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Short communication

Discrepancies of polygenic effects on symptom dimensions between adolescents and adults with ADHD

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A B S T R A C T

A significant proportion of individuals with attention-deficit/hyperactivity disorder (ADHD) show persistence into adulthood. The genetic and neural correlates of ADHD in adolescents versus adults remain poorly characterized. We investigated ADHD polygenic risk score (PRS) in relation to previously identified gray matter (GM) patterns, neurocognitive, and symptom findings in the same ADHD sample (462 adolescents & 422 adults from the NeuroIMAGE and IMpACT cohorts). Significant effects of ADHD PRS were found on hyperactivity and impulsivity symptoms in adolescents, hyperactivity symptom in adults, but not GM volume components. A distinct PRS effect between adolescents and adults on individual ADHD symptoms is suggested.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset neuropsychiatric disorder characterized by inattention and/or hyperactivity-impulsivity (American Psychiatric Association, 2013). The disorder is associated with alterations of brain structure and function mostly found in the caudate nucleus, right globus palidus and putamen, fronto-striatal-parietal pathway, and cerebellum (Dickstein et al., 2006; Faraone et al., 2005; Frodl and Skokauskas, 2012; Halperin and Schulz, 2006; Hoogman et al., 2017; Nakao et al., 2011; Polanczyk and Rohde, 2007; Valera et al., 2007). ADHD is also often marked by impairments in cognitive functioning; including deficits in working memory, inhibitory control, and cognitive flexibility (Alderson et al., 2013; Lijffijt et al., 2005; Martinussen et al., 2005; Tarver et al., 2014). The persistence rate of ADHD from childhood into adulthood is estimated between 15 and 60%, depending on the definition of persistence (Chandra et al., 2016).

Symptom profiles, neuroanatomical features, and cognitive deficits also appear to differ between children and adults with ADHD. In children, hyperactivity is the more common presentation, whereas inattention, restlessness, and working memory deficits are more common in adulthood (Agnew-Blais et al., 2016). In addition, previous literature has shown different neuroanatomical features between the age groups with adolescents showing more significant alterations in the bilateral

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Crus I, insula, caudate, thalamus, and middle occipital gyrus, adults showing moresignificant alterations in the middle frontal gyrus (Duan et al., 2018; Jiang et al., 2019), and children (age 4–9 years) having the greatest reduction in cortical surface area among all the age groups (Hoogman et al., 2019).

ADHD is considered among the most heritable psychiatric disorders with a heritability percentage estimate of 76% (Biederman et al., 1990; Wolfers et al., 2016). Twelve independent loci on 11 different chromosomes were identified as surpassing genome-wide significance to carry the risk to ADHD (Demontis et al., 2019). However, only a small percentage of heritability was accounted for, indicating a need for further investigation into the common variants of ADHD (Demontis et al., 2019).

Given the differing symptom profiles, neuroanatomical features, and cognitive deficits, examination of the genetic underpinnings of adult ADHD is needed. We aimed to investigate the differences in genetic effects between adolescents and adults with ADHD. Specifically, we investigated how ADHD polygenic risks scores (PRS) based on a genome wide association children and adult study from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH; https://ipsych.au.dk/downloads/) may influence brain structures and symptoms in ADHD that has persisted into adulthood, and how these genetic effects differ from those in adolescence (Duan et al., 2018; Jiang et al., 2019).

2. Methods

2.1. Participants

This study included adolescents and adults with ADHD, siblings of individuals with ADHD, and unrelated healthy controls (462 adolescent participants from the NeuroIMAGE cohort, 278 adult participants from the NeuroIMAGE cohort, and 144 adult participants from the Dutch IMpACT consortium). The NeuroIMAGE projects included relatives of both the adolescent participants and the adult participants, while the IMpACT cohort were unrelated. Participant breakdown and demographics are further explained in Supplemental Appendix 1. Participant recruitment, consent process, and enrollment are detailed in the original studies (Mostert et al., 2015; Onnink et al., 2016; von Rhein et al., 2015).

2.2. Clinical and neurocognitive measures

In brief, individuals with ADHD were included if they met the DSM-IV (NeuroIMAGE project) (American Psychiatric Association, 1994) or DSM-IV-TR (IMpACT consortium) (American Psychiatric Association, 2000) criteria for ADHD. Two symptom domains, inattention and hyperactivity/impulsivity, were evaluated between the two cohorts based on the 18 DSM-IV symptom questions (American Psychiatric Association, 1994). The symptom scores for both domains ranged from 0 to 9, with larger scores indicating more severe symptoms (Duan et al., 2018; Noordermeer et al., 2017). To examine working memory capacity, the WAIS Digit Span test (Wechsler et al., 2000) with maximum forward and backward scores was assessed in both NeuroIMAGE and IMpACT participants. Further assessment information is detailed in Supplemental Appendix 1.

