The opposite end of the attention deficit hyperactivity disorder continuum: genetic and environmental aetiologies of extremely low ADHD traits

Corina U. Greven, Andrew Merwood, Jolanda M. J. van der Meer, Claire M. A. Haworth, Nanda Rommelse, and Jan K. Buitelaar

Background: Although attention deficit hyperactivity disorder (ADHD) is thought to reflect a continuously distributed quantitative trait, it is assessed through binary diagnosis or skewed measures biased towards its high, symptomatic extreme. A growing trend is to study the positive tail of normally distributed traits, a promising avenue, for example, to study high intelligence to increase power for gene-hunting for intelligence. However, the emergence of such a ‘positive genetics’ model has been tempered for ADHD due to poor phenotypic resolution at the low extreme. Overcoming this methodological limitation, we conduct the first study to assess the aetiologies of low extreme ADHD traits. Methods: In a population-representative sample of 2,143 twins, the Strength and Weaknesses of ADHD Symptoms and Normal behaviour (SWAN) questionnaire was used to assess ADHD traits on a continuum from low to high. Aetiological influences on extreme ADHD traits were estimated using DeFries–Fulker extremes analysis. ADHD traits were related to behavioural, cognitive and home environmental outcomes using regression. Results: Low extreme ADHD traits were significantly influenced by shared environmental factors (23–35%) but were not significantly heritable. In contrast, high-extreme ADHD traits showed significant heritability (39–51%) but no shared environmental influences. Compared to individuals with high extreme or with average levels of ADHD traits, individuals with low extreme ADHD traits showed fewer internalizing and externalizing behaviour problems, better cognitive performance and more positive behaviours and positive home environmental outcomes. Conclusions: Shared environmental influences on low extreme ADHD traits may reflect passive gene-environment correlation, which arises because parents provide environments as well as passing on genes. Studying the low extreme opens new avenues to study mechanisms underlying previously neglected positive behaviours. This is different from the current deficit-based model of intervention, but congruent with a population-level approach to improving youth wellbeing. Keywords: Attention deficit hyperactivity disorder; quantitative trait; twin; extremes; positive genetics.

Introduction

Attention deficit hyperactivity disorder as a quantitative trait

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder affecting around 6–7% of children and adolescents (Willcutt, 2012). Multifactorial disorders like ADHD are assumed to be influenced by many genes and environments of small effect resulting in a bell-shaped quantitative trait distribution (Coghill & Sonuga-Barke, 2012; Willcutt, 2005). Nonetheless, violating the assumption of a normal distribution, mental health disorders are assessed through binary diagnosis or measures biased towards the high, symptomatic extreme. Case–control studies typically lump together unaffected individuals in a single ‘no symptoms’ group, ignoring meaningful variation in the lower range of scores (Fair, Bathula, Nikolas, & Nigg, 2012). Further, traditional interview and questionnaire measures allow fine-scaled assessment of variability at the high extreme of mental health continua, but attenuate variability at the low, unaffected end, reflected in skewed measure distributions. Overcoming this methodological limitation, this is the first study to assess the genetic and environmental aetiologies of low extreme ADHD scores.

