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RESEARCH ARTICLE

A polygenic risk score analysis of ASD and ADHD across emotion recognition subtypes

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Abstract

This study investigated the genetic components of ADHD and ASD by examining the cross-disorder trait of emotion recognition problems. The genetic burden for ADHD and ASD on previously identified emotion recognition factors (speed and accuracy of visual and auditory emotion recognition) and classes (Class 1: Average visual, impulsive auditory; Class 2: Average-strong visual & auditory; Class 3: Impulsive & imprecise visual, average auditory; Class 4: Weak visual & auditory) was assessed using ASD and ADHD polygenic risk scores (PRS). Our sample contained 552 participants: 74 with ADHD, 85 with ASD, 60 with ASD + ADHD, 177 unaffected siblings of ADHD or ASD probands, and 156 controls. ADHD- and ASD-PRS, calculated from the latest ADHD and ASD GWAS meta-analyses, were analyzed across these emotion recognition factors and classes using linear mixed models. Unexpectedly, the analysis of emotion recognition factors showed higher ASD-PRS to be associated with faster visual emotion recognition. The categorical analysis of emotion recognition classes showed ASD-PRS to be reduced in Class 3 compared to the other classes (p value threshold [pT] = 1, $p = .021$). A dimensional analysis identified a high ADHD-PRS reduced the probability of being assigned to the Class 1 or Class 3 ($pT = .05$, $p = .028$ and $p = .044$, respectively). Though these nominally significant results did not pass FDR correction, they potentially indicate different indirect causative chains from genetics via emotion recognition to ADHD and ASD, which need to be verified in future research.

KEYWORDS

ADHD, ASD, emotion recognition, polygenic risk score, subtyping

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1 | INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are frequently comorbid disorders that are highly heritable. Recent studies have calculated the heritability of ADHD at $h^2 = 0.74$ (Faraone & Larsson, 2019) and of ASD at $h^2 = 0.83$ (Sandin et al., 2017). Individuals with ASD and their relatives have an increased risk of ADHD and vice versa (Ghirardi et al., 2018; Oerlemans et al., 2015; Septier et al., 2019). Recent genome-wide association studies (GWAS) have identified genomic loci associated with each disorder (Demontis et al., 2019; Grove et al., 2019), and there is evidence for genetic sharing among them (Nijmeijer et al., 2010). In addition, the associated genetic variants also seem to contribute to the cognitive deficits seen in the two disorders (Campbell et al., 2011; LoParo & Waldman, 2015; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2015; Nigg et al., 2018). For example, polygenic risk scores for ADHD are associated with a lower educational attainment as well as with deficits in working memory and social communication (Martin et al., 2015). Similarly, genetic risk variants for ASD have been found to be associated with social communication and general cognitive abilities (Clarke et al., 2016; Peñagarikano & Geschwind, 2012). Given their shared etiology, it may be unsurprising that ADHD traits, such as hyperactivity, have been found to contribute to the clinical presentation of ASD, just as ASD traits, including repetitive behaviors and social deficits, contribute to the presentation of ADHD (Cooper, Martin, Langley, Hamshere, & Thapar, 2014; Grzadzinski et al., 2011; Kotte et al., 2013; Meer et al., 2012).

The genetic risk of ASD and ADHD in relation to emotion recognition abilities, defined as the ability of identifying emotional facial expressions and emotional prosody (see Adolphs, 2003; Adolphs, Tranel, & Damasio, 2001; Bänziger, Grandjean, & Scherer, 2009), has received little attention (Coleman et al., 2017; Martin et al., 2015). This is surprising given that studies have highlighted an increase in ADHD and/or ASD symptoms is associated with an increase in the severity of emotion recognition problems, though some suggest that inattentive symptoms predominantly underlie these problems in ADHD (Oerlemans et al., 2014; Sinzig, Morsch, & Lehmkuhl, 2008; Waddington et al., 2018b). Yet contrary reports indicate that this deficit is heterogeneous and complex (Bora & Pantelis, 2016; Collin, Bindra, Raju, Gillberg, & Minnis, 2013; Harms, Martin, & Wallace, 2010). Our group has recently used factor mixture modeling, a hybrid of latent class and factor analysis, to identify more homogeneous emotion recognition subtypes, based on four factors capturing most variance in the assessment of this trait (Waddington et al., 2018a, 2018b), i.e., visual speed, visual accuracy, auditory speed, and auditory accuracy. The subtypes identified, hereinafter referred to as classes, ranged from strong-average performing classes, Class 1: Average visual, impulsive auditory and Class 2: Average-strong visual and auditory, to poorer performing classes, Class 3: Impulsive and imprecise visual, average auditory and Class 4: Weak visual and auditory. These classes were associated with ADHD and ASD symptoms; stronger and average-performing classes displayed fewer ADHD and

