A meta-analysis of genetic effects on neurodevelopmental disorders and co-occurring conditions.

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Abstract

A systematic understanding of the aetiology of neurodevelopmental disorders (NDDs) and their co-occurrence with other conditions during childhood and adolescence remains incomplete. In the current meta-analysis, we synthesised the literature on: (1) the contribution of genetic and environmental factors to NDDs, (2) the genetic and environmental overlap between different NDDs, and (3) the co-occurrence between NDDs and disruptive, impulse control and conduct disorders (DICCs). Searches were conducted across three platforms: Web of Science, Ovid Medline, and Ovid Embase. Studies were included only if 75% or more of the sample consisted of children and/or adolescents, and they had measured the aetiology of NDDs and DICCs using single-generation family designs or genomic methods. Studies that had selected participants based on unrelated diagnoses or injuries were excluded. We performed multilevel, random-effects meta-analyses on 296 independent studies, including over 4 million, partly overlapping, individuals. We further explored developmental trajectories and the moderating role of gender, measurement, geography, and ancestry. We found all NDDs to be substantially heritable (family-based h^2= 0.66 (0.03); SNP h^2= 0.19 (0.03)). Meta-analytic genetic correlations between NDDs were moderate (grand family based rA= 0.36 (0.12), grand SNP-based rG = 0.39 (0.19)) but differed substantially between pairs of disorders. The genetic overlap between NDDs and DICCs was strong (grand family-based rA = 0.62 (0.20)). While our work provides evidence to inform and potentially guide clinical and educational diagnostic procedures and practice, it also highlights the imbalance in the research effort that has characterized developmental genetics research.

Introduction

Neurodevelopmental disorders (NDDs) are complex health concern, starting from childhood[1]. NDDs affect around 15% of children and adolescents worldwide and lead to impaired cognition, communication, adaptive behavior, and psychomotor skills[2]. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) categorizes the following seven disorders under NDDs: intellectual disabilities, communication disorders, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), specific learning disorders, motor disorders and other neurodevelopmental disorders[3]. NDDs often have lifelong trajectories: they can manifest before 12 months of age[4] and can be diagnosed before children enter primary education[5,3].

While some NDDs (e.g. ASD and ADHD) may persist throughout adolescence and adulthood[6,7], others are more likely to alleviate as children get older (e.g., tic disorder[8] and communication disorders[9]); nevertheless, all NDDs can lead to social and behavioural difficulties and reduced independence over the lifespan[6,7,10]. For instance, ADHD in childhood has been associated with an increased risk of educational and occupational problems, risk-taking, and mood disorders in adulthood[11]; and an ASD diagnosis in childhood with increased occupational difficulties and a greater risk of psychopathologies in adulthood[12,13]. Difficulties are often more salient for those children diagnosed with more than one NDD[14].

A systematic understanding of the aetiology of NDDs remains incomplete. A disproportionate number of studies and systematic reviews have focused on ASD and ADHD, pointing to their substantial heritability – the extent to which observed individual differences are accounted for by underlying genetic differences. A meta-analysis of 7 twin studies of clinically diagnosed ASD in childhood and adolescent samples yielded a grand heritability estimate of 0.74[15]. Similarly sizeable heritability estimates have also been obtained from twin studies of ADHD in childhood and adolescence[16]. Heritability estimates were found to differ across the two major components of ADHD, with genetic factors playing a more substantial role in the aetiology of hyperactivity (h^2= 0.71), if compared to inattention (h^2= 0.56)[17]. However, other NDDs, despite showing similar prevalence rates and severity as ASD and ADHD, are less well understood and studied[18].

In line with what observed for all complex traits, heritability estimates for ASD and ADHD obtained from DNA data are lower than those obtained from twin and family designs[19]. Single nucleotide polymorphism (SNP) heritability can be calculated using large samples of individual-level genotype data[20] or summary statistics from genome-wide association studies (GWAS)[21], hypothesis-free studies aimed at discovering associations between genetic variation across the genome and individual differences in traits and disorders. The two largest studies to date that have estimated the SNP heritability of ASD and ADHD report estimates of h^2= 0.12 for ASD[22] and h^2= 0.22 for ADHD[23].

It is now well-established that NDDs often co-occur with one another, a phenomenon known as homotypic co-occurrence, and this points to a shared underlying liability between conditions[24,25]. Even in this instance, most studies have focused on examining the genetic correlations —the degree to which the same genetic variants contribute to the observed covariation between pairs of traits or disorders[26]— between ASD and

ADHD, resulting in a meta-analytic genetic correlation of 0.59[27] across twin and family studies, and a SNP-based genetic correlation of 0.35[28]. Aetiological sources of co-occurrence between all other NDDs have not been meta-analysed, but individual studies point to a moderate to strong shared liability between ASD/ADHD and other NDDs[29,30,31,32,33].

Another category of disorders that onset and progress through childhood and adolescence are Disruptive, Impulse Control and Conduct Disorders (DICCs), which the DSM-5 describes as disorders that share the underlying features of impulsive behavior, aggressiveness, and pathological rule breaking[3]. The DSM-5 identifies eight main DICC categories: Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Pyromania, Kleptomania, Other Specified DICC Disorder, and Unspecified DICC Disorders[3] (Figure 1). Similar to NDDs, DICCs have been linked to impaired social, emotional, and educational outcomes[34,35,36,37].

The developmental nature of DICCs makes them an ideal primary target for the investigation of how NDDs co-occur with other disorders (i.e., heterotypic co-occurrence) during childhood and adolescence. However, the distinction between NDDs and DICCs in the published literature is often blurred, particularly for disorders that include clinical features that overlap across NDD and DICC categories, such as ADHD. The most investigated example of symptom overlap between NDDs and DICCs involve ADHD and conduct disorder[38,39], and ADHD and oppositional defiant disorder[40]. Studies highlight how these disorders are characterised by disturbances in emotion regulation, attention problems, cognitive inflexibility, and impaired inhibition[39,41,42]. A shared symptomatology has also been observed between ASD and antisocial behaviour/personality disorder (that we refer to as conduct disorder in the current work since antisocial personality disorder describes adult diagnoses)[3,43,44] . However, studies on the association between NDDs and DICCs are characterized by a great deal of heterogeneity and inconsistencies across co-occurring conditions[45,46].

With three core aims (Figure 1), the current meta-analysis bridges gaps in our knowledge of the aetiology of NDDs and their co-occurrence with other developmental conditions in childhood and adolescence. First, we meta-analysed studies on the relative contribution of genetic and environmental influences to all NDD categories described in the DSM-5. Second, we meta-analysed estimates for the genetic and environmental overlap between different NDDs (homotypic co-occurrences). Third, given their developmental onset and progression and partly shared symptomatology, we examined the aetiology of the co-occurrence between NDDs and DICCs (heterotypic co-occurrences). In addition to addressing each disorder individually, we take a transdiagnostic approach by combining data across NDDs and including categorical (i.e., presence or absence of a disorder) and quantitative (i.e., continuously measured symptoms) measures. Clarifying the genetic and environmental aetiology of all NDDs and their homotypic and heterotypic co-occurrences will advance our knowledge of how developmental disorders cluster together, which could in turn inform educational and clinical practice[47].