Towards a ‘positive genetics’ model of ADHD

An increasing trend in the literature is to focus on ‘positive genetics’; that is the study of adaptive tails of normally distributed traits, a promising avenue...
applied in the field of high intelligence to increase power for gene-hunting for intelligence (Plomin & Deary, 2015). This research is based on the continuity hypothesis, that is, the strong evidence that distribution extremes of quantitative traits are influenced by the same genetic and environmental aetiologies affecting the rest of normal variation (Plomin, Haworth, & Davis, 2009). In contrast, the discontinuity hypothesis assumes that the aetiologies of distribution extremes differ qualitatively from the normal distribution; for example, severe cognitive disability and extreme height deviations are often caused by rare genetic abnormalities, whereas normal population variation in these attributes is thought to be influenced by many genes of small effect (Plomin & Deary, 2015; Shiang et al., 1994). Quantitative genetic DeFries-Fulker (DF) extremes analysis (DeFries & Fulker, 1988) investigates genetic factors explaining why individuals at the distribution extreme, as a group, differ from the rest of the population, known as group heritability (h^2_g). Significant group heritability (h^2_g) that is similar in size to the heritability across the range of individual differences, suggests that extreme scores are heritable, and that there are genetic links between extreme scores and normal population variance, consistent with continuity. In contrast, nonsignificant h^2_g and significant heritability of individual differences would suggest that extreme scores are not significantly influenced by genetic factors, or that there are no genetic links between extreme scores and normal population variance, consistent with discontinuity. Like all common mental health continua (Plomin, DeFries, Knopik, & Neiderhiser, 2013), ADHD shows significant h^2_g (Larsson, Anckarsater, Råstam, Chang, & Lichtenstein, 2012; Willcutt, 2005), similar to heritability of individual differences in ADHD traits across the entire range of scores (around 70% for parent and teacher, somewhat lower for self-ratings) (Greven, Asherson, Rijsdijk, & Plomin, 2011; Greven, Rijsdijk, & Plomin, 2011; Merwood et al., 2013; Willcutt, 2005). However, such an approach has still to be applied to low extreme ADHD traits.

The low extreme: adaptive or maladaptive?

Whether low extremes of mental health continua represent positive (adaptive, desired) outcomes, or may also come with disadvantages remains a topic for empirical investigation (Plomin, 2013; Plomin et al., 2009). On the one hand, low extreme ADHD traits may be thought to reflect excellent attention, motor and impulse control coupled with good academic performance and low levels of comorbid behaviour problems. On the other hand, extreme deviations in either direction (low and high) on mental health continua may both represent maladaptive outcomes. Low extreme hyperactivity may reflect inertia or even behavioural rigidity; low extreme inattentiveness may reflect overfocusing and less flexible attentional shifting. From an evolutionary perspective, scoring in the midrange of the continuum may represent a favourable trade-off between advantages and disadvantages of extreme polygenic liabilities (Nettle, 2006). Evidence suggests that personality dimensions related to ADHD (Parker, Majeski, & Collin, 2004) that are traditionally regarded as adaptive (e.g. extraversion, emotional stability, agreeableness, conscientiousness) may become dysfunctional when one has ‘too much of a good thing’ (McCord, Joseph, & Grijalva, 2014). For example, for introversion/extroversion personality traits, extreme scores in either direction have been shown to be associated with worse performance outcomes (Grant, 2013). Very high levels of conscientiousness share considerable overlap with obsessive-compulsive tendencies, and are related to more negative effect, lower well-being and more adverse reactions to negative life events (Carter, Guan, Maples, Williamson, & Miller, 2015). However, such a trade-off hypothesis remains to be tested for ADHD traits.

The current study

Few measures exist that provide resolution at the low extreme of mental health continua. For ADHD, the Strength and Weaknesses of ADHD Symptoms and Normal behaviour (SWAN) questionnaire (Hay, Bennett, Levy, Sergeant, & Swanson, 2007) assesses ADHD traits on a continuum from low to high (Arnett et al., 2011; Hay et al., 2007; Van der Meer et al., 2014). Here, we obtained self-reports on the SWAN from a population sample of 2143 adolescent twins with two aims: First, to examine the genetic and environmental aetiologies of low extreme ADHD (SWAN) traits; second, to test the hypothesis that extreme deviations in either direction on ADHD (SWAN) traits represent maladaptive outcomes. The SWAN allows differentiation of two ADHD subdimensions: inattentiveness and hyperactivity-impulsivity. Given evidence for partial genetic separation, as well as differential correlates of these subdimensions (Greven et al., 2011, 2011), results were also explored separately for each (see Appendix S1).

