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ORIGINAL CONTRIBUTION

Increased risk of ADHD in families with ASD

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Abstract

Attention Deficit and Hyperactive Disorder (ADHD) and Autism Spectrum Disorders (ASD) are frequent comorbid neurodevelopmental conditions and the overlap between both disorders remains to be delineated. A more complete understanding of the shared genetic and environmental factors is needed. Using a family-based method, we evaluated the risk of ADHD in a group of relatives with an ASD proband (ASD−) and a group of relatives with an ASD and ADHD proband (ASD+). We enrolled 1245 individuals in the study: 499 probands, their 746 first-degree relatives and 140 controls. We used a multivariate generalized estimating equation (GEE) model, in which the dependent variable was the ADHD diagnosis in the relatives and the independent variable the ASD+ or ASD− in probands. We adjusted for sociodemographic factors (age, sex, IQ) and for the nature of the familial relationship with the affected proband (parent or sibling). Among the probands, there were 287 ASD− and 212 ASD+ individuals. ADHD was more frequent in relatives (19%) than in the control group (7%) ($p = 0.001$). The risk of ADHD was higher in the ASD+ relatives group than in the ASD− relatives group (GEE model OR 1.58 [95% CI 1.04–2.38], $p = 0.032$). This result was found in parents (OR 1.96 [95% CI 1.14–3.36], but not in siblings (OR 1.28 [95% CI 0.84–1.94], $p = 0.434$). Our study provides a representative estimate of the family distribution of ADHD in relatives of ASD probands but supports the modest effect of shared genetic and environmental factors between both disorders.

Keywords Attention deficit hyperactivity disorder · Autism spectrum disorder · Familial aggregation · Siblings

Introduction

Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are two of the most common neurodevelopmental disorders with a prevalence

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between 5 and 7 [1] and 1%, respectively, in children [2]. ADHD is characterized by symptoms of inattention, impulsivity and hyperactivity, and ASD by a deficit in social communication as well as restrictive, repetitive and stereotyped patterns of behavior [3]. Until the fourth edition of the Diagnostic and Statistical Manual of Mental Health (DSM), a comorbid diagnosis of ADHD and ASD could not be made because of the deep clinical/cognitive overlap between ASD and ADHD [4]. Most children with ASD, not only those with a comorbid intellectual disability (ID), display impulsive, inattentive and hyperkinetic symptoms. Approximately 40–70% of them fulfill the criteria for ADHD [5–7]. Likewise, patients with ADHD are deeply impacted in different areas of their lives from early stages of development, specifically in social integration at school or communication with family and friends. 18–22% of the subjects with ADHD, without ID, displayed significant symptoms of social communication impairment and lack of flexibility [8, 9] and 10% reached criteria for ASD [10]. The course of symptoms from childhood to adulthood [11], the impact on cognitive functions (specifically executive functions) [12, 13] and, to a lesser extent, the frequent aggressive and defiant behaviors or the sleep difficulties reported in these patients, contribute to the idea that both ADHD and ASD could belong to a single clinical entity, in which ADHD and ASD would be located at opposite poles [14]. The issue of phenotypic overlap between ASD and ADHD has been raised many times in the literature, most often excluding patients with intellectual disabilities. As example, we can mention the following recent studies: a causal modelling work excluding subjects with IQ below 70 [15] or a diffusion tensor imaging (DTI) study focusing on the neuro-anatomical expression of the clinical overlap between these two troubles and excluding subjects with IQ below 80 [16].

Genetically, ASD and ADHD are both of complex determinism and under the effects of similar pleiotropic influences including environmental and susceptibility genes factors [17]. Results from family, adoption and twin studies converge to suggest that both ASD and ADHD have a high heritability (90 and 75%, respectively) [18, 19]. They provide preliminary evidence that part of this heritability is shared by both disorders [20–22]. An increased incidence of ADHD was reported in the unaffected relatives of probands with ASD and vice versa [9, 23–25]. For example, a registry-based study which enrolled 1,899,654 individuals, showed that probands with ASD and their relatives were at a higher risk for ADHD than subjects without ASD (and their relatives) [26]. However, this study did not explore if the over-risk for ADHD was associated to the presence of attention deficit, hyperactive symptoms and impulsivity—frequently observed in probands with ASD—or only to the ASD status. In the end, the increased risk of ADHD commonly reported in families with ASD may be largely related to the ADHD comorbidity displayed by probands with ASD.