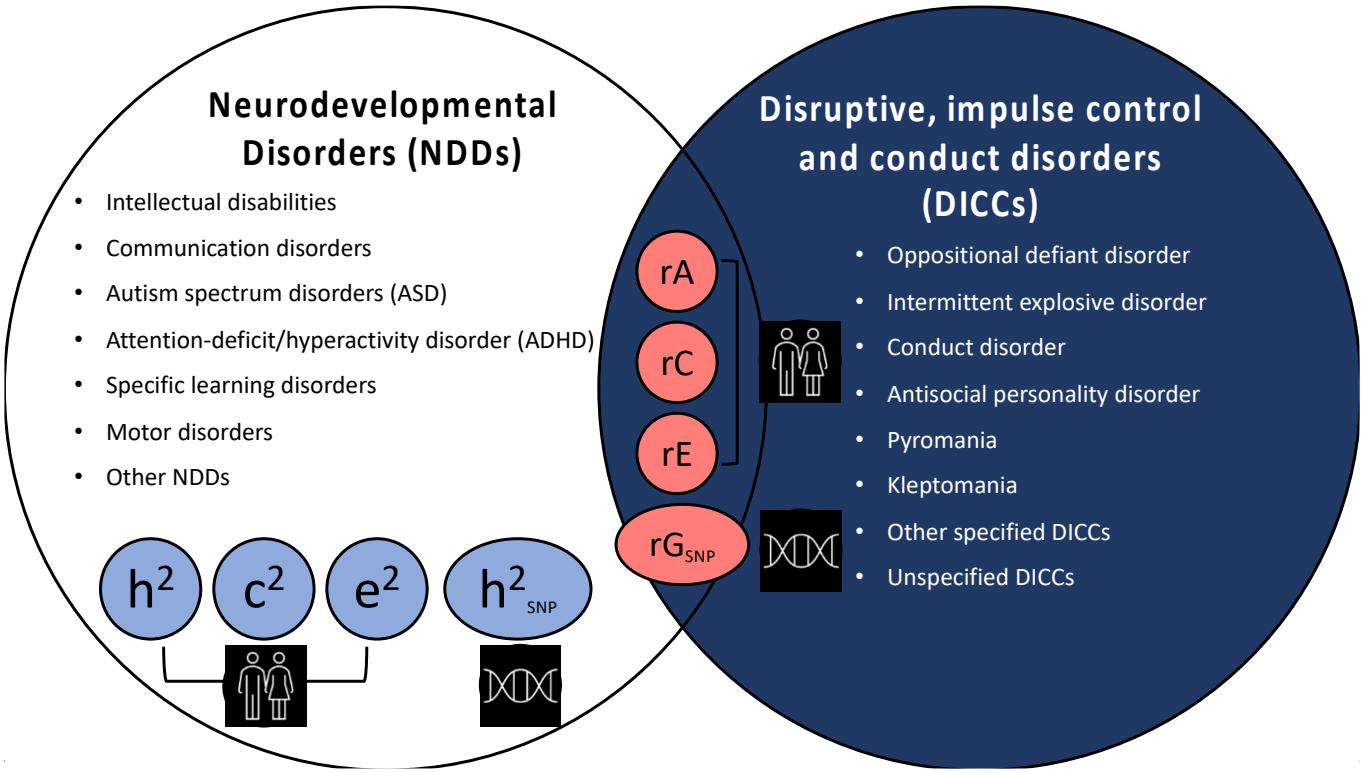

Figure 1. Visual summary of the three core aims of the current meta-analysis. Aim 1 (orange & light blue): estimate family-based genetic (h^2), shared environmental (c^2) and nonshared environmental (e^2) influences, as well as SNP heritability (h^2_{SNP}) for all neurodevelopmental disorders (NDDs) identified by the DSM-5. Aim 2 (orange & red): Provide grand estimates of family-based genetic (rA), shared environmental (rC) and nonshared environmental (rE) correlations and SNP-based genetic correlations (rG_{SNP}) between different NDDs. Aim 3 (navy blue & red): Provide grand estimates of rA, rC, rE and rG_{SNP} between NDDs and disruptive, impulse control and conduct disorders (DICCs). Results for c^2, e^2, rC and rE are presented in Supplementary Note 1.

Results

This Results section presents meta-analytic findings on genetic influences on NDDs and on their genetic overlap with other NDDs and DICCs. Meta-analytic estimates for shared and nonshared environmental factors and their overlap are presented in Supplementary Note 1. Results for all sub-categories of NDDs and DICCs are reported in Supplementary Note 2, Supplementary Figures 2 and 3 and Supplementary Tables 2, 4 and 6.

Searches and screening

Studies for this meta-analysis were selected during 3 screening stages including title and abstract screening, full text screening, and reference list screening (see Method for a detailed description). This selection process resulted in a total of 296 studies (292 family-based and 34 SNP-based studies) included in the current meta-analysis (Figure 2). The number of family-based and SNP-based studies do not add up because some studies provided both family-based and SNP-based estimates. These studies were counted only once towards the grand total but included separately in family-based and SNP-based categories.

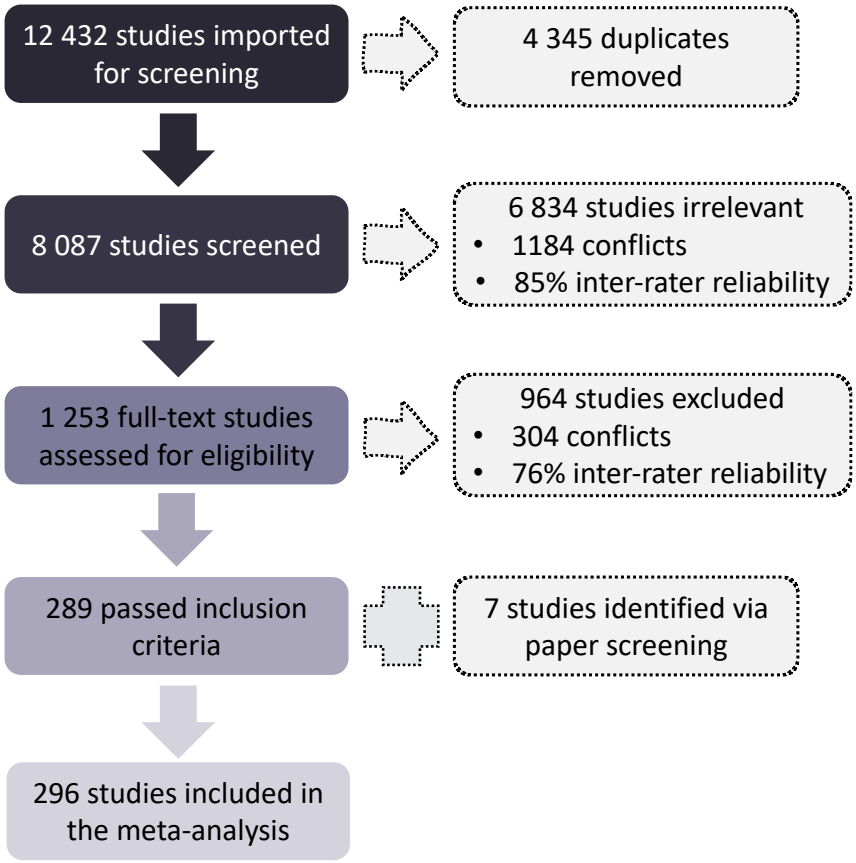

Figure 2. Diagram of searches and screening. This diagram presents an overview of the screening and selection process across primary and secondary searches, along with statistics of inter-rater reliability.

Heritability of NDDs

Our first aim was to obtain reliable estimates of the contribution of genetic factors to individual differences in all NDDs. We considered two broad categories of methods that allow for the estimation of heritability: family-based designs including related individuals (such as sibling comparisons and twin studies) and SNP heritability[48] (see Method). Given the substantial differences in methodology and outcomes, findings across these two broad categories were meta-analyzed separately.

Family-based heritability (h^2)

We identified a total of 236 family-based studies, comprising 2,792,511 partly overlapping individuals, that investigated the proportion of variance in NDDs that is accounted for by genetic factors. Out of the total, 121 studies (N= 682,340) investigated ADHD, 89 studies (N= 360,920) specific learning disorders, 36 studies (N= 1,821,970) ASD, 23 (N= 130,757) studies communication disorders, 6 studies (N= 52,278) motor disorders and 2 studies (N= 9,036) intellectual disabilities. Across all NDDs and 236 studies, the grand h^2 estimate was 0.66 (SE= 0.03). Grand h^2 estimates differed, albeit not significantly, across NDD categories, ranging from 0.86 (SE= 0.44) for intellectual disabilities to 0.62 (SE= 0.04) for specific learning disorders (see Figure 3 and Supplementary Table 1). Distributions of genetic influences across studies and NDDs are presented in Supplementary Figure 1.