Method

Sample

Participants were part of the Twins Early Development Study (TEDS), a U.K. population-representative sample of twins born in England and Wales between 1994 and 1996 (Haworth, Davis, & Plomin, 2013). Families were excluded following severe pre- or perinatal complications, a severe medical condition in twins (e.g. a chromosomal disorder, brain damage, global developmental delay, autism, blindness, death of either twin), and if sex or zygosity were uncertain. This study included 2,143 twins (mean age 16.32 years; SD 0.68; range 14.91–18.76) from 1083 twin pairs: 415 monozygotic (MZ;
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Cognitive performance outcomes. School grades in English and Mathematics were obtained from postal questionnaire and telephone interview (for details see (Krapohl et al., 2014)) assessing the highest grade achieved in the General Certificate of Secondary Education (GCSE), an academic qualification taken by students in England, Wales and Northern Ireland at the end of compulsory education, or in alternative equivalent qualifications if GCSEs were not taken. Children's general cognitive ability was assessed using a mean composite of the Mill Hill Vocabulary Test (Raven, Raven, & Court, 1998) and Raven's Standard Progressive Matrices (Raven, Court, & Raven, 1996), gathered via validated web-based testing (Haworth et al., 2013).

Home environmental outcomes. Parents' use of negative discipline strategies (e.g. shouting, smacking or slapping) was assessed using a child-rated 4-item web-based questionnaire (Viding, Fontaine, Oliver, & Plomin, 2009). The web-based child-rated Confusion, Hubbub and Order Scale (CHAOS) scale assessed disorganization in the home environment (Matheny, Wachs, Ludwig, & Phillips, 1995).

Analyses

To examine the aetiologies of extreme ADHD traits (aim 1), DF extremes analyses were conducted on low- and high extreme 5%, 10%, 15% and 20% cut-offs on the SWAN, using Mx (Boker et al., 2011). DF extremes analysis is based on differential regression of ADHD scores of co-twins of ADHD probands to the population mean for ADHD, where ADHD probands are selected for having extreme high or high ADHD traits (DeFries & Fulker, 1988). Group heritability (h^2g) addresses to what extent genetic factors explain why those at the extreme, as a group, differ from the rest of the population. Likewise group-shared (e^2g) and nonshared (e^2g) environment can be estimated, which refer to environmental factors contributing to twin similarity and dissimilarity respectively. We also obtained A (heritability), C (shared environmental) and E (nonshared environmental) estimates for the entire distribution of individual differences in ADHD traits using full-information maximum likelihood estimation on raw data in Mx, creating residual scores, corrected for sex and age by means of regression (McGue & Bouchard, 1984). Because of a lack of power to examine sex differences within the extreme scoring groups, the standard approach was taken to exclude opposite-sex twins from analyses for aim 1.

To test the hypothesis that extreme deviations in either direction on ADHD traits represent maladaptive outcomes (aim 2), polynomial regression analyses were conducted including the linear and nonlinear (quadratic) terms of ADHD traits as predictors (centred scores), age and gender as covariates, and behavioural, cognitive and home environmental measures as outcomes. Linear relations between ADHD traits and outcomes would indicate low extreme ADHD traits represent more adaptive outcomes than high-extreme ADHD traits. Curvilinear relations could suggest low and high-extreme traits are both associated with maladaptive outcomes, depending on the shape of the curve. Further, mean outcome measure scores were plotted of individuals with the highest and lowest 10% scores on the ADHD trait distribution, and children scoring above the average 10%. Outcome measures were standardized into z-scores. The skewed SDQ and MFQ measures transformed using Van der Waerden transformation. Corrections were applied for the nonindependence of data due to including twin pairs ('cluster' command in STATA (Williams, 2000)) and multiple testing (False Discovery Rate; \(p \leq 0.05\) (Benjamini & Hochberg, 1995)).
Results