ASD symptoms. Based on such findings, we hypothesized that partially different mechanisms may contribute to emotion recognition features captured in the defined factors and classes. Their potential differential association with genetic risk for ADHD and ASD may underlie the earlier observed lack of association of such genetic risk with emotion recognition (Coleman et al., 2017; Martin et al., 2015). An example of such work is given by the study by Veatch and colleagues, who used hierarchical clustering to partition phenotypic heterogeneity in ASD and found cluster assignment to be influenced by genetics (Veatch, Veenstra-VanderWeele, Potter, Pericak-Vance, & Haines, 2014). The hierarchical clustering approach that was used in this study is limited to analyzing data from a categorical perspective and disregards associations that may be present between variables utilized to define clusters. Other subtyping techniques that utilize a dimensional approach to define more homogeneous phenotypes may be more suitable and powerful for genetic analyses.

The current study aimed to yield further insight into the genetic components of ADHD and ASD, by examining emotion recognition problems, which are observed as a cross-disorder trait in these disorders; in this, we took into account existing heterogeneity of emotion recognition by investigating potentially more homogeneous factors and classes. The influence of genetic burden for ADHD and ASD on emotion recognition factors and classes identified in Waddington et al., (2018a, 2018b) was assessed using polygenic risk scores (PRS) based on the latest ADHD GWAS (Demontis et al., 2019) and ASD GWAS (Grove et al., 2019). We hypothesized that higher ADHD- and ASD-PRS would be linked to slower and/or less accurate identification of emotions. Consequently, individuals in the weakest emotion recognition class, defined by slow and inaccurate visual and auditory emotion recognition factors, were expected to have the highest genetic burden for these disorders compared to individuals in the stronger emotion recognition classes. To our knowledge, this is the first study to investigate the genetic burden of ADHD and ASD in relation to emotion recognition factors and classes.

2 | SUBJECTS AND METHODS

2.1 | Sample

Genotype and phenotype data were available from the NeuroIMAGE and Biological Origins of Autism (BOA) cohorts. The NeuroIMAGE cohort (Von Rhein et al., 2015) of children with ADHD, their unaffected siblings and controls, is a follow-up to the IMAGE study (Müller et al., 2011a; Müller et al., 2011b; Nijmeijer et al., 2009; Rommelse & Buitelaar, 2008), whereas the BOA cohort is a study of children with pure ASD or comorbid ASD + ADHD, their unaffected siblings and controls, the design of which was based on (Neuro)IMAGE (van Steijn et al., 2012). Both of these studies recruited participants from the Netherlands. All participants from the BOA study were assessed in Nijmegen. The NeuroIMAGE study conducted 49% of assessments in Amsterdam and the remainder in Nijmegen. Patient families were included in these cohort studies if they had one child with a clinical

diagnosis of ADHD (NeuroIMAGE) or ASD (BOA) and at least one biological sibling (regardless of possible clinical diagnosis) willing to participate. Control families for each cohort were included if they had at least one child with no formal or suspected ADHD or ASD diagnosis themselves, nor in any of their first-degree relatives. Participants in both cohorts were of European descent. These cohorts used some of the same exclusion criteria, such as Full Scale IQ (FSIQ) <70, diagnosis of epilepsy, and known genetic syndromes (e.g., Down-syndrome or Fragile-X-syndrome). The NeuroIMAGE cohort had as an additional exclusion criterion a clinical diagnosis of ASD based on DSM-IV criteria.

The sample analyzed in original emotion recognition subtyping study by Waddington et al. (2018a) included a total of 675 participants, of which 275 were from the NeuroIMAGE cohort and 400 were from the BOA cohort. Genetic data were not available for all participants in our original study (i.e., due to some participants not contributing with genetic material or low quality of DNA samples or genotyping). Therefore, the current study consisted of 552 participants, of which there were 74 ADHD participants, 60 unaffected siblings of ADHD, 85 ASD participants, 60 ASD + ADHD participants, 117 unaffected siblings of ASD and ASD + ADHD, and 156 controls (41 from NeuroIMAGE and 115 from BOA). Participants age ranged from 7 to 18 years. Of the included NeuroIMAGE participants, the average IQ was 100 ranging from 70 to 139, with 51.4% being male. Similarly, the BOA sample included in the present study had an average IQ of 103, ranging from 70 to 155, and 59.7% were male.

2.1.1 | Clinical measures

For an in-depth description of the clinical measures accessed in the NeuroIMAGE and BOA cohorts, see von Rhein et al. (2015) and Van Steijn et al. (2012), respectively. In summary, any children who were previously diagnosed with ADHD and/or ASD, their siblings and the control children were screened for the presence of ADHD and ASD symptoms using the parent-reported Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003) and the parent- and teacher-reported Conners Rating Scales-Revised (CPRS and CTRS, respectively; Conners, 1997).