A more complete understanding of the interactions between ADHD and ASD is crucial for the clarification of the etiology and pathogenesis of these complex disorders. Family studies are a way to shed a new light on the relationship between these neurodevelopmental disorders. The aim of this study was to examine differences in ADHD prevalence among first-degree relatives of cases with ASD + ADHD or ASD only. We hypothesized that the risk for ADHD in families with ASD would be correlated to the ADHD status of the proband (i.e., prevalence of ADHD increased in the ASD+ group vs. ASD− group) and to a lesser extent, correlated to the ASD status of the proband (i.e., prevalence of ADHD increased in the ASD− group vs. controls).

Methods

Subjects

A sample of 1245 individuals composed of 499 probands with ASD, their 746 first-degree relatives (siblings and parents) and a group of 140 controls (age range 4.1–55.3 years) were enrolled in the study. Relatives were divided into two groups: one group of relatives of probands with ASD and ADHD (referenced in the article as the ASD+ group) and one group of relatives of probands with ASD only (referenced in the article as the ASD− group). Three centers located in France (Bordeaux, Creteil and Paris) recruited this cohort of subjects. Probands were included after a clinical and medical check-up including psychiatric and neuropsychological examinations, negative blood test results for Fragile-X and exclusion of subjects carrying a large deletion over 2 Mb detected by Illumina SNPs array). Final diagnosis of ASD was based on the DSM-IV-TR criteria and made by summing up the information from the Autism Diagnostic Interview-Revised (ADI-R) [27], the Autism Diagnostic Observation Schedule (ADOS) [28] and data from clinical reports experts in the field. For the relatives, the evaluation of ASD was systematically performed using the social responsiveness scale-II [29]. Similar to the assessment of probands, the relatives were explored using the ADI-R and the ADOS when the SRS *t* score made them "at risk for ASD" or above.

Psychiatric comorbidities (according to DSM-IV TR criteria) were screened in probands and their relatives with a semi-standardized direct interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version (K-SADS-PL) [30] for children and the Diagnostic Interview for Genetic Studies (DIGS) [31] for adults. Since ADHD is not screened by the DIGS,

our group developed a semi-structured interview to ascertain this disorder in adults (lifetime diagnosis). The diversity and intensity of ADHD symptoms were assessed in all subjects in the study using the family self-report questionnaire designed by the Tourette Syndrome Association Genetic Consortium (January 1995 version) [32] and the ADHD-Rating Scale [33]. Both instruments were used as parental hetero-questionnaires for children and as self-questionnaires for adults. Finally, expert clinicians (MS and HP) reviewed symptom ratings to confirm the final diagnosis of ADHD. Both raters were blind to the subjects' status (probands/relative) and his family relationships (sibling, parent, control). Inter-rater agreement was good ($K=0.93$). Intellectual functioning of all subjects was estimated with the Raven's Progressive Matrices (RPM), or with the Wechsler Intelligence Scales. The Raven's Progressive Matrices were used in probands with severe behavioral and language difficulties. Indeed, they allow a more reliable measure of intelligence than the Wechsler Intelligence Scales in such patients [34]. Among the ASD+ group, 9.0% ($N=19$) were tested with the Raven's Progressive Matrices and 11.9% ($N=34$) in ASD− probands. The proportion of probands tested with the Raven's Progressive Matrices was similar in both groups (in probands with ASD and ADHD and probands with ASD without ADHD). Physical comorbidities were also systematically explored using a semi-structured interview developed by our group.

A sample of 140 volunteers from the general population was also included in the study as our control group. Exclusion criteria were (1) a personal or a familial history of ASD or with a total score over 40 (≥ 55th percentile) at the Social Responsiveness Scale [35], (2) a personal history of neurological condition including traumatic brain injury, severe prematurity (< 1850 g at birth) or epilepsy, (3) a personal history of psychiatric illness requiring a psychotropic treatment or medical care by a psychiatrist except for ADHD. All participants meeting inclusion and exclusion criteria were screened for symptoms of ADHD (with the ADHD-Rating Scale and the family self-report questionnaire designed by the Tourette Syndrome Association Genetic Consortium) and non-verbal intelligence [using the Raven's Progressive Matrices (RPM)].

The local Institutional Review Board approved this study. Written informed consent was obtained from all participants. For the patients who were unable to consent for themselves, a parent or legal guardian consented to the study on their behalf.

