risk of psychosis to also encompass those presenting with mood and other developmental and anxiety disorders. This approach creates several significant challenges. For example, some youth with depressive and anxiety disorders will ultimately develop psychotic or bipolar disorders; likewise, only a proportion of those receiving a diagnosis of bipolar disorders will consistently receive this diagnosis over the following 10 years.[1] The lack of diagnostic stability in help-seeking youth reflects the evolving disease process and means that the illness trajectory is less certain than for older adults with established illness.[2 3] From a research perspective, the use of dimensional approaches to phenomenology has helped us to understand illness progression in these early clinical stages, whilst from a clinical perspective, care and treatment have increasingly considered transdiagnostic interventions addressing core factors that may influence prognosis irrespective of cross-sectional diagnosis (e.g., anxiety, depressive or negative symptoms; sleep disturbances).[4 5] These approaches have highlighted that, in youth, a more meaningful measure of outcome may be functioning rather than change in diagnosis-specific symptoms. There is evidence to support this approach as level of functioning or disengagement (e.g., not being in education, employment or training, referred to as being NEET) is associated with early transition to major mental disorder[6] and with poor outcome of acute illness episodes.[7 8] However, to optimize interventions that target functioning it is important to understand the demographic and clinical factors that contribute to level of functioning at clinical presentation. For instance, as well as transdiagnostic symptom dimensions, it is likely that other factors such as neurocognitive functioning and alcohol or substance use will also affect overall functioning. Disentangling the contribution and magnitude of any effects of these

factors on functioning is important to determine which factors may be amenable to modification and allow clinicians to design a multidimensional intervention package.

The proposal that social and occupational functioning should be a primary target for mental health interventions is not new and is increasingly promoted for older adults with established illness. For example, senior policy experts in the U.S. have stipulated that recovery-oriented treatments should form the overarching goal of mental health care and the foundation of strategic health policy.[9] The recognition that more personalized interventions are urgently needed to enhance functioning and quality of life rather than simply targeting diagnosis-specific symptoms is also emphasized by the World Health Organization.[10] Given this interest in enhancement of functioning across all stages of mental illness and for youth and adults presenting to mental health services, it is useful to examine the role of demographic and clinical factors in determining functioning.

Most path modelling studies to date have used small, and single- or dual-diagnosis cohorts, predominantly in individuals with a chronic mental illness. Findings consistently demonstrate that neurocognition and negative symptoms are robust predictors of functional outcome in schizophrenia and bipolar disorder.[7 11 12] By contrast, the impact of affective and positive symptoms on functioning remains more equivocal. Overall, these findings have been replicated in large schizophrenia cohort studies more recently,[13 14] although the vast majority of existing studies have focused solely on schizophrenia. There have been no well-powered studies examining a mental disorder other than schizophrenia, such as affective disorders, despite depression being the leading cause of disability worldwide.[15] Studies have also largely sidestepped the issue of psychotropic medication use. Furthermore, given that more than 75% of mental illnesses emerge before the age of 25,[3] examining younger cohorts is critically important for the development of novel approaches to early intervention since most studies to date have targeted older individuals.[15]

In order to build upon prior research, a transdiagnostic and dimensional approach is ideally positioned to disentangle the factors that are associated with functioning. Key to this research strategy is the examination of shared constructs (e.g., neurocognition) with clear links to pathophysiology,[16-18] which can inform novel therapeutics that target specific neural circuitries.[17 19] Transdiagnostic studies are also able to harness the variance across disorders, with the goal of developing robust, unifying models that are *explanatory* in nature.[2] Data showing that physiological and genetic risk factors for mental illness extend across, rather than are bound by, traditional diagnoses,[20] further supports this paradigm, as does the frequent prescription of psychotropic medications for off-label use across diagnostic boundaries.[21] Transdiagnostic studies are also superior to single-diagnosis case-control studies in that they can determine which relationships are *shared* across various diagnoses and which are *unique* to a particular disorder.

In this study, we sought to determine whether: (i) neurocognition; (ii) core clinical dimensions; and (iii) alcohol and substance use, are associated with social and occupational functioning and the magnitude of these associations. In keeping with prior research,[7 12 22] it was hypothesized that neurocognition and negative symptoms would make the greatest contribution to level of social and occupational functioning irrespective of the cross-sectional diagnosis applied to cases at the time of inclusion in the cohort.

METHODS

This study was approved by the University of Sydney Human Research Ethics Committee. Data included in the current study represent the baseline assessments conducted at entry to the cohort study, and were collected between April 2008 and May 2016.

Participants

Participants were recruited into the Brain and Mind Youth Cohort from youth mental health outpatient services at the Brain and Mind Centre.[23 24] Referred participants were 12–36 years of age and presented with a major affective, psychotic or developmental/behavioral syndrome. Participants were excluded if they (or their guardians, if aged under 16 years) were unwilling or unable to provide written informed consent, or if they had a pre-existing neurological condition, clinically assessed impaired English language skills and/or intellectual disability that precluded completion of study self-ratings. Eligible participants completed a series of observer and self-rated questionnaires.

Procedure

Treating clinicians recorded clinical diagnoses and these were reviewed at consensus meetings by senior, treating psychiatrists (e.g., IBH, EMS) and formal diagnoses recorded based on the DSM-IV-TR (Table 1 provides details of diagnoses and sample characteristics). All participants received their prescribed course of medications and interventions, as independently determined in consultation with their treating clinicians.

Treating clinicians (i.e., psychiatrists, clinical psychologists, mental health nurses) provided an evaluation of each participant's social and occupational functioning. Next, clinical psychologists, clinical neuropsychologists, or trained research psychologists (supervised by RSCL to ensure a sufficient level of inter-rater reliability), conducted structured clinical interviews, neuropsychological testing, as well as an additional assessment of social and occupational functioning to improve the reliability of this single, clinician-rated score (approximately 80% were conducted within a month of the treating clinician assessment).

Measures

- *Social and occupational functioning* was indexed using the Social and Occupational Assessment Functioning Scale (SOFAS[25]). Scores were averaged across the treating clinician and researcher assessments (ICC = 0.70), as previously done.[26] This composite score was derived to obtain a more reliable estimate of real-world functioning and, secondarily, to conserve free parameters and increase stability of parameter estimates.[22 27]

- *Neurocognition* was assessed using a broad neuropsychological battery with demographic normative-adjustments (previously described[22]), and was chosen on the basis of sound psychometric properties[28] and relevance to the disorders under study.[29] Predicted IQ was estimated using the Wechsler Test of Adult Reading (WTAR) or Wide Range Achievement Test—fourth edition (WRAT-4, for participants younger than 16 years). Psychomotor speed and mental flexibility were measured using Trail Making Test—Part A (TMT-A) and -Part B (TMT-B). Verbal learning and memory were indexed using the five-trial total and delayed recall scores from the Rey Auditory Verbal Learning Test (RAVLT). Verbal fluency was comprised of the letter (FAS) and category (animals) fluency subtests of the Controlled Oral Word Association Test.

- *Core clinical symptom dimensions* were measured across two validated scales. Symptoms were rated on the expanded Brief Psychiatric Rating Scale (BPRS) using empirically-derived symptom sub-scores (depression and anxiety, mania, positive symptoms, negative symptoms, and disorientation[30]). The BPRS does not capture sleep profiles as a separate dimension so, as in previous studies,[31] disturbed sleep was indexed using the sum of the three sleep items from the Hamilton Depression Rating Scale (HDRS[32]).

- *Alcohol and substance use* were measured across two validated scales. Alcohol use was indexed using the Alcohol Use Disorders Identification Test (AUDIT[33]) total score. Substance use for tobacco, cannabis, and other illicit substances was measured using the 'current frequency' sub-scale (past 3 months) from the World Health Organization – Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) questionnaire.[34]

Data Analysis

Statistical analyses were conducted using IBM SPSS 20.0 and AMOS 20.0. Maximum likelihood estimation (MLE) was employed for all structural equation modelling (SEM) analyses. MLE was chosen as it is the most robust approach in the potential event of statistical assumption violations and performs best in heterogeneous samples [35]. Missing data was also handled by MLE, which does not involve data imputation, but uses all available data to compute maximum likelihood estimates. Diagnostic and demographic data were available for all participants. Each analysis (univariate and multivariate) had at least 80% of cases with complete data.

We first used SEM to evaluate the best-fitting *measurement model* for the following predictors: 1/ neurocognition; 2/ clinical symptoms and disturbed sleep; and 3/ alcohol and substance use. Then, we used SEM to test the *structural model* (i.e., the relationship between predictors and social and occupational functioning) at both the single-predictor and the overall levels in order to explore potential predictors and delineate unique contributions. All analyses used a model-trimming approach through an iterative process in which non-significant paths with the smallest contribution were sequentially eliminated from a saturated model (where all variables were allowed to freely co-vary), until a best fitting model was derived to best

explain the relationships between predictors and functional impairment. Finally, modification indices generated by AMOS were used to optimise model fit (i.e., to inform which paths and parameters should be added or removed to increase model adequacy), although these were only used when deemed theoretically meaningful. Residuals were allowed to correlate if theoretically justified (e.g., common measurement variance between neuropsychological subtests).

Model fit was determined using: (1) the absolute fit $\chi 2$ statistic; and (2) the relative fit indices: Bentler comparative fit index (CFI[36]), Bentler-Bonnett non-normed fit index (NFI[37]) and Root Mean Square Error of Approximation (RMSEA[38]) with 90% confidence interval. An excellent-fitting model is typically indicated by a non-significant $\chi 2$ test (indicating a non-significant difference between the covariance matrix of the data and the model), a CFI and NFI of greater than .90 (indicating that the current model was superior to a null model where all paths are constrained to zero), and a RMSEA of less than .05 with an upper confidence interval bound of less than .08 (indicating that the error of approximation of the model compared with the data was acceptable). In small samples (ie, less than 200), the $\chi 2$ statistic has been shown to be an adequate index of absolute model fit.[35] However, as sample size increases, the $\chi 2$ statistic (relative to a constant degrees of freedom; df) disproportionately increases, and is nearly always significant and inappropriately rejects the model irrespective of specified parameters.[39 40] An alternative solution is to compute a relative, $\chi 2$/df ratio, with a value between 2 and 5 considered excellent to adequate fit,[39 41-43] although primary emphasis will be placed on the relative fit indices as is the established convention.[13]

Moderator analyses were conducted using the multiple-group analysis procedure in AMOS, which compares the parameter estimates between specified sub-groups to determine how predictors of social and occupational functioning in the final model are moderated by demographic and clinical factors (these were dichotomous to maintain statistical power within

sub-groups for this categorical procedure). We sought to specifically test whether predictors in affective-spectrum disorders (anxiety, depressive and bipolar disorders) were similarly associated with functional impairment compared with psychotic, developmental or behavioral conditions. We chose to include primary affective disorders (i.e. major depression, bipolar disorder or an anxiety disorder) as a moderator since these disorders have been shown to have carry less neurocognitive burden in recent-onset mood disorders[44 45] and, as such, could potentially influence the role of neurocognition and the magnitude of effects in the statistical models.

RESULTS

Sample Characteristics

In total, 1003 patients were recruited. As shown in Table 1, cross-sectional diagnoses comprised of depressive (n = 449), bipolar (n = 178), psychotics (n = 193), anxiety (n = 109), and developmental or behavioral disorders (n = 74). The mean age was 20.4 years (SD = 4.7), with 54.0% being female (n = 542). Mean educational attainment was 11.7 years (SD = 2.5), with an average predicted IQ of 101.9 (SD = 10.8). The mean SOFAS score was 61.2 (SD = 11.4), indicating moderate levels of impairment. Of the participants with medication data available (87.4%, n = 877), 64.8% were prescribed psychotropic medications (n = 568). Of these 568 cases, 40.6% were prescribed an antidepressant (n = 356), 14.8% were prescribed lithium or an anticonvulsant (n = 130), 33.1% were prescribed any antipsychotic (n = 290), and 4.8% were prescribed a stimulant (n = 42).

[Insert Table 1 about here]

Single-Predictor Models

A. *Neurocognition.* The best fitting factor structure for the neuropsychological measures was a one-factor model with all tests loading on a single latent variable. Factor loadings were all significant and ranged from 0.51 to 0.69 (see Figure 1A and legend). Neurocognition was a significant contributor to functional level ($\beta = 0.39$, $p < 0.001$), explaining 15% of the variance. This model was a good fit for the data ($\chi2 = 57.3$, df = 17, $p < 0.001$, CFI = 0.980, NFI = 0.972, RMSEA = 0.055, 90% CI = 0.040–0.071).

B. *Core clinical symptom dimensions.* Only three dimensions [depression and anxiety ($\beta = -0.18$, $p < 0.001$), positive symptoms ($\beta = -0.17$, $p < 0.001$), and negative symptoms ($\beta = -0.26$, $p < 0.001$)] were associated with functioning. The model demonstrated an excellent fit ($\chi2 = 8.6$, df = 8, $p < 0.379$, CFI = 0.999, NFI = 0.986, RMSEA = 0.009, 90% CI = 0.000–0.043), with the three dimensions explaining a total of 18% of the variance in functioning (see Figure 1B).

C. *Alcohol and substance use.* A two-factor model emerged as the best fitting measurement model for alcohol and substance use, whereby tobacco, cannabis and other illicit substance use loaded on a single 'substance use' latent variable (Figure 1C and legend), as distinct from alcohol use. Only substance use was predictive of functioning ($\beta = -0.10$, $p < 0.05$), explaining 1% of the variance. The model was an excellent fit for the data ($\chi2 = 7.4$, df = 4, $p < 0.116$, CFI = 0.995, NFI = 0.990, RMSEA = 0.033, 90% CI = 0.000–0.069).

[Insert Figure 1 about here]

Final Model

In the overall model, all the factors identified in the single predictor models remained significant, except for substance use (Figure 2). Neurocognition showed the strongest unique contribution to social and occupational functioning ($\beta = 0.36$, $p < 0.001$); depressive

symptoms were next (β = -0.24, p < 0.001), followed by negative symptoms (β = -0.15, p < 0.001) and finally positive symptoms (β = -0.10, p < 0.001). Together, these four clinical features independently accounted for 31% of the variance in functioning, with the final model being a very good fit for the data ($\chi 2$ = 279.8, df = 119, p < 0.000, CFI = 0.956, NFI = 0.926, RMSEA = 0.037, 90% CI = 0.031–0.042). Mania, disorientation, and alcohol and substance use, all significantly correlated with these four significant features (p's < 0.05).

[Insert Figure 2 about here]

Moderator Analyses

- *Age.* As shown in Table 2, positive symptoms were no longer a significant contributor to functioning in the 12- to 20-year-old group (β = -0.06, p = 0.178). The model with older individuals explained 18% more variance in functional impairment than the model with younger individuals. This was driven in large part by a difference in predictive strength of neurocognition, whereby it was more predictive in older (β = 0.44, p < 0.001) than younger individuals (β = 0.27, p < 0.001).

- *Gender.* Positive symptoms were non-significant in the male sub-group (β = -0.07, p = 0.145), whereas all other clinical features remained significant (p's < 0.001). In females, negative symptoms became non-significant (β = -0.07, p = 0.105), whilst the other contributors remained significant. The final model was comparable across genders in terms of the total variance explained.

[Insert Table 2 about here]

- *Primary affective disorder diagnosis.* Neurocognition, depression and anxiety, and negative symptoms remained significant contributors to functional level irrespective of affective disorder diagnosis (see Table 3). By contrast, positive symptoms no longer remained significant in both the affective disorder (β = -0.63, p = 0.097) and psychosis,

developmental or behavioral disorders (β = -0.102, p = 0.123) sub-groups. An additional 14% of the variance in functioning was explained in individuals with a psychotic, developmental or behavioral disorder, primarily owing to the greater predictive strength of neurocognition (0.30 vs. 0.43, p's < 0.001).

