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GUEST EDITORIAL

Introduction to the Special Issue on 'The Genetic Architecture of Neurodevelopmental Disorders'

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Neurodevelopmental Disorders ADHD and ASD

Neurodevelopmental disorders encompass a range of psychopathological conditions that are characterized by an early life onset. Examples include learning disabilities, intellectual disability, conduct disorder, Attention Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD). This special issue of *Behavior Genetics* addresses the genetic architecture of neurodevelopmental disorders with a focus on the two most common, highly heritable conditions, namely ADHD and ASD.

ADHD has a worldwide prevalence of 4–7% (Polanczyk et al. 2014) (Mohammadi et al. 2019) and often persists into adulthood (Faraone et al. 2006). Main symptoms of ADHD are inattention, and hyperactive and impulsive behaviors (American Psychiatric Association 2013), but the extent and combination of symptoms differ between affected individuals. ADHD is at a phenotypic and genetic level associated with negative long term outcomes such as low educational attainment (Polderman et al. 2010; Demontis et al. 2018), substance use (Chang et al. 2012; Liu et al. 2019), anxiety and depression (Li 2019; Nigg et al. 2020), and risk taking behaviors (Karlsson Linnér et al. 2019).

ASD has a prevalence of 1–5% (Brugha et al. 2011; Delobel-Ayoub et al. 2020), and is characterized by impairments in social skills and communication, by repetitive, restricted and stereotyped behaviors, and by hypo or hyper sensory sensitivity (American Psychiatric Association 2013). Like ADHD, ASD affected individuals show a heterogeneous manifestation of symptoms, and in addition, ASD is associated with the full range of cognitive functioning; from severe intellectually disability, to individuals performing at the high end of cognitive functioning (Charman et al. 2011; Lord et al. 2020). Similarly to ADHD, ASD is associated with an array of adverse outcomes across the lifespan, such as psychiatric disorders (Simonoff et al. 2008), premature mortality (Hirvikoski et al. 2016), and poor physical health (Croen et al. 2015).

Themes: Comorbidity, Measurement Strategies, and a Monogenic Neurodevelopmental Disorder

This special issue will address three main themes that are associated with the genetic architecture of neurodevelopmental disorders. The first theme centers on the observation that neurodevelopmental disorders are often comorbid with other psychiatric and psychological problems. This observation has led researchers to suggest the presence of a shared etiological risk for psychopathology, the so-called P-factor (Ronald 2019). Several tools can be used to investigate the etiology of comorbidity and the presence of a potential P-factor, such as polygenic risk scores (Jansen et al. 2019; Riglin et al. 2019; de Zeeuw et al. 2020), twin models (Pan et al. 2019), and adoption designs (Sellers et al. 2020). The second theme of this issue is the value of different measurement strategies to assess neurodevelopmental problems. For instance, Castelbaum et al. (2019) add more nuances to the twin discordant design by adding a continuous trait measure, and Dolan et al. (2020) investigates the added value of multiple measures of an individual by different raters and/or instruments and how to harmonize those. A study by Gagne et al. (2020) uses parent reported and lab-based measures of inhibitory control to test the association with

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ADHD problems in a longitudinal twin design. A last theme focuses on monogenic neurodevelopmental disorders and their potential value in disentangling the genetic architecture of neurodevelopmental disorders.

This editorial aims connecting the different studies as presented in this issue, and put them in the context of current scientific knowledge. In addition, it will discuss how to move forward in improving our understanding of the genetic architecture of neurodevelopmental disorders.

Comorbidity and a Shared Etiological Risk

As is observed for many psychiatric conditions, comorbid problems are highly prevalent in neurodevelopmental disorders. ADHD and ASD frequently co-occur (Rommelse et al. 2010), and both disorders are in addition often comorbid with other problems such as anxiety, depression and sleep problems (Mohammadi et al. 2019). Twin studies showed that genetic factors my partly explain this comorbidity (Ronald et al. 2014; Taylor et al. 2013; Polderman et al. 2014), and recent large genome wide association studies (GWAS) confirm these observations. For instance, (Grove et al. 2019) reported a genetic correlation of 0.36 between ADHD and ASD. In addition, a recent analysis across eight psychiatric disorders showed that major depressive disorder (MDD) also shared genetic factors with ADHD (r_g 0.44) and ASD (r_g 0.46) (Cross-Disorder Group of the Psychiatric Genomics Consortium 2019; Liu et al. 2019) showed a genetic correlation between ADHD and smoking (r_g 0.41). Capitalizing on the large recent GWAS for multiple psychiatric disorders, several authors of the current special issue investigated genetic correlations and polygenic risk score predictions (i.e., an estimate of the cumulative effect of genetic variants associated with a trait in one individual) with ADHD and ASD to obtain more insights in the etiology of comorbidity.

