Attention-deficit/hyperactivity disorder and other neurodevelopmental disorders in offspring of parents with depression and bipolar disorder

L. Propper1,2, A. Sandstrom1,3, S. Rempe1,3, E. Howes Vallis1,3, S. Abidi1,2, A. Bagnell1,2, D. Lovas1,2, M. Alda1,3, B. Pavlova1,3 and R. Uher1,3

1Department of Psychiatry, Dalhousie University, Halifax, NS, Canada; 2IWK Health Centre, Halifax, NS, Canada and 3Nova Scotia Health Authority, Halifax, NS, Canada

Abstract

Background. Offspring of parents with major mood disorders (MDDs) are at increased risk for early psychopathology. We aim to compare the rates of neurodevelopmental disorders in offspring of parents with bipolar disorder, major depressive disorder, and controls.

Method. We established a lifetime diagnosis of neurodevelopmental disorders [attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, communication disorders, intellectual disabilities, specific learning disorders, and motor disorders] using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version in 400 participants (mean age 11.3 ± S.D. 3.9 years), including 93 offspring of parents with bipolar disorder, 182 offspring of parents with major depressive disorder, and 125 control offspring of parents with no mood disorder.

Results. Neurodevelopmental disorders were elevated in offspring of parents with bipolar disorder [odds ratio (OR) 2.34, 95% confidence interval (CI) 1.23–4.47, p = 0.010] and major depressive disorder (OR 1.87, 95% CI 1.03–3.39, p = 0.035) compared to controls. This difference was driven by the rates of ADHD, which were highest among offspring of parents with bipolar disorder (30.1%), intermediate in offspring of parents with major depressive disorder (24.2%), and lowest in controls (14.4%). There were no significant differences in frequencies of other neurodevelopmental disorders between the three groups. Chronic course of mood disorder in parents was associated with higher rates of any neurodevelopmental disorder and higher rates of ADHD in offspring.

Conclusions. Our findings suggest monitoring for ADHD and other neurodevelopmental disorders in offspring of parents with MDDs may be indicated to improve early diagnosis and treatment.

Introduction

Neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), communication disorders, intellectual disabilities, specific learning disorders, and motor disorders, are a group of conditions with onset in the early developmental period (American Psychiatric Association, 2013; Rutter & Uher, 2012). These disorders frequently co-occur (Simonoff et al., 2008) and are associated with higher rates of major psychiatric disorders that develop later in life (Cooper, Smiley, Morrison, Williamson, & Allan, 2007; Meier et al., 2018; Sandstrom, Perroud, Alda, Uher, & Pavlova, 2021; Schalbroeck, Termorshuizen, Visser, van Amelsvoort, & Selten, 2019).

Children of parents with major mood disorders (MDDs) often present with early behavioral and emotional problems (Rasic, Hajek, Alda, & Uher, 2014; Schalbroeck et al., 2019) and are more likely to develop childhood onset disorders including anxiety disorders (Ellersgaard et al., 2018; Rasic et al., 2014). This developmental psychopathology may represent antecedents which predict and precede MDDs (Meier et al., 2018; Pine & Fox, 2015).

Some studies suggest that elevated rates of ADHD in offspring of affected parents may reflect abnormal neurodevelopmental processes, particularly in young offspring of parents with schizophrenia (Sanchez-Gistau et al., 2015), and that neurodevelopmental abnormalities may be antecedents in a subgroup of high-risk children of parents with bipolar disorder (Duffy, 2012). High rates of disruptive behavior disorders and ADHD have been reported in offspring of parents with bipolar disorder when compared with offspring of healthy parents and parents with non-bipolar disorders (Birmaher et al., 2009), and there is evidence that ADHD may be associated with liability to bipolar disorder (Meier et al., 2018). Observed attentional problems are elevated in offspring of parents with major depressive disorder.
and bipolar disorder (Ellersgaard et al., 2018; Sandstrom et al., 2020), and childhood ADHD may be an early manifestation of risk for depression and bipolar disorder in offspring at risk (Duffy, 2012; Rice et al., 2019). The negative neurodevelopmental outcomes of children having parents with depression have been reported (Kingston et al., 2018; Wolford et al., 2017). Both paternal depression and maternal depression in the pre-pregnancy, perinatal and postnatal periods increase risks of ADHD and ASD in offspring; these risks may further increase with the duration of parental depression and with the additive effect of paternal and maternal depression (Chen et al., 2020).