- *Medication usage.* All factors associated with functional impairment remained significant in participants who were unmedicated. By contrast, positive symptoms no longer remained significant in medicated individuals (β = -0.06, p = 0.117).

[Insert Table 3 about here]

DISCUSSION

In a large, clinical, transdiagnostic cohort of youth with early-stage mental disorders, impaired neurocognition was the clinical feature most significantly associated with functional impairment. The role of neurocognition was attenuated in those with an affective disorder diagnosis and in the youngest age group. The findings are relevant as they demonstrate that whilst neurocognitive impairment may undermine functioning in those with psychotic disorders, they are not specific to such cases.

Depressive, anxiety and negative symptom dimensions also contributed significantly to level of social and occupational functioning; findings which support previous disorder-specific research.[11 13 27] Importantly, the contributions of these factors to level of functioning were largely independent of one another, and do not appear to be moderated by other clinical or demographic factors. By comparison, the role of positive symptoms diminished considerably in the final model; this finding differs from other research in psychotic and bipolar disorders, and may reflect the lower prevalence of positive symptoms in our cohort in

contrast to previous studies.[11 13 27] However, it was notable that positive symptoms in older, unmedicated females remained significantly associated with functioning.

Intriguingly, neither alcohol and substance use, nor sleep disturbances, were directly associated with functional impairment, although these factors remained significantly associated with neurocognition and clinical symptoms. Therefore, their role in social and occupational functioning does not appear to be direct, but may operate indirectly (e.g. substance use may impair cognition, which in turn may impair functioning). The indirect effects of alcohol and substance use, as well as sleep and circadian disruptions, warrant more detailed examination and causal analysis in longitudinal datasets.

The current findings have important implications for the transdiagnostic, dimensional approach to psychiatry. Research examining the underlying mechanisms of functional impairment in single- or dual-diagnosis cohorts have been unable to capture the unique contributions of a comprehensive range of neurocognitive, symptom, sleep and circadian factors, as well as other psychoactive exposures (ie, substance use, prescribed medications).[46] In particular, neuropsychological studies in older adults with chronic schizophrenia have not routinely and concurrently assessed depression and anxiety symptoms, hypomania and full-threshold mania, substance misuse, and sleep disturbance. That is not to say that categorical, nosological approaches have had little to contribute to the field. Indeed, the key argument underpinning a DSM-approach is to allow for comparability across studies and so diagnostic determinations are often necessary. However, in youth diagnoses tend to be unstable[1] and, as such, as not as useful. One plausible way forward for dimensional psychiatry is to ensure that the samples used in transdiagnostic studies are characterised as clearly and as comprehensively as possible,[16 47 48] as was attempted in the present investigation.

In terms of limitations, the current analyses were cross-sectional, and future research investigating moderator and mediator analyses would benefit from cross-lagged, longitudinal

path modelling to disentangle causality.[49] Secondly, the measures used to index alcohol and substance use, as well as sleep and circadian disturbances, were not as comprehensive as is typical in the addiction and sleep literatures. Future studies would benefit from including more detailed questionnaires, as well as real-time tracking technologies (e.g. substance use monitoring using smartphones, actigraphy monitoring of physical activity and sleep quality). Thirdly, medication data were not available for the full sample (12.6% were missing) and, as such, the moderating role of medication status requires further corroboration. Finally, a phenotype-approach, as attempted in the current study, would necessarily require converging genetic and neuroimaging evidence to ensure that the neurocognitive and symptom dimensions identified as predictive of functioning are linked to specific neural circuitries (eg, cortico-basal ganglia systems[50]) and genotype, which would ultimately facilitate the development of next-generation and neuroscience-informed pharmacotherapies.

This was the first study to examine a broad range of illness-related factors and associations with functional impairment in a well-powered and broadly transdiagnostic, clinical cohort of more than one thousand young people with mental illness. A significant contribution of the present findings to the established literature was evidence showing that neurocognition is a strong and reliable, unique predictor of social and occupational functioning irrespective of diagnosis – in a cohort predominantly comprised of affective disorders, which has not been previously demonstrated before at this scale. As such, the functional importance of neurocognitive functions clearly extends beyond the psychosis and developmental disorders spectrum and appears to become more pronounced with increasing age. Future studies should attempt to replicate these findings, as well as to clarify the directions of cause and effect.

Author statement

RSCL, DFH, SLN, AJG, NG, JS, EMS and IBH contributed to the conception of the study; RSCL, DFH, MK undertook the data collection, processing and analysis; RSCL wrote the first draft of the manuscript. All authors contributed to data interpretation, discussion and have approved the final manuscript.

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Competing interests

(1) No authors have support from any company for the submitted work; (2) no authors have relationships with any company that might have an interest in the submitted work; (3) no author, their spouses, partners, or children have financial relationships that may be relevant to the submitted work and; (4) no authors have any non-financial interests that may be relevant to the submitted work.

Ethical approval

This study was approved by the University of Sydney Human Research Ethics Committee (reference 12130; protocol no. 2012/1631).

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the breadth and sensitivity of data collected, which may have implications for individual privacy, but are available from the corresponding author on reasonable request.

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Table 1 Demographic, clinical and functional characteristics across diagnostic sub-groups

	ANXIETY[1] (n = 109)		DEPRESSION[2] (n = 449)		BIPOLAR[3] (n = 178)		PSYCHOSIS[4] (n = 193)		DEV/BEHAV[5] (n = 74)	
	M	SD	M	SD	M	SD	M	SD	M	SD
Age	19.9	4.8	19.8	4.3	21.6	4.8	22.2	4.6	17.0	4.6
Education (years)	11.5	2.7	11.6	2.4	12.3	2.2	12.0	2.4	10.0	2.8
Premorbid IQ	102.7	9.6	103.3	10.5	102.8	9.1	100.0	10.5	95.3	14.8
BPRS Depression (/7)	2.3	0.9	2.4	0.8	2.2	0.8	2.1	0.9	1.7	0.7
BPRS Mania (/7)	1.4	0.4	1.3	0.5	1.5	0.6	1.4	0.4	1.5	0.7
BPRS Positive (/7)	1.4	0.5	1.3	0.4	1.4	0.5	1.8	0.7	1.3	0.4
BPRS Negative (/7)	1.5	0.7	1.5	0.6	1.3	0.5	1.9	0.8	1.5	0.6
BRPS Disorientation (/7)	1.2	0.5	1.2	0.5	1.1	0.5	1.2	0.6	1.2	0.5
HDRS Sleep (/6)	1.5	1.5	2.0	1.8	1.7	1.7	1.3	1.6	1.8	1.7
AUDIT Alcohol Use (/40)	4.4	6.4	6.8	7.4	9.0	8.4	6.2	8.0	5.1	7.5
WHO-ASSIST Tobacco Use (/4)	1.0	1.5	1.3	1.6	1.6	1.7	1.7	1.9	1.4	1.7
WHO-ASSIST Cannabis Use (/4)	0.4	0.9	0.7	1.2	0.7	1.3	0.4	1.0	0.7	1.3
WHO-ASSIST Other Illicit Substance Use (/4)	0.1	0.3	0.1	0.3	0.1	0.3	0.1	0.2	0.1	0.3
SOFAS	63.2	11.1	61.8	10.7	63.9	11.5	55.9	12.1	61.7	9.8
	N	%	N	%	N	%	N	%	N	%
Gender (female)	58	53.2	277	61.7	129	72.5	58	30.1	20	27.0
Medicated†	37	45.7	231	60.0	128	77.6	140	77.3	32	49.2
Antidepressants	25	30.9	201	52.2	63	38.2	55	30.4	12	18.5
Lithium/Anticonvulsants	6	7.4	28	7.3	69	41.8	24	13.3	3	4.6
Antipsychotics	9	11.1	71	18.4	77	46.7	125	69.1	8	12.3
Stimulants	4	4.9	14	3.6	7	4.2	3	1.7	14	21.5

AUDIT–Alcohol Use Disorders Identification Test; BPRS–Brief Psychiatric Rating Scale; DEV/BEHAV– Developmental/Behavioral; HDRS–Hamilton Depression Rating Scale; SOFAS–Social and Occupational Functioning Assessment Scale; WHO-ASSIST–World Health Organization – Alcohol, Smoking and Substance Involvement Screening Test

[1] Panic Disorder (n=4), Social Phobia (n=29), Obsessive-Compulsive Disorder (n=11), Posttraumatic Stress Disorder (n=5), Generalised Anxiety Disorder (n=60)

[2] Major Depressive Disorder (n=313), Dysthymic Disorder (n=4), Depressive Disorder Not Otherwise Specified (n=132)

[3] Bipolar I Disorder (n=13), Bipolar II Disorder (n=25), Cyclothymic Disorder (n=1), Bipolar Disorder Not Otherwise Specified (n=139)

[4] Schizophrenia (n=53), Schizophreniform Disorder (n=15), Schizoaffective Disorder (n=26), Brief Psychotic Disorder (n=11), Substance-Induced Psychotic Disorder (n=14), Psychotic Disorder Not Otherwise Specified (n=74)

[5] Asperger's Disorder (n=16), Attention-Deficit/Hyperactivity Disorder (n=47), Conduct Disorder (n=7), Oppositional Defiant Disorder (n=4)

† Medication data was available in 877 individuals (87.4%), with missing data for the typologies of Depression (n=64), Bipolar (n=13), Psychosis (n=12), Anxiety (n=28), Developmental (n=9)

Table 2 Analyses of age and gender as moderators of the relationships between neurocognition, core clinical symptoms and functioning

	Age[†]				Gender[‡]			
	12-20 Years *(n = 539)*		21-36 Years *(n = 464)*		Male *(n = 461)*		Female *(n = 542)*	
	β	*p-value*	β	*p-value*	β	*p-value*	β	*p-value*
Neurocognition	**.27**	*.000*	**.44**	*.000*	**.35**	*.000*	**.35**	*.000*
Depression and Anxiety	**-.28**	*.000*	**-.22**	*.000*	**-.23**	*.000*	**-.30**	*.000*
Positive Symptoms	**-.06**	*.178*	**-.14**	*.002*	**-.07**	*.145*	**-.12**	*.004*
Negative Symptoms	**-.13**	*.005*	**-.18**	*.000*	**-.19**	*.000*	**-.07**	*.105*

[†] 12-20 Years (Subgroup Model, R^2=.24); 21-36 Years (Subgroup Model, R^2=.40)

[‡] Male (Subgroup Model, R^2=.32); Female (Subgroup Model, R^2=.29)

Table 3 Analyses of primary affective disorder and medication usage as moderators of the relationship between neurocognition, core clinical symptoms and functioning

	Primary Affective Disorder†				Medication Usage‡			
	Yes *(n = 736)*		No *(n = 267)*		Nil *(n = 309)*		Medicated *(n = 568)*	
	β	*p-value*	β	*p-value*	β	*p-value*	β	*p-value*
Neurocognition	**.30**	*.000*	**.43**	*.000*	**.38**	*.000*	**.38**	*.000*
Depression and Anxiety	**-.29**	*.000*	**-.24**	*.000*	**-.15**	*.007*	**-.24**	*.000*
Positive Symptoms	**-.06**	*.097*	**-.10**	*.123*	**-.22**	*.000*	**-.06**	*.117*
Negative Symptoms	**-.12**	*.003*	**-.16**	*.009*	**-.19**	*.000*	**-.13**	*.002*

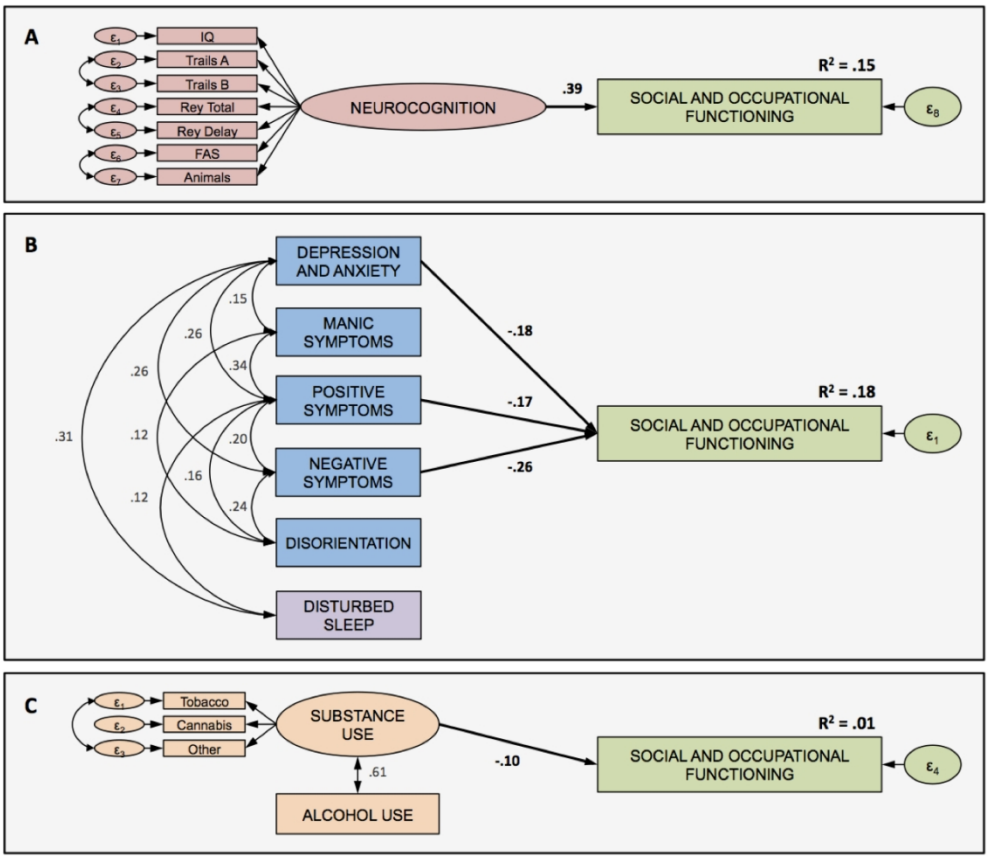
† Yes (Subgroup Model, R^2=.24); No (Subgroup Model, R^2=.38)
‡ Nil (Subgroup Model, R^2=.38); Medicated (Subgroup Model, R^2=.29)

Figure 1 Combined measurement and structural models for functioning and (**A**) neurocognition, (**B**) core clinical symptoms, and (**C**) alcohol and substance use.

Legend:
All unidirectional (correlation) and directional (regression) paths are significant at $p < .001$ (except path between substance use and functional outcome; where $p < .05$)
Factor Loadings for (A) Neurocognition (all p's < .001): IQ (.58), Trails A (-.51), Trails B (-.55), Rey Total (.69), Rey Delay (.59), FAS (.57), Animals (.51)
Factor Loadings for (C) Substance Use (all p's < .001): Tobacco (.81), Cannabis (.64), Other (.68)

Figure 2 Final model.

Legend:
All unidirectional (correlation) and directional (regression) paths are significant at $p < .001$ (except correlation between substance use and positive symptoms, where $p < .05$). Where no path is drawn it denotes no significant relationship between the variables (see Figure 1 for all factor loadings of latent variables).