Potential ADHD and/or ASD clinical cases were identified by raw scores of ≥ 10 on the SCQ Total score and by ≥ 63 T-score (a score that accounts for the child's age) on the either the parents' or teachers' Conners DSM-IV Inattention, Hyperactivity-Impulsivity, or Combined scales. Children who scored above cut-off on any of the screening questionnaires underwent full clinical ADHD assessment; in NeuroIMAGE cohort this was done using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS; Kaufman et al., 1997) and in BOA cohort using the Parental Account of Childhood Symptoms ADHD subversion (PACS) for ADHD (Taylor, Sandberg, Thorley, & Giles, 1991). Clinical assessment for ASD in the BOA cohort was performed using the Autism Diagnostic Interview-Revised (ADI-R) structured interview for ASD (Le Couteur, Lord, & Rutter, 2003). In NeuroIMAGE, the clinical assessment for ASD was performed using the Parental Account of Childhood Symptoms (PACS;

Taylor et al., 1986). Children from control families were required to obtain nonclinical scores (i.e., a raw score < 10 on the SCQ and T-score < 63 on both CPRS and CTRS) to qualify for this study.

2.1.2 | Cognitive measures intelligence

An estimate of the Full Scale Intelligence Quotient (FSIQ) was derived from the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children version III (WISC-III; Wechsler, 2000a) for participants younger than 16 years ($n = 510$), or the Wechsler Adult Intelligence Scale version III (WAIS-III; Wechsler, 2000b), for participants 16 years and older ($n = 42$).

2.1.3 | Emotion recognition factors and classes

Emotion recognition was assessed through speed and accuracy performance in the Facial Expressions Identification and Affective Prosody Tasks from the Amsterdam Neuropsychological Test (ANT; De Sonneville, 1999). Briefly, in the Facial Expressions Identification task, participants were shown pictures of emotional expressions on a computer screen. Participants had to click a yes or no button to confirm if they did or did not see the target emotion (happy, sad, fearful or angry) in these photos. In the Affective Prosody task, participants listened to a sentence of neutral content and had to identify the prosody (happy, sad, fearful, or angry) of the sentence they heard.

Exploratory and confirmatory factor analyses had previously been used to identify a common factor structure across the NeuroIMAGE and BOA cohorts (Waddington et al., 2018b). The emotion recognition classes/profiles were identified based on participants' performance on these four factors through factor mixture modeling, as described in Waddington et al. (2018a). In brief, the results of the exploratory and confirmatory factor analyses of this data identified four emotion recognition factors: (a) speed of visual emotion recognition; (b) accuracy of visual emotion recognition; (c) speed of auditory emotion recognition; and (d) accuracy of auditory emotion recognition. The identified emotion recognition classes, derived from these factors, were then labeled according the characteristics of their emotion recognition profiles: class 1—average visual, impulsive auditory; class 2—average-strong visual and auditory; class 3—impulsive/imprecise visual, average auditory; and class 4—weak visual and auditory (see Figure 1). Participants were assigned to one of these classes based on the probability of belonging to each class. Of all the participants in class 1, 93% had a probability $> .50$. Similarly, 95 and 91% of classes 2 and 4, respectively, also achieved this probability, whereas this was only the case for 78% of participants of class 3.

2.1.4 | Genotype data of NeuroIMAGE and BOA cohorts

In both cohorts, DNA was obtained from blood or saliva samples. Genotyping of the NeuroIMAGE and BOA samples was performed



FIGURE 1 Emotion recognition subtypes identified in Waddington et al. (2018a). Each line represents the emotion recognition class (mean factor scores—speed and accuracy of Identification of Facial Expressions and Affective Prosody tasks, from the Amsterdam Neuropsychological Test battery, ± 1 SE) for each class. Lower scores represent faster reaction time and fewer errors made

using the Illumina Infinium PsychArray-24 v1.2 BeadChip genotyping platform. Quality control, principal components analysis (PCA), and imputation were performed using RICOPII, the Psychiatric Genomics Consortium (PGC) pipeline for GWAS (Lam et al., 2019). RICOPII default quality control parameters were used extensively. PCA was used to identify and exclude population outliers during quality control and the first four principal components were included as covariates to account for population stratification during association analyses. Imputation was carried out using as reference the European ancestry subset of the 1000 Genomes Phase 3 reference panel (1000 Genomes Project Consortium, 2015). SNPs with a minor allele frequency (MAF) $< .01$, an imputation score of INFO $< .8$, were excluded prior to the analyses, resulting in 5,064,466 SNPs in the NeuroIMAGE dataset and 4,935,261 SNPs in the BOA dataset.

