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Published in:
European Neuropsychopharmacology

DOI:
10.1016/j.euroneuro.2022.07.182

European Neuropsychopharmacology 62 (2022) 63–73

www.elsevier.com/locate/euroneuro

Polygenic risk scores for antisocial behavior in relation to amygdala morphology across an attention deficit hyperactivity disorder case-control sample with and without disruptive behavior

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https://doi.org/10.1016/j.euroneuro.2022.07.182

Received 17 January 2022; received in revised form 13 July 2022; accepted 15 July 2022

KEYWORDS
Structural imaging;
Polygenic risk scores;
Conduct disorders;
Pediatric psychiatry

Abstract
Antisocial and aggressive behaviors show considerable heritability and are central to disruptive behavior disorders (DBDs), but are also frequently observed in attention deficit hyperactivity disorder (ADHD). While the amygdala is implicated as a key neural structure, it remains unclear whether common genetic variants underlie this brain-behavior association. We hypothesized that polygenic (risk) scores for antisocial and aggressive behaviors (ASB-PRS) would be related to amygdala morphology. Using the Broad Antisocial Behavior Consortium genome-wide association study (GWAS; mostly population based cohorts), we calculated ASB-PRS in the NeuroIMAGE I ADHD case-control sample with varying levels of DBD symptomatology (n=679 from 379 families, aged 7 - 29). We first investigated associations of several ASB-PRS *p* value thresholds with the presence of DBD symptoms and self-reported antisocial behavior (ASB) to determine the threshold for further analyses. This PRS was then related to amygdala volume and shape using regression and vertex-wise analyses. Our results showed associations of ASB-PRS with the presence of DBD symptoms, self-reported ASB, and left basolateral amygdala shape, independent of ADHD symptom severity and ADHD-PRS, with a relative outward displacement of the vertices. No associations of ASB-PRS, DBD symptoms or self-reported ASB with amygdala volume were found. Our results indicate that genetic risk for antisocial and aggressive behaviors is related to amygdala shape alterations, and point to genetic sharing across different DBD and ASB and aggression-related phenotypes as a spectrum of genetically related quantitative traits. Additionally, our findings support the utility of vertex-based shape analyses in genetic studies of ASB, aggression, and DBDs.

1. Introduction

Antisocial and aggressive behavior include a heterogeneous set of behaviors that cause harm or damage to others, objects, or the environment, and/or break accepted social rules. These behaviors often start in childhood and exist as continuous traits, which may at the upper end of the distribution become highly maladaptive when occurring in an intensity, frequency, severity, and/or duration disproportionate to preceding events or the social context. The latter is a criterion for disruptive behavior disorders (DBDs), comprising oppositional defiant disorder (ODD) and conduct disorder (CD) (American Psychiatric Association, 2013), but is also often observed in attention-deficit hyperactivity disorder (ADHD) (Saylor & Amann, 2016). Notably, DBDs are the most frequent comorbid conditions among youth with ADHD (Larson et al., 2011; Smalley et al., 2007), the presence of which is associated with a wide range of poorer psychosocial outcomes often persisting into adulthood (Fergusson et al., 2005; Huesmann et al., 2009).

Antisocial and aggressive behavior show substantial heritability, with family and twin studies indicating that half of their variance can be explained by genetic factors (Odintsova et al., 2019; Veroude et al., 2016). In search of the contribution of specific common genetic variants, genome-wide association studies (GWASs) have reported some genome-wide significant loci related to phenotypic variance in antisocial and aggressive behaviors as well as to the presence of DBD diagnoses across community and clinical samples (Demontis et al., 2021; Ip et al., 2021; Pappa et al., 2016; Tielbeek et al., 2017). Although larger samples are needed to discover additional susceptibility loci in GWASs, current GWAS summary statistics can be used to aggregate the effects of multiple single-nucleotide polymorphisms (SNPs) into risk scores on the individual level. The use of these polygenic (risk) scores (PRS) is an increasingly popular approach to study the genetics of complex traits, including antisocial and aggressive behaviors.

While the number of studies using PRS for antisocial and aggressive behavior is still limited, results so far point to genetic sharing among different operationalizations of antisocial behavior and aggression. In this respect, shared genetic etiology was found between childhood aggression and uncaring and unemotional traits in a sample enriched for ADHD (Ruisch et al., 2020), and between a broad spectrum of antisocial behavior and the presence of antisocial personality disorder (the adult equivalent of CD) (Raine, 2018) in a forensic cohort (Tielbeek et al., 2017). In addition, the results of a recent study on the genetics of DBDs in the context of ADHD indicate a genetic risk component including common risk variants associated with antisocial and aggressive behaviors, but also with ADHD and lower educational attainment and intelligence, to the DBD part of the ADHD+DBD phenotype (Demontis et al., 2021). Thus,

polygenic scores for antisocial and aggressive behaviors may be informative across both community samples and clinical populations with DBD diagnoses, with and without comorbid ADHD.