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Factor Loadings for (C) Substance Use (all p's < .001): Tobacco (.81), Cannabis (.64), Other (.68)

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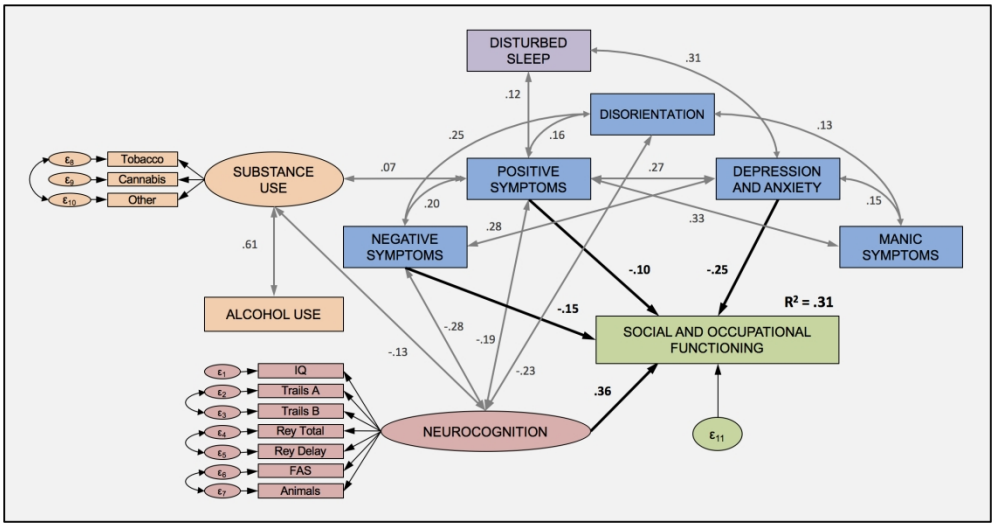

Figure 2 Final model.

Legend:
All unidirectional (correlation) and directional (regression) paths are significant at p < .001 (except correlation between substance use and positive symptoms, where p < .05). Where no path is drawn it denotes no significant relationship between the variables (see Figure 1 for all factor loadings of latent variables).

393x208mm (144 x 144 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

RE: "***A cross-sectional study of clinical, neurocognitive, and demographic factors associated with functional impairment in the Brain and Mind Youth Cohort***"

	Item No	Recommendation	Authors Response
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Pg. 1	Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Pg. 2	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Pg. 4-6	Yes
Objectives	3	State specific objectives, including any prespecified hypotheses Pg. 6	Yes
Methods			
Study design	4	Present key elements of study design early in the paper Pg. 6-7	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Pg. 7	Yes
Participants	6	(*a*) ~~*Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up~~ ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants Pg. 7	Yes
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Pg. 7-11	Yes
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Pg. 8	Yes
Bias	9	Describe any efforts to address potential sources of bias Pg. 10-11	Yes
Study size	10	Explain how the study size was arrived at Pg. 10	Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Pg. 9-11	Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Pg. 9-11	Yes
		(*b*) Describe any methods used to examine subgroups and interactions Pg. 10-11	Yes
		(*c*) Explain how missing data were addressed Pg. 9	Yes
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed ~~*Case-control study*—If applicable, explain how matching of cases and controls~~	NA

~~was addressed~~

~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~

(*e*) Describe any sensitivity analyses NA

Continued on next page

Results			**Authors Response**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Pg. 11	Yes
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Pg. 11	Yes
		(b) Indicate number of participants with missing data for each variable of interest Pg. 9	Yes
		© *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	~~*Cohort study*—Report numbers of outcome events or summary measures over time~~	Yes
		~~*Case-control study*—Report numbers in each exposure category, or summary measures of exposure~~	
		Cross-sectional study—Report numbers of outcome events or summary measures Pg. 11	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Pg. 12-13	Yes
		(*b*) Report category boundaries when continuous variables were categorized Pg. 10-11	Yes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Pg. 11-14	Yes
Discussion			
Key results	18	Summarise key results with reference to study objectives Pg. 14-15	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Pg. 15-16	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Pg. 14-16	Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results Pg. 16	Yes
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Pg. 17	Yes

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

A cross-sectional study of clinical, neurocognitive, and demographic factors associated with functional impairment in the Brain and Mind Youth Cohort

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	neurocognition, transdiagnostic, functional impairment, mental illness, symptom dimensions, alcohol use

A CROSS-SECTIONAL STUDY OF CLINICAL, NEUROCOGNITIVE, AND DEMOGRAPHIC FACTORS ASSOCIATED WITH FUNCTIONAL IMPAIRMENT IN THE BRAIN AND MIND YOUTH COHORT

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ABSTRACT

Objectives: We sought to determine the unique and shared contributions of clinical, neurocognitive and demographic factors to functional impairment in a large, transdiagnostic, clinical cohort of adolescents and young adults.

Design: Cross-sectional baseline data from a prospective, cohort study.

Setting: Help-seeking youth referred from outpatient services were recruited to the *Brain and Mind Youth Cohort* (2008-2016) in Sydney, Australia.

Participants: In total, 1003 outpatients were recruited, aged between 12 and 36 years (M = 20.4 years, 54% female), with baseline diagnoses of affective, psychotic, developmental or behavioural disorders.

Interventions: Treatment as usual.

Primary outcome measures: Social and occupational functioning was used to index level of functional impairment. Structural equation modelling was used to examine associations between neurocognition, core clinical symptoms, and alcohol and substance use, and clinician- and researcher-rated functional impairment. Moderator analyses were conducted to determine the potential influence of demographic and clinical factors (e.g. medication exposure).

Results: Independent of diagnosis, we found that neurocognitive impairments, and depressive, anxiety and negative symptoms, were significantly associated with functioning. The association of neurocognition with social and occupational functioning remained significant even when constraining age (only 15- to 25-year olds) or diagnosis (affective disorder) in the final model.

Conclusions: This study demonstrates that, in a clinically representative sample of youth, the key determinants of functioning may not be disorder specific. Further, evidence of neurocognitive

dysfunction suggests that interventions that target cognition and functioning should not necessarily be reserved only for older adults with established illness.

Keywords: Neurocognition; transdiagnostic; functional impairment; mental illness; symptom dimensions; alcohol use.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This was one of the largest studies to date (N > 1,000) to examine the associations between a broad range of illness characteristics and functional impairment in a mostly adolescent and young adult, clinical sample.
- Given the transdiagnostic approach, this study was equipped to disentangle the shared and unique associations between core illness phenotypes and functional impairment across a range of common mental disorders.
- The use of latent-variable, structural equation modelling controlled for aspects of measurement imprecision.

INTRODUCTION

In recent decades, early intervention services for youth with emerging mental disorders have extended their targets beyond those at risk of psychosis to also encompass those presenting with mood as well as other developmental and anxiety disorders. This approach creates several significant challenges. For example, some youth with depressive and anxiety disorders will ultimately develop psychotic or bipolar disorders; likewise, only a proportion of those receiving a diagnosis of bipolar disorders will consistently receive this diagnosis over the following 10 years.[1] The lack of diagnostic stability in help-seeking youth reflects the evolving disease process and means that the illness trajectory is less certain than for older adults with established illness.[2 3] From a research perspective, the use of dimensional approaches to phenomenology has helped us to understand illness progression in these early clinical stages, whilst from a clinical perspective, care and treatment have increasingly considered transdiagnostic interventions addressing core factors that may influence prognosis irrespective of cross-sectional diagnosis (e.g., anxiety, depressive or negative symptoms; sleep disturbances).[4 5] These approaches have highlighted that, in youth, a more meaningful measure of outcome may be functioning rather than change in diagnosis-specific symptoms. There is evidence to support this approach as level of functioning or disengagement (e.g., not being in education, employment or training, referred to as being NEET) is associated with early transition to major mental disorder[6] and with poor outcome of acute illness episodes.[7 8] However, to optimize interventions that target functioning it is important to understand the factors that contribute to level of functioning at clinical presentation. For instance, as well as transdiagnostic symptom dimensions, it is likely that other factors such as neurocognitive functioning and alcohol or substance use will also affect overall functioning. Disentangling the contribution and magnitude of any effects of these factors on functioning is important to determine which factors may be amenable to modification and allow clinicians to design a multidimensional intervention package.

The proposal that social and occupational functioning should be a primary target for mental health interventions is not new and is increasingly promoted for older adults with established illness. For example, senior policy experts in the U.S. have stipulated that recovery-oriented treatments should form the overarching goal of mental health care and the foundation of strategic health policy.[9] The recognition that more personalized interventions are urgently needed to enhance functioning and quality of life rather than simply targeting diagnosis-specific symptoms is also emphasized by the World Health Organization.[10] Given this interest in enhancement of functioning across all stages of mental illness and for youth and adults presenting to mental health services, it is also useful to examine the role of other, key clinical (e.g., medication exposure) and demographic factors (e.g., age, gender) in determining functioning, which would contribute to prognosis and attempts at personalised medicine.

Most path modelling studies to date have used small, single- or dual-diagnosis cohorts, predominantly in individuals with a chronic mental illness. Findings consistently demonstrate that neurocognition and negative symptoms are robust predictors of functional outcome in schizophrenia and bipolar disorder.[7 11 12] By contrast, the impact of affective and positive symptoms on functioning remains more equivocal. More recently, these findings have been replicated in large cohort studies,[13 14] although the vast majority of existing studies have focused exclusively on schizophrenia. There have been no well-powered studies examining a mental disorder other than schizophrenia, such as affective disorders, despite depression being the leading cause of disability worldwide.[15] Studies have also largely sidestepped the issue of psychotropic medication use. Furthermore, given that more than 75% of mental illnesses emerge before the age of 25,[3] examining younger cohorts is critically important for the development of novel approaches to early intervention since most studies to date have targeted older individuals.[15]

In order to build upon prior research, a transdiagnostic and dimensional approach is ideally positioned to disentangle the factors associated with functioning. Key to this research strategy is the examination of shared constructs (e.g., neurocognition) with clear links to pathophysiology,[16-18]

which can inform novel therapeutics that target specific neural circuitries.[17 19] Transdiagnostic studies are also able to harness the variance across disorders, with the goal of developing robust, unifying models that are *explanatory* in nature.[2] Data showing that physiological and genetic risk factors for mental illness extend across, rather than are bound by, traditional diagnoses,[20] further supports this paradigm, as does the frequent prescription of psychotropic medications for off-label use across diagnostic boundaries.[21] Transdiagnostic studies are also superior to single-diagnosis case-control studies in that they can determine which relationships are *shared* across various diagnoses and which are *unique* to a particular disorder.

In this study, we sought to determine whether: (i) neurocognition; (ii) core clinical dimensions; and (iii) alcohol and substance use, are associated with social and occupational functioning and the magnitude of these associations. The rationale for examining clinical symptoms and functioning alongside neurocognition, sleep changes, and substance use, is underscored by a recent systematic review highlighting the transdiagnostic relevance of these key domains in youth with mental illness.[22] In keeping with prior research,[7 12 23] it was hypothesized that neurocognition and negative symptoms would make the greatest contribution to level of social and occupational functioning irrespective of the cross-sectional diagnosis applied to cases at the time of inclusion in the cohort. Given the high degree of heterogeneity expected in a transdiagnostic youth sample, we secondarily sought to determine the influence of demographic (e.g., age, gender) and clinical factors (e.g., diagnosis, medication exposure) on findings.

METHODS

This study was approved by the University of Sydney Human Research Ethics Committee. Data included in the current study represent the baseline assessments conducted at entry to the cohort study, and were collected between April 2008 and May 2016.

Participants

Participants were recruited into the Brain and Mind Youth Cohort from youth mental health outpatient services at the Brain and Mind Centre.[24 25] Referred participants were 12–36 years of age and presented with a major affective, psychotic or developmental/behavioral syndrome. Participants were excluded if they (or their guardians, if aged under 16 years) were unwilling or unable to provide written informed consent, or if they had a pre-existing neurological condition, clinically assessed impaired English language skills and/or intellectual disability that precluded completion of study self-ratings. Eligible participants completed a series of observer and self-rated questionnaires.

Procedure

Treating clinicians recorded clinical diagnoses and these were reviewed at consensus meetings by senior, treating psychiatrists (e.g., IBH, EMS) and formal diagnoses recorded based on the DSM-IV-TR (Table 1 provides details of diagnoses and sample characteristics). Any disagreements in diagnosis were resolved at these consensus meetings with the relevant treating team. All participants received their prescribed course of medications and interventions, as independently determined in consultation with their treating clinicians.

Board-certified treating clinicians (i.e., consultant psychiatrists, clinical psychologists, mental health nurses) provided an evaluation of each participant's social and occupational functioning. Next, board-certified clinical psychologists, clinical neuropsychologists, or trained research psychologists (i.e., graduate-level academic psychologists; supervised by RSCL to ensure a sufficient level of inter-rater reliability), conducted structured clinical interviews, neuropsychological testing, as well as an additional assessment of social and occupational functioning to improve the reliability of this single, clinician-rated score (approximately 80% were conducted within a month of the treating clinician assessment).

Measures

- *Social and occupational functioning* was indexed using the Social and Occupational Assessment Functioning Scale (SOFAS[26]). Scores were averaged across the treating clinician and researcher assessments (ICC = 0.70), as previously done.[27] This composite score was derived to obtain a more reliable estimate of real-world functioning and, secondarily, to conserve free parameters and increase stability of parameter estimates.[23 28] A higher score denotes better functioning.

- *Neurocognition* was assessed using a broad neuropsychological battery with demographic normative-adjustments (previously described[23]), and was chosen on the basis of sound psychometric properties[29] and relevance to the disorders under study.[30] Predicted IQ was estimated using the Wechsler Test of Adult Reading (WTAR) or Wide Range Achievement Test—fourth edition (WRAT-4, for participants younger than 16 years). Psychomotor speed and mental flexibility were measured using Trail Making Test—Part A (TMT-A) and -Part B (TMT-B). Verbal learning and memory were indexed using the five-trial total and delayed recall scores from the Rey Auditory Verbal Learning Test (RAVLT). Verbal fluency was comprised of the letter (FAS) and category (animals) fluency subtests of the Controlled Oral Word Association Test. A higher score indicates better functioning.

- *Core clinical symptom dimensions* were measured across two validated scales. Symptoms were rated on the expanded Brief Psychiatric Rating Scale (BPRS) using empirically-derived symptom sub-scores (depression and anxiety, mania, positive symptoms, negative symptoms, and disorientation[31]). The BPRS does not capture sleep profiles as a separate dimension so, as in previous studies,[32] disturbed sleep was indexed using the sum of the three sleep items from the Hamilton Depression Rating Scale (HDRS[33]). A higher score denotes greater severity of symptoms.

- *Alcohol and substance use* were measured across two validated scales. Alcohol use was indexed using the Alcohol Use Disorders Identification Test (AUDIT[34]) total score. Substance use for tobacco, cannabis, and other illicit substances was measured using the 'current frequency' sub-scale (past 3 months) from the World Health Organization – Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) questionnaire.[35] A higher score indicates greater alcohol or substance use.

Patient and public involvement

Participants were not involved in the development of research question(s), design and outcome measures, nor was the study informed by their priorities, experience, and preferences. We did not formally assess the burden of time required to participate in the research.

Data Analysis

Statistical analyses were conducted using IBM SPSS 20.0 and AMOS 20.0. Maximum likelihood estimation (MLE) was employed for all structural equation modelling (SEM) analyses. MLE was chosen as it is the most robust approach in the potential event of statistical assumption violations and performs best in heterogeneous samples [36]. Missing data was also handled by MLE, which does not involve data imputation, but uses all available data to compute maximum likelihood estimates. Diagnostic and demographic data were available for all participants. In total, 9.1% of data were missing for functioning, 18.8% for neurocognition, 12.7% for clinical symptoms and disturbed sleep, and 17.7% were missing for alcohol and substance use. Each analysis had >80% of cases with complete data. Normality was assessed through inspection of Q-Q plots, given inferential measures of non-normality (e.g., Shapiro-Wilk statistic) are overly sensitive in large datasets and almost always return a significant finding [37]. All endogenous variables (e.g., SOFAS) met normality assumptions on visual inspection.