2.2 | Data analysis

2.2.1 | Polygenic risk scores (PRS)

The summary statistics of the latest GWAS meta-analyses for ADHD and ASD were used as discovery datasets (Demontis et al., 2019 & Grove et al., 2019, respectively) to calculate ADHD-PRS and ASD-PRS, for the participants from the NeuroIMAGE and BOA cohorts (hereafter referred to as target samples). More specifically, the ADHD GWAS is composed by samples from the Lundbeck Foundation

Initiative for Integrative Psychiatric Research (iPSYCH) and the PGC samples of European ancestry (Demontis et al., 2019; summary statistics available at <https://www.med.unc.edu/pgc/results-and-downloads>). Prior to all analyses from the current study, leave-one-out analyses were performed, and the GWAS results excluding the NeuroIMAGE cohort are used here as ADHD discovery dataset in order to avoid sample overlap in the PRS analyses. Genetic variants with a MAF $< .01$ and an INFO $< .8$ were excluded. Therefore, this ADHD GWAS summary statistics were derived from 34,697 individuals ($N = 13,960$ cases and $N = 20,737$ controls) and, after the exclusion of SNPs with MAF $< .01$ and INFO $< .8$, it contained a total of $N = 8,094,095$ genetic variants. On the other hand, since BOA is not included as a cohort in the ASD GWAS, the results from the European-only GWAS could be used directly. These were derived from 46,351 participants ($N = 18,382$ cases and $N = 27,969$ controls) and summary statistics are available at <https://www.med.unc.edu/pgc/results-and-downloads>. Similar to the ADHD GWAS, variants were excluded if they had a MAF $< .01$ and an info score $< .8$, resulting in 9,112,387 genetic variants. In order to minimize the possibility of batch effect between cohorts, SNPs common to both NeuroIMAGE and BOA were identified and nonoverlapping SNPs were removed, resulting in 4,479,126 SNPs in the target sample.

For each participant of the target samples (i.e., NeuroIMAGE and BOA), PRS were computed as the sum of trait-associated alleles, weighted by the odds ratio obtained in the discovery GWASs (i.e., ASD and ADHD GWAS), using PRSice v1.25 software (Euesden,

TABLE 1 SNPs per p -value threshold used in the generation of ADHD-PRS and ASD-PRS

Threshold	No. SNPs ASD GWAS	No. SNPs ADHD GWAS
GWAS significance 5×10^{-8}	1	8
GWAS suggestive significance 10^{-6}	9	29
$pT = .05$	16,523	17,180
$pT = 1$	117,648	114,022

Lewis, & O'Reilly, 2015). In order to remove SNPs in linkage disequilibrium, clumping was performed using PRSice default values ($r^2 > 0.1$ within a 250-kb window). PRS were calculated from SNPs according to different association thresholds in the discovery GWASs, including only those SNPs with p -value lower than: 5×10^{-8} (GWAS Significance), 10^{-6} (GWAS Suggestive Significance), .05, and 1 (see Table 1).

2.2.2 | Statistical analyses

The current study comprises a subset of participants who had valid emotion recognition data and for whom genetic data were available (Waddington et al., 2018a). Therefore, it was necessary to check if the age, IQ, and gender proportions were similar to those reported in the previous study (Waddington et al., 2018a). ANOVAs were used to compare differences in age and IQ of participants in the emotion recognition classes in the current study. Potential differences in the proportion of males in each class were assessed using the chi-square statistic.

Differences in mean ADHD and ASD-PRS were assessed across diagnostic groups. The comorbid diagnostic group contains individuals who reached criteria for ASD and ADHD diagnoses in the BOA cohort, whereas those with a diagnosis of ASD or ADHD were assigned to the ASD-only and ADHD-only groups, respectively. Due to the small number of unaffected siblings of individuals with comorbid ASD + ADHD, these siblings were placed into the same group as unaffected siblings of individuals with ASD. The control group consisted of controls from the BOA and NeuroIMAGE cohorts.

Linear mixed models that accounted for family structure (modeled as a random effect), age, gender, IQ, and population stratification (i.e., using the first four principal components, as described above) were used to test the associations between ADHD-PRS/ASD-PRS and emotion recognition factors and classes. Given that factors of speed and accuracy are not mutually exclusive variables, the overarching model of the emotion recognition factors was analyzed. The individual factors were analyzed, irrespective of the significance of the overarching model. These analyses of individual factors were also modeled with their modality counterpart (i.e., speed of visual emotion recognition was modeled with accuracy of visual emotion recognition, whereas speed of auditory emotion recognition was modeled with

accuracy of auditory emotion recognition). All of these models also included ADHD and ASD diagnostic status as covariates.

Emotion recognition classes can be utilized as a categorical variable. Alternatively, the probability of a participant being assigned to a particular class can be used as a continuous variable. Both approaches were explored in the current study.