SNP heritability (SNP h^2)

Out of the total of 29 SNP-based studies, involving 893,896 partly overlapping individuals, the only disorders that were addressed by at least two independent studies[49], included ASD (15 studies; N= 637,240), ADHD (14 studies; N= 725,168), specific learning disorders (9 studies; N= 40,637) and communication disorders (4 studies; N= 14,894). SNP heritability across all NDDs was moderate (0.19, SE= 0.03) and ranged between 0.15 (SE= 0.04) for ASD to 0.30 (SE= 0.14) for communication disorders (Figure 3 and Supplementary Table 1). SNP heritability estimates were not found to differ significantly across disorders, although the degree of precision in the estimates varied substantially depending on the sample size and number of individual studies included per disorder.

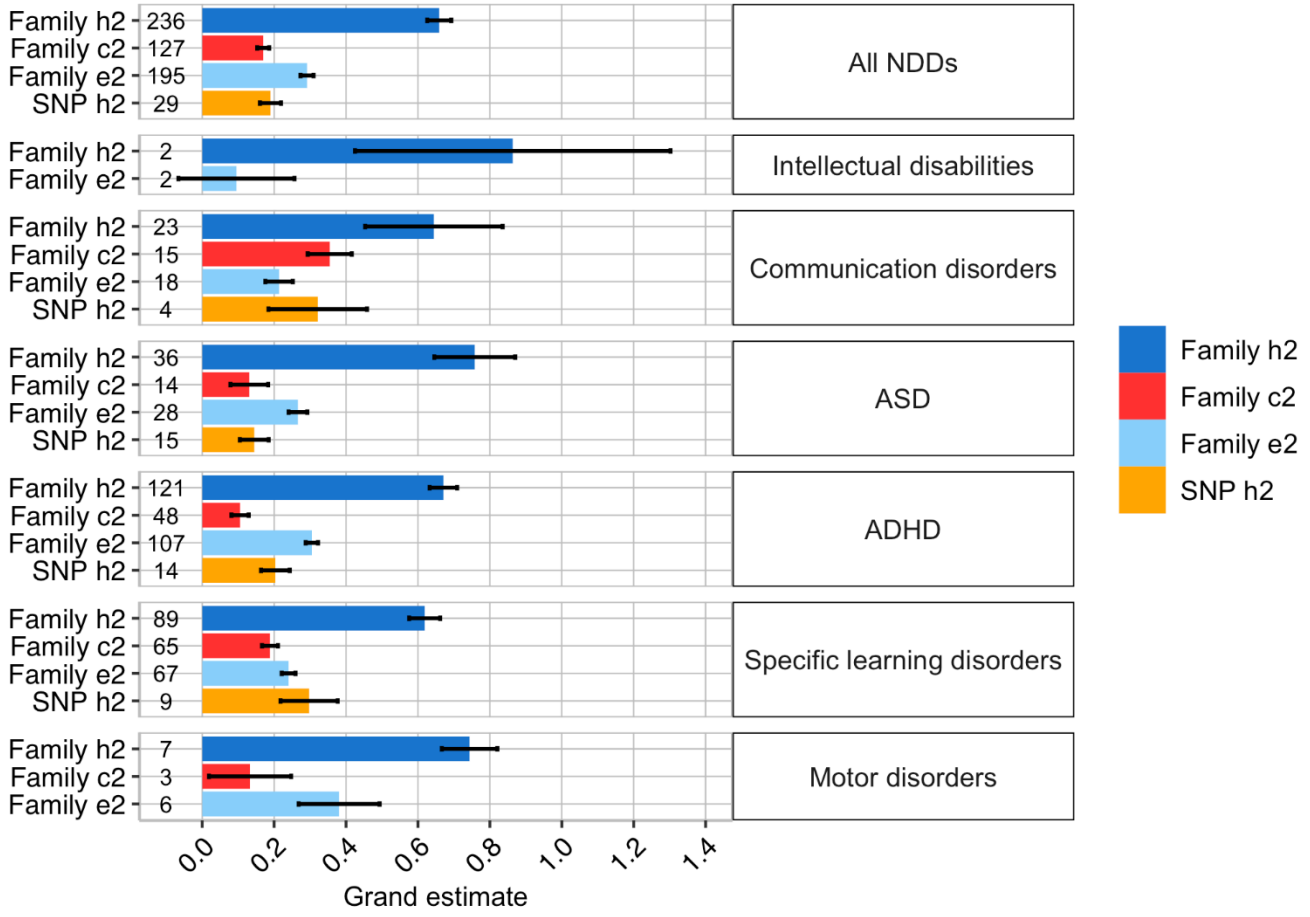

Figure 3. Genetic and environmental sources of variation in neurodevelopmental disorders (NDDs). Meta-analytic family and SNP-based heritability (h2) shared environmental influences (c2) and nonshared environmental influences (e2) on variation in NDDs. Numbers preceding bars on the y-axis denote the number of studies identified that provided estimates for specific NDDs. Error bars signify standard errors of the grand estimates. The results for c^2 and e^2 are discussed in Supplementary Note 1.

Genetic overlap between NDDs

When compared to the vast number of studies that had examined the aetiology of individual differences in each NDD, only a limited body of research (37 studies, N= 212,569) had investigated the co-occurrence

between NDDs in childhood and adolescence. In fact, for some of the disorders, we were unable to find two independent statistics[49], and therefore could not provide a meta-analytic estimate.

Family-based genetic correlations (rA)

When considering family-based designs (see Method and Supplementary Note 3), a sufficient number of studies to allow for meta-analysis was obtained for the following NDD pairs: ADHD & specific learning disorders (15 studies; N= 67,039), ASD & ADHD (6 studies; N= 58,518), ADHD & motor disorders (2 studies; N= 8,748), communication disorders & motor disorders (2 studies; N= 3,950), and communication disorders & specific learning disorders (2 studies; N= 42,098). Only one study was identified for the following pairs of NDDs: ASD & communication disorders (N= 12,174), ASD & specific learning disorders (N= 6,858), ASD & motor disorders (N= 6,858), and specific learning disorders & motor disorders (N= 6,858), therefore these studies could only be included in the transdiagnostic meta-analysis, capturing the degree of genetic and environmental co-occurrence across all NDD pairs. In addition, 9 studies (N= 46,000) examined the co-occurrence between subtypes of specific learning disorders, such as dyslexia & dyscalculia, these studies have been included in the transdiagnostic meta-analysis and results of these finer-grained analyses are reported in Supplementary Note 2.

We first meta-analyzed genetic correlations across all NDD categories (transdiagnostic genetic co-occurrence), this yielded a moderate grand estimate of rA= 0.36 (SE= 0.12). When considering NDD categories separately, the strongest genetic overlaps were found between ADHD & motor disorders (rA= 0.90, SE= 0.82), and between ASD & ADHD (rA= 0.67, SE= 0.30), while the weakest genetic correlation was found for the association between ADHD & specific learning disorders (rA= 0.07, SE= 0.12; Figure 4 and Supplementary Table 3). However, given the considerable differences in sample size used to derive genetic correlations between pairs of disorders, for example between ASD & ADHD or communication disorders & motor disorders, the strength of these correlations may be difficult to compare. Low correlations could also reflect low power to detect the true overlap.

SNP-based genetic correlations (rG_{SNP})

SNP-based designs in childhood and adolescent samples exclusively focused on the association between ASD & ADHD (5 studies; N= 242,543) and subtypes of specific learning disorders (1 study; N= 4,500). The transdiagnostic genetic correlation obtained meta-analyzing SNP-based designs was 0.39 (SE= 0.19) (Supplementary Table 8), in line with the estimate obtained from family-based designs. A grand genetic correlation of 0.20 (SE= 0.14) was found for the co-occurrence between ADHD and ASD. The one remaining study examined the co-occurrence between dyslexia & dyscalculia-related traits, specifically reading and mathematics abilities, which were strongly correlated (rG_{SNP}= 0.74, SE= 0.17)[50].

Genetic overlap between NDDs and DICCs

Our third aim was to obtain meta-analytic estimates of the genetic associations between NDDs and DICCs. Our search yielded only 15 eligible family-based studies (N= 42,718), and no SNP-based studies. Meta-analytic genetic correlations could only be calculated for a few NDD and DICC pairs, namely ADHD & conduct disorder (6 studies; N= 11,308), ADHD & oppositional defiant disorder (6 studies; N= 10,748) and

ASD & conduct disorder (3 studies; N= 24,564). In addition, we identified 1 study (N= 360) that examined the co-occurrence between specific learning disorders & disruptive behaviour, finding a weak negative genetic correlation (rA= -0.14, SE= 0.06)[51].