Jansen et al. (2019) aimed to test the predictive value of a polygenic risk score (PRS) of ADHD, ASD, and Schizophrenia. They tested if the PRS of these three disorders could distinguish controls from cases that had an ADHD or ASD diagnosis, or both diagnoses. To their surprise, only the ADHD PRS was significantly associated with case–control status. A further investigation learned that this association was primarily driven by ADHD diagnostic status, and not ASD, suggesting that the ADHD PRS captures ADHD specific genetic effects, and no genetic effects that are shared with ASD. These results contradict the findings of genetic correlations between ADHD and ASD as reported in previous twin studies in children (Taylor et al. 2013), and the latest ASD GWAS (Grove et al. 2019). An explanation may be that specific sample characteristics play a role here, and therefore, testing the ADHD and ASD PRS in an independent child psychiatric sample would be highly interesting.

It has been discussed to what extent a PRS captures purely genetic effects, or whether also gene-environment correlation effects play a role. In a recent study, Kong et al. (2018) aimed to disentangle these genetic and environmental effects by investigating if the prediction of a PRS based on parent–child transmitted alleles differed from the prediction of a PRS based on non-transmitted alleles. In other words, they investigated if genetically mediated effects predicted children's outcomes to a similar extent as environmentally mediated effects. Kong coined the term 'genetic nurture' to describe the latter; the environment that parents create is after all partly based on their genetic make-up. de Zeeuw et al. (2020) tested the 'genetic nurture' effect in their contribution to this special issue. In a sample of trios (i.e., parents and child), they constructed a PRS of EA and of ADHD based on the parent–child transmitted alleles, and, for both traits, a PRS based on the non-transmitted alleles. They observed some evidence for 'genetic nurturing' for EA in adults offspring. The other associations with offspring ADHD and EA were only present for the transmitted EA and ADHD PRS, leading the authors to conclude that offspring outcomes in their sample are mainly attributable to the shared genes between parents and offspring and to a lesser extent to their shared environment. (Riglin et al. 2019) also investigated for this issue shared genetic factors between traits, but focused specifically on the general psychopathology factor, the so-called P-factor. Based on several questionnaires assessing emotional, behavioral, social-communication and neurodevelopmental problems at age 7/8 and at age 13, a P-factor and specific factors for each age were constructed. The ADHD and Schizophrenia PRS were both associated with the P-factor at both ages. The Schizophrenia PRS is interesting as this is considered a late-onset, adult disorder, while in this study they tested for an association in a children's sample. Additionally, apart from the association with the P-factor, a suggestive association was observed for the specific 'emotional problems factor' at age 7 (capturing anxiety, depression, and phobia) and the Schizophrenia PRS. A related finding was reported previously in a population based sample where the Schizophrenia PRS was associated with internalizing problems assessed in children at age 3, 6 and 10 years old (Jansen et al. 2018). Both findings suggest that the distinction between early and late onset disorders is not present regarding the biological basis that might be shared between these disorders.

Pan et al. (2019) investigated for this special issue the association between ASD and somatic traits in a co-twin control design using a sample enriched for autistic traits. The study focused on immunological, gastrointestinal, cardiovascular, infectious disease, and neurological problems, as there is some evidence that these particular problems are elevated in individuals with ASD. Their findings showed that in particular neurological and immunological conditions were

associated with ASD. Since somatic conditions seriously affect the quality of life and potentially increase autistic symptoms, this research is an important first step in obtaining a better understanding of the complexity of somatic conditions in ASD. This study also supports current hypotheses that link psychiatric traits to somatic traits such as the immunological system to schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014), and eating disorders to metabolic traits (Watson et al. 2019).

An adoption design allows one to examine the effects of parent–offspring dynamics on resulting behaviors in both parties, and disentangle genetic from environmental influences. For instance, depressive behavior of parents can result in ADHD symptoms in offspring, or ADHD symptoms in offspring can evoke aggression in parents. In addition, a shared genetic risk may contribute to the manifestation of these behaviors. An important finding of Sellers et al. in this issue, was that hostile maternal behavior of adoptive mothers was associated with ADHD symptoms and aggressive behavior in their (genetically unrelated) offspring, suggesting an environmental effect instead of passive gene-environment correlation in this association.