ADHD and ASD PRS derived from the GWAS Significance, GWAS Suggestive Significance, $pT = .05$ and $pT = 1$ thresholds were transformed into z -scores, to reduce scale bias and improve stability of the linear mixed models of the emotion recognition classes and factors. The number of SNPs present at each threshold used to calculate the ASD and ADHD PRS can be seen in Table 1. FDR corrections for multiple testing were performed. In case none of the PRS associations remained significant after correction, nominally significant findings are presented and later discussed in an exploratory manner.

3 | RESULTS

3.1 | Descriptive statistics

3.1.1 | Differences between groups defined by emotion recognition classes

There was no significant difference in age between the classes, ($F[3, 548] = 1.87, p = .13$) (Table 2). A significant difference in IQ was observed between the classes, ($F[3, 548] = 11.91, p < .001$), with class 4 having a lower IQ than class 1 ($p < .001$), class 2 ($p < .001$), and class 3 ($p = .017$). Furthermore, a significantly greater proportion of males than females was present in our sample ($\chi^2[1] = 11.02, p = .001$); class 4 had significantly more males than females ($\chi^2[1] = 20.81, p < .001$).

3.1.2 | Differences in mean ADHD-PRS across diagnostic groups

There were no differences in mean ADHD-PRS between the healthy controls and ADHD patients, ASD patients, ADHD+ASD patients, ADHD-unaffected siblings, and ASD(+ADHD) unaffected siblings, respectively, at the GWAS Significance ($F[5,491.44] = 0.93, p = .46$) or at the GWAS Suggestive Significance ($F[5,494.75] = 0.76, p = .58$) thresholds. However, we did find differences in the mean ADHD-PRS between the diagnostic groups at the $pT = .05$ ($F[5,512.45] = 2.74, p = .019$) and the $pT = 1$ ($F[5,520.66] = 2.70, p = .020$) thresholds. As expected, the ADHD-only and the ASD + ADHD participants both had a significantly higher ADHD-PRS than controls.

3.1.3 | Differences in mean ASD-PRS across diagnostic groups

There were no differences in mean ASD-PRS between the diagnostic groups at the GWAS Significance ($F[5,491.44] = 0.93, p = .46$), GWAS

TABLE 2 Emotion recognition class characteristics

Class	Factor 1: Speed of visual emotion recognition M	Factor 2: Accuracy of visual emotion recognition M	Factor 3: Speed of auditory emotion recognition M	Factor 4: Accuracy of auditory emotion recognition M	ASD + ADHD n	ASD n	ADHD n	ASD (+ADHD) unaffected siblings n	ADHD unaffected siblings n	Controls n	Age M SD	IQ M SD Range	Male (%)
1. N = 134	-0.86	-0.21	-4.19	1.13	9	11	15	22	18	59	12.54 2.50	104.85 14.34 73-139	46.27
2. N = 254	0.31	-1.13	0.89	-1.63	27	45	30	60	28	64	12.67 2.34	103.37 15.01 70-155	55.12
3. N = 39	-3.79	2.96	0.65	-0.25	2	8	5	11	6	7	11.69 2.41	101.31 14.85 76-130	64.10
4. N = 125	1.51	1.52	2.89	2.26	22	21	24	24	8	26	12.50 2.46	95.17 13.31 70-133	70.40
Total N = 552	n.a.	n.a.	n.a.	n.a.	60	85	74	117	60	156	12.53 2.41	101.72 14.88 70-155	57.07

Notes: ASD + ADHD, ASD, ASD (+ADHD) Unaffected Siblings and Controls (N = 115) are from the BOA cohort. ADHD probands, ADHD Unaffected Siblings, and Controls (N = 41) are from the NeuroIMAGE cohort.

Class 1: average visual, impulsive auditory emotion recognition. This class had average speed and accuracy at visually identifying emotions, but very fast and inaccurate auditory emotion recognition.

Class 2: average-strong visual and auditory emotion recognition. This class was reasonably fast and accurate at visual and auditory emotion recognition.

Class 3: impulsive/imprecise visual, average auditory emotion recognition. This class was very fast and inaccurate at visually identifying emotions, but average speed and accuracy at auditory emotion recognition.

Class 4: weak visual and auditory emotion recognition. This class was slow and inaccurate visual and auditory emotion recognition.

Suggestive Significance ($F[5,494.75] = 0.76, p = .58$), $pT = .05$ ($F[5,515.89] = 1.65, p = .14$), or the $pT = 1$ ($F[5,509.97] = 1.93, p = .088$) thresholds.

3.2 | ADHD and ASD-PRS association analyses

We tested the association between ADHD and ASD-PRS and the emotion recognition factor and classes separately. None of the findings survived FDR corrections for multiple testing. Below, we present the nominally significant findings in an exploratory context.