Evidence from a study using data from the Psychiatric Genomics Consortium suggests that ASD and affective disorders, such as bipolar and depressive disorders may have a shared etiology (Psychiatric Genomics Consortium, 2019), and epidemiological studies have found that children of parents with bipolar and depressive disorders have a 20–90% increased risk of developing ASD in later life (Chen et al., 2020; Rai et al., 2013; Sullivan et al., 2012). In addition, a recent meta-analysis found that parental affective, depressive, and bipolar disorders, as well as maternal affective and depressive disorders increased the risk of ASD in offspring (Ayano, Maravilla, & Alati, 2019). Some studies suggest that maternal antidepressant use during pregnancy may be associated with an increased risk of ASD (Rai et al., 2013), but it has been a widespread clinical finding that maternal depression was associated with offspring ASD regardless of antidepressant use in the perinatal period (Hagberg, Robijn, & Jick, 2018; Rai et al., 2017).

There is limited literature on other neurodevelopmental disorders in offspring of parents with MDDs. Studies of high-risk offspring suggest cognitive deficits, particularly deficits in working memory, visual–spatial memory, and cognitive planning prior to the onset of bipolar disorder (Lin et al., 2017). A meta-analysis of neurocognition in youth with familial high risk for bipolar disorder found significant deficits in several cognitive domains, including visual memory, verbal memory, processing speed and sustained attention (Bora & Ozerdem, 2017), and a recent meta-analysis of cognitive performance in first-degree relatives of individuals with major depressive disorder found impairment across all measures of cognition (including full-scale IQ, verbal intelligence, perceptual intelligence, academic performance, and language) as a feature of familial disposition for major depressive disorder (MacKenzie, Uher, & Pavlova, 2019).

In summary, neurodevelopmental traits may be a feature of familial disposition for mood disorders (Rice et al., 2019), thus early identification of high-risk offspring with neurodevelopmental psychopathology may be clinically useful, as it may indicate which children would most benefit from early interventions aimed at reducing the risk of severe mental illness (Beardslee, Gladstone, & O’Connor, 2011; Nurnberger, Jr. et al., 2011).

Although several previous studies examined the rates of ADHD and ASD in offspring of parents with MDDs (Ayano et al., 2019; Birmaher et al., 2009; Chen et al., 2020; Duffy, 2012; Sullivan et al., 2012), literature on other neurodevelopmental disorders in the offspring is rather limited, and there has been no previous study of the full spectrum of neurodevelopmental disorders in offspring of parents with MDDs. Therefore, the first aim of the current study is to compare the rates of the spectrum of neurodevelopmental disorders in offspring of parents with bipolar disorder and offspring of parents with major depressive disorder with control offspring.

A family history of mood disorders has been associated with an early age at onset and chronic course of major depressive disorder (Lieb, Isensee, Hofer, Pfister, & Wittchen, 2002; Musliner et al., 2015) and bipolar disorder (Baldessarini et al., 2012; Ortiz et al., 2011). A recent meta-analysis suggests that people with mood disorders have significantly elevated rates of concurrent ADHD (Sandstrom et al., 2021). Childhood onset of bipolar disorder may be associated with the highest rates of comorbid ADHD (Propper et al., 2015). Another study highlighted a link between early onset mood symptoms and genetic liability to ADHD (Rice et al., 2019). Potential explanations for the relationship between neurodevelopmental problems and mood disorders include shared genetic factors (Anttila et al., 2018) and environmental factors (Dvir, Ford, Hill, & Frazier, 2014; Zwicker et al., 2020). This raises the question whether ADHD and other neurodevelopmental disorders, which have an early age at onset and chronic course, may be particularly common in familial cases of MDDs that are marked by early age at onset and chronic course (Chen et al., 2020). However, the relationship between the familial history of MDDs, illness course in affected parent, and neurodevelopmental disorders in offspring at risk, is yet to be examined. Therefore, the second aim of the current study is to examine the relationship between course of the illness in affected parents and rates of neurodevelopmental disorders in offspring at risk, as an early onset and chronic course of parent’s mood disorder may be associated with a common genetic disposition for neurodevelopmental disorders in offspring.