DF extremes analysis of low and high-extreme ADHD traits

DeFries–Fulker extremes analyses showed that, across 5%, 10%, 15% and 20% cut-offs, $h^2_g$ was significant for high extreme ($h^2_g = 39–51%$), but not for low extreme ADHD traits. In contrast, $c^2_g$ was nonsignificant for high extreme, but significant for low extreme ADHD traits ($c^2_g = 23–35%$; exception: $c^2_g$ was nonsignificant at the low 5% cut-off, due to the smaller sample). However, estimates of $h^2_g$ and $c^2_g$ at low and high extremes did not differ significantly as 95% confidence intervals overlapped (Table 1). $e^2_g$, was significant for both high ($e^2_g = 49–61%$) and low ($e^2_g = 50–55%$) extremes (Table 1). Results were similar after correction for age and gender (Table B.S1, Appendix S2). Post hoc, we ran DF extremes analyses for less extreme cut-offs. At 30%, 40% and 50% low extreme cut-offs, $c^2_g$ of low extreme ADHD traits was no longer significant, whereas $h^2_g$ reached significance (Figure 1).

Genetic ($A = 46%$) and nonshared environmental ($E = 48%$) estimates for the entire distribution of individual differences in ADHD traits were significant, whereas shared environmental influences were nonsignificant ($C = 6%$) (Table B.S2 in Appendix S2). Do low and high-extreme ADHD traits represent maladaptive outcomes?

Polynomial regression analyses revealed that ADHD traits showed significant linear associations with all outcomes measures, whereas curvilinear associations were nonsignificant (the only exception was that five measures showed significant linear as well as curvilinear associations, as explained in Table B.S3 and Figure B.S2 in Appendix S2). Individuals at the low extreme of ADHD traits, relative to those at the high extreme, had lower internalizing and externalizing behaviour scores, higher general cognitive ability and school grades in English and Mathematics, showed more prosocial behaviour, greater life satisfaction, happiness and grit, were more likely to have a special ability or striking skill, and reported fewer negative parental discipline strategies and less confusion and disorganization at home. Individuals with average levels of ADHD traits tended to score intermediate to those at either extreme of the SWAN distribution (Figures 2 and 3). Individuals at low and high 10% extremes differed between 0.36 and 1.60 standard deviations (SDs) of a standard normal distribution ($M = 0.00$, $SD = 1.00$) on behaviour problems, between 0.71 and 1.19 SDs on cognitive performance, between 0.61 and 1.4 SDs on the continuous child positive outcomes, and 0.75 and 1.3 SDs on home environmental outcomes, indicating moderate to large effect sizes (Figure 2).

Discussion

This study examined the genetic and environmental aetiologies of low extreme ADHD traits, and tested the hypothesis that low and high-extreme ADHD trait scores may both be maladaptive. As a main novel finding, and in contrast to our hypothesis, low extreme ADHD traits were not significantly heritable, but were significantly influenced by group-shared (23–35%) and nonshared environment (50–55%). This is a striking finding as shared environmental influences on high extreme and individual differences in ADHD traits are typically nonsignificant and close to zero (Burt, 2009; Willcutt, 2005). Consistent with the literature (Larsson et al., 2012; Willcutt, 2005), high-extreme ADHD traits showed significant group heritability (39–51%) and group nonshared environmental (49–61%), but nonsignificant group-shared environmental effects; estimates that resembled genetic and environmental contributions to individual differences in ADHD traits. This suggests that there are genetic links between the high

Table 1 Results of DeFries-Fulker (DF) extremes analyses for ADHD traits using low and high 5%, 10%, 15% and 20% extreme cut-offs