3.3 | Association between ADHD-PRS and emotion recognition factors

We found no association of the ADHD-PRS with the overarching emotion recognition factor model at the GWAS Significance ($F[1,522.27] = 0.25, p = .62$), GWAS Suggestive Significance ($F[1,486.65] = 0.01, p = .95$), $pT = .05$ ($F[1,468.44] = 0.21, p = .65$), or $pT = 1$ ($F[1,477.20] = 2.08, p = .15$) thresholds. For exploratory purposes, the four individual emotion recognition factors (speed of visual emotion recognition; accuracy of visual emotion recognition; speed of auditory emotion recognition; accuracy of auditory emotion recognition) were also analyzed. However, these analyses, with and without modality counterpart covariates, also did not find any significant effect of the ADHD-PRS on these factors (see Table 3).

3.4 | Association between the ASD-PRS and emotion recognition factors

Similar to the ADHD-PRS association analyses, there was no effect of the ASD-PRS on the overarching combined emotion recognition factor model at any of the p -value thresholds tested. Upon further analysis of the individual emotion recognition factors, we observed a single association, for the speed of visual emotion recognition factor (Factor 1) at the $pT = .05$ threshold (Table 3; column a : $F[1,499.24] = 4.17, p = .042, d = .17$), with a higher ASD-PRS associated with faster visual emotion recognition. This association remained when the modality counterpart, accuracy of visual emotion recognition, was included as a covariate (Table 3; column b : $F[1,499.60] = 4.56, p = .033, d = .18$). No other effects of the ASD-PRS on any other thresholds and other individual factors were seen.

3.5 | Association between ADHD-PRS and emotion recognition classes

There was no significant difference in the ADHD-PRS between the different emotion recognition classes at the GWAS Significance threshold ($F[3,518.92] = 0.67, p = .57$), the GWAS Suggestive Significance threshold ($F[3,465.96] = 1.45, p = .23$), the $pT = .05$ threshold

TABLE 3 Results of exploratory association analysis of ADHD-PRS and ASD-PRS with individual emotion recognition factors (*p*-values)

	GWAS significance 5×10^{-8}		GWAS suggestive significance 10^{-6}		pT = .05		pT = 1	
	<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>
ADHD								
Factor 1: Speed of visual emotion recognition	.76	.82	.22	.28	.79	.77	.25	.24
Factor 2: Accuracy of visual emotion recognition	.55	.58	.24	.31	.90	.86	.79	.67
Factor 3: Speed of auditory emotion recognition	.98	.97	.93	.96	.22	.27	.50	.44
Factor 4: Accuracy of auditory emotion recognition	.32	.32	.74	.74	.13	.16	.25	.23
ASD	<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>
Factor 1: Speed of visual emotion recognition	.96	.86	.82	.84	.042	.033	.27	.20
Factor 2: Accuracy of visual emotion recognition	.36	.35	.84	.87	.64	.45	.27	.20
Factor 3: Speed of auditory emotion recognition	.99	.91	.60	.72	.51	.56	.84	.77
Factor 4: Accuracy of auditory emotion recognition	.15	.15	.051	.055	.32	.34	.25	.25

Notes: *a*: Analysis includes covariates of age, sex, IQ, cohort, diagnosis, population stratification, and family structure. *b*: Analysis includes covariates listed in *a* and modality counterpart as an additional covariate.

($F[3,466.39] = 1.61, p = .19$), or the pT = 1 threshold ($F[3,481.75] = .84, p = .47$) (Figure 2).

3.6 | Association between ASD-PRS and emotion recognition classes

The ASD-PRS was associated with emotion recognition classes at the pT = 1 threshold ($F[3,461.58] = 3.26, p = .021$; Figure 3); class 3 (impulsive/imprecise visual, average auditory emotion recognition) had a significantly reduced ASD-PRS compared to class 1 (average visual, impulsive auditory emotion recognition; $p = .005$), class 2 (average-strong visual and auditory emotion recognition; $p = .002$), and class 4 (weak visual and auditory emotion recognition; $p = .010$). No association was observed with any of the other thresholds and for any of the other classes.

3.7 | Association between PRS and emotion recognition class probabilities

Exploring the use of probabilities of belonging to a class in the association analyses with PRS (Table 4), we found that the ADHD-PRS affected the probability of being assigned to class 1 and class 2 at the pT = .05 threshold ($p = .028$ and $p = .044$, respectively), as well as class 3 at the GWAS Suggestive Significance threshold ($p = .040$). For the ASD-PRS, no associations were observed.