Method

Participants

Participants of this study were offspring of parents with bipolar disorder, major depressive disorder, and offspring of parents without a major psychiatric disorder (controls) who provided diagnostic information as part of the Families Overcoming Risks and Building Opportunities for Wellbeing project (FORBOW) (Uher et al., 2014). Offspring of parents with bipolar disorder and offspring of parents with major depressive disorder were enrolled through affected parents receiving inpatient and outpatient psychiatric services in Nova Scotia, Canada, where clinicians systematically inquire whether patients with an MDD have biological children in the eligible age range. Control offspring were enrolled through schools serving the geographic areas from which high-risk offspring were recruited. Inclusion criteria were availability of at least one biological parent for assessment and age of offspring between 4 and 24 years. We aimed to be inclusive. We chose 4 years as the minimum age when at least some neurodevelopmental disorders (e.g. ASDs) can be reliably diagnosed. We chose a maximum age of 24 as a maximum age when it is still possible to reliably collect developmental history through parent report. Offspring in the eligible age range were enrolled irrespective of psychopathology. Exclusion criteria were unavailability of both biological parents for assessment, and severe psychopathology (including non-affective psychotic disorders) other than an MDD in the parents. Parents with common mental disorders other than mood disorders (e.g. anxiety disorders and substance use disorders) were included in the control group.

The study protocol was approved by the Nova Scotia Health Authority Research Ethics Board. All participants with capacity provided written informed consent. For children who did not have the capacity to make a fully informed decision about participating, a parent or guardian provided written informed consent, and the child gave an assent.
Parent assessment

Parents and children were assessed by separate teams of assessors. The parents’ assessors established parent DSM-IV and DSM-5 lifetime diagnosis with the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott & Spitzer, 1979) and the Structured Clinical Interview for DSM Disorders (SCID) (First, Williams, Karg, & Spitzer, 2014). Parent diagnoses were confirmed in consensus meetings with licensed psychiatrists blind to child psychopathology. We recorded an early age at onset if the first major mood episode occurred before the age of 21 years (Preisig et al., 2016). We classified the course of parental mood disorders as episodic (with full or partial remissions between mood episodes) or chronic (fluctuating or persistent without remissions) according to the Diagnostic Interview for Genetic Studies (Nurnberger, Jr. et al., 2011). In addition to the mental disorders of adulthood, we recorded the symptoms and history of ADHD in parents. We used the Family Interview for Genetic Studies to collect diagnostic data on biological co-parent who were not available for direct interview.

Offspring assessment

The youth assessors blind to parent diagnosis interviewed the youth participants and their parents or other care-givers regarding child psychopathology with the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 2013). For offspring aged 18 or older both the K-SADS-PL and SCID-5 (First et al., 2014) were completed.

All diagnoses of intellectual disability and specific learning disorders in offspring were made based on formal cognitive assessments, including not limited to the Wexler Abbreviated Scale of Intelligence (MacKenzie et al., 2019). Communication disorders were assessed using the Clinical Evaluation of Language Fundamentals (CELF-5) and test of narrative speech, evaluated by a licensed speech and language pathologist. Observational data were obtained to inform motor disorders in offspring. The Autism Diagnostic Observation Schedule (ADOS) assessment and a detailed developmental history were used to determine an ASD diagnosis in offspring. School reports and psycho-educational assessment reports were obtained from the parents as additional information.

All youth DSM-IV and DSM-5 lifetime diagnoses were confirmed in consensus meetings with licensed child and adolescent psychiatrists presented with all available information on offspring, but blind to information on parents. The diagnoses were recorded without hierarchy. For example, the diagnosis of ADHD was recorded if symptomatic criteria were met, irrespective of whether a diagnosis of ASD was present. ADHD, ASD, mild to moderate intellectual disabilities, specific learning disorder, and motor disorders were included as neurodevelopmental disorders.