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>$N$ probands (individuals)</th>
<th>Proband mean</th>
<th>Co-twin mean</th>
<th>Twin group correlation</th>
<th>$h^2_g$ (95% CI)</th>
<th>$c^2_g$ (95% CI)</th>
<th>$e^2_g$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD, low (unaffected)</td>
<td>5</td>
<td>41</td>
<td>38</td>
<td>1.51</td>
<td>1.53</td>
<td>2.35</td>
<td>2.64</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>82</td>
<td>74</td>
<td>1.76</td>
<td>1.77</td>
<td>2.64</td>
<td>2.75</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>130</td>
<td>110</td>
<td>1.94</td>
<td>1.93</td>
<td>2.64</td>
<td>2.75</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>165</td>
<td>133</td>
<td>2.04</td>
<td>2.01</td>
<td>2.64</td>
<td>2.75</td>
</tr>
<tr>
<td>ADHD, high (symptomatic)</td>
<td>5</td>
<td>33</td>
<td>41</td>
<td>1.51</td>
<td>1.53</td>
<td>2.35</td>
<td>2.64</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>82</td>
<td>74</td>
<td>1.76</td>
<td>1.77</td>
<td>2.64</td>
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<td></td>
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<td>20</td>
<td>165</td>
<td>133</td>
<td>2.04</td>
<td>2.01</td>
<td>2.64</td>
<td>2.75</td>
</tr>
</tbody>
</table>

ADHD = ADHD total score on the SWAN measure. $h^2_g$ = group heritability; $c^2_g$ = group-shared environment; $e^2_g$ = group nonshared environment. Twin group correlation = the extent to which the mean standardized quantitative trait score of co-twins is as low/high as the mean standardized score of probands selected for low/high ADHD traits. Doubling the difference in MZ and DZ group twin correlation gives a rough estimate $h^2_g$. 95% confidence intervals (CIs) that include zero indicate nonsignificance; nonoverlapping CIs indicate two estimates differ significantly.

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distribution extreme and normal variation in ADHD traits. We found no evidence to support an evolutionary trade-off hypothesis (Nettle, 2006), that is that those scoring in the average range would show the most favourable outcomes. Instead, low extreme ADHD traits, compared to the high extreme or average levels of ADHD traits, were related to fewer behavioural problems, better cognitive performance, more positive traits, less chaotic homes and less negative parental discipline. Results are consistent with a recent study in a population sample of 378 children (6–13 years) which found lower SWAN scores to be linked to fewer parent-rated internalizing and externalizing behaviour problems and better performance on neurocognitive tasks (Greven et al., 2015); and a...
findings is passive rGE, which arises because biolog-
et al., 2002). A potential mechanism explaining our
of environmental moderation of heritability (Wichers
shown to decrease and those of shared and non-
genetic factors on problem behaviour have been
cross the continuum of ADHD traits. For example,
environments on ADHD traits may be nonlinear
comes and low ADHD traits was greater in nonadop-
correlation between such family environmental out-
Direct evidence for passive rGE would arise if the
adaptive parenting styles and nutritional factors.
family environmental influences such as high SES,
late this may be a result of a combination of positive
reflecting a single environmental source, we specu-
tal component (Plomin et al., 2013). Rather than
on genes and which inflates the shared environmen-
tors changes over the continuum. Genetic and envi-
mental effects do not operate in isolation, but
interact in the form of gene-environment interaction
and correlation (r GE). Hence, the effect of genes and
environments on ADHD traits may be nonlinear
across the continuum of ADHD traits. For example,
in the presence of perinatal insults, influences of
factor on problem behaviour have been
shown to decrease and those of shared and non-
shared environmental factors to increase, suggestive
of environmental moderation of heritability (Wichers
et al., 2002). A potential mechanism explaining our
findings is passive rGE, which arises because biological
relatives provide environments as well as passing
on genes and which inflates the shared environmen-
tal component (Plomin et al., 2013). Rather than
reflecting a single environmental source, we specu-
late this may be a result of a combination of positive
family environmental influences such as high SES,
adaptive parenting styles and nutritional factors.
Direct evidence for passive rGE would arise if the
correlation between such family environmental out-
comes and low ADHD traits was greater in nonadop-
tive than adoptive families (Rijssdijk & Sham, 2002).
Second, our findings suggest that there may be
additional, shared environmental, factors contribut-
ing to variation in low extreme ADHD traits that are
not operating across the normal variation in ADHD
traits or high-extreme traits, consistent with the
discontinuity hypothesis. This, in combination with
the nonsignificant group heritability, suggests that
extremely low ADHD traits may not be connected
with the construct we know as ADHD at the high
extreme or represent different aetiological mecha-
nisms. This requires further investigation in larger
samples, as estimates of group heritability and
shared environment did not differ significantly
between opposite ADHD trait extremes, hence the
continuity hypothesis could not be rejected entirely.
Of note, power to detect shared environment is lower
in twin studies than that to detect heritability,
adding further emphasis to the role of shared envi-
ronmental influences on low extreme traits.
Third, finding nonsignificant group heritability
could also be consistent with reduced reliability in
measurement of the low extreme. However, similar
internal consistency of below and above average
SWAN scores (see Method) and the pretty level group
nonshared environment estimates (which include
measurement error) across the distribution suggest
that there is no difference in measurement error at
high and low ends, supporting the quality of the
measurement at the low extreme.
Fourth, shared environment in ADHD deserves
further attention. Typically influence of shared envi-
ronment decreases with age, and tends to be minimal
for ADHD, whereas heritability increases (Burt,
2009; Plomin et al., 2013). Participants were in their
midadolescence, hence finding influences of shared
environment on ADHD traits is striking. In contrast
to nonshared environments and genetic effects,
shared environmental influences represent a more
readily identifiable and persistent source of variabil-
ity in childhood and adolescence (Burt, 2014). If we
can identify positive and protective environments
influencing low ADHD traits, this could provide clues
for relevant factors that could be targeted in inter-
ventions for those with clinically elevated ADHD
scores or to prevent individuals from growing into
deficit.