Investigations into the neural correlates underlying antisocial and aggressive behavior have implicated the amygdala as one of the key structures through its role in motivational and affective aspects of cognitive processing, such as reinforcement learning and emotional processing (Blair et al., 2018; Matthys et al., 2012). In line with these findings, negative associations between amygdala volume and aggression have been shown in the general population (Matthies et al., 2012; Pardini et al., 2014). Moreover, neuroimaging studies have consistently provided evidence structural (i.e., smaller volumes) and functional amygdala abnormalities in DBDs irrespective of ADHD comorbidity as well as compared to ADHD-only groups, indicating these abnormalities may be specific for ODD/CD rather than for ADHD (Noordermeer et al., 2016). Still, a mega-analysis using data from the large EGNIMA consortium has provided support for smaller amygdala volumes in children with ADHD compared to those without ADHD (Hoogman et al., 2017). Currently, it remains unclear to what extent DBDs are related to smaller amygdala volumes in the context of ADHD.

Structural and functional amygdala abnormalities may link genetics to antisocial and aggressive behavior (Blair, 2013). In line with this, a cross-trait genetic meta-analysis identified one gene (*AVPR1A*) related to both aggression and amygdala volume (van Donkelaar et al., 2018). In addition to studies of individual genes, the use of PRS may provide a particularly useful approach to investigate the shared genetic basis of antisocial and aggressive behavior and amygdala morphology at the genomic level, and thereby contribute to our knowledge of the etiology of antisocial and aggressive behaviors and DBDs. Accordingly, the main aim of our study was to use PRS to investigate genetic sharing between antisocial and aggressive behavior and amygdala morphology in an ADHD case-control sample with and without symptoms of DBDs (NeuroImage I) (von Rhein et al., 2015). We first assessed amygdala volume and subsequently investigated shape using a more novel and sophisticated surface-based vertex analysis to identify localized morphological changes that may show specific associations with genetic influences and behavior beyond gross volume (Mancke et al., 2018; Naaijen et al., 2020; Roshchupkin et al., 2016).In particular, this method has the potential to localize changes more precisely compared to voxel-based morphometry (Patenaude et al., 2011). A secondary aim was to evaluate the genetic overlap between antisocial and aggressive behavior and the presence of DBD symptoms in our sample. To this end, we calculated PRS for antisocial and aggressive behavior (ASB-PRS) based on a GWASs of a broad spectrum of antisocial and aggressive behaviors mostly including population-based samples (Tielbeek et al., 2017). We expected associations of ASB-PRS with amygdala morphology, assessed by volumetric analyses and the more novel and sophisticated approach of vertex-based shape analyses of magnetic resonance imaging (MRI) images (Roshchupkin et al., 2016), as well as associations with the presence of clinically relevant DBD symptoms and self-reported antisocial behavior.

2. Experimental procedures

2.1. Participants

Our study included 679 participants (aged between 7 - 29; from 379 families) from the NeuroIMAGE I sample, a follow-up cohort of the Dutch part of the International Multicenter ADHD Genetics case-control study (IMAGE) (Müller et al., 2011a, 2011b), which included families with at least one child with ADHD and at least one biological sibling (regardless of ADHD diagnosis), and control families (that had no ADHD diagnosis in any first-degree family members). Inclusion criteria for children included in the IMAGE study were: age between 5 and 17 years, European Caucasian descent (based on clinical judgement and birth places of the child's grandparents), and an IQ $\geq$ 70 (estimated with the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for or Wechsler Adult Intelligence Scale) (Wechsler, 2000); exclusion criteria were diagnoses of autism, learning disorders, neurological diseases, or genetic syndromes. All Dutch IMAGE participants were invited for re-assessment as part of the NeuroIMAGE I study (follow-up rate: ADHD families, 75.6%; control families, 75.1%; mean [SD] time between measurements, 5.9 [0.74] years). In addition, 43 ADHD, and 34 control families were newly recruited. Ethical approval for the study was obtained from the regional ethics committee and the medical ethical committee of the VU University Medical Center. All participants provided written informed consent (parents gave consent for children younger than 12; between 12 and 18 years old consent was also obtained from both parents and child).