Statistical analysis

Categorical variables were analyzed using Chi^2 test and continuous variables using the parametric Student t test. To further examine the association between ASD and ADHD, we built a multivariate generalized estimating equation (GEE) model, in which the dependent variable was the ADHD diagnosis in relatives and the independent variable the ASD+/ASD− status, adjusting for sociodemographic factors (age, sex, IQ) and the nature of the familial relationship with the affected proband (parent or sibling). The GEE model was used here to take into account the family relatedness among participants (i.e., non-independence of observations) as Stewart et al. in the analysis of family relationships between TD and ADHD. To address this issue dimensionally, we also performed GEE models in which the dependent variable was the ADHD symptom scores in relatives and the dependent variable the ASD+/ASD− status, adjusting for sociodemographic factors (age, sex, IQ) and the nature of the familial relationship with the affected proband (parent or sibling). A two-sided p value < 0.05 was considered as statistically significant. All statistical analyses were conducted using SAS statistical software (version 9.4, Cary, North Carolina).

Results

Clinical and demographic characteristics of probands with ASD and their relatives are summarized in Table 1. In our study, there were two groups of probands: a group of ASD− probands ($n=287$, 57.5%) and a group of ASD+ probands ($n=212$, 42.4%). ASD+ probands were more likely to be males (85.9 vs. 78.8%, $X^2=4.13$, $p=0.04$) and they were younger (16.3 ± 10.4 vs. $20.1. \pm 17.8$, $t=3.87$, df (497), $p<0.001$). The severity of symptoms measured with the ADI-R and the ADOS was not significantly different between groups. Both groups had similar non-verbal IQ scores [91.2 (24.0) in ASD+ vs. 93.7 (2.6) in ASD−] and a similar proportion of individuals with Performance IQ below 85 (33.6% of ASD+ and 28.3% of ASD−; $p=0.3$). However, the SRS t score was higher in the ASD+ probands (74.8 ± 11.8 vs. 57.9 ± 16.3, $t=10.2$, $p<0.001$).

Main clinical and demographic characteristics of the relatives in both groups were not significantly different (Table 1). The proportion of mothers, fathers and siblings was very similar in both ASD+ and ASD− groups. As hypothesized, the prevalence of ADHD was higher in the ASD+ relatives group (22.4%) than in ASD− relatives group (15.3%) ($X^2=6.0$, $p=0.014$) (Table 2). Whatever the status of the relative (ASD+ or ASD−), the prevalence of ADHD in relatives was higher than in the control group (19 vs. 7.1%, $X^2=1.31$, $p=0.001$). This difference remained significant after adjustment for age and IQ ($U=10.9$, $p=0.001$). Controls were younger than the relatives at inclusion (26.0 ± 15.5 vs. $37.7. \pm 18.3$, $t=6.99$, df (886), $p<0.001$) and had a lower normal range non-verbal IQ (103.4 ± 20.4 vs. 111.2 ± 20.7, $t=4.59$, df (886), $p=0.004$).

Table 1 Clinical and demographic characteristics of probands with ASD and their relatives enrolled in the study

	ASD+	ASD−	ASD+ vs. ASD− [*p*] (*df* = 497)	Statistical test
Probands, no.	212	287		
Males, %	85.9	78.8	0.042*	$X^2 = 4.13$
Current age, year (SD)	16.3 (10.4)	20.1 (17.8)	< 0.001*	$t = 3.87$
Performance IQ (SD)	91.2 (24.0)	93.7 (23.6)	0.370	$t = 0.90$
ADI-R				
ADI-R—social (SD)	16.4 (9.4)	17.1 (10.0)	0.509	$t = 0.66$
ADI-R—communication (SD)	12.4 (7.8)	11.3 (7.6)	0.262	$t = 1.12$
ADI-R—repetitive behaviors (SD)	5.5 (3.6)	4.8 (3.5)	0.098	$t = 1.66$
ADOS				
ADOS—communication (SD)	4.79 (1.96)	4.66 (1.94)	0.552	$t = 0.60$
ADOS—social (SD)	3.49 (2.99)	2.95 (2.81)	0.119	$t = 1.57$
ADOS—repetitive behaviors (SD)	1.66 (1.55)	1.93 (1.93)	0.196	$t = 1.30$
SRS *t* score (SD)	74.8 (11.8)	57.9 (16.3)	< 0.001*	$t = 10.2$
Relatives, no.	388	358		
Males, %	48.2	47.2	0.787	$X^2 = 0.07$
Current age, year (SD)	37.4 (18.2)	37.7 (18.5)	0.837	$t = 0.84$
Full-scale IQ (SD)	110.7 (23.0)	111.7 (18.0)	0.659	$t = 0.44$
Father, no. (%)	127 (32.7)	114 (31.8)	0.955	$X^2 = 0.09$
Mother, no. (%)	143 (37.0)	132 (37.1)		
Siblings, no. (%)	118 (30.3)	112 (31.2)		
Brothers, no. (%)	64 (54.7)	56 (50.0)	0.477	$X^2 = 0.50$