We first used SEM to evaluate the best-fitting *measurement model* for the following predictors: 1/ neurocognition; 2/ clinical symptoms and disturbed sleep; and 3/ alcohol and substance use. Then, we used SEM to test the *structural model* (i.e., the relationship between predictors and social and occupational functioning) at both the single-predictor and the overall levels in order to explore potential predictors and delineate unique contributions. This was done in a two-step process – first, by testing individual predictors and then by testing the combined predictors - to quantify the amount of overlapping and unique explanatory power. All analyses used a model-trimming approach through an iterative process in which non-significant paths with the smallest contribution were sequentially eliminated from a saturated model (where all variables were allowed to freely co-vary), until a best fitting model was derived to best explain the relationships between predictors and functional impairment. Finally, modification indices generated by AMOS were used to optimise model fit (i.e., to inform which paths and parameters should be added or removed to increase model adequacy), although these were only used when deemed theoretically meaningful. Residuals were allowed to correlate if theoretically justified (e.g., common measurement variance between neuropsychological subtests).

Model fit was determined using: (1) the absolute fit $\chi 2$ statistic; and (2) the relative fit indices: Bentler comparative fit index (CFI[38]), Bentler-Bonnett non-normed fit index (NFI[39]) and Root Mean Square Error of Approximation (RMSEA[40]) with 90% confidence interval. An excellent-fitting model is typically indicated by a non-significant $\chi 2$ test (indicating a non-significant difference between the covariance matrix of the data and the model), a CFI and NFI of greater than .90 (indicating that the current model was superior to a null model where all paths are constrained to zero), and a RMSEA of less than .05 with an upper confidence interval bound of less than .08 (indicating that the error of approximation of the model compared with the data was acceptable). In small samples (i.e., less than 200), the $\chi 2$ statistic has been shown to be an adequate index of absolute model fit.[36] However, as sample size increases, the $\chi 2$ statistic (relative to a constant degrees of freedom; df) disproportionately increases, and is nearly always significant and

inappropriately rejects the model irrespective of specified parameters.[41 42] An alternative solution is to compute a relative, $\chi 2$/df ratio, with a value between 2 and 5 considered excellent to adequate fit,[41 43-45] although primary emphasis will be placed on the relative fit indices as is the established convention.[13]

Moderator analyses were conducted allowing a model to be tested in separate sub-groups, comparing the parameter estimates to determine how predictors of social and occupational functioning in the final model are moderated by demographic and clinical factors (these were dichotomous to maintain statistical power within sub-groups for this categorical procedure). For instance, the median-split on age was performed to determine whether the model held for both younger and older individuals whilst maintaining statistical power. We sought to specifically test whether predictors in affective-spectrum disorders (anxiety, depressive and bipolar disorders) were similarly associated with functional impairment compared with psychotic, developmental or behavioral conditions. We chose to include primary affective disorders (i.e. major depression, bipolar disorder or an anxiety disorder) as a moderator since these disorders have been shown to have carry less neurocognitive burden in recent-onset mood disorders[46 47] and, as such, could potentially influence the role of neurocognition and the magnitude of effects in the statistical models.

RESULTS

Sample Characteristics

In total, 1003 patients were recruited. As shown in Table 1 and 2, cross-sectional diagnoses comprised of depressive (n = 449), bipolar (n = 178), psychotic (n = 193), anxiety (n = 109), and developmental or behavioral disorders (n = 74). The mean age was 20.4 years (SD = 4.7), with 54.0% being female (n = 542). Mean educational attainment was 11.7 years (SD = 2.5), with an average predicted IQ of 101.9 (SD = 10.8). The mean SOFAS score was 61.2 (SD = 11.4),

indicating moderate levels of impairment. Of the participants with medication data available (87.4%, n = 877), 64.8% were prescribed psychotropic medications (n = 568). Of these 568 cases, 40.6% were prescribed an antidepressant (n = 356), 14.8% were prescribed lithium or an anticonvulsant (n = 130), 33.1% were prescribed any antipsychotic (n = 290), and 4.8% were prescribed a stimulant (n = 42).

[Insert Table 1 about here]

Single-Predictor Models

A. *Neurocognition.* Inspecting the scree plot, exploratory factor analyses identified two potential latent structures. The one-factor model was a very good fit for the data ($\chi 2 = 57.3$, df = 17, $p < 0.001$, CFI = 0.980, NFI = 0.972, RMSEA = 0.055, 90% CI = 0.040–0.071), and was a better fit than a two-factor model, whereby Trails A, Trails B and IQ loaded on one latent factor, and IQ, Rey Total, Rey Delay, FAS and Animals loaded on a second latent factor ($\chi 2 = 76.499$, df = 11, $p < 0.001$, CFI = 0.967, NFI = 0.962, RMSEA = 0.077, 90% CI = 0.061–0.094). Factor loadings on the one-factor model were all significant and ranged from 0.51 to 0.69 (see Figure 1A and legend). Neurocognition was a significant contributor to functional level ($\beta = 0.39$, $p < 0.001$), explaining 15% of the variance.

B. *Core clinical symptom dimensions.* Only three clinical dimensions [depression and anxiety ($\beta = -0.18$, $p < 0.001$), positive symptoms ($\beta = -0.17$, $p < 0.001$), and negative symptoms ($\beta = -0.26$, $p < 0.001$)] were associated with functioning, whereas mania and disorientation were not significantly associated (p's > 0.05). The model demonstrated excellent fit ($\chi 2 = 8.6$, df = 8, $p < 0.379$, CFI = 0.999, NFI = 0.986, RMSEA = 0.009, 90% CI = 0.000–0.043), with the three dimensions explaining a total of 18% of the variance in functioning (see Figure 1B).

C. *Alcohol and substance use.* Exploratory factor analyses determined that alcohol use did not load with the other substance use variables. Only a two-factor latent model was possible given

the number of observed variables and statistical constraints. The two-factor model emerged as an excellent fit for the data ($\chi 2 = 7.4$, df = 4, $p < 0.116$, CFI = 0.995, NFI = 0.990, RMSEA = 0.033, 90% CI = 0.000–0.069), whereby tobacco, cannabis and other illicit substance use loaded on a single 'substance use' latent variable as distinct from alcohol use (Figure 1C and legend). Only substance use was predictive of functioning ($\beta = -0.10$, $p < 0.05$), explaining 1% of the variance.

[Insert Figure 1 about here]

Final Model

In the overall model, all the factors identified in the single predictor models remained significant, except for substance use (Figure 2). Neurocognition showed the strongest unique contribution to social and occupational functioning ($\beta = 0.36$, $p < 0.001$); depressive symptoms were next ($\beta = -0.24$, $p < 0.001$), followed by negative symptoms ($\beta = -0.15$, $p < 0.001$) and finally positive symptoms ($\beta = -0.10$, $p < 0.001$). Together, these four clinical features independently accounted for 31% of the variance in functioning, with the final model being a very good fit for the data ($\chi 2 = 279.8$, df = 119, $p < 0.000$, CFI = 0.956, NFI = 0.926, RMSEA = 0.037, 90% CI = 0.031–0.042). Mania, disorientation, and alcohol and substance use, all significantly correlated with these four significant features (p's < 0.05).

[Insert Figure 2 about here]

Moderator Analyses

- *Age.* As shown in Table 3, positive symptoms were no longer a significant contributor to functioning in the 12- to 20-year-old group ($\beta = -0.06$, $p = 0.178$). The model with older individuals explained 18% more variance in functional impairment than the model with younger individuals. This was driven in large part by a difference in predictive strength of

neurocognition, whereby it was more predictive in older (β = 0.44, p < 0.001) than younger individuals (β = 0.27, p < 0.001).

- *Gender.* Positive symptoms were non-significant in the male sub-group (β = -0.07, p = 0.145), whereas all other clinical features remained significant (p's < 0.001). In females, negative symptoms became non-significant (β = -0.07, p = 0.105), whilst the other contributors remained significant. The final model was comparable across genders in terms of the total variance explained.

[Insert Table 2 about here]

- *Primary affective disorder diagnosis.* Neurocognition, depression and anxiety, and negative symptoms remained significant contributors to functional level irrespective of affective disorder diagnosis (see Table 4). By contrast, positive symptoms no longer remained significant in both the affective disorder (β = -0.63, p = 0.097) and psychosis, developmental or behavioral disorders (β = -0.102, p = 0.123) sub-groups. An additional 14% of the variance in functioning was explained in individuals with a psychotic, developmental or behavioral disorder, primarily owing to the greater predictive strength of neurocognition (0.30 vs. 0.43, p's < 0.001).

- *Medication usage.* All factors associated with functional impairment remained significant in participants who were unmedicated. By contrast, positive symptoms no longer remained significant in medicated individuals (β = -0.06, p = 0.117).

[Insert Table 3 about here]

Sensitivity Analysis

Restricting the full sample to individuals aged 15-25 years of age (N = 794) yielded a very good fitting model as well ($\chi 2$ = 240.1, df = 119, p < 0.000, CFI = 0.959, NFI = 0.924, RMSEA = 0.036, 90% CI = 0.029–0.042). The explained variance remained the same (31% explained). Importantly,

all predictors remained significant with the same effect sizes, with the exception of depression and anxiety, which became slightly more predictive (-0.25 → -0.26), and neurocognition, which became slightly less predictive (0.36 → 0.35).

DISCUSSION

In a large, clinical, transdiagnostic cohort of youth with mental disorders, impaired neurocognition was the clinical feature most significantly associated with functional impairment. The role of neurocognition was attenuated in those with an affective disorder diagnosis and in the younger age group. The findings are relevant as they demonstrate that whilst neurocognitive impairment may undermine functioning in those with psychotic disorders, or in chronic or recurrent mental disorders, they are not specific to such cases. That is, neurocognitive dysfunction has traditionally been argued as a core, underlying feature of social and occupational impairments in chronic schizophrenia. However, our current findings support the burgeoning position that the role of neurocognitive deficits cut across diagnosis and clinical stage. Nevertheless, it appears that neurocognitive disturbances are more pronounced in those with psychotic, developmental, or behavioural disorders, converging with evidence of more pronounced cognitive deficits in children who will go on to develop psychosis compared with those who develop depression or bipolar disorder [48-50]. Mechanistically, whether neurocognitive dysfunction drives functional impairment as a few past studies have found [7 28], and is a consequence of poor functioning remains to be clarified.

Depressive, anxiety and negative symptom dimensions also contributed significantly to level of social and occupational functioning, supporting previous disorder-specific research.[11 13 28] Importantly, the contributions of these factors to level of functioning were largely independent of one another, and do not appear to be moderated by other clinical or demographic factors. By comparison, the role of positive symptoms diminished considerably in the final model. This finding differs from other research in psychotic and bipolar disorders, and may reflect the lower prevalence of positive symptoms in our cohort in contrast to previous studies.[11 13 28] However, it was notable that positive symptoms in older, unmedicated females remained significantly associated with

functioning. As with neurocognition however, the directionality of findings remains unclear, with some evidence suggesting that it may be bidirectional in the case of negative symptoms [7 28 51].

Intriguingly, neither alcohol and substance use, nor sleep disturbances, were directly associated with functional impairment, although these factors remained significantly associated with neurocognition and clinical symptoms. Therefore, their role in social and occupational functioning does not appear to be direct, but may operate indirectly (e.g., substance use may impair cognition, which in turn may impair functioning). The indirect effects of alcohol and substance use, as well as sleep and circadian disruptions, warrant more detailed examination and causal analysis in longitudinal datasets. Moreover, the lack of a direct association between alcohol and substance use and functioning may be related to the domains of neurocognitive functions currently tested. That is, the impact of substance use on functioning may be greatest in other neurocognitive functions that are more directly linked to driving and maintaining alcohol and substance use behaviours, such as those subserved by the fear, reward and self-control circuitries not covered in the current neuropsychological battery (e.g., reward-related cue learning, habit formation, response inhibition).

The current findings have important implications for the transdiagnostic, dimensional approach to psychiatry. Research examining the underlying mechanisms of functional impairment in single- or dual-diagnosis cohorts have been unable to capture the unique contributions of a comprehensive range of neurocognitive, symptom, sleep and circadian factors, as well as other psychoactive exposures (i.e., substance use, prescribed medications).[22] In particular, neuropsychological studies in psychosis have not routinely and concurrently assessed depression and anxiety symptoms, hypomania and full-threshold mania, substance misuse, and sleep disturbance. That is not to say that categorical, nosological approaches have had little to contribute to the field. Indeed, the key argument underpinning a DSM-approach is to allow for comparability across studies and so diagnostic determinations are often necessary. However, in youth, diagnoses tend to be unstable[1] and, as such, not as useful. One plausible way forward for dimensional

psychiatry is to ensure that the samples used in transdiagnostic studies are characterised as clearly and as comprehensively as possible,[16 52 53] as was attempted in the present investigation.

In terms of limitations, the current analyses were cross-sectional, and future research investigating moderator and mediator analyses would benefit from cross-lagged, longitudinal path modelling to disentangle causality.[54] Secondly, the measures used to index clinical symptoms, sleep disturbance, and alcohol and substance use were not as comprehensive as is typical in the sleep and addiction literatures, and some were not originally designed for use in certain clinical disorders, which may have reduced sensitivity to detect symptoms (e.g., mania). More detailed examination of these dimensions in the future will help more definitively determine whether the impact of neurocognition on functioning is as large as currently identified. Future studies would also benefit from using real-time, ecological momentary assessment technologies (e.g., substance use monitoring using smartphones, actigraphy monitoring of physical activity and sleep quality). Thirdly, medication data were not available for the full sample (12.6% were missing) and, as such, the moderating role of medication status requires further corroboration (as with the role of medication type). Fourthly, clinical diagnoses assigned to cases in the current study were by treating psychiatrists and future studies should consider more structured approaches (e.g., Structured Clinical Interview for DSM), including consideration of the influence of other comorbid diagnoses (e.g., personality disorders). Further, the age range included in the current study meant that individuals on the opposite ends of the age spectrum were at different stages of their cognitive and emotional development (e.g., executive functioning, emotional regulation), although our sensitivity analyses supports the argument that our findings hold irrespective of age. Finally, a phenotype-approach, as attempted in the current study, would necessarily require converging genetic and neuroimaging evidence to ensure that the neurocognitive and symptom dimensions identified as predictive of functioning are linked to specific neural circuitries (e.g., cortico-basal ganglia systems[55]) and genotype, which would ultimately facilitate the development of next-generation and neuroscience-informed pharmacotherapies.

This was the first study to examine a broad range of illness-related factors and associations with functional impairment in a well-powered and broadly transdiagnostic, clinical cohort of more than one thousand young people with mental illness. A significant contribution of the present findings to the established literature was evidence showing that neurocognition is a strong and reliable, unique predictor of social and occupational functioning irrespective of diagnosis – in a cohort predominantly comprised of affective disorders, which has not been previously demonstrated before at this scale. As such, the functional importance of neurocognitive functions clearly extends beyond the psychosis and developmental disorders spectrum and appears to become more pronounced with increasing age. Future studies should attempt to replicate these findings, as well as to clarify the directions of cause and effect.

AUTHORSHIP

RSCL, DFH, SLN, AJG, NG, JS, EMS and IBH contributed to the conception of the study; RSCL, DFH, MK undertook the data collection, processing and analysis; RSCL wrote the first draft of the manuscript. All authors contributed to data interpretation, discussion and have approved the final manuscript.

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COMPETING INTERESTS

(1) No authors have support from any company for the submitted work; (2) no authors have relationships with any company that might have an interest in the submitted work; (3) no author, their spouses, partners, or children have financial relationships that may be relevant to the submitted work and; (4) no authors have any non-financial interests that may be relevant to the submitted work.

ETHICAL APPROVAL

This study was approved by the University of Sydney Human Research Ethics Committee (reference 12130; protocol no. 2012/1631).

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analysed during the current study are not publicly available due to the breadth and sensitivity of data collected, which may have implications for individual privacy, but are available from the corresponding author on reasonable request.