Out of 1069 participants (751 from ADHD families, 318 from control families) who were involved in NeuroIMAGE I, we included those with available genetic information, behavioral questionnaire data, and a T1-weighted scan that survived quality control (see MR acquisition and processing) in the current study. This resulted in the inclusion of 466 participants from 258 ADHD families and 213 participants from 121 control families.

2.2. Diagnostic information

ADHD diagnoses were determined using a diagnostic algorithm combining information obtained from a semi-structured diagnostic interview (Kiddie Schedule for Affective Disorders and Schizophrenia [K-SADS]) (Kaufman et al., 1997), based on DSM-IV-TR criteria (American Psychiatric Association, 2000), and the Conners ADHD questionnaires (CTRS- R:L for participants $<$ 18 years or CAARS-S:L for participants $\geq$ 18) (Conners et al., 1997, 1998). See (von Rhein et al., 2015) for more information.

2.3. Behavioral measures

The presence of ODD and CD symptoms was also ascertained by the K-SADS (Kaufman et al., 1997). The K-SADS includes disorder-specific screening sections and follow-up supplementary modules for full diagnostic assessment if any of the screening items, reflecting the core symptoms of a disorder, are endorsed as clinically relevant (exceeding the range of

normal in terms of frequency, pervasiveness, and/or severity). In the current study, we focused on screen positives (yes/no; across both ADHD and control families), without the requirement to meet full diagnostic DSM-IV-TR criteria for ODD and/or CD. Dichotomous measures were created for ODD and CD screen positives separately and for ODD and/or CD screen positives combined. Moreover, a continuous measure of antisocial behavior was obtained from the from the Observed Antisocial Behavior Questionnaire (OAB; *Vragenlijst Waargenomen AntiSociaal gedrag*) (Slot et al., 1998), which is based on the Self-report of Antisocial Behavior Scale designed for children from the age of 7 onwards (Loeber et al., 1989), and has been widely used in samples aged 5-12 (Cohn et al., 2012; Van Domburgh et al., 2019). The OAB includes 42 items on several forms of antisocial and delinquent behavior, such as theft, violence, vandalism and rule-breaking. For each item, participants indicated whether a certain behavior applied to them. All behaviors endorsed were combined into a total life-time score (with range 0 – 42). T-scores on the parent-rated Conners' ADHD questionnaires (Conners et al., 1998) were used as an ADHD severity score across participants with and without ADHD diagnoses.

2.4. Genotyping and polygenic risk scores

Genotyping was carried out using the Illumina Psych-Array 24 v1.1A, which has been developed in collaboration with the Psychiatric Genomics Consortium for the (genome-wide) analyses of psychiatric phenotypes (Logue et al., 2015) and assesses ~560,000 markers. Imputation was performed using the RICOPILI-pipeline (Lam et al., 2020). Quality control exclusions were based on Impute Information scores (<0.8), minor allele frequency (MAF<0.05), Hardy-Weinberg equilibrium test (*p* cut-off 1E-06), single nucleotide polymorphism (SNP) call rate (<0.98) and individual call rate (<0.98). A total of 2,611,627 SNPs was available in our target sample.

ASB-PRS were estimated based on the summary statistics of the BroadABC GWAS (Tielbeek et al., 2017), which adopted a broad quantitative measure of antisocial and aggressive behavior across 5 large population-based cohorts with different age ranges. A total of 2,154,067 SNPs could be included for PRS-analyses. The PRSice2-software (Choi & O'Reilly, 2019) was used to calculate ASB-PRS at eight 'broad' *p* value thresholds (i.e. 0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1). To address linkage disequilibrium (LD), SNPs were clumped using the PRSice2 default settings (i.e. a bidirectional 250Kb-window and R^2-threshold of 0.1). After LD-clumping, a total of 67,450 independent SNPs was used for generating ASB-PRS.