ADHD Attention Deficit Hyperactivity Disorder, *ADI-R* Autism Diagnostic Interview Revised, *ADOS* Autism Diagnostic Observation Schedule; *ASD* Autism Spectrum Disorder, *ASD*− Autism Spectrum Disorder only, *ASD*+ Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder, *IQ* Intellectual Quotient, *SD* standard derivation, *SRS* Social Responsiveness Scale

Table 2 Clinical and demographic characteristics of relatives and controls

	Relatives $N = 748$	ASD+ relatives $N = 388$	ASD− relatives $N = 358$	Controls $N = 140$	Controls vs. relatives	Controls vs. ASD+ relatives	Controls vs. ASD− relatives
Males, % (no.)	47.7	48.2	47.2	42.5	0.253	0.244	0.339
Current age, year (SD)	37.7 (18.3)	37.4 (18.2)	37.9 (18.3)	26.0 (15.5)	< 0.001*	< 0.001*	< 0.001*
Full-scale IQ (SD)	111.2 (20.7)	110.7 (23.0)	111.7 (18.0)	103.4 (20.4)	0.004*	0.020*	0.002*
ADHD	19.0	22.4	15.3	7.1	0.001*	< 0.001*	0.017*
					0.001[a]	< 0.001[a]	0.008[a]

ADHD Attention Deficit Hyperactivity Disorder, *ASD* Autism Spectrum Disorder, *ASD*− Autism Spectrum Disorder only, *ASD*+ Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder, *IQ* Intellectual Quotient, *n/a*: not applicable, *SD* standard derivation

*Significant; $p < 0.05$

[a]Adjusted for age and IQ

[b]Mean (SD)

The derived odds ratios and *p* values of our GEE model are reported in Table 3. This analysis showed that ADHD in relatives was significantly associated with the presence of ADHD symptoms in the probands with ASD (OR 1.58 [95% CI 1.04–2.38], $p = 0.032$). This association remained significant in parents (OR 1.96 [95% CI 1.14–3.36], $p = 0.016$) but not in siblings (OR 1.28 [95% CI 0.84–1.94], $p = 0.434$). In GEE models with ADHD symptoms scores in relatives as dependent variables, the differences between ASD+ or ASD− were in the same direction but not significant ($\beta = 0.12$ (SD = 0.08; *p* value = 0.143), $\beta = 0.12$ (SD = 0.07; *p* value = 0.120)

Table 3 Univariate logistic models with ADHD diagnosis in relatives as the dependent variable and ASD+ vs. ASD− in probands as the independent variable

	ASD+ relatives vs. ASD− relatives		ASD+ parents vs. ASD− parents		ASD+ siblings vs. ASD− siblings	
	OR [95% CI]	*p* value	OR [95% CI]	*p* value	OR [95% CI]	*p* value
ADHD (unadjusted)	1.58 [1.04–2.38]	0.032	1.96 [1.14–3.36]	0.016	1.28 [0.84–1.94]	0.424
ADHD (adjusted)	1.59 [1.03–2.47]	0.037[a]	1.82 [1.06–3.15]	0.031[b]	1.30 [0.69–2.46]	0.426[b]

ASD Autism Spectrum Disorder, *ADHD* Attention Deficit Hyperactivity Disorder, *ASD+* Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder, *ASD−* Autism Spectrum Disorder only, *OR* odds ratio, *CI* confidence interval

[a]Adjusted for ASD status, socio-demographics (age and sex) and the familial relationship with the affected proband

[b]Adjusted for ASD status, socio-demographics (age and sex)

in parents and $\beta = 0.15$ (SD = 0.16; p value = 0.248) in siblings).