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Table 1 Demographic, clinical and functional characteristics across diagnostic sub-groups

	DEPRESSION[1] (n = 449)		BIPOLAR[2] (n = 178)		PSYCHOSIS[3] (n = 193)		ANXIETY[4] (n = 109)		DEV/BEHAV[5] (n = 74)	
	M	*SD*	**M**	*SD*	**M**	*SD*	**M**	*SD*	**M**	*SD*
Age	**19.8**	*4.3*	**21.6**	*4.8*	**22.2**	*4.6*	**19.9**	*4.8*	**17.0**	*4.6*
Education (years)	**11.6**	*2.4*	**12.3**	*2.2*	**12.0**	*2.4*	**11.5**	*2.7*	**10.0**	*2.8*
BPRS Depression (/7)	**2.4**	*0.8*	**2.2**	*0.8*	**2.1**	*0.9*	**2.3**	*0.9*	**1.7**	*0.7*
BPRS Mania (/7)	**1.3**	*0.5*	**1.5**	*0.6*	**1.4**	*0.4*	**1.4**	*0.4*	**1.5**	*0.7*
BPRS Positive (/7)	**1.3**	*0.4*	**1.4**	*0.5*	**1.8**	*0.7*	**1.4**	*0.5*	**1.3**	*0.4*
BPRS Negative (/7)	**1.5**	*0.6*	**1.3**	*0.5*	**1.9**	*0.8*	**1.5**	*0.7*	**1.5**	*0.6*
BRPS Disorientation (/7)	**1.2**	*0.5*	**1.1**	*0.5*	**1.2**	*0.6*	**1.2**	*0.5*	**1.2**	*0.5*
HDRS Sleep (/6)	**2.0**	*1.8*	**1.7**	*1.7*	**1.3**	*1.6*	**1.5**	*1.5*	**1.8**	*1.7*
AUDIT Alcohol Use (/40)	**6.8**	*7.4*	**9.0**	*8.4*	**6.2**	*8.0*	**4.4**	*6.4*	**5.1**	*7.5*
WHO-ASSIST Tobacco Use (/4)	**1.3**	*1.6*	**1.6**	*1.7*	**1.7**	*1.9*	**1.0**	*1.5*	**1.4**	*1.7*
WHO-ASSIST Cannabis Use (/4)	**0.7**	*1.2*	**0.7**	*1.3*	**0.4**	*1.0*	**0.4**	*0.9*	**0.7**	*1.3*
WHO-ASSIST Other Illicit Substance Use (/4)	**0.1**	*0.3*	**0.1**	*0.3*	**0.1**	*0.2*	**0.1**	*0.3*	**0.1**	*0.3*
SOFAS	**61.8**	*10.7*	**63.9**	*11.5*	**55.9**	*12.1*	**63.2**	*11.1*	**61.7**	*9.8*
	N	**%**	*N*	**%**	*N*	**%**	*N*	**%**	*N*	**%**
Gender (female)	*277*	**61.7**	*129*	**72.5**	*58*	**30.1**	*58*	**53.2**	*20*	**27.0**
Medicated[†]	*231*	**60.0**	*128*	**77.6**	*140*	**77.3**	*37*	**45.7**	*32*	**49.2**
Antidepressants	*201*	**52.2**	*63*	**38.2**	*55*	**30.4**	*25*	**30.9**	*12*	**18.5**
Lithium/Anticonvulsants	*28*	**7.3**	*69*	**41.8**	*24*	**13.3**	*6*	**7.4**	*3*	**4.6**
Antipsychotics	*71*	**18.4**	*77*	**46.7**	*125*	**69.1**	*9*	**11.1**	*8*	**12.3**
Stimulants	*14*	**3.6**	*7*	**4.2**	*3*	**1.7**	*4*	**4.9**	*14*	**21.5**

AUDIT–Alcohol Use Disorders Identification Test; BPRS–Brief Psychiatric Rating Scale; DEV/BEHAV–Developmental/Behavioral; HDRS–Hamilton Depression Rating Scale; SOFAS–Social and Occupational Functioning Assessment Scale; WHO-ASSIST–World Health Organization – Alcohol, Smoking and Substance Involvement Screening Test

[1] Major Depressive Disorder (n=313), Dysthymic Disorder (n=4), Depressive Disorder Not Otherwise Specified (n=132)

[2] Bipolar I Disorder (n=13), Bipolar II Disorder (n=25), Cyclothymic Disorder (n=1), Bipolar Disorder Not Otherwise Specified (n=139)

[3] Schizophrenia (n=53), Schizophreniform Disorder (n=15), Schizoaffective Disorder (n=26), Brief Psychotic Disorder (n=11), Substance-Induced Psychotic Disorder (n=14), Psychotic Disorder Not Otherwise Specified (n=74)

[4] Panic Disorder (n=4), Social Phobia (n=29), Obsessive-Compulsive Disorder (n=11), Posttraumatic Stress Disorder (n=5), Generalised Anxiety Disorder (n=60)

[5] Asperger's Disorder (n=16), Attention-Deficit/Hyperactivity Disorder (n=47), Conduct Disorder (n=7), Oppositional Defiant Disorder (n=4)

[†] Medication data was available in 877 individuals (87.4%), with missing data for the typologies of Depression (n=64), Bipolar (n=13), Psychosis (n=12), Anxiety (n=28), Developmental (n=9)

Table 2 Neuropsychological functioning across diagnostic sub-groups

	DEPRESSION *(n = 449)*		BIPOLAR *(n = 178)*		PSYCHOSIS *(n = 193)*		ANXIETY *(n = 109)*		DEV/BEHAV *(n = 74)*	
	M	*SD*	**M**	*SD*	**M**	*SD*	**M**	*SD*	**M**	*SD*
IQ[1]	**103.25**	*10.49*	**102.82**	*9.08*	**99.99**	*10.47*	**102.66**	*9.59*	**95.30**	*14.83*
Trails A[2]	**-0.01**	*1.32*	**0.16**	*1.06*	**-0.31**	*1.01*	**0.12**	*0.96*	**-0.03**	*1.07*
Trails B[2]	**-0.44**	*1.53*	**-0.47**	*1.92*	**-1.22**	*2.23*	**-0.50**	*1.59*	**-0.85**	*2.16*
Rey Total[2]	**-0.06**	*1.27*	**-0.18**	*1.20*	**-1.12**	*1.46*	**0.09**	*1.93*	**-0.48**	*1.42*
Rey Delay[2]	**0.03**	*1.34*	**-0.27**	*1.38*	**-1.07**	*1.51*	**0.18**	*2.29*	**-0.29**	*1.22*
FAS[2]	**-0.31**	*1.15*	**-0.04**	*1.07*	**-0.56**	*1.00*	**-0.37**	*1.15*	**-0.86**	*1.09*
Animals[2]	**0.23**	*1.20*	**0.45**	*1.25*	**-0.28**	*1.08*	**0.26**	*1.17*	**-0.03**	*0.94*

[1] Age-adjusted; normative M = 100; SD = 15.
[2] Demographically-adjusted; normative M= 0.00; SD = 1.00.

Table 3 Analyses of demographic factors (age, gender) as moderators of the relationships between predictors and functional outcome in the final model

	Age[†]				Gender[‡]			
	12-20 Years (*n = 539*)		21-36 Years (*n = 464*)		Male (*n = 461*)		Female (*n = 542*)	
	β	*p-value*	β	*p-value*	β	*p-value*	β	*p-value*
Neurocognition	**.27**	*.000*	**.44**	*.000*	**.35**	*.000*	**.35**	*.000*
Depression and Anxiety	**-.28**	*.000*	**-.22**	*.000*	**-.23**	*.000*	**-.30**	*.000*
Positive Symptoms	**-.06**	*.178*	**-.14**	*.002*	**-.07**	*.145*	**-.12**	*.004*
Negative Symptoms	**-.13**	*.005*	**-.18**	*.000*	**-.19**	*.000*	**-.07**	*.105*

[†] 12-20 Years (Subgroup Model, R^2=.24); 21-36 Years (Subgroup Model, R^2=.40)

[‡] Male (Subgroup Model, R^2=.32); Female (Subgroup Model, R^2=.29)

Table 4 Analyses of clinical factors (primary affective disorder, medication usage) moderating the relationship between predictors and functional outcome in the final model

	Primary Affective Disorder†				Medication Usage‡			
	Yes *(n = 736)*		No *(n = 267)*		Nil *(n = 309)*		Medicated *(n = 568)*	
	β	*p-value*	β	*p-value*	β	*p-value*	β	*p-value*
Neurocognition	**.30**	*.000*	**.43**	*.000*	**.38**	*.000*	**.38**	*.000*
Depression and Anxiety	**-.29**	*.000*	**-.24**	*.000*	**-.15**	*.007*	**-.24**	*.000*
Positive Symptoms	**-.06**	*.097*	**-.10**	*.123*	**-.22**	*.000*	**-.06**	*.117*
Negative Symptoms	**-.12**	*.003*	**-.16**	*.009*	**-.19**	*.000*	**-.13**	*.002*

† Yes (Subgroup Model, R^2=.24); No (Subgroup Model, R^2=.38)
‡ Nil (Subgroup Model, R^2=.38); Medicated (Subgroup Model, R^2=.29)

Figure 1 Combined measurement and structural models for functioning and (**A**) neurocognition, (**B**) core clinical symptoms, and (**C**) alcohol and substance use.

Legend:
All unidirectional (correlation) and directional (regression) paths are significant at $p < .001$ (except path between substance use and functional outcome; where $p < .05$)
Factor Loadings for (A) Neurocognition (all p's < .001): IQ (.58), Trails A (-.51), Trails B (-.55), Rey Total (.69), Rey Delay (.59), FAS (.57), Animals (.51)
Factor Loadings for (C) Substance Use (all p's < .001): Tobacco (.81), Cannabis (.64), Other (.68)

Figure 2 Final model.

Legend:
All unidirectional (correlation) and directional (regression) paths are significant at $p < .001$ (except correlation between substance use and positive symptoms, where $p < .05$). Where no path is drawn it denotes no significant relationship between the variables (see Figure 1 for all factor loadings of latent variables).

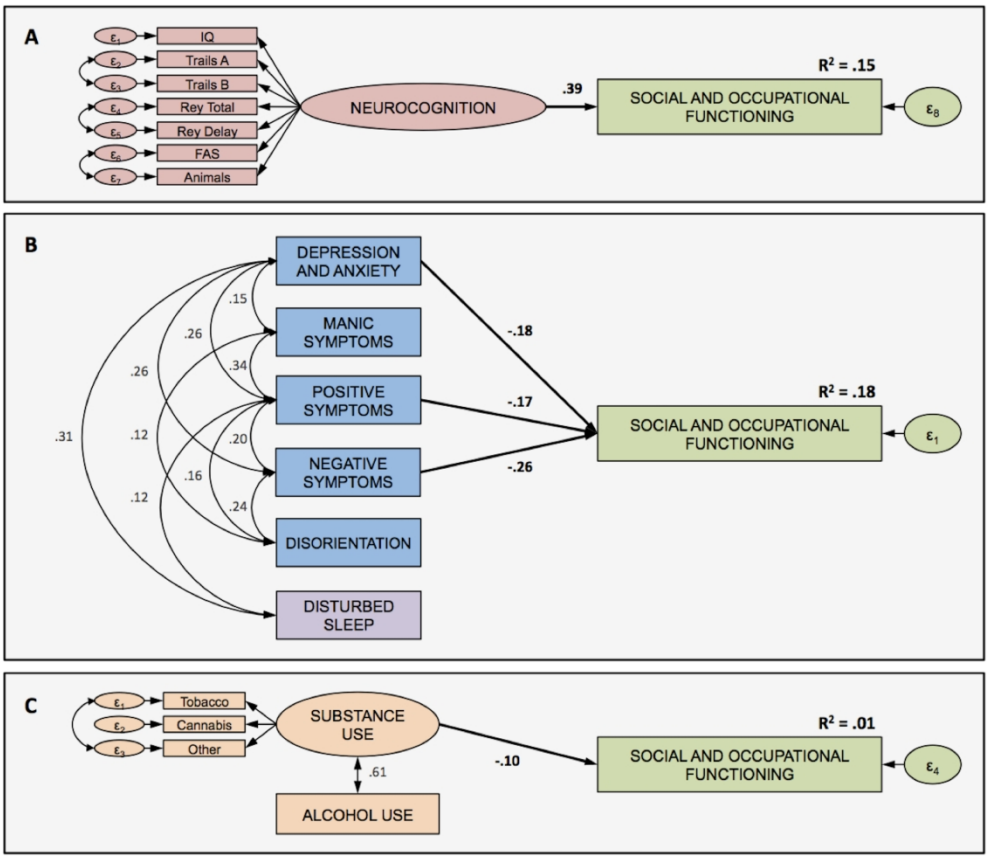

Figure 1 Combined measurement and structural models for functioning and (A) neurocognition, (B) core clinical symptoms, and (C) alcohol and substance use.

Legend:
All unidirectional (correlation) and directional (regression) paths are significant at $p < .001$ (except path between substance use and functional outcome; where $p < .05$)
Factor Loadings for (A) Neurocognition (all p's < .001): IQ (.58), Trails A (-.51), Trails B (-.55), Rey Total (.69), Rey Delay (.59), FAS (.57), Animals (.51)
Factor Loadings for (C) Substance Use (all p's < .001): Tobacco (.81), Cannabis (.64), Other (.68)

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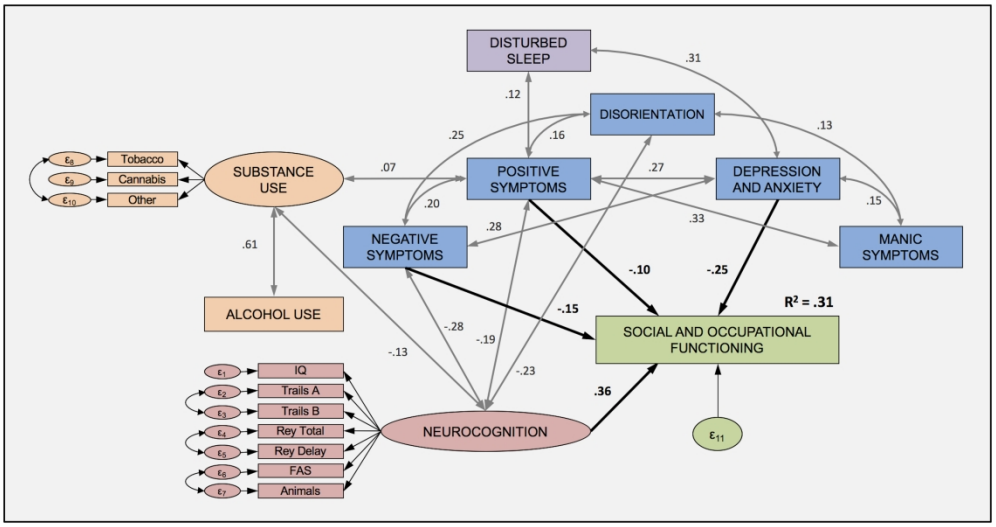

Figure 2 Final model.

Legend:
All unidirectional (correlation) and directional (regression) paths are significant at p < .001 (except correlation between substance use and positive symptoms, where p < .05). Where no path is drawn it denotes no significant relationship between the variables (see Figure 1 for all factor loadings of latent variables).