**Strengths and limitations**

This is the first study to test the group heritability of
low extreme ADHD traits and uses an established
twin sample. Findings are based on adolescents’ self-
report and should be replicated in childhood, using
parent- and teacher-report, and in a larger sample.
Using self-report is also a strength as self-reported
ADHD traits are relatively underexplored in twin
research (Merwood et al., 2013). Whether beha-
vours at the low extreme form a stable trait and
represent resilience, that is, reduced vulnerability to
environmental adversity (Rutter, 2012), was not
addressed in this study. Hence, whether those at
low extreme do better or relatively well even in the


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face of experiencing risk remains unclear. Future studies could test this using propensity score matching to test if children differing only in being low or high ADHD traits, but not on other risks (e.g. SES, parental diagnostic status), have different outcomes. Standard assumptions and limitations of the twin method applied to this study (Plomin et al., 2013).

Conclusions and implications

Continuously distributed measures of ADHD provide value beyond improved psychometric properties and advantages of parametric testing, through allowing assessment of previously poorly measured behaviours at the low extreme. A focus on the low extreme might be relevant if we wish to nurture individual strengths, helping those with positive ADHD-related behaviours to reach their full potential. This is different from the current, deficit-based model of intervening only to assist those with high-extreme ADHD traits or at risk of adverse psychosocial outcomes, but is congruent with a population-level approach to improving youth wellbeing (Sanders et al., 2008).

Supporting information

Additional Supporting Information may be found in the online version of this article:
Appendix S1. Subdimensions of ADHD traits.
Appendix S2. ADHD traits (total score).

Key points

- Mental disorders such as ADHD are assessed through binary diagnosis or skewed measures biased towards the high, symptomatic extreme. This violates the fundamental assumption that mental disorders are multifactorial and normally distributed, and has tempered research progress.
- Overcoming this methodological limitation, this is the first study to assess the aetiologies of low extreme ADHD traits in a population sample of twins.
- In contrast to the high extreme, extremely low ADHD traits represented better-than-average adaptive behaviours and cognition. These low traits were significantly influenced by shared and nonshared environmental, but not genetic factors.
- The study paves the way for new possibilities to study mechanisms underlying previously neglected positive behaviours.

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Correspondence

Corina U. Greven, Department of Cognitive Neuroscience, Donders Institute for Brain, Radboud University Medical Center, Cognition and Behaviour, internal post 204, Nijmegen, The Netherlands; Email: corina.greven@donders.ru.nl

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