2.3. Neuroimaging

T1-weighted images were acquired from three 1.5T scanners (Amsterdam using Siemens SONATA and Siemens AVANTO, and Nijmegen using Siemens SONATA). The imaging preprocessing procedure was the same as in previous studies and is further detailed in Supplemental Appendix 2. In brief, the Jacobian-scaled modulated images were regressed for age, sex, and site prior to analyses.

2.4. Structural brain decomposition

The preprocessed images went through component estimation using the minimum description length algorithm (Rissanen, 1978). Twenty distinct gray matter (GM) components were computed by the infomax algorithm (Bell and Sejnowski, 1995) ICA (Xu et al., 2009) within the GIFT toolbox (http://mialab.mrn.org/software/gift). ICASSO (Himberg et al., 2004) with 10 ICA runs was used to ensure the stability of components. Detailed information about the GM brain components identified in the previous studies is described in Supplemental Appendix 3.

2.5. Genetic data and PRS construction

We used PRSice-2 (https://www.prsice.info/) for PRS calculations (Choi and O'Reilly, 2019). Detailed information of genetic data and preprocessing is further described in Supplemental Appendix 4. The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH; https://ipsych.au.dk/downloads/) child and adult ADHD summary statistics were used as the base file, and the preprocessed genetic data were used as the target file for adolescent and adult samples.

2.6. Association analyses of PRS, structural brain components, and behavior data

Our previous research identified GM components, which were greater in controls than individuals with ADHD (Duan et al., 2018; Jiang et al., 2019). The association between PRS and those GM components that showed differences between cases and controls, symptom score, or neurocognitive differences were analyzed in separate linear mixed models (LMM). In the LMMs, the GM component was the dependent variable. Age, diagnosis, medication use (yes/no), and PRS were included as fixed effect with family as a random effect on the intercept. The quadratic effect of age^2 (testing possible non-linear age effects) was added into the fixed effect for adolescents only.

The associations between PRS and symptom score and neurocognitive data were also tested with similar LMMs. The individual ADHD symptoms of hyperactivity and inattention, and the working memory assessments of WAIS digital span forward and backward, were included in four separate LMMs as dependent variables. Again, age, sex, medication, and PRS were included as fixed effect with family as a random effect on the intercept. Significance corrections for multiple comparisons were done using false discovery rate (FDR) correction ($p < 0.05$) (Genovese et al., 2002).

3. Results

Detailed demographic information can be found in Supplementary Tables 1 and 2 for adolescents and adults, respectively. In the adolescent sample, the p-value threshold to compute PRS was 0.0025 with 3% of the case vs. control variance explained ($p = 1.29E-04$) (Fig. 1a). Using this threshold, a total of 1789 SNPs were included in the PRS model. In the adult sample, the p-value threshold to compute PRS was 0.065 with 5.6% of the case vs. control variance explained ($p = 2.94E-04$). A total of 15,908 SNPs were included in this model (Fig. 1b).

In adolescents, there were no significant associations between PRS and any of the GM components previously reported (Supplemental Appendix 5). In adolescents, PRS were positively related to hyperactivity scores ($\beta = 0.10$, $p = 7.52E4$ (FDR corrected)) and inattention scores ($\beta = 0.09$, $p = 0.02$ (FDR corrected)) after controlling for age, sex, and medication. In adults, PRS were positively related to hyperactivity scores ($\beta = 0.19$, $p = 3.58E-03$ (FDR corrected)) while controlling for age, sex, and medication, but not inattention scores ($\beta = 0.06$, $p = 0.15$ (FDR corrected)). There were no significant associations with the previously reported GM components for adults (Supplemental Appendix 6).