Discussion

In the present study, we investigated the risk of ADHD in a large sample of first-degree relatives of probands with ASD and explored our results further using a multivariate GEE model which takes into account the family relatedness of participants. We identified a significant increase of the prevalence of ADHD in the relatives of probands with ASD whether these ASD subjects presented with ADHD. Our results reinforce preliminary evidence that ADHD shares common ground with ASD.

A higher risk of ADHD in the relatives of individuals with ASD has already been suggested in previous studies which found a significant correlation between ADHD in the parents and ASD in their offspring [36, 37]. As we reported in our study, the observed prevalence of ADHD in the relatives of ASD subjects was 2–3 times higher than in the control population [38]. This risk seems to be correlated to the intensity of autistic symptoms in the proband [39]. In our study, the ASD severity, measured with the ADOS or the ADI-R, was not significantly different between probands with or without ADHD, and thus did not play a role in the increased frequency of ADHD in the ASD+ relatives group vs. the ASD− relatives group. However, we observed that the proband ASD+ group scored significantly more on the SRS than the proband ASD− group. Several studies have investigated the potential influence of ADHD symptoms on the SRS score in patients with ASD. They showed a higher SRS total score regardless of the autistic symptoms severity suggesting that this score is sensitive to ADHD symptoms [39].

The risk of ADHD in families with ASD is partially dependent on the ADHD status of the proband (prevalence of ADHD increased in the ASD+ relatives group vs. ASD− relatives group), but also on the ASD status of the proband (prevalence of ADHD increased in the ASD− relatives group vs. controls). A difficulty to differentiate clinical symptoms between ADHD and ASD could be one of the factors to explain the familial aggregation of ADHD in the relatives of probands with ASD. For example, the lack of awareness of the feelings of others or the reduced comprehension of the consequences of their behavior toward others [40] have been recurrently described in patients with ADHD but also belong to the core symptoms of ASD. Similarly, the lack of motivation for tasks which have a social valence is frequently interpreted as attention deficit in patients with ASD [41, 42]. Thus, symptoms of ADHD could be a partial phenocopy of ASD in specific contexts [43]. Misdiagnosis, among other things, seems to be due to the high phenotypic heterogeneity of neurodevelopmental disorders. Specifically in ADHD, the clinical expression varies in early vs. late onset of symptoms [44], the behavioral (hyperactivity) or cognitive expression of symptoms (attention deficit) [45], the sex-dependent phenotype variability [46], the course of symptoms over time [47] and the associated comorbidity [48]. Even if the DSM-5 considered ASD and ADHD as distinct clinical entities, both disorders seem to belong to a single entity underlined by a shared genetic background [36]. A recent study, which estimated the association between ASD and ADHD in a complex pattern of familial relationships (including more than 1.8 billion of subjects), observed that relatives of probands with ASD were at a higher risk for ADHD than the relatives of individuals without ASD. Although they did not take into account the presence of ADHD symptoms in the proband, they reported a significantly higher risk of ADHD (OR 4.3–4.6) in subjects who shared 50% of the genetic background with the proband compared to controls [36]. These results are in accordance with those observed in our study since we observed a 3–4 times higher prevalence of ADHD in the siblings of patients with ASD than in controls.

Despite the shared heritability between ASD and ADHD, the identification of frequent variants associated with both disorders was unfruitful. Several candidate-genes studies

performed in samples of patients with ADHD and ASD symptoms remained inconclusive [49]. Most of them were without replication groups or displayed insufficient power to detect a robust association. Similarly, genome-wide association studies (GWAS) have not yielded many significant findings [50, 51]. The lack of significant results obtained through GWAS, reinforced early hypotheses suggesting that the mode of inheritance of ASD and ADHD was polygenic, i.e., the result of the action of many risk alleles in one individual. However, additional molecular studies focused on rare mutations associated with ASD or ADHD and shed new light on the puzzle of genes involved in the determinism of both disorders. Whole-genome microarray studies revealed submicroscopic deletions and duplications, called copy-number variants, affecting many loci, inherited and de novo. Some of them have been associated with ASD and ADHD.