Family-based genetic correlations (rA)

Across all co-occurrences between NDDs and DICCs (15 studies), the grand genetic correlation was 0.62 (SE= 0.20). A similarly strong genetic correlation was observed between ADHD & conduct disorder (6 studies) and ADHD & oppositional defiant disorder (6 studies): rA= 0.66 (SE= 0.36) and rA= 0.66 (SE= 0.18), respectively; a similar level of aetiological overlap to that observed between strongly genetically correlated NDDs such as for example ADHD & ASD (Supplementary Table 5). On the other hand, the genetic overlap between ASD & conduct disorder (3 studies) was much weaker, with a meta-analytic genetic correlation of 0.35 (SE= 0.10; Figure 4). The similar extent of genetic overlap between ADHD & conduct disorder or ADHD & oppositional defiant disorder and ADHD & ASD may not be free from biases introduced by an unbalanced sample size used to derive these meta-analytic estimates. In addition, large meta-analytic standard errors make assessing the significance of differences between the estimates difficult.

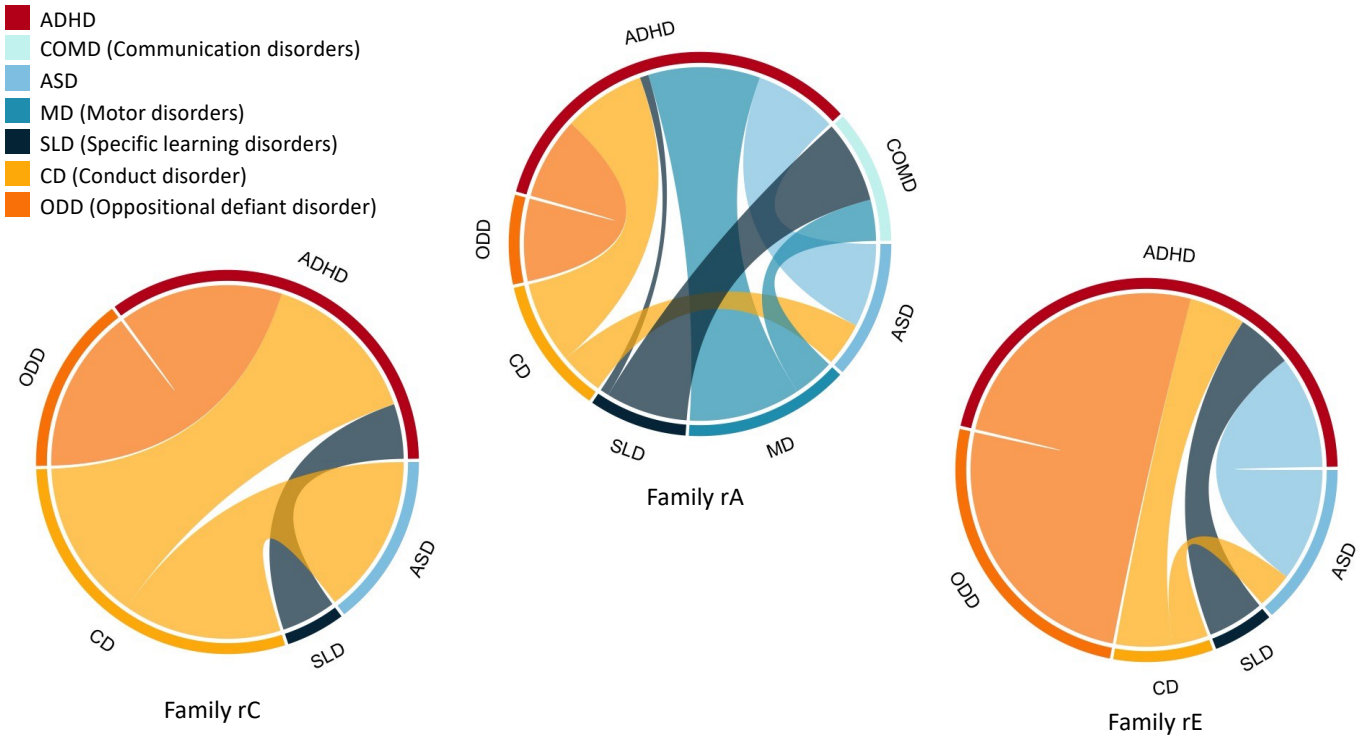

Figure 4. Genetic and environmental correlations between NDDs and DICCs. Strength of the meta-analytic genetic (rA), shared environmental (rC) and nonshared environmental (rE) correlations between neurodevelopmental disorders (NDDs) and their homotypic (other NDDs) and heterotypic (disruptive, impulse control and conduct disorders (DICCs)) co-occurrences. The outer layer of each circle shows all the different NDDs and DICCs for which meta-analytic correlation estimates could be computed. Each colored connector path indicates the strength of association between disorders, the thicker the connector path, the stronger the correlation between two disorders. The results for family rC and rE are presented in Supplementary Note 1.

Sex differences

Some NDDs do not affect males and females equally, for instance males are four times more likely to be diagnosed with ASD[52,53] and twice as likely to be diagnosed with ADHD[54]. Studies have suggested that these differences in prevalence may be caused by quantitative genetic sex differences, differences in the degree to which genes influence variation in NDDs in males versus females[55]. To provide an overview of sex differences in NDDs, we conducted separate meta-analyses including all studies that had reported sex-specific estimates.

Family-based heritability (h^2)

We identified 68 family-based studies that investigated the genetic aetiology of individual differences in NDDs in male samples and 67 studies that reported estimates for female samples. Out of all studies involving sex-stratified samples, 38 studies focused on ADHD, 21 studies on ASD, 8 studies on specific learning disorders, 4 studies on communication disorders and 2 studies on motor disorders. Across all NDDs, family-based heritability was not significantly different between males and females (h^2= 0.65, SE= 0.06 in males and 0.67, SE= 0.06 in females). Distributions of sex-specific family-based variance components for all NDDs, except for motor disorders for which a sufficient number of studies (>1) was not identified, are presented in Figure 5 and Supplementary Table 16.

SNP heritability (SNP h^2)

Marked differences in SNP heritability were observed between males and females across all NDDs (0.19, SE= 0.07 for males and 0.09, SE= 0.10 for females). However, these estimates were based on the only two studies to date that had calculated the SNP heritability of ASD and ADHD separately by sex (Supplementary Table 16).

Sex differences in genetic overlap between NDDs

We identified only 4 family-based studies that had examined homotypic co-occurrences of NDDs in males and only 2 studies in females. Half of these studies considered the overlap between ASD & ADHD. The other half had considered the co-occurrence between ASD & communication disorders (1 study in both male and female) and between developmental coordination disorder & tic disorder, two subtypes of motor disorder (1 study in males only). The grand family-based genetic correlation across all NDDs was estimated at 0.86 (SE= 0.58) for males and 0.25 (SE= 0.36) for females (Supplementary Table 17).

Sex-specific grand estimates of family-based genetic correlations between specific disorders could not be calculated due to the limited number of available studies. The only exception was the co-occurrence between ASD & ADHD in males, where 2 studies were identified (rA= 0.79, SE= 0.42) (Supplementary Table 17). SNP-based genetic correlations between NDDs could not be calculated for males and females separately due to a lack of studies that examined these associations separately by sex in samples of children and adolescents.

Sex differences in genetic overlap between NDDs and DICCs

Sources of co-occurrence between NDDs and DICCs could only be estimated between ADHD & conduct disorder and only in in females. In fact, one out of the only two studies that examined the sex-specific co-occurrence between ADHD and conduct disorders used a female-only sample. Hence, we could only meta-

analyse the co-occurrence between ADHD & conduct disorder in females. We found a meta-analytic genetic correlation of 0.75 (SE= 0.58) (Supplementary Table 18).