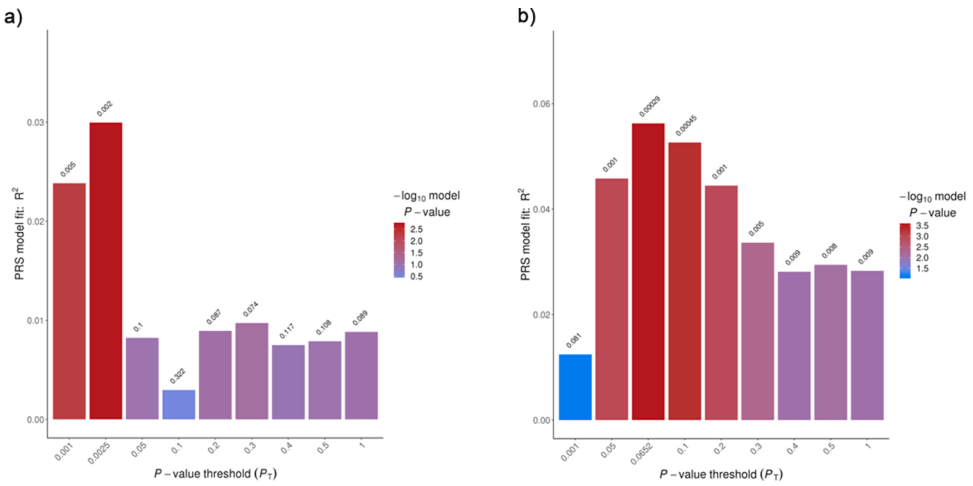

Fig. 1. Polygenic Risk Model Estimation. a) The polygenic risk model estimation based on iPSYCH data and case/control phenotypes in adolescent sample. The risk scores set at P value threshold of 0.0025 were included in the following analyses. b) The polygenic risk model estimation based on iPSYCH data and case/control phenotypes in adult sample. The risk scores set at P value threshold of 0.0652 were included in the following analyses.

4. Discussion

In this study, we assessed PRS effects on ADHD diagnosis, symptoms, and brain networks implicated in ADHD separately in two age cohorts: adolescents and adults. Our findings did not show a PRS effect on any of the previously identified GM components (see Supplemental Appendices 5 and 6) related to ADHD in either adolescents or adults (Duan et al., 2018; Jiang et al., 2019). However, our results did show a PRS effect on individual symptom domains of ADHD; in adolescents this held for both hyperactivity and inattention scores, while in adulthood this was only found for hyperactivity scores.

Inattention is the prominent symptom profile of adults with ADHD, not hyperactivity (Spencer et al., 2007). Previous PRS literature has shown associations between PRS and individual externalizing symptoms, hyperactivity among others, but not internalizing symptoms including inattention (Brikell et al., 2018). Our findings are in line with this previous literature. This may partially explain why our results showed no association between PRS and inattention in adults. In adolescents, symptoms of hyperactivity and inattention were highly correlated, and therefore, the dual results could be capturing the same behavioral presentation. These results may offer new insights into the genetic effects of the different behavioral phenotypes of ADHD through the lifespan.

The variable persistence rate of ADHD from childhood to adulthood has previous lead to the speculation that adults with ADHD may present a more homogeneous phenotype of ADHD. Therefore, children with ADHD could be a more muddled representation of ADHD; perhaps representing varied phenotypes, environmental factors, or eventually simply “grow out” of their clinical diagnosis. Adults who have had the diagnosis of ADHD persist through adolescence into their adulthood, may be a more severe and consistent representation of the disorder. A recent study by Rovira and colleagues also found that the PRS for persistent ADHD (or adulthood ADHD) relates to a more severe and consistent clinical phenotype when compared to the PRS for childhood ADHD (Rovira et al., 2020). Our previous and current results support this notion that adulthood ADHD differs from childhood ADHD in phenotypic presentation, in the affected brain structures, and now, genetically.

Limitations in our study include a relatively broad age range for the adolescent data (7 to 18 years old; mean = 14.65, SD = 2.24) that we counteracted by completing a voxelwise correction with the quadratic effect of age (age^2) in the analyses. Our sample sizes are also relatively small and should be replicated with larger samples as these results are meant to serve as preliminary findings for ADHD in adolescents and adults.

In conclusion, the finding of different age groups with ADHD presenting with distinct symptom profiles partially explained by PRS is an important addition to the ADHD literature. We demonstrated a difference between adolescents and adults in the effects of PRS on individual symptom domains. These results may be explained by differences in the genetic effects of the symptom domains of ADHD and should serve as a starting point for future genetic studies of adults with ADHD.

Author contributions

J.T., J.L., and W.J. designed the study. J.O., J.B, D.H., B.F. and A.A.V. acquired the data and A.A.V and E.S consulted on the interpretation. W. J., K.R.M., and K.D. analyzed the data. W.J. and K.R.M. wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

Declaration of Competing Interest

Barbara Franke has received educational speaking fees from Shire and Medice. Other authors report no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2021.111282.

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