In sum, the studies on comorbidity and shared genetic risk in this issue almost all suggest genetic overlap between neurodevelopmental disorders and multiple related traits, varying from educational attainment to emotional problems, to somatic traits, to adult onset disorders such as schizophrenia. These findings may have implications for treatment, disorder classification, and for future etiological research that aims to obtain a better understanding of underlying causes of neurodevelopmental problems.

Neurodevelopmental Disorders as Dimensional Trait or Diagnostic Classification

How best to measure neurodevelopmental disorders is a long-standing discussion. Diagnostic manuals currently draw a dichotomy between individuals with and without these conditions, and this is mirrored in a majority of molecular genetic studies of these disorders, which adopt case–control approaches. Yet it is clear that milder traits that characterize neurodevelopmental disorders are continuously distributed throughout the general population (Constantino and Todd 2003). A growing body of evidence from both twin and molecular genetic studies also indicates that the genetic factors that influence clinical neurodevelopmental disorders also influence subthreshold variation in traits of these conditions (Taylor et al. 2019). This suggests that a dimensional assessment of traits may capture additional valuable variation compared to a case–control assessment only. This evidence is especially robust for neurodevelopmental disorders, such as ASD and ADHD (Robinson et al. 2011; Larsson et al. 2012) opening up a multitude of possible approaches to measuring neurodevelopmental disorders, many of which are applied in innovative ways in this special issue.

If we can use dimensional measures of neurodevelopmental disorders, then who should complete these measures? Parental reports are commonplace, and some studies also utilize self-reports and teacher reports. Are all these different raters assessing the same construct? And can conclusions of genetic studies based on one rater be extrapolated to another? This is the issue at the core of a paper by Dolan et al. (2020) in this issue. Using ADHD measures collected from participants in the Netherlands Twin Register, they performed a multivariate twin study aiming to assess whether similar genetic factors contributed to both parent and teacher ratings of ADHD, using four different measures. For measures of hyperactivity, genetic correlations averaged at approximately 0.50, and 0.55 for measures of inattention. Furthermore, hyperactivity and inattention were strongly genetically correlated, regardless of measure. These results thus indicate that ADHD measures taken from different raters are, to a degree, influenced by some of the same genetic factors and so large-scale GWAS meta-analyses could benefit from including data from multiple raters. Notably, the environmental correlations were lower, however, indicating that some caution might be needed to generalizing results from studies of environmental risks across raters. Further, there is a dearth of evidence on whether measures of other neurodevelopmental disorders taken from multiple raters have generalizable results (Ronald et al. 2008). It would be beneficial to see if Dolan et al.'s (2020) results apply to other neurodevelopmental disorders as well.

Another paper in this special issue emphasizes that it is not just a question of *who* completed measures of the phenotypes we study; the method used is also of substantial importance. Gagne et al. (2020) highlight that inhibitory control (IC) is a potential early risk factor for subsequent ADHD. They therefore carried out a twin study that aimed to assess the association between IC at age 2 and ADHD symptoms at age 3, and tested whether the observed associations were due to shared genetic factors. Importantly, they carried out two sets of analyses: one where IC was assessed using parental reports and one where IC was assessed using laboratory-based measures. They found statistically significant associations between IC at age 2 and ADHD at age 3, and report negative genetic correlations between these measures. Of importance, however, is the finding that the correlations are smaller for laboratory-based measures of IC. Thus, as well as adding new evidence on the association between early IC and ADHD symptoms, this study highlights the need for a multi-rater, multi-method approaches in behavior genetics.

It is thus increasingly clear that continuous measures of neurodevelopmental disorders are of considerable value in

disentangling their genetic architecture. Typically, these measures are applied to large-scale, general population samples, which include small numbers of individuals with diagnoses of neurodevelopmental disorders. Since there is such strong evidence that similar genetic factors influence these measures to differing severity levels, one might assume that these measures would behave very similarly in clinical groups compared to the general population. Castelbaum et al. (2019) turn this notion on its head, however. They collected data from twin samples including twin pairs where at least one twin had a diagnosis of ASD. They then examined quantitative trait severity in these individuals using two established measures [the Autism Diagnostic Observation Schedule (Lord et al. 1989) and Social Responsiveness Scale (Constantino and Gruber 2012)]. They performed twin analyses of these measures in these clinically affected twins. Their results were very surprising. We know very well from prior studies that measures of autistic traits are highly heritable in the general population (Ronald et al. 2006; Hoekstra et al. 2007; Castelbaum et al. 2019) replicated this finding in showing that the heritability of autistic traits in those without a diagnosis of ASD was 57%. Yet among clinically affected pairs, genetic variation accounted for only 5–7% of the variance in autistic traits. These surprising findings indicate that quantitative trait measures of ASD behave differently in clinical samples, and that severity of ASD symptoms among clinical cases may be more linked to nonshared environmental variation. These striking findings have the potential to change the way we think about ASD symptoms, and need to be replicated in other samples.