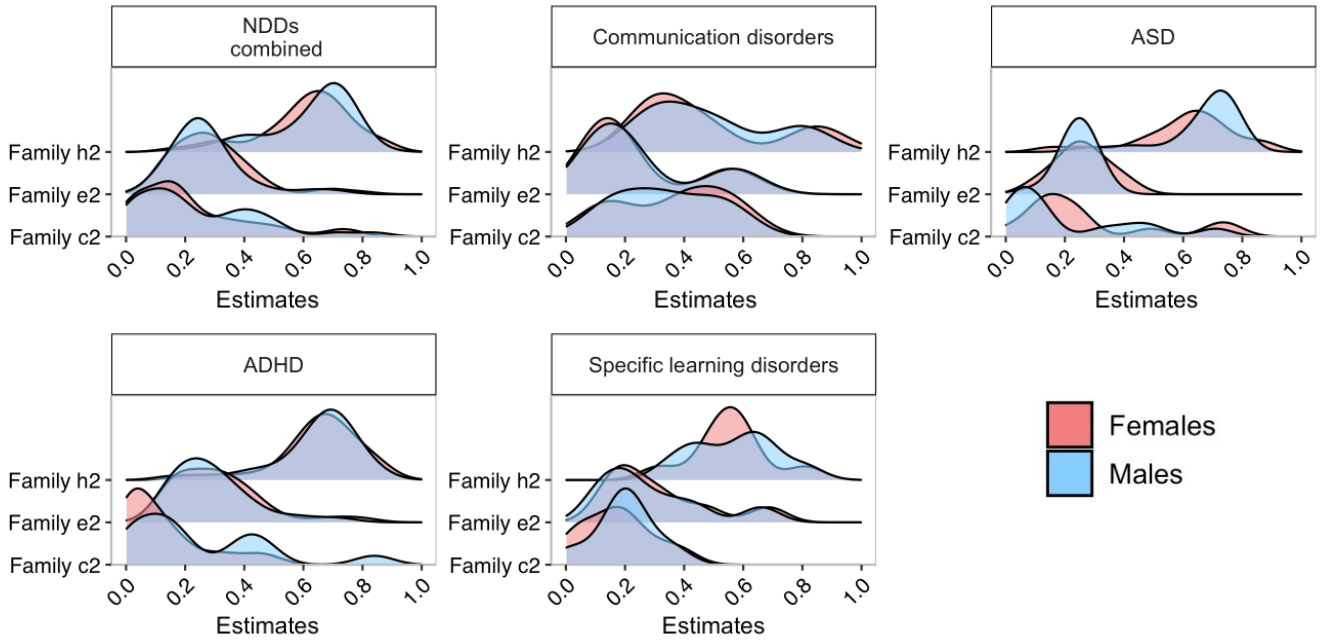

Figure 5. Sex differences. Distributions of the sex-specific meta-analytic estimates for the heritability (h2) and environmental contributions to neurodevelopmental disorders (NDDs). The top left panel shows the distributions of sex-specific estimates for the transdiagnostic meta-analysis, while the remaining panels the same estimates for specific NDDs for which a sufficient number of studies (>2) reporting sex-specific estimates was identified. The results for sex-specific c^2, e^2, rC and rE estimates are presented in Supplementary Note 1.

Developmental trajectories

We investigated developmental change and continuity in the relative contribution of genetic factors to NDDs by examining age-related differences in their aetiology and sources of their homotypic and heterotypic co-occurrences. We distinguished between the three following developmental stages: childhood (4-7 years), middle childhood (8-10 years) and adolescence (11-24 years). We grouped estimates in either of those three categories or across multiple categories, for example childhood & middle childhood (4-10 years), middle childhood & adolescence (8-24 years) and childhood & adolescence (4-24 years).

Family-based heritability (h^2)

Across all NDDs, 54 family-based studies reported estimates in childhood (4-7 years), 54 studies reported estimates in middle childhood (8-10 years) and 79 studies reported estimates in adolescence (11-24 years). The remaining studies involved populations whose age range spanned across categories, i.e., childhood & middle childhood (4-10 years; 14 studies), middle childhood & adolescence (8-24 years; 50 studies) and childhood & adolescence (4-24 years; 40 studies). We investigated age-related differences in heritability including all NDD categories (Figure 6A), with the exception of motor disorders for which we did not identify enough studies (>1) per age category. All estimates with standard errors, including those for age cross-categories are presented in Supplementary Table 19.

Across all NDDs, grand heritability remained relatively stable developmentally, with the estimate of 0.63 (SE= 0.03) in childhood, slight increase in middle childhood (0.68, SE= 0.04) and a subsequent drop back to 0.62 (SE= 0.08) in adolescence. This trend was consistent for some specific disorders (e.g., ASD and ADHD) but not for others (e.g., communication disorders and specific learning disorders) for which genetic influences decreased developmentally (Figure 6A; Supplementary Table 19).

SNP heritability (SNP h^2)

Out of a total of 29 SNP-based studies that were identified, 13 included adolescent samples, 7 samples in middle childhood and 6 samples in childhood, while 11 studies reported estimates across childhood & adolescence. SNP heritability was stable developmentally across NDDs, and the developmental trajectory mirrored that of family-based heritability (SNP h^2= 0.24, SE= 0.11 in childhood; 0.26, SE= 0.08 in middle childhood and 0.23, SE= 0.07 in adolescence) (Figure 6B; Supplementary Table 19). For ASD, ADHD and specific learning disorders, the specific NDDs for which grand estimates could be calculated, the developmental trends were consistent with those observed for family-based heritability (Figure 6B; Supplementary Table 19).

Developmental trajectories in genetic overlap between NDDs

Overall, we could not explore developmental trends in genetic correlations using either method due to a lack of available studies, the only exceptions were grand estimates for adolescence and across age categories (see Supplementary Tables 20-21). Genetic correlations obtained for adolescent samples only were in line with those obtained for the total sample (for example, when considering the co-occurrence between ASD & ADHD the genetic correlation was 0.66 (0.49) in adolescent samples and 0.67 (0.30) across all age categories).