2.5. Magnetic resonance imaging data acquisition and processing

MRI data were acquired on 1.5 T scanners (Siemens SONATA at VU University, Amsterdam; Siemens AVANTO at the Radboud University Medical Center, Nijmegen; Siemens, Erlangen, Germany) with the same product 8-channel headcoil. Whole-brain high-resolution T1-weighted anatomical images were acquired in the sagittal plane: magnetization-prepared rapid acquisition gradient echo (MP-RAGE), echo time (TE)=2.95 ms, repetition time (TR)=2730 ms, inversion time (TI)=1000 ms, flip angle = 7°, using generalized auto-calibrating partially parallel acquisition (GRAPPA) with 176 sagittal slices, voxel size $1\times1\times1$ mm^3, and field of view 256 mm. The quality of the T1 anatomical scans was rated on a 4-point scale by two independent raters. From each participant, the structural acquisition of highest quality was selected. Only scans with no/mild distortions were accepted, with all scans indicating incidental findings, poor data quality, or motion artifacts excluded from the analysis. This resulted in the exclusion of data from 21 participants (8 participants from control families, 13 participants from ADHD families). T1-weighted images were processed with the FMRIB Software Library (FSL) (Smith et al., 2004). Segmentation of the amygdala was performed by applying the automated FMRIB integrated registration and segmentation tool (FIRST) (Patenaude et al., 2011) which included affine registration to MNI space and used information on shape and intensity for accurate segmentation. FIRST uses a training set of manually labeled brain image data of 336 individuals encompassing a wide age range (4.2 to 72 years), and the Bayesian framework alleviates problems associated with a limited amount of training data (Patenaude et al., 2011). Therefore, variations in the developing brain can be captured by this approach. Segmentation was visually inspected for all participants by a trained researcher, after which amygdala volumes (mm^3) were extracted for statistical analysis. Amygdala shape was determined by applying vertex analysis, in which surface meshes were created overlaying the left and right amygdala using a deformable mesh model. Localized shape alterations were then calculated using the displacements from each individuals' vertices to the average vertices. Meshes were reconstructed in MNI space, with preservation of local pose and volume differences (i.e. using the -ReconMNI option).

2.6. Statistical analyses

2.6.1. ASB-PRS threshold selection - associations with behavioral measures

We first investigated which of the eight ASB-PRS *p* value thresholds (.001, .05, 0.1, 0.2, 0.3, 0.4, 0.5, 1) was most predictive of the ODD, CD, and ODD/CD screen positives and self-reported antisocial behavior (OAB scores) to check whether the ASB-PRS association strength was comparable between these behavioral measures and with thresholds used in earlier studies (Taylor et al., 2019). To limit the number of analyses, and given that we were not particularly interested in small differences regarding associations between ASB-PRS and each specific behavioral measure, we chose the threshold that overall showed the highest associations for subsequent analyses on amygdala volume and shape. Although not the main aim of the current study, these analyses also provide valuable information on genetic sharing of ASB-PRS (based on a broad definition of ASB) with the presence of clinically relevant DBD symptomatology. Associations of the ASB-PRS thresholds with the presence of ODD and/or CD screen positives across the entire sample were assessed by logistic regression analyses (using generalized

linear mixed-effect models with a logit link function). Associations of ASB-PRS with OAB scores were assessed by linear regression models. In order to adjust for sibling relatedness, we built mixed effects models in R (lme4 package) (Bates et al., 2015), where family was included as a random effect, and sex, age, genotyping batch, and the first 4 genetic principal components for ancestry were included as fixed effects. Predictors were standardized to compare effects among ASB-PRS including different numbers of SNPs. *P* values were corrected for multiple testing by applying the false discovery rate (FDR) approach (Benjamini & Hochberg, 1995) on the total number of PRS thresholds and phenotypes (8 PRS thresholds, 4 phenotypes; 32 tests in total) investigated. For the *p* value threshold used in the subsequent analyses, we reran the analyses with ADHD severity added as an additional covariate to assess the specificity of the ASB-PRS effect.

2.6.2. Amygdala volume and shape

Associations of respectively ASB-PRS and behavioral measures (ODD, CD, and ODD/CD screen positives, and OAB scores) as between-subject variables of interest with left and right amygdala volumes were analyzed using linear mixed effects models (again using the lme4 package in R; Bates et al., 2015). Separate models were fitted using left and right amygdala volumes as dependent measures. All models included the following confounds and covariates of non-interest (age, sex, scanning site, and for the PRS analysis also genotyping batch and the first four genetic principal components). Then, we refitted all models that showed significant effects of the predictor of interest, now including possible additional explanatory covariates (IQ, total brain volume [TBV], and ADHD severity) to investigate if effects were specific to the predictor of interest. Family was included as a random factor to correct for sibling relatedness in all models. All continuous predictors were standardized prior to analysis.

Statistical shape analyses were performed using FSL randomise (Winkler et al., 2014) with 5,000 random permutations and threshold-free cluster enhancement (TFCE) (Smith & Nichols, 2009). Variables of interest, confounds and covariates of non-interest, and potential additional explanatory covariates (except TBV, as reconstruction in MNI space already normalizes for brain size) were similar to the volume analyses. Family-wise error (FWE) corrected p values < 0.05 were considered statistically significant. Localization of voxels and clusters were determined using the Juelich Histological Atlas (Eickhoff et al., 2007), which provides cytoarchitectonically verified probabilistic maps of the amygdala.