Data analysis

We defined the binary primary dependent variable as the lifetime diagnosis of any neurodevelopmental disorder in offspring (0 = absent, 1 = present). We tested the effect of parent’s diagnosis on the presence of neurodevelopmental disorders in the offspring using logistic regression with robust standard errors to account for non-independence of siblings within families, implemented in STATA 16 (StataCorp LP, 2019). Parent’s diagnosis was classified into three subgroups: (1) lifetime diagnosis of bipolar disorder; (2) lifetime diagnosis of major depressive disorder; or (3) no diagnosis of a major psychiatric disorder. Parent’s course of an MDD was classified into two subgroups: (1) chronic course or (2) episodic course.

We controlled for offspring’s age and sex, as potential confounders. For each of the two high risk groups, we compared the rates of neurodevelopmental disorders (ADHD, ASD, intellectual disabilities, specific learning disorders, and motor disorders) against the control group. We reported the effect size of comparisons as odds ratios (ORs) and their 95% confidence intervals (95% CIs). OR greater than 1 indicates an increased risk of the outcome in the high-risk group compared to the control group. Since we expected that the high-risk offspring groups would differ from the control group on the primary variable of neurodevelopmental disorders as well as specific tests of individual disorders, we report all results with p < 0.05 as nominally statistically significant. To assess the probability of type 1 error in the context of multiple testing of specific diagnoses, we also report statistical significance corrected for the number of tests (12 tests, corrected p-value <0.0042). Assuming that the rate of neurodevelopmental disorders among offspring of parents with mood disorders may be twice that of control offspring (Raslic et al., 2014), we had statistical power of 72% and 86% to detect such difference for offspring of parents with bipolar disorder and offspring of parents with major depressive disorders, respectively, at a nominal level of significance (α = 0.05). At a level of significance corrected for multiple testing, the power drops to 38% and 54% for offspring of parents with bipolar disorder and major depressive disorder, respectively.

Results

Participants

Between February 2013 and December 2018, we assessed 400 participants aged 4–24 years, including 93 offspring of parents with bipolar disorder, 182 offspring of parents with major depressive disorder, and 125 control offspring. The mean age of the offspring at the time of assessment was 11.3 years (s.d. = 3.9). Sample characteristics for each group by familial history are shown in Table 1.

Parent mood disorder and neurodevelopmental disorders in offspring

The rates of neurodevelopmental disorders in offspring of parents with bipolar disorder, offspring of parents with major depressive disorder and control offspring are shown in Table 2. The diagnosis of any neurodevelopmental disorder was more frequent in offspring of parents with bipolar disorder (OR 2.34, 95% CI 1.23–4.47, p = 0.010) and offspring of parents with major depressive disorder (OR 1.87, 95% CI 1.03–3.39, p = 0.040) than that in control offspring (Fig. 1).

The rate of any neurodevelopmental disorder did not significantly differ between offspring of parents with major depressive disorder and offspring of parents with bipolar disorder (p = 0.421).

The odds of ADHD were significantly increased in offspring of parents with bipolar disorder (OR 2.67, 95% CI 1.35–5.27, p = 0.005) and in offspring of parents with major depressive disorder (OR 1.99, 95% CI 1.05–3.79, p = 0.035) compared to the control offspring (Fig. 1). The rate of ADHD did not significantly differ
between the offspring of parents with major depressive disorder and the offspring of parents with bipolar disorder (p = 0.344). There was no significant difference in the rates of other neurodevelopmental disorders: ASD, intellectual disabilities, specific learning disorder, and motor disorders, between the three groups (all p > 0.1; Table 2). For number of neurodevelopmental disorders and overlap between neurodevelopmental disorders, see online Supplementary Tables S1–S3.