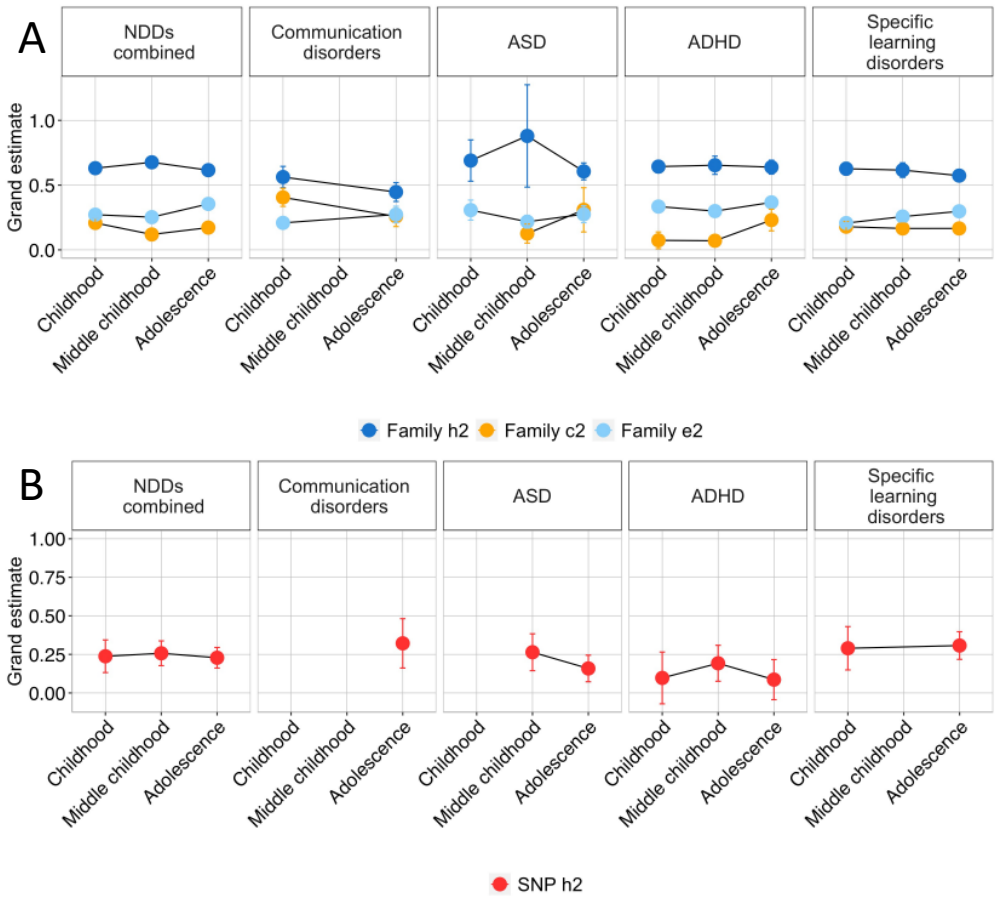

Figure 6. Developmental trajectories. Age-related differences in family-based heritability (h2), shared (c2) and nonshared (e2) environmental influences on neurodevelopmental disorders (NDDs) (panel A) and SNP heritability (panel B). Developmental stages include childhood (4-7 years), middle childhood (8-10 years) and adolescence (11-24 years). Error bars represent standard errors of grand estimates. For intellectual disabilities and motor disorders we could not identify a sufficient number of studies (>1) reporting age-dependent estimates and we were consequently unable to derive meta-analytic estimates. The results for age-stratified c^2, e^2, rC and rE are reported in Supplementary Note 1.

Categorical versus continuous measurement

Although we meta-analysed categorical (binary phenotypes, such as clinical diagnoses and cut-offs) and quantitative (sub-threshold symptom counts or test/questionnaire scores) measures together, we also report separate grand estimates for both measurement types. Across all NDDs, categorical measures were observed to yield significantly higher family-based heritability estimates if compared to continuous phenotypes (0.77, SE= 0.07 vs. 0.64, SE= 0.03). However, the opposite was found for SNP-based heritability (0.17, SE= 0.03 for categorical measures vs. 0.25, SE= 0.06 for quantitative assessments). Differences in sources of variation in specific NDDs, as well specific homotypic and heterotypic co-occurrences are presented in Supplementary Note 4, Supplementary Figure 26, and Supplementary Tables 28-30.

Geography and ancestry

Research into the genetic aetiology of NDDs and of their homotypic and heterotypic co-occurrences is largely limited to Western countries, even though, according to the Global Burden of Disease study[56], the prevalence of diagnosed NDDs is not uniform across the globe. Furthermore, individuals of European ancestry represent 16% of the global population but 80% of participants in genomic (i.e., DNA-based) research[57]. This Eurocentric bias[58] has created a major gap in our knowledge of the genetic aetiology of NDDs and their co-occurrences in non-White populations. In the following section we provide an overview of how behaviour genetics research into NDDs is distributed across countries and continents and how the estimates differ as a function of geographical location. Supplementary Note 5, Supplementary Figure 27, and Supplementary Tables 25-27 contain meta-analytic results of how heritability and genetic correlations differ at different levels of sample ancestral diversity. We created a moderator with four levels of percentage of European ancestry participants in samples: less than 50%, more than 50% but less than 75%, more than 75% but less than 100% and 100%.

Family-based heritability (h^2)

Out of the 236 studies investigating sources of individual differences in NDDs, 41% (96 studies) involved samples and cohorts based in the United Kingdom, 77 studies samples based in the United States, 24 studies Swedish samples, 19 studies Dutch samples, 11 studies Australian samples, 7 studies Canadian samples, 4 studies samples from China, and 2 studies samples from Norway. Other countries that contributed to the total grand estimate but did not have enough estimates for separate meta-analysis (i.e., only 1 study found from each country), included Finland, Japan, South Korea, and Italy. Estimates differed significantly across Countries. Considering all NDDs, the highest meta-analytic family-based heritability was estimated for Australian and Swedish samples (0.76, SE= 0.17 and 0.74 SE= 0.05, respectively), while the lowest was obtained for Canadian cohorts (0.43, SE= 0.09) (Figure 7A; Supplementary Table 22).

When considering specific NDDs, these were investigated with different frequencies across countries: the aetiology of intellectual disabilities was exclusively investigated in Swedish cohorts (2 out of 2 studies), from where most studies addressing sources of variance in motor disorders also came from (4 out of a total of 7 studies). Communication disorders were mostly researched in the United Kingdom (17 out of a total of 23 studies), as were ASD (20 out of a total of 36 studies) and ADHD (42 out of a total of 121 studies). On the other hand, 47 out of a total of 89 studies investigating specific learning disorders were carried out in the United States.

SNP heritability (SNP h^2)

Studies exploring SNP heritability of NDDs focused entirely on European cohorts and were primarily conducted in the United Kingdom and the Netherlands (14 and 3 out of 29 SNP-based studies in total) (Supplementary Table 22).

Geography and ancestry-related differences in the genetic overlap between NDDs

Sources of homotypic co-occurrence with NDDs were investigated in 37 independent family-based studies, out of which the majority was conducted in the United Kingdom (49%) and United States (30%). The highest genetic correlation across all co-occurrences was estimated in Swedish cohorts (0.80, SE= 0.26 across 3 studies), while the lowest grand genetic overlap was estimated in Canadian samples (-0.44, SE=

0.24 across only 2 studies which investigated the association between ADHD and specific learning disorders; Figure 7B; Supplementary Table 23).

The genetic aetiology of the co-occurrence between ASD & ADHD during childhood and adolescence was exclusively researched in the United Kingdom and Sweden (3 out of a total of 6 studies each). The co-occurrence between ADHD & motor disorders was only explored by two studies, one conducted in Sweden and the other one in Australia. Most studies examining the genetic overlap between ADHD & specific learning disorders came from the United States (8 out of a total of 18 studies), whereas the overlap between communication disorders & motor disorders was only addressed by 2 studies conducted in the United Kingdom and Japan.

SNP-based studies (6 in total) addressing the co-occurrence between NDDs were exclusively conducted in combined samples from the United Kingdom and Denmark (Supplementary Table 23).

Geography and ancestry-related differences in the genetic overlap between NDDs and DICCs

A total of 15 family-based studies addressing the co-occurrence between NDDs and DICCs were identified, 40% of which were conducted in the United Kingdom, 20% in the United States and 20% in Sweden. Studies yielded consistently strong estimates of genetic correlations across the three regions: genetic correlations of 0.60 (SE= 0.29); 0.42 (SE= 0.15) and 0.68 (SE= 0.41), respectively (Supplementary Figure 28 and Supplementary Table 24). The remaining 20 % of studies were conducted in Australia, Finland, and South Korea, but could not be meta-analysed separately as only one estimate was available for each country.

In terms of specific co-occurrences between NDDs and DICCs, half of the studies that explored genetic overlap between ADHD & conduct disorder, and ADHD & oppositional defiant disorder were conducted in the United States (3 studies each). Three out of 4 studies examining the association between ASD & conduct disorder were conducted in the United Kingdom and 1 study in Sweden.