Monogenic Forms of Neurodevelopmental Disorders

The previous section discussed continuous traits of neurodevelopmental disorders, and their genetic links with clinical disorders. The dimensional model of neurodevelopmental disorders makes the assumption that these disorders arise following cumulative exposure to multiple risk factors of varying effect sizes. In this issue, however, Kaczorowski et al. (2020) draw our attention back to potential cases of neurodevelopmental disorders associated with monogenic disorders. Neurodevelopmental disorders are known to be elevated among individuals with certain monogenic disorders; for example, the very widely reported association between ASD and Fragile X syndrome. Kaczorowski et al., however, set out a detailed roadmap for understanding the genetic architecture of neurodevelopmental disorders based on monogenic disorders. They set out the example of neurofibromatosis type I, a rare monogenic disease caused by mutations in the NF1 gene, which causes tumors to grow along the nerves. Individuals with neurofibromatosis type I have elevated rates of ASD, ADHD, and learning disabilities. Quite a lot is currently known about the genetic underpinnings of neurofibromatosis, and so Kaczorowski et al. propose that it can yield valuable insights into the genetic architecture of neurodevelopmental disorders. For example, they argue that stratifying samples based on neurofibromatosis type I could be informative.

Conclusions and Future Directions

The studies published in this special issue further reconfirm a number of important findings within behavioral genetic studies. First, they once again reiterate that neurodevelopmental disorders are strongly heritable, reinforcing that they are among the most heritable of behavioural phenotypes (Polderman et al. 2015). They also confirm that genetic risks for neurodevelopmental disorders are likely to be shared with other neurodevelopmental disorders, as well as with psychiatric disorders.

This, however, brings us to the first important extension of prior work offered by this special issue. Although it is increasingly clear that genetic risks are shared between different neurodevelopmental and psychiatric phenotypes, the results published here indicate that neurodevelopmental disorders also share genetic risks with various non-psychiatric phenotypes. For example, in this issue we see evidence that genetic risks for ADHD might, to a degree, influence educational attainment, while it also appears that genetic risks for neurodevelopmental disorders might influence somatic outcomes. This highlights just how wide reaching the impact of the genetics of neurodevelopmental disorders might be, and which research questions lay ahead of us.

This special issue also further confirms the substantial value in utilizing dimensional measurements of neurodevelopmental disorders, and their application here is especially interesting. First, they are valuable tools in large longitudinal population studies, due to their relative ease of administration and hence low costs. The size of these studies allows for drawing firm conclusions on associations between neurodevelopmental psychopathological conditions and predictors or outcome measures. Second, these measures seem to be robust across raters and highlight the need to consider multiple sources of information. Lastly, using these instruments in clinical samples is highly relevant too as within clinical samples we observe substantial heterogeneity in the manifestation of symptoms and symptom severity. Dimensional instruments provide excellent data to capture this variation in the clinical population, and should be encouraged in future research.

A final point to raise relates to the importance of investigating the etiology of monogenic neurodevelopmental disorders. In recent years, there has been strong interest in

polygenic scores and dimensional measures; concepts that heavily draw on the notion of multiple variants of smaller effect size contributing to neurodevelopmental disorders. Yet this special issue reminds us that some cases might be linked to monogenic disorders. Some of these disorders have a rich array of evidence about their biology, and may as such provide unique additional information to our understanding of neurodevelopmental disorders in this era of polygenic risk scores.

In sum, this special issue provides exciting new studies in the field of genetics of neurodevelopmental disorders. Findings support future research that includes multiple raters, that uses dimensional measures (also in clinical samples), that focus on the genetic overlap between comorbid phenotypes, eventually extended to a general genetic (P) risk factor, and research that studies monogenic disorders, as this may potentially provide mechanistic insights into the etiology of neurodevelopmental disorders.

Compliance with Ethical Standards

Conflict of interest Mark J. Taylor and Tinca J. C. Polderman declare that they have no conflict of interest.

Human and animal rights and Informed consent This article did not include research with human or animal subjects and informed consent is not required.

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