To further investigate the specificity of significant ASB-PRS effects on amygdala volume and/or shape, we performed sensitivity analyses by adding ADHD-PRS (see supplementary methods) instead of ADHD symptom severity scores to the models as a covariate, after first exploring associations of the ADHD-PRS with our behavioral measures. We also ran sensitivity analyses with stimulant use as a covariate, as this is the most commonly prescribed psychotropic medication in our (ADHD enriched) sample.

3. Results

3.1. Descriptive statistics

The descriptive statistics of the included participants from NeuroIMAGE can be found in Table 1. The ODD and/or CD screen positive group consisted of more males and more individuals with an ADHD diagnosis, had a lower IQ, and higher self-reported ASB and ADHD severity relative to the ODD and/or CD screen negative group.

3.2. ASB-PRS threshold selection - associations with behavioral measures

Based on the effect sizes and significance levels of the eight *p* value thresholds used for ASB-PRS generation in relation to the behavioral measures (see Supplementary Table 1) and analogous to previous studies (Taylor et al., 2019),we used the ASB-PRS at the threshold of $p = 0.5$ for further analyses. As shown in Table 2, this ASB-PRS was significantly associated with the presence of ODD, CD, ODD/CD screen positives and self-reported antisocial behavior (OAB scores). Associations with all behavioral measures remained significant after adjusting for ADHD severity.

3.2.1. Amygdala volume and shape

ASB-PRS nor any of the behavioral measures showed associations with amygdala volume, see Supplementary Table 2 for model estimates. The primary vertex-wise shape analyses showed significant positive ($P_{FWE} = .010$; peak voxel $x = 121$, $y = 125$, $z = 50$, cluster size = 103 voxels; peak voxel $x = 108$, $y = 124$, $z = 53$, cluster size = 4 voxels) and negative ($P_{FWE} = .035$; peak voxel $x = 109$, $y = 118$, $z = 53$, cluster size = 28 voxels; peak voxel $x = 117$, $y = 120$, $z = 57$, cluster size = 8 voxels) effects of ASB-PRS on vertices in the left amygdala. The largest positive effect, mainly located in the basolateral region and indicating regional outward displacement in subjects with higher ASB-PRS, remained significant when IQ and ADHD severity were added as additional covariates ($p_{FWE} = 0.017$; peak voxel $x = 121$, $y = 125$, $z = 50$, cluster size = 76 voxels), see Fig. 1. No effects of ASB-PRS on right amygdala shape were found, whereas self-reported antisocial behavior (OAB score) showed a negative association with right amygdala shape ($P_{FWE} = .022$; peak voxel $x = 60$, $y = 121$, $z = 48$, cluster size = 134 voxels) in the primary analysis. This effect, however, was no longer significant after adding IQ and ADHD severity to the model. No other effects of the ODD, CD, ODD/CD measures and self-reported antisocial behavior (OAB score) on amygdala shape were found, see Supplementary Table 3 for peak *p* values.

3.2.2. Sensitivity analyses

ADHD-PRS were associated with the ODD ($B = 0.325$, $SE = 0.101$, FDR $Q = 0.005$) and ODD/CD ($B = 0.232$, $SE = 0.100$, FDR $Q = 0.011$), but not with the CD measure or self-reported antisocial behavior (OAB score), nor with amygdala shape or volume. The positive effect of the ASB-PRS on the left basolateral amygdala remained significant after correcting for ADHD-PRS (peak $p_{FWE} = 0.011$, cluster size = 98) or stimulant use (peak $P_{FWE} = 0.0024$, cluster size = 223). No

Table 1 Descriptive statistics of the current sample (N = 679) by family type and ODD and/or CD screen positives