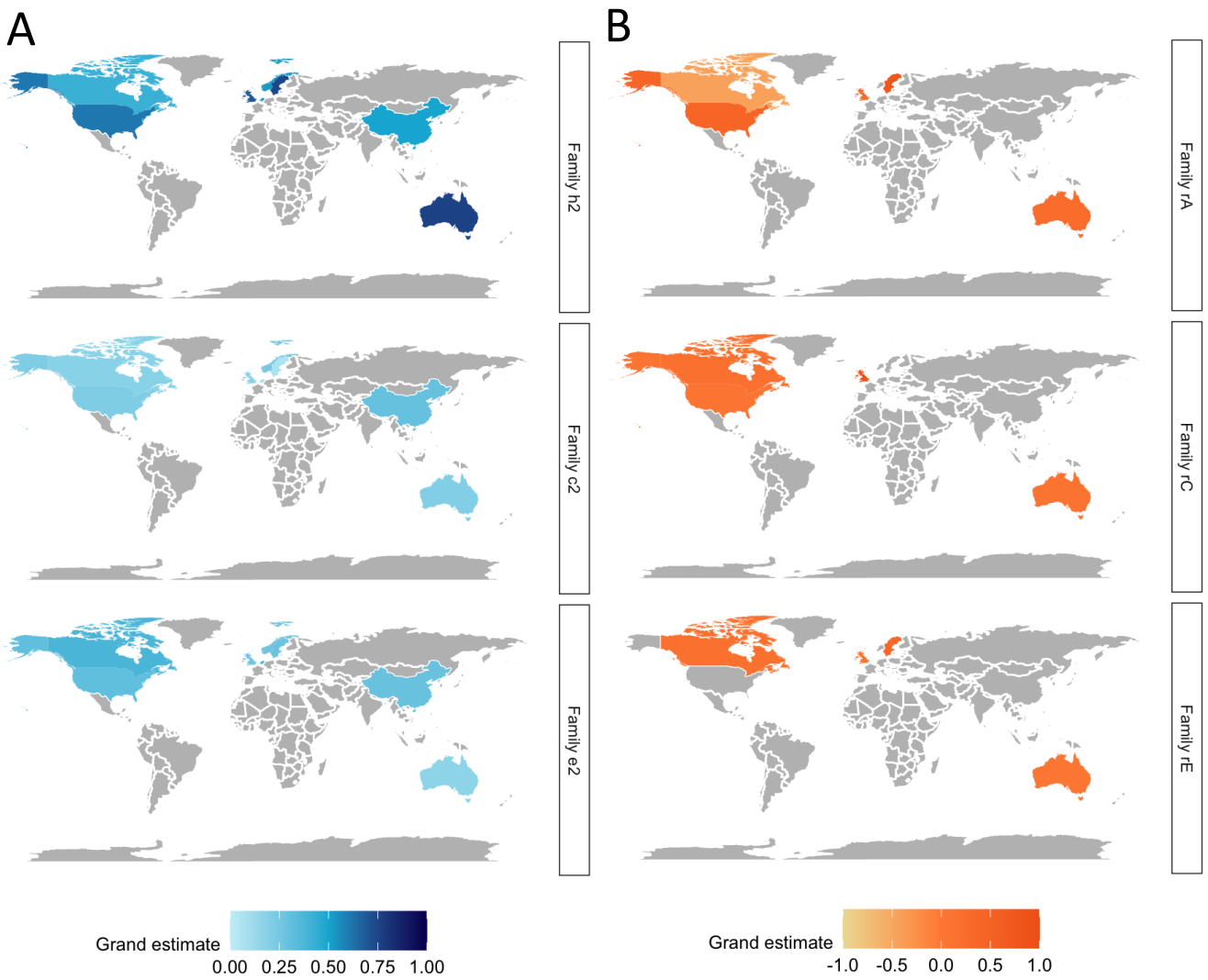

Figure 7. Geographical differences. Panel A illustrates differences in family-based heritability (h2) shared environmental (c2) and nonshared environmental (e2) influences across all neurodevelopmental disorders (NDDs). Panel B illustrates geographical differences in the genetic (rA), shared environmental (rC) and nonshared environmental (rE) overlap between NDDs. The areas shaded in grey are regions for which not enough relevant studies were identified (<2 studies). Geographical differences in rA, rC and rE between NDDs and disruptive, impulse control and conduct disorders (DICCs) are presented in Supplementary Figure 28. The results for c^2 and e^2 as well as rC and rE are discussed in Supplementary Note 1.

Bias and heterogeneity assessment

We applied I^2 statistics to assess heterogeneity in the estimates, followed by outlier and influential cases identification analyses. The results of these analyses are reported in Supplementary Note 6, Supplementary Tables 7-12, and Supplementary Figures 4-7. We applied Egger's regression and inspected funnel plots to examine the impact of publication bias on our results, the outcomes of these analyses are reported in Supplementary Note 7 and Supplementary Tables 13-15 and Supplementary Figures 8-24. Results of the risk of bias assessment are presented in Supplementary Figure 25, where, 93.8% of studies showed low risk of bias across the 9 quality checklist items, and the remaining 6.2% moderate risk.

Discussion

The findings of the current meta-analysis synthesise the current state of knowledge on NDDs and have important implications that can guide future research strategies, clinical and educational practice. First, by providing estimates of the relative contribution of genetic factors to all NDDs, our work responds to the need of moving beyond the nearly exclusive research focus on ASD and ADHD. Second, by providing an account of the genetic overlap between NDDs, we highlight how genetic influences are implicated in the co-occurrence between multiple NDDs, identifying patterns of shared aetiological liability. Third, by synthesising the literature on the co-occurrence between NDDs and DICCs we highlight how disorders from these two separate groups identified by the DSM-5 share as much of their genetic aetiology as do disorders all classified as NDDs.

Our work provides meta-analytic evidence for the substantial heritability of all NDDs, particularly when considering family-based studies, which indicated that around two thirds of the variation in NDDs is accounted for by genetic differences between children and adolescents. Although males are up to four times more likely to be diagnosed with ASD and ADHD than females [52,53,54], we showed that, when meta-analysed, genetic effects on NDDs do not differ by sex. We also showed that genetic sources of variation in NDDs are remarkably stable across developmental stages, and this developmental stability was observed across all NDDs. Genetic effects were also mostly consistent when we separated studies that had considered diagnoses and clinical cut-offs from studies that had quantified NDDs as continuous traits.

Interestingly, we found that the genetic contributions to NDDs differed substantially as a function of geography. This highlights how estimates of genetic effects on disorders are sensitive to different environmental contexts[59,60]. Our work on geographical differences also highlighted the major gap in our knowledge of the aetiology of NDDs in non-Western countries, a gap that is only exceeded by the lack of ancestral diversity observed across all studies of NDDs. Importantly, the current study pointed to how genetic influences on NDDs were substantially reduced in more ancestrally diverse samples, again highlighting how heritability estimates are inextricably linked to our social context[61,62], in a sense that increased ancestral homogeneity within the sample likely entails increased environmental homogeneity, reducing environmental variability and inflating heritability in these populations.

The lack of diversity in genetic research remains its most striking limitation to date, particularly when considering DNA-based methods, limiting the extension of genetic findings to the entire population[63,64]. Limited research resources in under-represented populations are likely to have profound cascading effects for future advances in clinical practice, including pharmacological and behavioural treatment. Fortunately, there are major initiatives underway to re-balance these biases[65,66,67].

Our second aim was to provide a clear account of how close NDDs are to one another aetiologically. We found that, while meta-analytic estimates indicated moderate genetic overlap, the degree of heterogeneity in these associations across disorders was large. We found a substantial genetic correlation between ASD and ADHD, ADHD and motor disorders, and communication disorders and specific learning disorders. On the other hand, genetic overlap was only moderate between communication disorders and motor disorders, and very weak between ADHD and specific learning disorders, which is consistent with the degree of symptom resemblance across these disorders.

Although we were able to explore general patterns of variation and co-occurrence, the aetiology of specific NDDs and of their associations could not be comprehensively characterised. The research gaps that we identified highlight an imbalance in focus across NDDs in developmental behaviour genetics research. When considering our first aim, we could only identify 2 family-based studies that investigated the genetic contributions to intellectual disabilities, if compared to 121 family-based and 14 SNP-based studies identified for ADHD, and 36 family-based and 15 SNP-based studies identified for ASD. This lack of research on intellectual disabilities, a neurodevelopmental disorder affecting 2.5% of children in the United Kingdom[68,] more than double the prevalence rate of ASD[70] is reflected in, and likely partly due to, the lack of funding bodies devoted to researching NDDs other than ASD and ADHD, as well as a lack of publicly available data repositories and resources (e.g., [71,72,73]).

We also identified very few studies that had examined the aetiology of motor disorders, another neurodevelopmental condition showing significant prevalence rates of 5-6% in school aged children[74]. This unbalanced research focus, that extends far beyond genetically informative research to touch developmental and therapeutic research[75,76,77,78], has led to an uneven distribution of knowledge, which could lead to limited access to interventions for children with NDDs other than ASD, ADHD, and Dyslexia[79].