### Table 1. Offspring characteristics by parent diagnosis

<table>
<thead>
<tr>
<th>Parent diagnosis (N)</th>
<th>No diagnosis (N = 125)</th>
<th>Major depressive disorder (N = 182)</th>
<th>Bipolar disorder (N = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at assessment (years), mean (s.d.)</td>
<td>11.3 ± 3.4</td>
<td>11.2 ± 3.8</td>
<td>11.5 ± 4.6</td>
</tr>
<tr>
<td>Socioeconomic status (range 0–5), mean (s.d.)</td>
<td>3.57 ± 1.16</td>
<td>2.85 ± 1.42</td>
<td>2.88 ± 1.30</td>
</tr>
<tr>
<td>Gender, female: N (%)</td>
<td>59 (47)</td>
<td>95 (52)</td>
<td>47 (51)</td>
</tr>
<tr>
<td>Ethnicity, white: N (%)</td>
<td>111 (89)</td>
<td>162 (89)</td>
<td>91 (98)</td>
</tr>
<tr>
<td>Living with both parents: N (%)</td>
<td>92 (74)</td>
<td>107 (59)</td>
<td>57 (61)</td>
</tr>
<tr>
<td>Parent disorder onset before age 21: N (%)</td>
<td>NA</td>
<td>99 (54)</td>
<td>45 (48)</td>
</tr>
<tr>
<td>Parent disorder chronic course: N (%)</td>
<td>NA</td>
<td>72 (40)</td>
<td>45 (48)</td>
</tr>
</tbody>
</table>

### Table 2. Rates of neurodevelopmental disorders for offspring based on parent diagnosis

<table>
<thead>
<tr>
<th>Parent diagnosis (N)</th>
<th>No diagnosis (N = 125)</th>
<th>Major depressive disorder (N = 182)</th>
<th>Bipolar disorder (N = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime diagnosis of neurodevelopmental disorder: N (%)</td>
<td>28 (22)</td>
<td>59 (32)</td>
<td>32 (34)</td>
</tr>
<tr>
<td>Attention-deficit/hyperactivity disorder: N (%)</td>
<td>18 (14)</td>
<td>44 (24)</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Autism spectrum disorder: N (%)</td>
<td>5 (4)</td>
<td>8 (4)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Communication disorders: N (%)</td>
<td>8 (6)</td>
<td>14 (8)</td>
<td>6 (6.5)</td>
</tr>
<tr>
<td>Intellectual disabilities: N (%)</td>
<td>3 (2)</td>
<td>10 (5)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Specific learning disorder: N (%)</td>
<td>2 (2)</td>
<td>7 (4)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Motor disorders: N (%)</td>
<td>8 (6)</td>
<td>14 (7)</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

**Parent ADHD and neurodevelopmental disorders in offspring**

Lifetime diagnosis of ADHD was present in 43 parents (20 mothers and 23 fathers) and was higher among parents with mood disorders (n = 34, 12.5%) than among control parents (n = 9, 7.4%). To confirm whether the association between parent mood disorder and neurodevelopmental disorders in offspring was independent of the influence of comorbid ADHD in parents, we completed a sensitivity analysis controlling for lifetime ADHD diagnosis in parents. In this analysis, any neurodevelopmental disorder in offspring was independently associated with parents’ mood disorder (OR 2.03, 95% CI 1.16–3.71, p = 0.013) and parents’ ADHD (OR 2.16, 95% CI 1.23–3.79, p = 0.007).

When we separated parent mood disorders into bipolar and depression while controlling for parents’ ADHD, the association between parents’ bipolar disorder and offspring neurodevelopmental disorder remained strong and statistically significant (OR 2.76, 95% CI 1.43–5.36, p = 0.003), but the association between parental depression and offspring neurodevelopmental disorders got attenuated and was no longer statistically significant (OR 1.70, 95% CI 0.93–3.11, p = 0.084).

**Parent course of illness and neurodevelopmental disorders in offspring**

We further explored whether the age at onset or the course of mood disorder in the parent affected the risk of neurodevelopmental disorders in their offspring. Among offspring of parents with MDDs, early onset of parental mood disorder was not significantly associated with the rates of neurodevelopmental disorders (all p > 0.1; Fig. 2). However, a chronic course of the parental illness was associated with higher odds of any neurodevelopmental disorder (OR 2.14, 95% CI 1.16–3.94, p = 0.015) and higher odds of ADHD (OR 2.03, 95% CI 1.10–3.78, p = 0.025). The relationship between the parent’s course of the illness and the offspring’s risk of neurodevelopmental disorders was similar whether the parent’s diagnosis was major depressive disorder or bipolar disorder (Table 3).