393x208mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

RE: "***A cross-sectional study of clinical, neurocognitive, and demographic factors associated with functional impairment in the Brain and Mind Youth Cohort***"

	Item No	Recommendation	Authors Response
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Pg. 1	Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Pg. 2	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Pg. 4-6	Yes
Objectives	3	State specific objectives, including any prespecified hypotheses Pg. 6	Yes
Methods			
Study design	4	Present key elements of study design early in the paper Pg. 6-7	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Pg. 7	Yes
Participants	6	(*a*) ~~*Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up~~ ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants Pg. 7	Yes
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Pg. 7-11	Yes
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Pg. 8	Yes
Bias	9	Describe any efforts to address potential sources of bias Pg. 10-11	Yes
Study size	10	Explain how the study size was arrived at Pg. 10	Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Pg. 9-11	Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Pg. 9-11	Yes
		(*b*) Describe any methods used to examine subgroups and interactions Pg. 10-11	Yes
		(*c*) Explain how missing data were addressed Pg. 9	Yes
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed ~~*Case-control study*—If applicable, explain how matching of cases and controls~~	NA

	~~was addressed~~ ~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~	
	(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			Authors Response
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Pg. 11	Yes
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Pg. 11	Yes
		(b) Indicate number of participants with missing data for each variable of interest Pg. 9	Yes
		© *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	~~*Cohort study*—Report numbers of outcome events or summary measures over time~~	Yes
		~~*Case-control study*—Report numbers in each exposure category, or summary measures of exposure~~	
		Cross-sectional study—Report numbers of outcome events or summary measures Pg. 11	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Pg. 12-13	Yes
		(*b*) Report category boundaries when continuous variables were categorized Pg. 10-11	Yes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Pg. 11-14	Yes
Discussion			
Key results	18	Summarise key results with reference to study objectives Pg. 14-15	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Pg. 15-16	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Pg. 14-16	Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results Pg. 16	Yes
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Pg. 17	Yes

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Clinical, neurocognitive, and demographic factors associated with functional impairment in the Australian Brain and Mind Youth Cohort Study (2008-2016)

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Secondary Subject Heading:	Mental health
Keywords:	neurocognition, transdiagnostic, functional impairment, mental illness, symptom dimensions, alcohol use

CLINICAL, NEUROCOGNITIVE, AND DEMOGRAPHIC FACTORS ASSOCIATED WITH FUNCTIONAL IMPAIRMENT IN THE AUSTRALIAN BRAIN AND MIND YOUTH COHORT STUDY (2008-2016)

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Manuscript word count: 4601

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ABSTRACT

Objectives: We sought to determine the unique and shared contributions of clinical, neurocognitive and demographic factors to functional impairment in a large, transdiagnostic, clinical cohort of adolescents and young adults.

Design: Cross-sectional baseline data from a prospective, cohort study.

Setting: Help-seeking youth referred from outpatient services were recruited to the *Brain and Mind Youth Cohort* (2008-2016) in Sydney, Australia.

Participants: In total, 1003 outpatients were recruited, aged between 12 and 36 years (M = 20.4 years, 54% female), with baseline diagnoses of affective, psychotic, developmental or behavioural disorders.

Interventions: Treatment as usual.

Primary outcome measures: Social and occupational functioning was used to index level of functional impairment. Structural equation modelling was used to examine associations between neurocognition, core clinical symptoms, and alcohol and substance use, and clinician- and researcher-rated functional impairment. Moderator analyses were conducted to determine the potential influence of demographic and clinical factors (e.g. medication exposure).

Results: Independent of diagnosis, we found that neurocognitive impairments, and depressive, anxiety and negative symptoms, were significantly associated with functioning. The association of neurocognition with social and occupational functioning remained significant even when constraining age (only 15- to 25-year olds) or diagnosis (affective disorder) in the final model.

Conclusions: This study demonstrates that, in a clinically representative sample of youth, the key determinants of functioning may not be disorder specific. Further, evidence of neurocognitive dysfunction suggests that interventions that target cognition and functioning should not necessarily be reserved only for older adults with established illness.

Keywords: Neurocognition; transdiagnostic; functional impairment; mental illness; symptom dimensions; alcohol use.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This was one of the largest studies to date (N > 1,000) to examine the associations between a broad range of illness characteristics and functional impairment in a mostly adolescent and young adult, clinical sample.
- Given the transdiagnostic approach, this study was equipped to disentangle the shared and unique associations between core illness phenotypes and functional impairment across a range of common mental disorders.
- The use of latent-variable, structural equation modelling controlled for aspects of measurement imprecision.

INTRODUCTION

In recent decades, early intervention services for youth with emerging mental disorders have extended their targets beyond those at risk of psychosis to also encompass those presenting with mood as well as other developmental and anxiety disorders. This approach creates several significant challenges. For example, some youth with depressive and anxiety disorders will ultimately develop psychotic or bipolar disorders; likewise, only a proportion of those receiving a diagnosis of bipolar disorders will consistently receive this diagnosis over the following 10 years.[1] The lack of diagnostic stability in help-seeking youth reflects the evolving disease process and means that the illness trajectory is less certain than for older adults with established illness.[2 3] From a research perspective, the use of dimensional approaches to phenomenology has helped us to understand illness progression in these early clinical stages, whilst from a clinical perspective, care and treatment have increasingly considered transdiagnostic interventions addressing core factors that may influence prognosis irrespective of cross-sectional diagnosis (e.g., anxiety, depressive or negative symptoms; sleep disturbances).[4 5] These approaches have highlighted that, in youth, a more meaningful measure of outcome may be functioning rather than change in diagnosis-specific symptoms. There is evidence to support this approach as level of functioning or disengagement (e.g., not being in education, employment or training, referred to as being NEET) is associated with early transition to major mental disorder[6] and with poor outcome of acute illness episodes.[7 8] However, to optimize interventions that target functioning it is important to understand the factors that contribute to level of functioning at clinical presentation. For instance, as well as transdiagnostic symptom dimensions, it is likely that other factors such as neurocognitive functioning and alcohol or substance use will also affect overall functioning. Disentangling the contribution and magnitude of any effects of these factors on functioning is important to determine which factors may be amenable to modification and allow clinicians to design a multidimensional intervention package.

The proposal that social and occupational functioning should be a primary target for mental health interventions is not new and is increasingly promoted for older adults with established illness. For example, senior policy experts in the U.S. have stipulated that recovery-oriented treatments should form the overarching goal of mental health care and the foundation of strategic health policy.[9] The recognition that more personalized interventions are urgently needed to enhance functioning and quality of life rather than simply targeting diagnosis-specific symptoms in a one-size-fits-all approach is also emphasized by the World Health Organization.[10] Given this interest in enhancement of functioning across all stages of mental illness and for youth and adults presenting to mental health services, it is therefore useful to examine the role of other, key clinical (e.g., medication exposure) and demographic factors (e.g., age, gender) in determining functioning, which would contribute to prognosis and attempts at personalised medicine.

Most path modelling studies to date have used small, single- or dual-diagnosis cohorts, predominantly in individuals with a chronic mental illness. Findings consistently demonstrate that neurocognition and negative symptoms are robust predictors of functional outcome in schizophrenia and bipolar disorder.[7 11 12] By contrast, the impact of affective and positive symptoms on functioning remains more equivocal. More recently, these findings have been replicated in large cohort studies,[13 14] although the vast majority of existing studies have focused exclusively on schizophrenia. There have been no well-powered studies examining a mental disorder other than schizophrenia, such as affective disorders, despite depression being the leading cause of disability worldwide.[15] Studies have also largely sidestepped the issue of psychotropic medication use. Furthermore, given that more than 75% of mental illnesses emerge before the age of 25,[3] examining younger cohorts is critically important for the development of novel approaches to early intervention since most studies to date have targeted older individuals.[15]

In order to build upon prior research, a transdiagnostic and dimensional approach is ideally positioned to disentangle the factors associated with functioning. Key to this research strategy is the examination of shared constructs (e.g., neurocognition) with clear links to pathophysiology,[16-18] which can inform novel therapeutics that target specific neural circuitries.[17 19] Transdiagnostic studies are also able to harness the variance across disorders, with the goal of developing robust, unifying models that are *explanatory* in nature.[2] Data showing that physiological and genetic risk factors for mental illness extend across, rather than are bound by, traditional diagnoses,[20] further supports this paradigm, as does the frequent prescription of psychotropic medications for off-label use across diagnostic boundaries.[21] Transdiagnostic studies are also superior to single-diagnosis case-control studies in that they can determine which relationships are *shared* across various diagnoses and which are *unique* to a particular disorder.

In this study, we sought to determine whether: (i) neurocognition; (ii) core clinical dimensions; and (iii) alcohol and substance use, are associated with social and occupational functioning and the magnitude of these associations. The rationale for examining clinical symptoms and functioning alongside neurocognition, sleep changes, and substance use, is underscored by a recent systematic review highlighting the transdiagnostic relevance of these key domains in youth with mental illness.[22] In keeping with prior research,[7 12 23] it was hypothesized that neurocognition and negative symptoms would make the greatest contribution to level of social and occupational functioning irrespective of the cross-sectional diagnosis applied to cases at the time of inclusion in the cohort. Given the high degree of heterogeneity expected in a transdiagnostic youth sample, we secondarily sought to determine the influence of demographic (e.g., age, gender) and clinical factors (e.g., diagnosis, medication exposure) on findings.

METHODS

This study was approved by the University of Sydney Human Research Ethics Committee. Data included in the current study represent the baseline assessments conducted at entry to the cohort study, and were collected between April 2008 and May 2016.

Participants

Participants were recruited into the Brain and Mind Youth Cohort from youth mental health outpatient services at the Brain and Mind Centre.[24 25] Referred participants were 12–36 years of age and presented with a major affective, psychotic or developmental/behavioral syndrome. Participants were excluded if they (or their guardians, if aged under 16 years) were unwilling or unable to provide written informed consent, or if they had a pre-existing neurological condition, clinically assessed impaired English language skills and/or intellectual disability that precluded completion of study self-ratings. Eligible participants completed a series of observer and self-rated questionnaires.

Procedure

Treating clinicians recorded clinical diagnoses and these were reviewed at consensus meetings by senior, treating psychiatrists (e.g., IBH, EMS) and formal diagnoses recorded based on the DSM-IV-TR (Table 1 provides details of diagnoses and sample characteristics). Any disagreements in diagnosis were resolved at these consensus meetings with the relevant treating team. All participants received their prescribed course of medications and interventions, as independently determined in consultation with their treating clinicians.

Board-certified treating clinicians (i.e., consultant psychiatrists, clinical psychologists, mental health nurses) provided an evaluation of each participant's social and occupational functioning. Next, board-certified clinical psychologists, clinical neuropsychologists, or trained research psychologists (i.e.,

graduate-level academic psychologists; supervised by RSCL to ensure a sufficient level of inter-rater reliability), conducted structured clinical interviews, neuropsychological testing, as well as an additional assessment of social and occupational functioning to improve the reliability of this single, clinician-rated score (approximately 80% were conducted within a month of the treating clinician assessment).

Measures

- *Social and occupational functioning* was indexed using the Social and Occupational Assessment Functioning Scale (SOFAS[26]). Scores were averaged across the treating clinician and researcher assessments (ICC = 0.70), as previously done.[27] This composite score was derived to obtain a more reliable estimate of real-world functioning and, secondarily, to conserve free parameters and increase stability of parameter estimates.[23 28] A higher score denotes better functioning.
- *Neurocognition* was assessed using a broad neuropsychological battery with demographic normative-adjustments (previously described[23]), and was chosen on the basis of sound psychometric properties[29] and relevance to the disorders under study.[30] Predicted IQ was estimated using the Wechsler Test of Adult Reading (WTAR) or Wide Range Achievement Test—fourth edition (WRAT-4, for participants younger than 16 years). Psychomotor speed and mental flexibility were measured using Trail Making Test—Part A (TMT-A) and -Part B (TMT-B). Verbal learning and memory were indexed using the five-trial total and delayed recall scores from the Rey Auditory Verbal Learning Test (RAVLT). Verbal fluency was comprised of the letter (FAS) and category (animals) fluency subtests of the Controlled Oral Word Association Test. A higher score indicates better functioning.
- *Core clinical symptom dimensions* were measured across two validated scales. Symptoms were rated on the expanded Brief Psychiatric Rating Scale (BPRS) using empirically-derived symptom sub-

scores (depression and anxiety, mania, positive symptoms, negative symptoms, and disorientation[31]). The BPRS does not capture sleep profiles as a separate dimension so, as in previous studies,[32] disturbed sleep was indexed using the sum of the three sleep items from the Hamilton Depression Rating Scale (HDRS[33]). A higher score denotes greater severity of symptoms.

- *Alcohol and substance use* were measured across two validated scales. Alcohol use was indexed using the Alcohol Use Disorders Identification Test (AUDIT[34]) total score. Substance use for tobacco, cannabis, and other illicit substances was measured using the 'current frequency' sub-scale (past 3 months) from the World Health Organization – Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) questionnaire.[35] A higher score indicates greater alcohol or substance use.

Patient and public involvement

Participants were not involved in the development of research question(s), design and outcome measures, nor was the study informed by their priorities, experience, and preferences. We did not formally assess the burden of time required to participate in the research.

Data Analysis

Statistical analyses were conducted using IBM SPSS 20.0 and AMOS 20.0. Maximum likelihood estimation (MLE) was employed for all structural equation modelling (SEM) analyses. MLE was chosen as it is the most robust approach in the potential event of statistical assumption violations and performs best in heterogeneous samples [36]. Missing data was also handled by MLE, which does not involve data imputation, but uses all available data to compute maximum likelihood estimates. Diagnostic and demographic data were available for all participants. In total, 9.1% of data were missing for functioning,

18.8% for neurocognition, 12.7% for clinical symptoms and disturbed sleep, and 17.7% were missing for alcohol and substance use. Each analysis had >80% of cases with complete data. Additional analyses revealed that data were not missing at random, and missing data were more likely to occur in younger participants [Welch's $F(1,102.54) = 4.85$, $p < 0.05$] and in those with an anxiety disorder [$\chi^2(4) = 26.09$, P , 0.001], albeit the effect sizes were small (Cohen's d = 0.26 and Cramer's V = 0.16, respectively).

Normality was assessed through inspection of Q-Q plots, given inferential measures of non-normality (e.g., Shapiro-Wilk statistic) are overly sensitive in large datasets and almost always return a significant finding [37]. All endogenous variables (e.g., SOFAS) met normality assumptions on visual inspection. Based on visual inspection of the frequency histograms and assessment of the Q-Q plot, the predictor/exogenous variables that departed from normality were positive symptoms, negative symptoms, mania, disorientation, TMT-A, and TMT-B, which were all observed to have a slight positive skew (no others were skewed). Prior studies have found that MLE methods are robust in cases where variables depart from normality where N > 600, as in the present case [38]. However, other approaches to non-normal data, such as asymptotically distribution free SEM, require no missing data and would unsatisfactorily affect the generalisability of findings as well as statistical power in the current analyses. As such, we utilised the MLE approach.

We first used SEM to evaluate the best-fitting *measurement model* for the following predictors: 1/ neurocognition; 2/ clinical symptoms and disturbed sleep; and 3/ alcohol and substance use. Then, we used SEM to test the *structural model* (i.e., the relationship between predictors and social and occupational functioning) at both the single-predictor and the overall levels in order to explore potential predictors and delineate unique contributions. This was done in a two-step process – first, by testing individual predictors and then by testing the combined predictors - to quantify the amount of overlapping and unique explanatory power. All analyses used a model-trimming approach through an iterative process in which non-significant paths with the smallest contribution were sequentially eliminated from

a saturated model (where all variables were allowed to freely co-vary), until a best fitting model was derived to best explain the relationships between predictors and functional impairment. Finally, modification indices generated by AMOS were used to optimise model fit (i.e., to inform which paths and parameters should be added or removed to increase model adequacy), although these were only used when deemed theoretically meaningful. Residuals were allowed to correlate if theoretically justified (e.g., common measurement variance between neuropsychological subtests).