4 | DISCUSSION

The aim of this study was to yield further insight into the genetic components of ASD and ADHD by examining the cross-disorder trait of emotion recognition problems. To investigate if the genetic burden

for ADHD and/or ASD differed across the earlier defined emotion recognition factors and classes, ADHD- and ASD-PRS were assessed. As expected, ASD + ADHD and ADHD participants had a higher average ADHD-PRS than controls; in contrast, the ASD-PRS did not seem to differ between ASD participants and controls. Though the analyses of the emotion recognition factors and classes only yielded nominally significant results, they were observed in an exploratory manner. For the emotion recognition factors, our exploration detected a possible link between a higher ASD-PRS and faster visual emotion recognition. In the analysis of the emotion recognition classes, the ASD-PRS appeared lower in emotion recognition class 3 (impulsive/imprecise visual, average auditory emotion recognition) compared to the other emotion recognition classes. In the analysis of class probabilities, we found that a high ADHD-PRS was associated with the reduced probability of being assigned to emotion recognition class 1 (average visual, impulsive auditory emotion recognition) or class 3 (impulsive/imprecise visual, average auditory emotion recognition), but a greater probability of being assigned to class 2 (average-strong visual and auditory emotion recognition). While this lack of significant association of emotion recognition and PRS corroborates findings from an earlier study—at least for ADHD (Martin et al., 2015), we feel that our findings merit discussion in an exploratory context below.

The impulsive/imprecise visual, average auditory emotion recognition class (class 3) demonstrated a lower ASD-PRS, which counterintuitively suggests a link between reduced genetic burden for ASD and poor task performance in this emotion recognition class. Similarly, high genetic burden for ADHD being linked to average to strong emotion recognition skills as seen in class 2 also appears to be counterintuitive. If these results were to be replicated, they would indicate that the causative chain from genetics via emotion recognition to disorders is indirect in ASD and ADHD. This may corroborate other neurocognitive studies supporting an indirect causative pathway (Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2014; McAuley, Crosbie, Charach, & Schachar, 2014; McAuley, Crosbie, Charach, &

Association between ADHD-PRS and emotion recognition classes

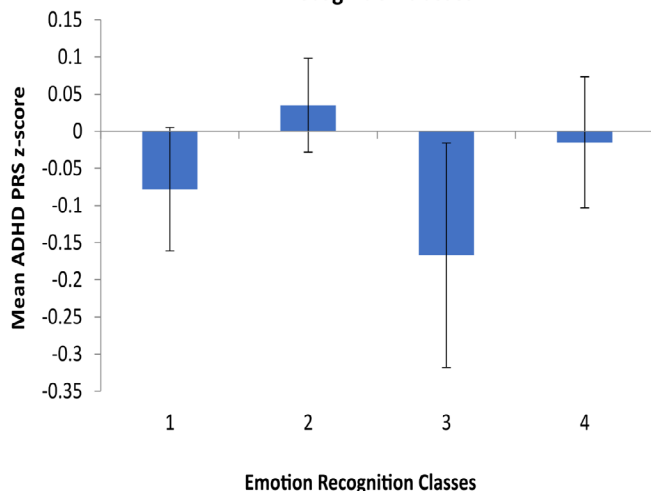


FIGURE 2 Mean ADHD PRS z-score for each emotion recognition class (+/- 1 SE); the $pT = 1$ threshold is shown as an example. Covariates included in the analysis were population stratification, family structure, age, sex and IQ

Association between ASD-PRS and emotion recognition classes

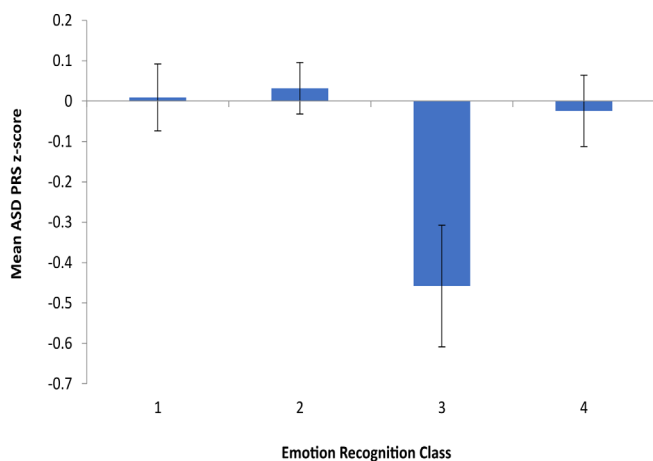


FIGURE 3 Mean ASD PRS z-score at the $p = 1$ threshold for each emotion recognition class (+/- 1 SE). Covariates included were population stratification, family structure, age, sex, and IQ

Schachar, 2017; van Lieshout et al., 2016). A moderation model, in which emotion recognition abilities might, for example, act as a buffer for the risk of developing ADHD and/or ASD, may also be plausible. The link of genetic burden for ADHD across emotion recognition factors and classes appeared to be different than the link of genetic burden for ASD with the factors and classes. Differences in ADHD and ASD genetic contribution to each of the emotion recognition variables potentially indicate that the indirect causative pathways in ASD and ADHD are different.