**Discussion**

We found that offspring of parents with MDDs, and in particular the children of parents living with bipolar disorder, had elevated rates of ADHD in comparison with control offspring. We did not find increased rates of neurodevelopmental disorders other than ADHD. We found that a chronic course of the mood disorder...
in parents was associated with higher rates of neurodevelopmental disorders and ADHD in offspring.

The finding of higher rates of ADHD in offspring of parents with bipolar disorder is consistent with previous literature (Birmaher et al., 2009; Rasic et al., 2014; Sanchez-Gistau et al., 2015). The significance of the overrepresentation of ADHD in young offspring of parents with bipolar disorder is a subject of ongoing debate. There has been controversy about the nature of the association between childhood ADHD and the development of bipolar disorder (Propper et al., 2015) and evidence from previous familial high-risk studies suggests that the clinical diagnosis of childhood ADHD may not be a strong predictor of the development of bipolar disorder (Akiskal et al., 1985; Duffy, Alda, Hajek, Sherry, & Grof, 2010). However, subjective problems with attention may form part of the early course of the illness, and neurodevelopmental abnormalities may be an antecedent in a subgroup of offspring of parents with bipolar disorder (Duffy, 2012). Thus, screening for ADHD in offspring at risk may be clinically useful.

In addition, the rates of comorbid ADHD are significantly higher in very early onset bipolar disorder (age at onset <15 years) (Propper et al., 2015). Childhood ADHD may have contributed to over-reporting of ‘manic-like’ symptoms and ‘ultra-rapid-cycling’ in earlier studies of juvenile onset bipolar disorder conducted on clinically referred children with ADHD (Biederman et al., 1996; Faraone, Biederman, Mennin, Wozniak, & Spencer, 1997; Wozniak et al., 1995). This highlights the clinical importance of differential diagnosis between childhood ADHD and early onset bipolar disorder, particularly in children of parents with bipolar disorder, as mood dysregulation secondary to impulsivity and hyperactivity in children with untreated ADHD may be confused with symptoms of early onset mania.

The finding that offspring of parents with major depressive disorder presented with higher rates of ADHD is consistent with previous studies suggesting that both paternal depression and maternal depression increase offspring ADHD and ASD risks, and these risks increase further with a longer duration of parental depression and with the additive effect of parental and maternal depression (Chen et al., 2020; Wolford et al., 2017). A meta-analysis showed that parents of children with ADHD had a higher major depressive disorder risk than did those of children without ADHD (Rasic et al., 2014) and longitudinal studies suggest that people with childhood ADHD are more likely to develop depressive symptoms in adolescence (Rice et al., 2019) or in adulthood (Meinzer et al., 2016). The finding that a chronic course of the mood disorder in parents was associated with higher rates of neurodevelopmental disorders and ADHD in offspring in the study further support evidence from the above studies that childhood ADHD may be an early manifestation of a broader disposition to psychopathology that may later develop into a more persistent subtype of major depressive disorder.

There are several potential explanations for the increased prevalence of childhood ADHD in offspring of parents with MDDs. Elevated ADHD in offspring at risk may be due to common genetic vulnerability. A genome-wide analysis across eight mental disorders reported a substantial overlap of genetic risk variants between ADHD and mood disorders, with a particularly strong genetic correlation between ADHD and MDD (Psychiatric Genomics Consortium, 2019). Genetic risk for ADHD may be particularly important to consider in early-onset depression, as cross-sectional and longitudinal cohort studies show heightened rates of depression in children with ADHD, which may be partly due to the strong genetic correlation between ADHD and early onset depression (Rice et al., 2019).