Variable	Families				DBD screen positives				Total Sample		
	ADHD(n = 466)		Control(n = 213)		Yes(n = 155)		No(n = 524)				
	n	***%***	***n***	***%***	***n***	***%***	***n***	***%***	***n***	***%***	
Families	258	-	121	-	-	-	-	-	377	-	
Sex (males)	277	59	106	50	106	68[4]	277	53[4]	383	56	
ADHD diagnosis	269	58	7[3]		130	84[4]	146	28[4]	276	41	
ODD screen positive[1]	144	31	2	1	146	94	0	0	146	22	
CD screen positive[1]	44	9	1	0.5	45	29	0	0	45	7	
ODD/CD screen positive[1]	152	33	3	1	155	100	0	0	155	23	
Stimulant use	248	53	2[3]	1	113	73[4]	137	26[4]	250	43	
	M	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***	**range**
Age (years)	17.1	3.5	16.6	3.5	16.8	3.1	17.0	3.6	16.9	3.5	7.7 - 29.2
IQ	99	15	106	14	95[4]	15	103[4]	14	101	15	70 - 147
OAB total score	8.7	7.4	6.0	5.2	11.1[4]	8.7	6.9[4]	5.9	7.9	6.9	0 - 36
ADHD severity[2]	61	15	47	7	70.6[4]	13.9	52.5[4]	12.0	57	45	40 - 90

Note. ADHD, attention-deficit hyperactivity disorder; CD, conduct disorder; DBD, disruptive behavior disorder; ODD, oppositional defiant disorder; OAB, Observed Antisocial Behavior scale; *M*, mean; *SD*, standard deviation. ADHD families also included non-affected siblings.
[1] Assessed by the K-SADS (28).
[2] Derived from the parent-reported Conners' ADHD questionnaire, CPRS-R:L.
[3] Some individuals from control families who participated in IMAGE had developed symptoms at reassessment in NeuroIMAGE.
[4] Significant differences between DBD screen positives and negatives.

Table 2 Associations of ASB-PRS (0.5 threshold) with ODD, CD, and ODD/CD screen positives and self-reported antisocial behavior.

Effect	**ODD screen positives**[1]				
	OR	***95% CI***	***p***	***Q*** FDR	**Nagelkerke's R^2**
ASB-PRS	1.30	1.07 - 1.58	.010	.023	.016
	CD screen positives[1]				
	1.54	1.13 - 2.10	.007	.022	.028
	ODD and/or CD screen positives[1]				
	1.31	1.08 - 1.59	.006	.022	.017
	Self-reported ASB (OAB score)[2]				
	β	***95% CI***	***p***	***Q*** FDR	**Nagelkerke's R^2**
	0.76	0.21 - 1.30	.006	.022	.011

Note. CD, conduct disorder; ODD, oppositional defiant disorder; OAB, Observed Antisocial Behavior scale. Regression coefficients (β), odds ratios (OR) and confidence intervals (CI) are shown. The analyses were adjusted for age, sex, genotyping batch and the first 4 genetic principal components. Sibling relatedness was accounted for by modelling a random intercept. All continuous predictors were standardized.
[1] Logistic regression model.
[2] Linear regression model.

effects of stimulant use (yes/no) on amygdala shape or volume were observed.

4. Discussion

The current study investigated the shared genetic background between antisocial and aggressive behaviors and amygdala structure by means of polygenic (risk) scores (PRS) in an ADHD case-control sample including individuals aged 7-29 with and without disruptive behavior. Our main finding points to genetic sharing of a broad spectrum of antisocial and aggressive behaviors with regional shape alterations in the left basolateral amygdala, independent of ADHD symptom severity and ADHD-PRS. In addition, our findings suggest that common genetic variants associated with antisocial and aggressive behaviors in the general population are also implicated in ODD and CD symptomatology in an ADHD enriched sample. Yet, although our results support the role of the amygdala as an important structure related to genetic risk for a broad spectrum of antisocial and aggressive behaviors, we did not find direct links of DBD symptomatology and antisocial behavior with left basolateral amygdala shape and amygdala volumes.

Our findings indicating associations of ASB-PRS with DBD symptomatology and self-reported ABS support a shared genetic background along a continuum of antisocial and aggressive behaviors and clinically relevant DBD symptomatology across population and (partly) clinical samples. This is in line with a recent study reporting high polygenic overlap

