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Predicting spectrums of adult mania, psychosis and depression by prospectively ascertained childhood neurodevelopment

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ABSTRACT

Background: We used a novel approach to investigate early neurodevelopmental factors of later adult spectrums of mania, depression and psychosis as a means to identify etiological similarities and differences among the three constructs.
Methods: Participants were from the Mater University Study of Pregnancy (MUSP), a pre-birth cohort study started in Brisbane, Australia in 1981. A range of neurodevelopmental variables were ascertained at age 5, including measures of cognitive ability, developmental delay and behaviour problems. At age 21, offspring were assessed using a semi-structured psychiatric interview. We used structural equation modelling to establish three latent factors of mania, depression and psychotic symptoms. We then regressed these factors on the neurodevelopmental variables and covariates.
Results: In both univariate and multivariate analysis premorbid cognitive ability predicted only psychotic symptoms, developmental delay predicted only manic symptoms, while behaviour problems predicted both depressive and psychotic symptoms. In a supplementary analysis the three factors were also found to have unique relationships with a number of outcomes also measured at age 21, including anxiety and substance use.
Conclusion: By assessing the impact of early childhood neurodevelopment on the continuous spectrums which underlie three serious adult psychiatric disorders in a general population sample, we provide unique evidence regarding potential etiological similarities and differences. Perhaps of most interest is that our findings suggest that the manic and depressive symptoms in bipolar depression, despite often overlapping in clinical presentations, may in fact be somewhat separate entities with origins that are at least partly unique to either disorder.

1. Introduction

Determining the etiologies of serious mental health problems including major depression, bipolar disorders and schizophrenia remains a priority in efforts to reduce the considerable morbidity and mortality associated with these disorders (Saha et al., 2005; Slade et al., 2009). One area of research has focused on pinpointing the childhood neurodevelopmental abnormalities which predict such psychiatric disorders in later life, in the hope of identifying at risk individuals for early intervention. Such research has highlighted a number of neurodevelopmental similarities and differences among the disorders. Impairments in cognitive ability, social functioning, attention and motor functioning have been found to predict schizophrenia (Dickson et al., 2012; Erlenmeyer-Kimling et al., 2000). While some studies suggest similar impairments are not associated with later onset bipolar disorders (Cannon et al., 2002; Murray et al., 2004), declines in early academic adjustment have been noted in individuals who later develop bipolar disorders (Payá et al., 2013). In addition, cognitive ability deficits are also associated with unipolar depression (Zammit et al., 2004).

Such research also plays a central role in establishing the nosological boundaries among these disorders by elucidating their impaired premorbid profiles (Zammit et al., 2004). However,

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conclusions about which neurodevelopmental factors predict which disorders and what this suggests about their etiologies are confounded by the high levels of comorbidity among the disorders. For example, a recent study discussed the conflicting findings with regard to the levels of premorbid adjustment observed in bipolar disorders, for which various previous studies support as being either better, the same or worse than controls (Payá et al., 2013). The authors suggest the differences may be due to subgroups within bipolar individuals who vary by the severity of psychotic symptoms. The importance of such comorbidity was again highlighted in a recent population register study which found that higher intelligence did predict bipolar disorder, but only in a minority of cases who had 'pure bipolar' (Gale et al., 2013), and by an earlier study which found a number of neurodevelopmental abnormalities predicted schizophrenia but not non-psychotic bipolar disorder (Reichenberg et al., 2002). Importantly, even studies which take comorbidity into account are likely to include participants with considerable sub-threshold levels of comorbid disorders, and therefore symptoms of another disorder which are unaccounted for in the analyses (Merikangas et al., 2011).

The comorbidity which complicates etiological enquiry is a defining feature of the prevailing diagnostic systems, which categorise and class disorders according to their primary features built upon expert determined thresholds of psychopathology (Goldberg et al., 2009; Linscott and van Os, 2010). Thus, approaches aimed at elucidating the unique or shared origins of related psychiatric disorders may benefit from employing alternative ways to define the disorders under study. One approach suggested in the literature, but yet to be implemented in a truly effective manner, is to incorporate the related psychiatric disorders into a single analysis, and to operationalise the disorders as spectrums thereby accounting for comorbidity even at sub-clinical levels (Cederlöf et al., 2013; Goldberg et al., 2009; Hickie, 2014). Accumulating research supports the dimensional structure of psychiatric disorders, whereby the distribution of symptoms in the general population forms a continuous spectrum (with perhaps more than a single spectrum underlying the symptoms) (Linscott and van Os, 2010; van Os et al., 2009), and where it may be reasonable to expect the increasing symptom load to linearly relate to distress, impairment and to the etiological factors found to precipitate the related clinical diagnoses (Blanchard et al., 2010; Kelleher et al., 2012).