Model fit was determined using: (1) the absolute fit $\chi 2$ statistic; and (2) the relative fit indices: Bentler comparative fit index (CFI[39]), Bentler-Bonnett non-normed fit index (NFI[40]) and Root Mean Square Error of Approximation (RMSEA[41]) with 90% confidence interval. An excellent-fitting model is typically indicated by a non-significant $\chi 2$ test (indicating a non-significant difference between the covariance matrix of the data and the model), a CFI and NFI of greater than .90 (indicating that the current model was superior to a null model where all paths are constrained to zero), and a RMSEA of less than .05 with an upper confidence interval bound of less than .08 (indicating that the error of approximation of the model compared with the data was acceptable). In small samples (i.e., less than 200), the $\chi 2$ statistic has been shown to be an adequate index of absolute model fit.[36] However, as sample size increases, the $\chi 2$ statistic (relative to a constant degrees of freedom; df) disproportionately increases, and is nearly always significant and inappropriately rejects the model irrespective of specified parameters.[42 43] An alternative solution is to compute a relative, $\chi 2$/df ratio, with a value between 2 and 5 considered excellent to adequate fit,[42 44-46] although primary emphasis will be placed on the relative fit indices as is the established convention.[13]

Moderator analyses were conducted allowing a model to be tested in separate sub-groups, comparing the parameter estimates to determine how predictors of social and occupational functioning in the final model are moderated by demographic and clinical factors (these were dichotomous to maintain statistical power within sub-groups for this categorical procedure). For instance, the median-

split on age was performed to determine whether the model held for both younger and older individuals whilst maintaining statistical power. We sought to specifically test whether predictors in affective-spectrum disorders (anxiety, depressive and bipolar disorders) were similarly associated with functional impairment compared with psychotic, developmental or behavioral conditions. We chose to include primary affective disorders (i.e. major depression, bipolar disorder or an anxiety disorder) as a moderator since these disorders have been shown to have carry less neurocognitive burden in recent-onset mood disorders[47 48] and, as such, could potentially influence the role of neurocognition and the magnitude of effects in the statistical models.

RESULTS

Sample Characteristics

In total, 1003 patients were recruited. As shown in Table 1 and 2, cross-sectional diagnoses comprised of depressive (n = 449), bipolar (n = 178), psychotic (n = 193), anxiety (n = 109), and developmental or behavioral disorders (n = 74). The mean age was 20.4 years (SD = 4.7), with 54.0% being female (n = 542). Mean educational attainment was 11.7 years (SD = 2.5), with an average predicted IQ of 101.9 (SD = 10.8). The mean SOFAS score was 61.2 (SD = 11.4), indicating moderate levels of impairment. Of the participants with medication data available (87.4%, n = 877), 64.8% were prescribed psychotropic medications (n = 568). Of these 568 cases, 40.6% were prescribed an antidepressant (n = 356), 14.8% were prescribed lithium or an anticonvulsant (n = 130), 33.1% were prescribed any antipsychotic (n = 290), and 4.8% were prescribed a stimulant (n = 42).

[Insert Table 1 about here]

Single-Predictor Models

A. *Neurocognition.* Inspecting the scree plot, exploratory factor analyses identified two potential latent structures. The one-factor model was a very good fit for the data ($\chi 2 = 57.3$, df = 17, $p < 0.001$, CFI = 0.980, NFI = 0.972, RMSEA = 0.055, 90% CI = 0.040–0.071), and was a better fit than a two-factor model, whereby Trails A, Trails B and IQ loaded on one latent factor, and IQ, Rey Total, Rey Delay, FAS and Animals loaded on a second latent factor ($\chi 2 = 76.499$, df = 11, $p < 0.001$, CFI = 0.967, NFI = 0.962, RMSEA = 0.077, 90% CI = 0.061–0.094). Factor loadings on the one-factor model were all significant and ranged from 0.51 to 0.69 (see Figure 1A and legend). Neurocognition was a significant contributor to functional level ($\beta = 0.39$, $p < 0.001$), explaining 15% of the variance.

B. *Core clinical symptom dimensions.* Only three clinical dimensions [depression and anxiety ($\beta = -0.18$, $p < 0.001$), positive symptoms ($\beta = -0.17$, $p < 0.001$), and negative symptoms ($\beta = -0.26$, $p < 0.001$)] were associated with functioning, whereas mania and disorientation were not significantly associated (p's > 0.05). The model demonstrated excellent fit ($\chi 2 = 8.6$, df = 8, $p < 0.379$, CFI = 0.999, NFI = 0.986, RMSEA = 0.009, 90% CI = 0.000–0.043), with the three dimensions explaining a total of 18% of the variance in functioning (see Figure 1B).

C. *Alcohol and substance use.* Exploratory factor analyses determined that alcohol use did not load with the other substance use variables. Only a two-factor latent model was possible given the number of observed variables and statistical constraints. The two-factor model emerged as an excellent fit for the data ($\chi 2 = 7.4$, df = 4, $p < 0.116$, CFI = 0.995, NFI = 0.990, RMSEA = 0.033, 90% CI = 0.000–0.069), whereby tobacco, cannabis and other illicit substance use loaded on a single 'substance use' latent variable as distinct from alcohol use (Figure 1C and legend). Only substance use was predictive of functioning ($\beta = -0.10$, $p < 0.05$), explaining 1% of the variance.

[Insert Figure 1 about here]

Final Model

In the overall model, all the factors identified in the single predictor models remained significant, except for substance use (Figure 2). Neurocognition showed the strongest unique contribution to social and occupational functioning ($\beta = 0.36$, $p < 0.001$); depressive symptoms were next ($\beta = -0.24$, $p < 0.001$), followed by negative symptoms ($\beta = -0.15$, $p < 0.001$) and finally positive symptoms ($\beta = -0.10$, $p < 0.001$). Together, these four clinical features independently accounted for 31% of the variance in functioning, with the final model being a very good fit for the data ($\chi 2 = 279.8$, $df = 119$, $p < 0.000$, CFI = 0.956, NFI = 0.926, RMSEA = 0.037, 90% CI = 0.031–0.042). Mania, disorientation, and alcohol and substance use, all significantly correlated with these four significant features (p's < 0.05).

[Insert Figure 2 about here]

Moderator Analyses

- *Age.* As shown in Table 3, positive symptoms were no longer a significant contributor to functioning in the 12- to 20-year-old group ($\beta = -0.06$, $p = 0.178$). The model with older individuals explained 18% more variance in functional impairment than the model with younger individuals. This was driven in large part by a difference in predictive strength of neurocognition, whereby it was more predictive in older ($\beta = 0.44$, $p < 0.001$) than younger individuals ($\beta = 0.27$, $p < 0.001$).
- *Gender.* Positive symptoms were non-significant in the male sub-group ($\beta = -0.07$, $p = 0.145$), whereas all other clinical features remained significant (p's < 0.001). In females, negative symptoms became non-significant ($\beta = -0.07$, $p = 0.105$), whilst the other contributors remained significant. The final model was comparable across genders in terms of the total variance explained.

[Insert Table 2 about here]

- *Primary affective disorder diagnosis.* Neurocognition, depression and anxiety, and negative symptoms remained significant contributors to functional level irrespective of affective disorder

diagnosis (see Table 4). By contrast, positive symptoms no longer remained significant in both the affective disorder (β = -0.63, p = 0.097) and psychosis, developmental or behavioral disorders (β = -0.102, p = 0.123) sub-groups. An additional 14% of the variance in functioning was explained in individuals with a psychotic, developmental or behavioral disorder, primarily owing to the greater predictive strength of neurocognition (0.30 vs. 0.43, p's < 0.001).

- *Medication usage.* All factors associated with functional impairment remained significant in participants who were unmedicated. By contrast, positive symptoms no longer remained significant in medicated individuals (β = -0.06, p = 0.117).

[Insert Table 3 about here]

Sensitivity Analysis

Restricting the full sample to individuals aged 15-25 years of age (N = 794) yielded a very good fitting model as well ($\chi 2$ = 240.1, df = 119, p < 0.000, CFI = 0.959, NFI = 0.924, RMSEA = 0.036, 90% CI = 0.029–0.042). The explained variance remained the same (31% explained). Importantly, all predictors remained significant with the same effect sizes, with the exception of depression and anxiety, which became slightly more predictive (-0.25 → -0.26), and neurocognition, which became slightly less predictive (0.36 → 0.35).

DISCUSSION

In a large, clinical, transdiagnostic cohort of youth with mental disorders, impaired neurocognition was the clinical feature most significantly associated with functional impairment. The role of neurocognition was attenuated in those with an affective disorder diagnosis and in the younger age group. The findings are relevant as they demonstrate that whilst neurocognitive impairment may undermine functioning in

those with psychotic disorders, or in chronic or recurrent mental disorders, they are not specific to such cases. That is, neurocognitive dysfunction has traditionally been argued as a core, underlying feature of social and occupational impairments in chronic schizophrenia. However, our current findings support the burgeoning position that the role of neurocognitive deficits cut across diagnosis and clinical stage. Nevertheless, it appears that neurocognitive disturbances are more pronounced in those with psychotic, developmental, or behavioural disorders, converging with evidence of more pronounced cognitive deficits in children who will go on to develop psychosis compared with those who develop depression or bipolar disorder [49-51]. Mechanistically, whether neurocognitive dysfunction drives functional impairment as a few past studies have found [7 28], and is a consequence of poor functioning remains to be clarified.

Depressive, anxiety and negative symptom dimensions also contributed significantly to level of social and occupational functioning, supporting previous disorder-specific research.[11 13 28] Importantly, the contributions of these factors to level of functioning were largely independent of one another, and do not appear to be moderated by other clinical or demographic factors. By comparison, the role of positive symptoms diminished considerably in the final model. This finding differs from other research in psychotic and bipolar disorders, and may reflect the lower prevalence of positive symptoms in our cohort in contrast to previous studies.[11 13 28] However, it was notable that positive symptoms in older, unmedicated females remained significantly associated with functioning. As with neurocognition however, the directionality of findings remains unclear, with some evidence suggesting that it may be bidirectional in the case of negative symptoms [7 28 52].

Intriguingly, neither alcohol and substance use, nor sleep disturbances, were directly associated with functional impairment, although these factors remained significantly associated with neurocognition and clinical symptoms. Therefore, their role in social and occupational functioning does not appear to be direct, but may operate indirectly (e.g., substance use may impair cognition, which in turn may impair

functioning). The indirect effects of alcohol and substance use, as well as sleep and circadian disruptions, warrant more detailed examination and causal analysis in longitudinal datasets. Moreover, the lack of a direct association between alcohol and substance use and functioning may be related to the domains of neurocognitive functions currently tested. That is, the impact of substance use on functioning may be greatest in other neurocognitive functions that are more directly linked to driving and maintaining alcohol and substance use behaviours, such as those subserved by the fear, reward and self-control circuitries not covered in the current neuropsychological battery (e.g., reward-related cue learning, habit formation, response inhibition).

The current findings have important implications for the transdiagnostic, dimensional approach to psychiatry. Research examining the underlying mechanisms of functional impairment in single- or dual-diagnosis cohorts have been unable to capture the unique contributions of a comprehensive range of neurocognitive, symptom, sleep and circadian factors, as well as other psychoactive exposures (i.e., substance use, prescribed medications).[22] In particular, neuropsychological studies in psychosis have not routinely and concurrently assessed depression and anxiety symptoms, hypomania and full-threshold mania, substance misuse, and sleep disturbance. That is not to say that categorical, nosological approaches have had little to contribute to the field. Indeed, the key argument underpinning a DSM-approach is to allow for comparability across studies and so diagnostic determinations are often necessary. However, in youth, diagnoses tend to be unstable[1] and, as such, not as useful. One plausible way forward for dimensional psychiatry is to ensure that the samples used in transdiagnostic studies are characterised as clearly and as comprehensively as possible,[16 53 54] as was attempted in the present investigation.

In terms of limitations, the current analyses were cross-sectional, and future research investigating moderator and mediator analyses would benefit from cross-lagged, longitudinal path modelling to disentangle causality.[55] Secondly, the measures used to index clinical symptoms, sleep

disturbance, and alcohol and substance use were not as comprehensive as is typical in the sleep and addiction literatures, and some were not originally designed for use in certain clinical disorders, which may have reduced sensitivity to detect symptoms (e.g., mania). More detailed examination of these dimensions in the future will help more definitively determine whether the impact of neurocognition on functioning is as large as currently identified. Future studies would also benefit from using real-time, ecological momentary assessment technologies (e.g., substance use monitoring using smartphones, actigraphy monitoring of physical activity and sleep quality). Thirdly, medication data were not available for the full sample (12.6% were missing) and, as such, the moderating role of medication status requires further corroboration (as with the role of medication type). Fourthly, clinical diagnoses assigned to cases in the current study were by treating psychiatrists and future studies should consider more structured approaches (e.g., Structured Clinical Interview for DSM), including consideration of the influence of other comorbid diagnoses (e.g., personality disorders). Further, the age range included in the current study meant that individuals on the opposite ends of the age spectrum were at different stages of their cognitive and emotional development (e.g., executive functioning, emotional regulation), although our sensitivity analyses supports the argument that our findings hold irrespective of age. Further, a phenotype-approach, as attempted in the current study, would necessarily require converging genetic and neuroimaging evidence to ensure that the neurocognitive and symptom dimensions identified as predictive of functioning are linked to specific neural circuitries (e.g., cortico-basal ganglia systems[56]) and genotype, which would ultimately facilitate the development of next-generation and neuroscience-informed pharmacotherapies. Finally, it remains to be seen whether the current findings hold in future studies with less missing data, as well as in studies using measures or approaches that can circumvent potential biases stemming from non-normally distributed data.

This was the first study to examine a broad range of illness-related factors and associations with functional impairment in a well-powered and broadly transdiagnostic, clinical cohort of more than one

thousand young people with mental illness. A significant contribution of the present findings to the established literature was evidence showing that neurocognition is a strong and reliable, unique predictor of social and occupational functioning irrespective of diagnosis – in a cohort predominantly comprised of affective disorders, which has not been previously demonstrated before at this scale. As such, the functional importance of neurocognitive functions clearly extends beyond the psychosis and developmental disorders spectrum and appears to become more pronounced with increasing age. Future studies should attempt to replicate these findings, as well as to clarify the directions of cause and effect.

AUTHORSHIP

RSCL, DFH, SLN, AJG, NG, JS, EMS and IBH contributed to the conception of the study; RSCL, DFH, MK undertook the data collection, processing and analysis; RSCL wrote the first draft of the manuscript. All authors contributed to data interpretation, discussion and have approved the final manuscript.

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COMPETING INTERESTS

(1) No authors have support from any company for the submitted work; (2) no authors have relationships with any company that might have an interest in the submitted work; (3) no author, their spouses, partners, or children have financial relationships that may be relevant to the submitted work and; (4) no authors have any non-financial interests that may be relevant to the submitted work.

ETHICAL APPROVAL

This study was approved by the University of Sydney Human Research Ethics Committee (reference 12130; protocol no. 2012/1631).

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analysed during the current study are not publicly available due to the breadth and sensitivity of data collected, which may have implications for individual privacy, but are available from the corresponding author on reasonable request.