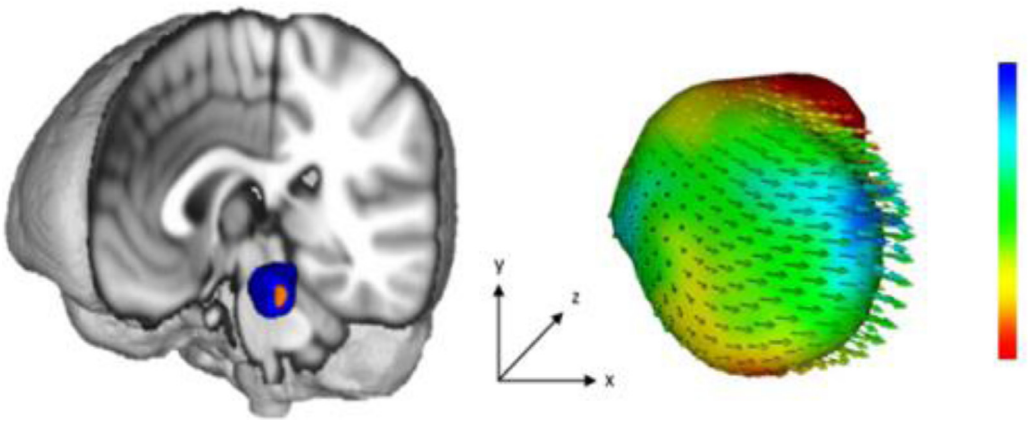

Fig. 1 Vertex analyses of shape alterations in the left amygdala. *Note*. The left panel shows the anatomical location of the shape alteration related to higher ASB-PRS (in orange). The right panel shows the results of the classical vector vertex analysis, with the colors on the surface of the mesh and the arrows indicating the Pillai's trace F-statistic. The direction of the arrows points to a relative outward displacement of the vertices.

of ADHD+DBDs with antisocial behavior and childhood aggression in the general population (Demontis et al., 2021). Together, these results point to genetic sharing across different DBD and ASB-related phenotypes as a spectrum of genetically related quantitative traits. Importantly, this genetic sharing was independent of ADHD symptom severity. Importantly, the current study points to a (partly) unique background of DBD symptomatology versus ADHD, as expected based on earlier twin studies (Anckarsäter et al., 2011; Bornovalova et al., 2010; Lahey et al., 2011). Further investigation of the genetics of antisocial behavior and aggression may help to identify biological mechanisms and substrates involved in DBDs and shed light on their etiology.

Our most important finding indicates genetic sharing between antisocial and aggressive behaviors and regional shape (expansion) in the left basolateral amygdala, providing support for the amygdala as one of the key structures related to these behaviors. In particular, the basolateral amygdala is implicated in associative emotional learning processes, which have often been found to be disrupted in DBDs (Matthys et al., 2012; Olsson & Phelps, 2007). Still, our findings of both positive and negative (the latter in relation to self-reported ASB and only significant without adjusting for IQ/ADHD severity) associations of the ASB-PRS with shape alterations indicate the complexity of this relation, which has also been observed in brain-behavior associations in the context of psychopathy (a personality disorder often accompanied by antisocial behavior) (Boccardi et al., 2011). Findings regarding the right amygdala are mixed; either pointing to smaller volumes or no volume reductions versus controls (Fairchild et al., 2013; Noordermeer et al., 2016; Waller et al., 2020)Thus, distinct genetic and behavioral components may be differentially associated with left versus right amygdala morphology.

Importantly, the positive link of ASB-PRS with amygdala shape was independent of ADHD severity scores and ADHD-PRS, as it could be argued that this association may actually be an ADHD effect (given the high genetic correlations of antisocial and aggressive behaviors and/or DBDs with ADHD) (Faraone & Larsson, 2019; Rodríguez-López et al., 2020). Yet, although we are not aware of previous studies on amygdala shape related to DBDs, a study in male adults with bipolar disorder did report a positive association between left basolateral amygdala shape and aggression (Mancke et al., 2018). In addition, larger grey matter volume in the left basolateral amygdala has been related to negative emotionality (Mincic, 2015). Notably, negative emotionality makes up a core dimension of ODD, often referred to as 'irritability' (which may most specifically reflect difficulties with affective behavior regulation) (American Psychiatric Association, 2013; Faraone et al., 2019) and previous evidence also indicates shared genetic influences between specifically negative emotionality and externalizing disorders (ODD/CD/ADHD) (Singh & Waldman, 2010). Negative emotionality may thus be an important dimension to consider in future genetic and imaging studies on DBDs and ADHD.

While previous studies have pointed to smaller amygdala volumes in DBDs (Noordermeer et al., 2016) as well as to pleiotropic genetic effects on amygdala volume and respectively aggression (e.g. of the gene *AVPR1A)* and ADHD (both at the single variant and genomic level) (Klein et al., 2019), we did not find significant associations of amygdala volume with ASB-PRS or behavioral measures. Still, noneof the previous imaging studies that also used the NeuroIMAGE I-sample have reported any differences in amygdala volume between healthy controls and those with ADHD or ADHD+ODD (Greven et al., 2015; Noordermeer et al., 2015). Notably, corresponding to our current findings, the results of a large population-based study on the heritability of the morphology of subcortical brain structures illustrate that genetic effects may be localized, affecting only specific vertices within a structure, and extend beyond influences on gross volume of subcortical structures(Roshchupkin et al., 2016). Hence, shape may provide more specific information relative to volume alone and may be particularly relevant in genetic studies.