Brain imaging studies have found that a global dysfunction of the cortico-striato-thalamo-cortical loop, which plays a critical role in the development of ADHD [52], is involved in the co-occurrence of ADHD and ASD [53, 54]. In a recent study [53], the authors reported that ADHD and ASD patients displayed a significant reduction of the activation of the bilateral striato-thalamic regions, the left dorsolateral prefrontal cortex and the superior parietal cortex. The under-activation of the left dorsolateral prefrontal cortex was more specifically associated with ADHD; indeed, its degree of inactivation was inversely correlated to the attention performance on a vigilance task. These results reinforce the hypothesis that ASD and ADHD may be seen as different manifestations of an overarching disorder [11]. As suggested by Buitelaars's group, both ADHD and ASD could belong to a single entity ranging from ADHD with few if any social handicaps, through ADHD with significant levels of socio-communicational impairment, to ASD as the most severe subtype with a deep deficit in social abilities [55].

Strengths and limitations

In the present study, we investigated the risk of ADHD in a large sample of first-degree relatives of probands with ASD and explored our results further using a multivariate GEE model which takes into account the family relatedness of participants. Our study differed from previous works on family aggregation of ADHD and ASD for two main reasons: (1) the strength of our study was mainly the intervention of senior psychiatrists who interviewed each proband, relative and control participant individually for inclusion in the study. Semi-structured interviews were conducted with the help of standardized tools to validate the axis I diagnosis according DSM-IV TR criteria. (2) Moreover, our study added to the existing literature by examining the prevalence of ADHD in relatives of ASD+ (with ADHD) and ASD− probands. To our knowledge, such analysis has never been performed on this specific query. Using a methodological approach developed by Stewart et al. [32], the present study reinforced the idea of a shared genetic and environmental influences in ASD and ADHD but using a distinct approach.

Several limitations should be acknowledged in this work. First, this study was based on cross-sectional data, which may be associated with recall bias. Second, the control group was significantly younger ($p < 0.001$) and had lower total IQ scores ($p = 0.004$) than the relatives of ASD probands group. However, statistical analyses controlled for age and total IQ as potential confounding factors. Third, the design of our study did not allow us to determine the prevalence of ASD and ADHD in relatives of probands with ADHD alone or in relatives of controls. Based on the results of the present study, we would have expected (1) a higher prevalence of ASD in relatives of probands with ADHD alone than in the control group and (2) a higher prevalence of ASD in relatives of probands with ASD and ADHD than in relatives of probands with ADHD alone. Further studies are needed to test these hypotheses. Fourth, the prevalence of ADHD in the control group was higher (7.1%) than the prevalence usually reported in general population-based epidemiological studies. A possible explanation for this might be that all participants were given a diagnosis of ADHD if they met DSM-IV criteria using a semi-structured diagnostic interview (DIGS or K-SADS-PL) or an ADHD-specific rating scale (ADHD-RS or the family self-report questionnaire designed by the Tourette Syndrome Association Genetic Consortium for children). This approach is inclusive and tends to overestimate symptoms of ADHD. However, we used the same approach in all groups (relatives ASD−, relatives ASD+, and controls) and there is no reason that this method was biased towards one particular group. Fifth, the presence of ADHD symptoms in probands with ASD was associated with ADHD in parents but not with ADHD in siblings. This result should be considered carefully given that (1) our sample of siblings was two times smaller than that of parents (leading to a lesser statistical power of the GEE model in siblings than in parents) and that (2) the 95% confidence intervals of the ORs (1.14–3.36 in parents and 0.84–1.94 in siblings) were largely overlapping (reinforcing the idea that the familial association of ADHD symptoms may not differ in parents and siblings of ASD probands). Finally, our sample of probands with low IQ was insufficient to conduct a sensitivity analysis on this specific population.

Conclusion

Our study provides a representative estimate of the family distribution of ADHD in relatives of ASD probands (with or without ADHD), supporting the importance of shared genetic and environmental influences. The categorical

approach which considers ADHD and ASD as distinct disorders should be reevaluated. In that respect, the Research Domain Criteria (RDoC) approach, initiated by the NIMH, has proposed to better take into account the multidimensionality of behaviors reported in patients (https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml). This approach is crucial to develop more accurate models which will better estimate the risk of developing specific symptoms or a specific pattern of symptoms related to impulsivity, inattention, sameness or social deficit. This will help revisit the interactions between ASD and ADHD on many subtle levels.

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Compliance with ethical standards

Conflict of interest This work was supported via collaboration with the Roche Institute for Research and Translational Medicine. F.B, G.H, C.B & M.L are employees of F. Hoffmann-La Roche Ltd who supported part of the study. The other authors did not receive any fees from Roche for this study. The remaining authors have no competing interests to declare.

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