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Table 1 Demographic, clinical and functional characteristics across diagnostic sub-groups

	DEPRESSION[1] *(n = 449)*		BIPOLAR[2] *(n = 178)*		PSYCHOSIS[3] *(n = 193)*		ANXIETY[4] *(n = 109)*		DEV/BEHAV[5] *(n = 74)*	
	M	*SD*	**M**	*SD*	**M**	*SD*	**M**	*SD*	**M**	*SD*
Age	**19.8**	*4.3*	**21.6**	*4.8*	**22.2**	*4.6*	**19.9**	*4.8*	**17.0**	*4.6*
Education (years)	**11.6**	*2.4*	**12.3**	*2.2*	**12.0**	*2.4*	**11.5**	*2.7*	**10.0**	*2.8*
BPRS Depression (/7)	**2.4**	*0.8*	**2.2**	*0.8*	**2.1**	*0.9*	**2.3**	*0.9*	**1.7**	*0.7*
BPRS Mania (/7)	**1.3**	*0.5*	**1.5**	*0.6*	**1.4**	*0.4*	**1.4**	*0.4*	**1.5**	*0.7*
BPRS Positive (/7)	**1.3**	*0.4*	**1.4**	*0.5*	**1.8**	*0.7*	**1.4**	*0.5*	**1.3**	*0.4*
BPRS Negative (/7)	**1.5**	*0.6*	**1.3**	*0.5*	**1.9**	*0.8*	**1.5**	*0.7*	**1.5**	*0.6*
BRPS Disorientation (/7)	**1.2**	*0.5*	**1.1**	*0.5*	**1.2**	*0.6*	**1.2**	*0.5*	**1.2**	*0.5*
HDRS Sleep (/6)	**2.0**	*1.8*	**1.7**	*1.7*	**1.3**	*1.6*	**1.5**	*1.5*	**1.8**	*1.7*
AUDIT Alcohol Use (/40)	**6.8**	*7.4*	**9.0**	*8.4*	**6.2**	*8.0*	**4.4**	*6.4*	**5.1**	*7.5*
WHO-ASSIST Tobacco Use (/4)	**1.3**	*1.6*	**1.6**	*1.7*	**1.7**	*1.9*	**1.0**	*1.5*	**1.4**	*1.7*
WHO-ASSIST Cannabis Use (/4)	**0.7**	*1.2*	**0.7**	*1.3*	**0.4**	*1.0*	**0.4**	*0.9*	**0.7**	*1.3*
WHO-ASSIST Other Illicit Substance Use (/4)	**0.1**	*0.3*	**0.1**	*0.3*	**0.1**	*0.2*	**0.1**	*0.3*	**0.1**	*0.3*
SOFAS	**61.8**	*10.7*	**63.9**	*11.5*	**55.9**	*12.1*	**63.2**	*11.1*	**61.7**	*9.8*
	N	**%**	*N*	**%**	*N*	**%**	*N*	**%**	*N*	**%**
Gender (female)	*277*	**61.7**	*129*	**72.5**	*58*	**30.1**	*58*	**53.2**	*20*	**27.0**
Medicated†	*231*	**60.0**	*128*	**77.6**	*140*	**77.3**	*37*	**45.7**	*32*	**49.2**
Antidepressants	*201*	**52.2**	*63*	**38.2**	*55*	**30.4**	*25*	**30.9**	*12*	**18.5**
Lithium/Anticonvulsants	*28*	**7.3**	*69*	**41.8**	*24*	**13.3**	*6*	**7.4**	*3*	**4.6**
Antipsychotics	*71*	**18.4**	*77*	**46.7**	*125*	**69.1**	*9*	**11.1**	*8*	**12.3**
Stimulants	*14*	**3.6**	*7*	**4.2**	*3*	**1.7**	*4*	**4.9**	*14*	**21.5**

AUDIT–Alcohol Use Disorders Identification Test; BPRS–Brief Psychiatric Rating Scale; DEV/BEHAV–Developmental/Behavioral; HDRS–Hamilton Depression Rating Scale; SOFAS–Social and Occupational Functioning Assessment Scale; WHO-ASSIST–World Health Organization – Alcohol, Smoking and Substance Involvement Screening Test

[1] Major Depressive Disorder (n=313), Dysthymic Disorder (n=4), Depressive Disorder Not Otherwise Specified (n=132)

[2] Bipolar I Disorder (n=13), Bipolar II Disorder (n=25), Cyclothymic Disorder (n=1), Bipolar Disorder Not Otherwise Specified (n=139)

[3] Schizophrenia (n=53), Schizophreniform Disorder (n=15), Schizoaffective Disorder (n=26), Brief Psychotic Disorder (n=11), Substance-Induced Psychotic Disorder (n=14), Psychotic Disorder Not Otherwise Specified (n=74)

[4] Panic Disorder (n=4), Social Phobia (n=29), Obsessive-Compulsive Disorder (n=11), Posttraumatic Stress Disorder (n=5), Generalised Anxiety Disorder (n=60)

[5] Asperger's Disorder (n=16), Attention-Deficit/Hyperactivity Disorder (n=47), Conduct Disorder (n=7), Oppositional Defiant Disorder (n=4)

[†] Medication data was available in 877 individuals (87.4%), with missing data for the typologies of Depression (n=64), Bipolar (n=13), Psychosis (n=12), Anxiety (n=28), Developmental (n=9)

Table 2 Neuropsychological functioning across diagnostic sub-groups

	DEPRESSION *(n = 449)*		BIPOLAR *(n = 178)*		PSYCHOSIS *(n = 193)*		ANXIETY *(n = 109)*		DEV/BEHAV *(n = 74)*	
	M	*SD*	**M**	*SD*	**M**	*SD*	**M**	*SD*	**M**	*SD*
IQ[1]	**103.25**	*10.49*	**102.82**	*9.08*	**99.99**	*10.47*	**102.66**	*9.59*	**95.30**	*14.83*
Trails A[2]	**-0.01**	*1.32*	**0.16**	*1.06*	**-0.31**	*1.01*	**0.12**	*0.96*	**-0.03**	*1.07*
Trails B[2]	**-0.44**	*1.53*	**-0.47**	*1.92*	**-1.22**	*2.23*	**-0.50**	*1.59*	**-0.85**	*2.16*
Rey Total[2]	**-0.06**	*1.27*	**-0.18**	*1.20*	**-1.12**	*1.46*	**0.09**	*1.93*	**-0.48**	*1.42*
Rey Delay[2]	**0.03**	*1.34*	**-0.27**	*1.38*	**-1.07**	*1.51*	**0.18**	*2.29*	**-0.29**	*1.22*
FAS[2]	**-0.31**	*1.15*	**-0.04**	*1.07*	**-0.56**	*1.00*	**-0.37**	*1.15*	**-0.86**	*1.09*
Animals[2]	**0.23**	*1.20*	**0.45**	*1.25*	**-0.28**	*1.08*	**0.26**	*1.17*	**-0.03**	*0.94*

[1] Age-adjusted; normative M = 100; SD = 15.

[2] Demographically-adjusted; normative M= 0.00; SD = 1.00.

Table 3 Analyses of demographic factors (age, gender) as moderators of the relationships between predictors and functional outcome in the final model

	Age†				Gender‡			
	12-20 Years *(n = 539)*		21-36 Years *(n = 464)*		Male *(n = 461)*		Female *(n = 542)*	
	β	*p-value*	β	*p-value*	β	*p-value*	β	*p-value*
Neurocognition	**.27**	*.000*	**.44**	*.000*	**.35**	*.000*	**.35**	*.000*
Depression and Anxiety	**-.28**	*.000*	**-.22**	*.000*	**-.23**	*.000*	**-.30**	*.000*
Positive Symptoms	**-.06**	*.178*	**-.14**	*.002*	**-.07**	*.145*	**-.12**	*.004*
Negative Symptoms	**-.13**	*.005*	**-.18**	*.000*	**-.19**	*.000*	**-.07**	*.105*

† 12-20 Years (Subgroup Model, R^2=.24); 21-36 Years (Subgroup Model, R^2=.40)
‡ Male (Subgroup Model, R^2=.32); Female (Subgroup Model, R^2=.29)

Table 4 Analyses of clinical factors (primary affective disorder, medication usage) moderating the relationship between predictors and functional outcome in the final model

	Primary Affective Disorder†				Medication Usage‡			
	Yes *(n = 736)*		No *(n = 267)*		Nil *(n = 309)*		Medicated *(n = 568)*	
	β	*p-value*	β	*p-value*	β	*p-value*	β	*p-value*
Neurocognition	**.30**	*.000*	**.43**	*.000*	**.38**	*.000*	**.38**	*.000*
Depression and Anxiety	**-.29**	*.000*	**-.24**	*.000*	**-.15**	*.007*	**-.24**	*.000*
Positive Symptoms	**-.06**	*.097*	**-.10**	*.123*	**-.22**	*.000*	**-.06**	*.117*
Negative Symptoms	**-.12**	*.003*	**-.16**	*.009*	**-.19**	*.000*	**-.13**	*.002*

† Yes (Subgroup Model, R^2=.24); No (Subgroup Model, R^2=.38)
‡ Nil (Subgroup Model, R^2=.38); Medicated (Subgroup Model, R^2=.29)

Figure 1 Combined measurement and structural models for functioning and (**A**) neurocognition, (**B**) core clinical symptoms, and (**C**) alcohol and substance use.

Legend:
All unidirectional (correlation) and directional (regression) paths are significant at $p < .001$ (except path between substance use and functional outcome; where $p < .05$)
Factor Loadings for (A) Neurocognition (all p's < .001): IQ (.58), Trails A (-.51), Trails B (-.55), Rey Total (.69), Rey Delay (.59), FAS (.57), Animals (.51)
Factor Loadings for (C) Substance Use (all p's < .001): Tobacco (.81), Cannabis (.64), Other (.68)

Figure 2 Final model.

Legend:
All unidirectional (correlation) and directional (regression) paths are significant at $p < .001$ (except correlation between substance use and positive symptoms, where $p < .05$). Where no path is drawn it denotes no significant relationship between the variables (see Figure 1 for all factor loadings of latent variables).

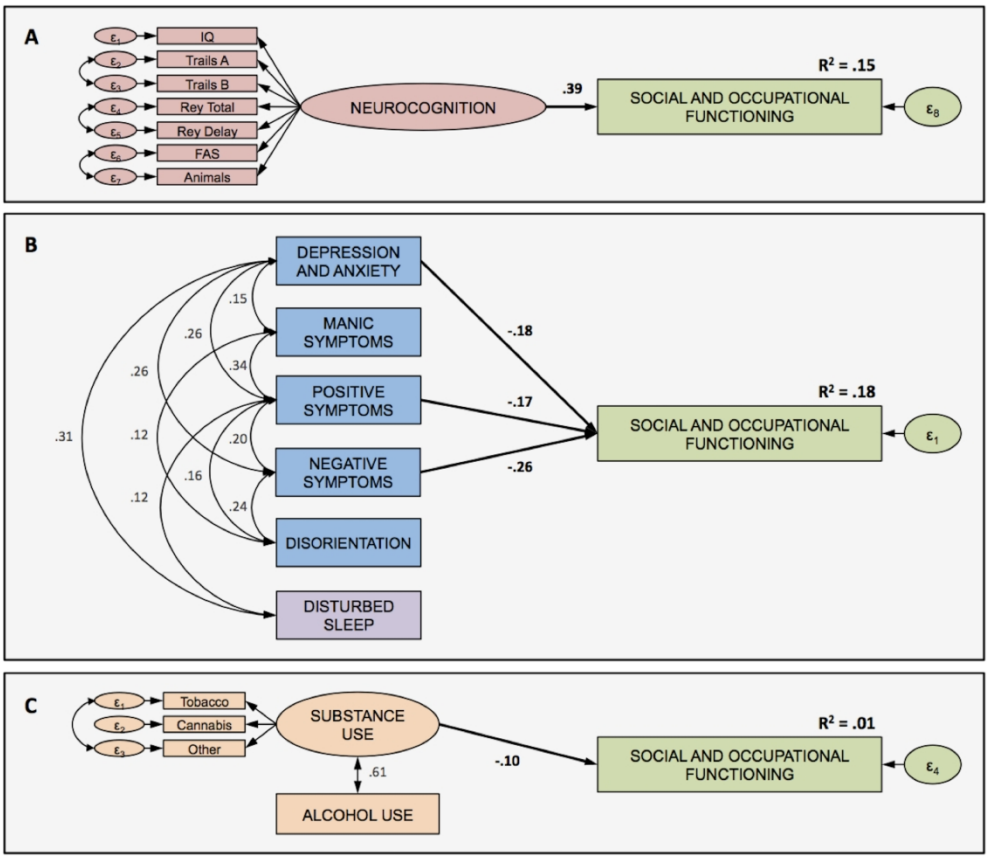

Figure 1 Combined measurement and structural models for functioning and (A) neurocognition, (B) core clinical symptoms, and (C) alcohol and substance use.

Legend:
All unidirectional (correlation) and directional (regression) paths are significant at $p < .001$ (except path between substance use and functional outcome; where $p < .05$)
Factor Loadings for (A) Neurocognition (all p's < .001): IQ (.58), Trails A (-.51), Trails B (-.55), Rey Total (.69), Rey Delay (.59), FAS (.57), Animals (.51)
Factor Loadings for (C) Substance Use (all p's < .001): Tobacco (.81), Cannabis (.64), Other (.68)

230x199mm (300 x 300 DPI)

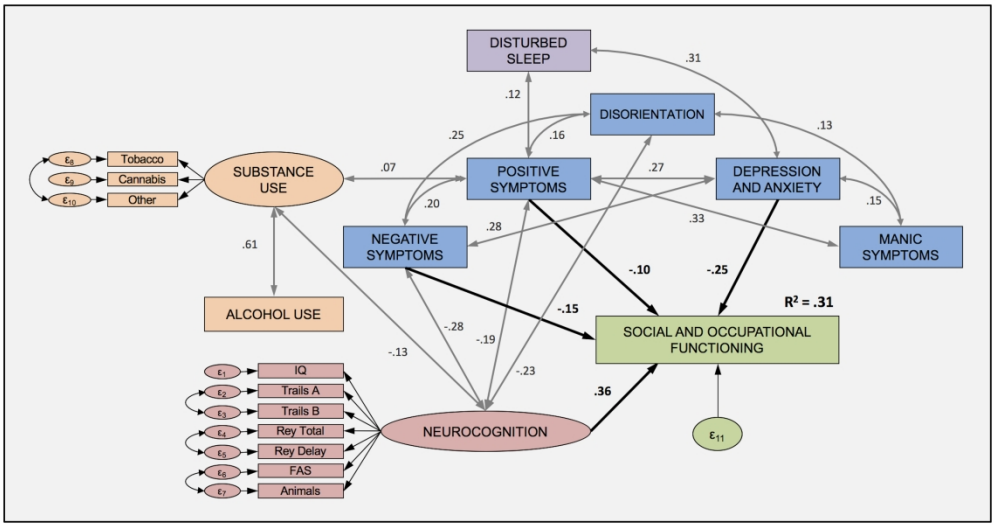

Figure 2 Final model.

Legend:
All unidirectional (correlation) and directional (regression) paths are significant at p < .001 (except correlation between substance use and positive symptoms, where p < .05). Where no path is drawn it denotes no significant relationship between the variables (see Figure 1 for all factor loadings of latent variables).

393x208mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

RE: "***A cross-sectional study of clinical, neurocognitive, and demographic factors associated with functional impairment in the Brain and Mind Youth Cohort***"

	Item No	Recommendation	Authors Response
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Pg. 1	Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Pg. 2	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Pg. 4-6	Yes
Objectives	3	State specific objectives, including any prespecified hypotheses Pg. 6	Yes
Methods			
Study design	4	Present key elements of study design early in the paper Pg. 6-7	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Pg. 7	Yes
Participants	6	(*a*) ~~*Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up~~ ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants Pg. 7	Yes
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Pg. 7-11	Yes
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Pg. 8	Yes
Bias	9	Describe any efforts to address potential sources of bias Pg. 10-11	Yes
Study size	10	Explain how the study size was arrived at Pg. 10	Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Pg. 9-11	Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Pg. 9-11	Yes
		(*b*) Describe any methods used to examine subgroups and interactions Pg. 10-11	Yes
		(*c*) Explain how missing data were addressed Pg. 9	Yes
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed ~~*Case-control study*—If applicable, explain how matching of cases and controls~~	NA

	~~was addressed~~ ~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~	
	(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			Authors Response
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Pg. 11	Yes
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Pg. 11	Yes
		(b) Indicate number of participants with missing data for each variable of interest Pg. 9	Yes
		© *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	~~*Cohort study*—Report numbers of outcome events or summary measures over time~~	Yes
		~~*Case-control study*—Report numbers in each exposure category, or summary measures of exposure~~	
		Cross-sectional study—Report numbers of outcome events or summary measures Pg. 11	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Pg. 12-13	Yes
		(*b*) Report category boundaries when continuous variables were categorized Pg. 10-11	Yes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Pg. 11-14	Yes
Discussion			
Key results	18	Summarise key results with reference to study objectives Pg. 14-15	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Pg. 15-16	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Pg. 14-16	Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results Pg. 16	Yes
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Pg. 17	Yes

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.