Our study is among the first to investigate shared genetic effects between antisocial and aggressive behavior and amygdala morphology on the individual level using ASB-PRS and the inclusion of vertex-wise shape analyses in addition to the more often reported volume analyses. Fur-

thermore, our partially clinical target sample covered the presence and absence of clinically relevant DBD symptoms and a continuum of antisocial behavior. Thus, our results point to the generalizability of the ASB-PRS across clinical and non-clinical populations and may increase our understanding of the genetic background of both DBDs as well as non-clinical aggressive traits across the general population. Still, some limitations should be noted. Although our ASB-PRS were based on the a GWAS using a broad definition of antisocial and aggressive behavior (Tielbeek et al., 2017) with the benefit of generalizability across clinical and non-clinical populations, a larger GWAS of a more homogeneous ASB related phenotype (e.g., clinical CD diagnoses) could increase power and result in a more sensitive PRS. Further, given the use of both genome-wide genotyping data and individual-level MRI data and in a sample enriched for antisocial and aggressive behavior, an independent cross-validation of our ASB-PRS *p* value threshold was not feasible and may be done in the future. Still, a *p* value threshold of 0.5 has been frequently used (Taylor et al., 2019). In addition, our sample was primarily an ADHD sample, with relatively few individuals with ODD and CD diagnoses; future studies may focus on more severely affected individuals.

In conclusion, our results show that localized variation in amygdala shape is related to genetic risk for antisocial and aggressive behavior across a sample of youth with and without ADHD. Furthermore, our study provides evidence for shared common genetic variants between antisocial and aggressive behavior in the general population and clinically relevant DBD symptomatology, which is consistent with a dimensional view of antisocial behaviors and diagnoses. Finally, our results show the utility of vertex-based shape analyses, in addition to ROI volume analyses, in genetic studies of antisocial and aggressive behavior. Future studies may therefore further focus on (the shape of) amygdala subregions as well as on more homogeneous operationalizations of antisocial behavior and aggression, and may also benefit from investigating a possible link with emotional learning and functional activations of the amygdala as well as amygdala connectivity.

Contributors

Renee Kleine Deters, Hyun Ruisch, Jilly Naaijen, Pieter Hoekstra and Andrea Dietrich designed the study. Renee Kleine Deters, Hyun Ruisch, and Jilly Naaijen undertook the statistical analyses. Renee Kleine Deters wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

Jan K. Buitelaar has been a consultant to/advisory board member of/and/or a speaker for Janssen Cilag BV, Eli Lilly, Shire, Lundbeck, Roche, and Servier. He is not an employee of any of these companies and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, or royalties. Stephen V Faraone received income, potential income, travel expenses continuing education support and/or research support from Takeda, OnDosis, Tris, Otsuka, Arbor, Ironshore, Rhodes, Akili Interactive Labs, Sunovion, Supernus and Genomind. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. He also receives royalties from books published by Guilford Press: Straight Talk about Your Child's Mental Health, Oxford University Press: Schizophrenia: The Facts and Elsevier: ADHD: Non-Pharmacologic Interventions. He is Program Director of www.adhdinadults.com. Barbara Franke has received educational speaking fees from Medice. All other authors declare that they have no conflicts of interest.

Acknowledgements

We are very grateful to all families who participated in the NeuroIMAGE-study, and the whole NeuroIMAGE-team, including interviewers, technicians, scientists, clinicians, volunteers, and managers of all involved organizations and facilities, for recruitment and collection, and preprocessing of the data used in this study.

Role of Funding Source

This work is supported by the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 603016 (MATRICS) and no. 602805 (Aggressotype) and by the European Community's Horizon 2020 Programme (H2020/2014 - 2020) under grant agreements n° 667302 (CoCA), and n° 728018 (Eat2beNICE). The NeuroIMAGE- project was supported by NIH Grant R01MH62873, NWO Large Investment Grant 1750102007010 and ZonMW Grant 60- 60600-97-193, and grants from Radboud University Nijmegen Medical Center, University Medical Center Groningen and Accare, and VU University Amsterdam. J. Naaijen is supported by an NWO Veni grant (VI.Veni.194.032). B. Franke is supported by funding for the Dutch National Science Agenda NeurolabNL project (grant 400-17-602). None of the funding sources had a further role in study design; in the collection, analysis and interpretation of the data; in the writing of the report; and in the decision to submit the paper for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.07.182.

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