In this study we used structural equation modelling to construct separate but correlated spectrums (continuous factors) of mania, depression and psychosis measured in early adulthood in a general population birth cohort. We then examined the relationships among a range of neurodevelopmental factors ascertained during early childhood (age 5) with these spectrums. We hypothesised that this unique methodology, which better accounts for comorbidity among the disorder spectrums (even at sub-clinical levels), may more explicitly demonstrate that the different disorders have partly unique underlying etiological factors. By providing a clearer picture of how specific disorders are linked with specific neurodevelopmental abnormalities we may have the potential to inform early intervention strategies.

2. Methods

2.1. Participants

Participants are from the Mater University Study of Pregnancy (MUSP), a prospective pre-birth cohort study following mothers and their children for over 20 years. A total of 7223 mothers attending their first clinic visit at Brisbane's Mater Misericordiae Hospital were recruited between 1981 and 1984, with subsequent follow-ups at birth, and child age 6 months, and 5, 14 and 21 years, further information found elsewhere (Najman et al., 2005). At 21 years 2566 offspring completed the Composite International Diagnostic Interview (CIDI-Auto 2.1) (World Health Organization, 1997), forming the sample for the measurement model. The CIDI is a fully structured and comprehensive diagnostic interview for the assessment of mental disorders and provides diagnosis by computerised algorithms, with the questions eliciting symptoms and behaviours from respondents and mapping these to diagnostic criteria. Regression analyses were limited to participants with values on all risk factors of interest and covariates ($n = 1934$).

2.2. Symptoms of mania, depression and psychosis

At the 21 year follow-up the lifetime version of the CIDI-Auto (World Health Organization, 1997) was administered by lay trained interviewers, including 11 symptoms of mania, 11 symptoms of depression and 12 symptoms of psychosis (see table one for symptom descriptions and prevalence). Due to the format of the interview, symptoms of mania were restricted to participants who had experienced at least four days of either (i) being so happy/excited it caused problems with friends, family or a doctor told them that they were manic, or (ii) being so irritable that they complained, started arguments, shouted at or hit people. Also due to the format of the interview, symptoms of depression were restricted to participants who for at least two weeks either (i) felt sad, empty or depressed for most of the day nearly every day, or (ii) had lost interest in things they usually enjoyed. The psychotic symptoms included delusions and hallucinations, for which positive responses were probed to be surer the experience was psychotic. Due to the low prevalence of a number of the symptoms items and the need to satisfy the requirements of the covariance matrix for the subsequent structural equation model, a number of the items were either combined or dropped as done in a previous study (Betts et al., 2014) (see Supplementary text 1).

2.3. Childhood neurodevelopmental factors

At 5 years mothers completed a shortened version of the Achenbach Child Behaviour Checklist (CBCL) (Achenbach, 1991), which included the most commonly occurring behaviours, assessing 10 items each from the internalising and externalising scales, and 10 items from the social/attention/thought sub-scales. These items were combined into a total behaviour problems scale (Alpha = 0.897), and dichotomised defining 'cases' using a cut-off consistent with the percentage of cases identified by Achenbach in a community sample (Bor et al., 1997). The correlation between the full form (ascertained on a subsample) and short form for total behaviour problems was found to be very high (r = 0.98) (Bor et al., 1997). Children completed the Peabody Picture Vocabulary Test – Revised (PPVT-R), requiring them to indicate which one of four illustrations best represented a word expressed verbally by the examiner, resulting in a score measuring the subjects verbal ability (Jongsma, 1982). The PPVT-R has been validated against other standardised intelligence tests used on children (Childers et al., 1994; Dunn, 1981; Johnson et al., 1993). Children were also administered the Denver Developmental Screening Test (DDST) (Frankenburg and Dodds, 1967), which assesses developmental delays in the four key sectors of gross motor, fine motor-adaptive, language and personal-social development. The DDST was administered by trained researchers and a standard algorithm determined if the child's performance on the relevant task was normal, questionable or abnormal (Frankenburg et al., 1973). In this study we classified any child with a rating of abnormal or questionable in