TABLE 4 The effect of ADHD-PRS and ASD-PRS on class probability assignment

	GWAS significance 5×10^{-8}	GWAS suggestive significance 10^{-6}	$pT = .05$	$pT = 1$
ADHD-PRS				
Class 1	.99	.98	.028	.38
Class 2	.60	.74	.044	.07
Class 3	.50	.040	.92	.72
Class 4	.48	.47	.78	.45
ASD-PRS				
Class 1	.59	.45	.28	.66
Class 2	.21	.29	.23	.10
Class 3	.34	.45	.86	.24
Class 4	.09	.35	.69	.40

Notes: Participants were assigned to an emotion recognition class based on the probability of belonging to that class. Ninety-three percent of participants in class 1 had a probability of being assigned to this class > 0.50, 95 and 91% of classes 2 and 4, respectively, also achieved this probability, whereas this was the case for 78% of participants in class 3.

Seemingly counter-intuitive results may not be entirely unusual, as a previous study found that association findings may potentially be explained by associations with other (unobserved) traits; in their case by cognitive ability (Hagenaars et al., 2016). We took IQ along in our own analyses in the present and previous studies. Though previously we did not find emotion recognition difficulties across classes to be directly attributable to low IQ (Waddington et al., 2018a), it should be noted that a positive association exists between the genetic risk for ASD and IQ, whereas a negative association between the risk for ADHD and IQ has been identified (Clarke et al., 2016). These associations also appear to be counterintuitive and complex, and potentially (partially) explain the findings in this study. It may also be worthwhile exploring other traits that have relevance to the association of emotion recognition abilities such as theory of mind and language abilities. Similar studies into these traits would be beneficial for our understanding of these indirect causative pathways in ASD and ADHD. Studies of the neural correlates of emotion recognition and potential mediators in the pathway from genotype to phenotype in ASD and ADHD may yield some answers.

This study has taken a novel approach to investigating the association between the genetic risk of ADHD and ASD and emotion recognition problems. More homogeneous subgroups are suggested to increase power in genetic association studies (Traylor, Markus, & Lewis, 2015). We tried to improve such work further by using quantitative in addition to categorical approaches in subgroup specification. The subgroups in the current study were based on our previous factor analysis of different emotion recognition domains and identification of subgroups using factor mixture modeling. This subtyping method uses probabilities to assign participants to classes, and therefore emotion recognition abilities could be investigated both as a continuous

and as a categorical variable. Nonetheless, studies that utilize a dimensional approach are still vulnerable to other limitations, as demonstrated by the current study. Limitations were brought about by sample size: although quite unique in size and depth of phenotyping, the sample we investigated here was small for genetic studies. A related limitation was the relatedness of participants. It was necessary to include this parameter in the analyses, but this reduced statistical power. In addition, the sample sizes of the GWAS used as a basis for the PRS were limited to detect small effect sizes. The power of the ASD GWAS was also lower than the ADHD GWAS, with fewer hits being identified in the former (Grove et al., 2019). This was exemplified by the lack of difference in the PRS of ASD participants and healthy controls. Together, the small target cohorts and the still limited discovery samples pose considerable restraints on statistical power and thus restrictions on our interpretations. Future studies will benefit from an increase in the sample size of the ASD and ADHD GWAS. Moreover, a multimodal emotion recognition GWAS that combines data from visual and auditory emotion recognition tasks could also be performed to improve our insight into the genetic basis of emotion recognition and its genetic links with ADHD and ASD.

This study aimed to investigate the genetics of ASD and ADHD through emotion recognition abilities. The results did not evidence strong support for a direct causative pathway from genetics to disorders via emotion recognition abilities, potential indirect pathways should be further investigated. Our findings tentatively suggest that potential pathways differ between ASD and ADHD, though replication is required to confirm this.

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CONFLICT OF INTEREST

Francesca Waddington, Catharina Hartman, Nanda Rommelse, and Nina Roth Mota have no conflicts of interest to declare. Barbara Franke has received educational speaking fees from Medice. In the

past 4 years, Buitelaar has been a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Organon/Shering Plough, UCB, Shire, Medice and Servier.

AUTHORS' CONTRIBUTIONS

Francesca Waddington, Nina Roth Mota and Barbara Franke were responsible for the study concept and design. Francesca Waddington performed the analyses under the supervision of Nina Roth Mota. Francesca Waddington drafted the manuscript. Nanda Rommelse, Barbara Franke, Jan K. Buitelaar, Catharina Hartman and Nina Roth Mota provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved the final version for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the NeuroIMAGE and BOA cohort studies. Restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data may be available with permission of the responsible persons of the NeuroIMAGE and BOA cohorts.

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