Environmental factors may contribute to attentional problems in offspring of parents with MDDs. For example, premature birth and childhood trauma associated with parental mental illness may increase the risk. Previous studies found that parental depression and stress during the pregnancy or postnatal period were both correlated with children’s hyperactivity and inattention problems or neurodevelopmental diagnoses (Beversdorf et al., 2005; Goodman et al., 2011; Kinney, Munir, Crowley, & Miller, 2008; Rodriguez & Bohlin, 2005; Say, Karabekiroglu, Babadagi, & Yuce, 2016). Family dysfunction, inconsistent parenting style, and maladaptive communication can be associated with an increased risk of ADHD in offspring at risk (Cussen, Sciberras, Ukoumunne, & Efron, 2012). However, there is growing debate about over-detection of ADHD in young children and an issue of misinterpreting their attentional and behavioral problems (Kazda, Bell, Thomas, McGeechan, & Barratt, 2019) that may be secondary to childhood maltreatment and other adverse environmental factors.

Untreated childhood ADHD may result in dysfunctional peer relationships and poor educational outcomes (Kessler et al., 2014), and subsequently in a lower self-esteem, which is a risk factor for...
mood disorders (Boden, Fergusson, & Horwood, 2008). Children with ADHD, and those with high genetic risk for ADHD are more likely to experience maltreatment in childhood, which may in turn contribute to the development of mood disorders (Capusan et al., 2016; Zwicker et al., 2020).

We did not find a significant association between any other neurodevelopmental disorder (ASD, intellectual disabilities, specific learning disorders, and motor disorders) and familial history of MDDs. Prior epidemiological (Ayano et al., 2019) and genetic (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019) studies suggest overlapping genetic and familial risk for mood and ASD. There is also evidence for family history of mood disorders to be associated with a lower cognitive ability (Lin et al., 2017; MacKenzie et al., 2019). Literature on mood disorders’ relationship with other types of neurodevelopmental disorders is limited. In the current study, the rates of ASD, intellectual disabilities, and specific learning disorders are nominally higher in offspring with family history of MDDs, but not significantly different from control offspring. This null finding may be the result of low statistical power. The smaller numbers of offspring with neurodevelopmental disorders other than ADHD reduces confidence in the current study’s findings for specific diagnoses. Larger samples will be required to conclusively establish to what extent the familial risk for mood disorders overlaps with diathesis to ASD, intellectual disabilities, specific learning disorders, and motor disorders.

Neurodevelopmental disorders start, by definition, at an early age and follow a chronic, persistent course (Uher & Rutter, 2012). We examined whether early age at onset and chronic course of mood disorders in parents are associated with the rate of neurodevelopmental disorders in offspring. We found that neurodevelopmental disorders were substantially more frequent among offspring of parents, whose mood disorder had taken a chronic or persistent course, irrespective of age at onset. This finding suggests that neurodevelopmental disorders may overlap with familial disposition to a subgroup of mood disorders that tend to run a chronic or persistent course (Uher, Mantere, Suominen, & Isometsa, 2013). On the contrary, the present data do not support a strong link between neurodevelopmental disorder and familial risk for early age at onset mood disorders with an episodic course (Preisig et al., 2016).

The distinction between early onset episodic and chronic forms of mood disorders may help explain discrepancies between previous studies of offspring in finding a higher rate of neurodevelopmental disorders or not (Duffy, 2012). We propose that the course typology of mood disorders may be informative of etiology (Uher & Rutter, 2012), with a chronic course being associated with neurodevelopmental factors.

**Clinical implications**

Our findings may remind clinicians regarding the importance of screening for ADHD and other neurodevelopmental disorders in offspring of parents with MDDs. Early diagnosis may allow for targeted treatment, and early interventions may in turn reduce risk of more severe mental illness later in the clinical course (Beardslee et al., 2011; Nurnberger, Jr. et al., 2011).

**Strengths and limitations**

To the best of our knowledge, this is the first study that has attempted to examine the rates of the spectrum of neurodevelopmental disorders in offspring of parents with bipolar and major depressive disorders. The study benefits from a substantial sample with comprehensive diagnostic assessments. However, our results must be interpreted in the context of several limitations. First, ADHD is more prevalent in the general pediatric population compared to other neurodevelopmental disorders (Thomas, Sanders, Doust, Beller, & Glasziou, 2015). Thus, we expected ADHD diagnoses to account for a large portion of the neurodevelopmental disorders in our sample. Apart from ADHD in offspring, rates of other neurodevelopmental disorders were low, and we were not able to fully interpret the findings due to low statistical power. Firm conclusions on whether the full spectrum of neurodevelopmental disorders is associated with familial liability to mood disorders may be only possible with larger combined datasets.

Second, given the relatively young age of offspring in the sample, we are unable to conclude whether ADHD or other neurodevelopmental disorders in offspring of parents with MDDs are associated with increased risk of developing mood disorders. Prospective longitudinal observation of large high-risk cohorts will determine if neurodevelopmental psychopathology is specifically associated with emerging MDDs later in life.

Wide variability in offspring age (including preschool children who might be diagnosed with ADHD and other neurodevelopmental disorders at a subsequent stage) potentially influenced rates of ADHD and other neurodevelopmental disorders in the study.

Third, we recorded a history of ADHD in parents, but we did not collect information on other neurodevelopmental disorders in

<table>
<thead>
<tr>
<th>Parent diagnosis, course of illness</th>
<th>Major depression, chronic (N = 72)</th>
<th>Major depression, episodic (N = 110)</th>
<th>Bipolar disorder, chronic (N = 45)</th>
<th>Bipolar disorder, episodic (N = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime diagnosis of any neurodevelopmental disorder: N (%)</td>
<td>26 (36)</td>
<td>33 (30)</td>
<td>19 (42)</td>
<td>13 (27)</td>
</tr>
<tr>
<td>Attention-deficit/hyperactivity disorder: N (%)</td>
<td>22 (31)</td>
<td>22 (20)</td>
<td>17 (38)</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Autism spectrum disorder: N (%)</td>
<td>3 (4)</td>
<td>4 (4)</td>
<td>3 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Communication disorders: N (%)</td>
<td>4 (6)</td>
<td>10 (9)</td>
<td>4 (9)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Intellectual disabilities: N (%)</td>
<td>3 (4)</td>
<td>7 (6)</td>
<td>4 (9)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Specific learning disorder: N (%)</td>
<td>2 (3)</td>
<td>5 (5)</td>
<td>3 (7)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Motor disorders: N (%)</td>
<td>4 (6)</td>
<td>10 (9)</td>
<td>2 (4)</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>
parents in the study. We speculate that some of the parents may have an undiagnosed neurodevelopmental disorder other than ADHD, but we were not able to confirm this without a formal testing in parents.

Fourth, the age at onset of mood disorders in parents was assessed retrospectively, often with a long delay. The inaccuracy of such retrospective assessment may have contributed to not finding an association between age at onset in parents and neurodevelopmental disorders in offspring.

Fifth, there is a potential selection bias in the study, as families of parents with an MDD may be more motivated to participate (e.g., they may be interested in assessing the offspring at risk) and this may limit generalization of the findings. In addition, there is a risk of over-detection of ADHD in young children with attentional and behavioral problems (Kazda et al., 2019).

Conclusion

We found elevated rates of ADHD in offspring of parents with MDDs, in particular in offspring of parents with bipolar disorder. No other neurodevelopmental disorders were specifically associated with the familial history of bipolar disorder or major depressive disorder. A chronic course of the parental MDD was associated with higher rates of any neurodevelopmental disorder and higher rates of ADHD in offspring.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721001951

Financial support. Research leading to this report was funded by the Canada Research Chairs Program (award number 231397), the Canadian Institutes of Health Research (Grant reference numbers 124976, 142738, and 148394), the Brain & Behavior Research Foundation (NARSAD) Independent Investigator Grant 24684, Nova Scotia Health Research Foundation (grants 275319, 1716, and 553892), the Windsor Foundation, the Sutton Mental Health Innovation Fund and the Dalhousie Medical Research Foundation. The funders had no role in the study design, data collection, data analysis, data interpretation, and preparation of the manuscript, or the decision to submit the manuscript for publication.

Conflict of interest. The authors declare no conflict of interest.

References


StataCorp LP (2019). STATA 16. College Station, TX: StataCorp.


Downloaded from https://www.cambridge.org/core. IP address: 54.70.40.11, on 30 Jun 2021 at 01:56:38, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1017/S0033291721001951