The lack of equity in focus across NDDs was pronounced in analyses addressing our third aim. Sources of co-occurrence between NDDs and DICCs could only be investigated between ADHD & conduct disorder, ADHD & oppositional defiant disorder and between ASD & conduct disorder. Considering that in the DSM-5 the DICCs category comprises 8 distinct disruptive disorders, this highlights a major gap in our knowledge.

To conclude, this meta-analysis provides a holistic view of genetic and environmental contributions to all NDDs and commonly co-occurring developmental disorders, revealing that NDDs are just as strongly genetically correlated with other NDDs, as most of them are with DICCs. Our work identifies a lack of balance in research across different NDDs, which calls for future genetic research to focus on less investigated disorders. We provide knowledge about patterns of aetiological co-occurrence between NDDs, as well as between NDDs and DICCs, which we hope will inform clinical and educational diagnostics and practice, resulting for example in expanded diagnostic screening.

Methods

The protocol for the current meta-analysis was registered with the international prospective register of systematic reviews (PROSPERO) and can be accessed at the following link: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=230158. Deviations from the registered protocol are described in Supplementary Note 8. This meta-analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[80]. PRISMA 2020 Checklist and PRISMA 2020 for Abstracts Checklist[80] are included in Supplementary Notes 9 and 10. Code and master extraction tables are available at https://github.com/CoDEresearchlab/Meta_analysis_NDDs_DICCs.

Identification of relevant studies

A total of 296 studies were included in the meta-analysis (Figure 2). Studies were identified during three searches: the primary search (Supplementary Figure 29A) conducted on the 20th of January 2021, the secondary (confirmatory) search (Supplementary Figure 29B) conducted on the 15th of April 2021 and the additional search of other relevant meta-analyses and reviews finalised on the 4th of May 2021. Searches were conducted across three platforms: Web of Science, Ovid Medline, and Ovid Embase and the outputs managed with the aid of Covidence (https://www.covidence.org/). An in-depth description of indexes, timespans, search strategy and key words is included in Supplementary Note 11. All studies included in the meta-analysis are listed in Supplementary Tables 31-36.

Screening and inclusion criteria

After the initial searches were conducted and duplicate studies removed, 8,087 studies met the criteria for the first stage of screening, which involved title and abstract scanning. All titles and abstracts were screened by two independent, blinded reviewers to ensure inter-rater agreement. Conflicts were resolved by a third independent reviewer and inter-rater reliability was calculated as the proportion of conflicts to the total number of studies screened (Figure 2). After this initial screening phase, 6,834 studies were excluded as deemed not relevant for the purpose of the current meta-analysis.

The title and abstract screening process resulted in a total of 1,253 potentially eligible studies. The full text of each study was screened by two independent, blinded reviewers. Reviewer discrepancies were identified and resolved by a third independent reviewer. Inter-rater reliability statistic was calculated (Figure 2). This resulted in 289 eligible articles. In addition, during full text screening, relevant review articles, meta-analyses, editorials, and conference abstracts were flagged to aid the potential discovery of further relevant studies by either screening the References sections or contacting the authors of conference abstracts. Through this process, 7 additional studies were identified, which resulted in a total of 296 studies included in the current meta-analysis (see Figure 2). Studies were considered relevant and selected to be included at the next screening stage based on the following criteria.

First, studies were only included if 75% or more of the sample consisted of children and/or adolescents. Based on guidelines from the World Health Organization (WHO; https://www.who.int/health-topics/adolescent-health#tab=tab_1), we defined the period from childhood to end of adolescence as ranging from age 4, the earliest age for compulsory schooling, to age 24, the end of adolescence. Second, we included studies that had measured NDDs and DICCs considering either formal clinical diagnoses, clinical cut-offs, and/or quantitative measures of symptoms. Third, studies were selected only if they featured data on at least one NDD (Aim 1), at least two NDDs (Aim 2), or at least one NDD and one DICC disorder (Aim 3).

Fourth, studies using family-based designs had to have reported at least one estimate of heritability (h^2), shared environmental (c^2) or nonshared environmental influence (e^2), or genetic or environmental correlations. We included only single-generation family designs, that is studies that had used twin design[81], sibling comparisons[82], or extended twin designs[83]. We excluded multiple-generation family designs (e.g., children-of-twins[84] and in-vitro fertilization[85]) due to the potential confounding in the genetic and

environmental estimates that could have resulted from including parental traits in the models decomposing the covariance between family members[86].

Fifth, studies using genomic designs were included only if they had reported at least one SNP-based heritability estimate and/or a genetic correlation (r_a). Eligible SNP-based methods to quantify the proportion of phenotypic variance accounted for by common SNPs included genome-based restricted maximum likelihood (GREML)[87], linkage-disequilibrium score regression (LDSC)[21] and SbayesS, which is a Bayesian approach to the analysis of GWA summary data[88]. Each method is described in greater detail in Supplementary Note 12. Sixth, studies that had selected participants based on other diagnoses not related to NDD or DICC categories or based on extreme vulnerability or environmental insult unrelated to NDDs or DICCs, such as alcohol abuse, were not included. Lastly, only studies published in English were included. Studies deemed eligible based on full-text scanning were also scored in terms of their scientific quality and risk of bias by two reviewers (see details on the quality scoring checklist in Supplementary Note 13).

Data extraction

Data extraction was conducted by the primary reviewer. Issues and uncertainties were resolved through discussion with co-authors. Missing data was requested from study authors via email or ResearchGate (for details, see Supplementary Note 14). Extracted data were compiled in a table, including information on study reference, project/cohort name, study design (e.g., classical twin study), model reported (e.g., full ACE model; when multiple models were reported, the best fitting model was selected for data synthesis), overall number of participants and number of participants in subgroups (e.g. number of monozygotic vs. dizygotic twins), average age and age range of the sample, cohort country(ies) of origin, participants ancestry (defined in terms on the percentage of participants of European ancestry in samples), broad types of NDD and DICC included (e.g., Specific Learning Disorder), sub-type of NDD and/or DICC included (e.g., dyslexia), specific phenotypes measured (e.g., reading fluency), measure statistics (e.g., binary (diagnosis) or continuous (symptoms continua)), measure (e.g., Conners rating scale for ADHD) and rater (e.g., parent reports), covariates included in the analyses (e.g., age and sex), statistics (e.g., family-based heritability, SNP-based genetic correlation etc.), and finally the estimated statistics and the provided index of measurement variance (e.g., standard error). Master extraction tables, 'Extraction_heritability' and 'Extraction_correlations' are available at https://github.com/CoDEresearchlab/Meta_analysis_NDDs_DICCs.
Estimates of heritability, shared and nonshared environmental influences were extracted as reported by individual studies. When studies only reported twin correlations, variance components were calculated using the Falconer's formula[89], as follows:

$$h^2 = 2(r_{MZ} - r_{DZ})$$
$$c^2 = 1 - (h^2 + e^2)$$
$$e^2 = 1 - \mathrm{r_{MZ}}$$

Where: h^2= family-based heritability; r_{MZ}= monozygotic twin correlation; r_{DZ}= dizygotic twin correlation; c^2= shared environmental influences; e^2= nonshared environmental influences.
Genetic, shared and nonshared environmental correlations were only extracted if reported by individual studies. For studies where neither standard deviation, standard errors nor 95% confidence intervals were reported, the 95% confidence intervals were calculated using the Cir function implemented in the R package

psychometric[90,91], based on the sample size of the study, and subsequently converted to standard errors via dividing the difference between upper and lower bound confidence intervals by 3.92[92].

Data synthesis

Heritability and environmental influences reported by selected studies were synthesised using a multilevel random-effects meta-analysis in metafor for R[55,]. We used heritability/environmental influences and genetic/environmental correlation coefficients, along with standard errors as the measures of effect size[27]. However, to avoid the risk of Type I error introduced by the distribution characteristics of the correlation coefficient[93], we transformed all estimates using Fisher's z. Effect sizes were then weighted by their inverse variance weight so that larger samples were given more weighting and the standard error for the common effect size resulted as a function of the allocated weights. For results presentation, Fisher's z was transformed back to variance components and correlation coefficients[94]. Multilevel random-effects models enabled varying true effect sizes across studies . We introduced a 2-level structure to account for nested effects underlying heterogeneity and clustering across studies (Level 1: individual clustering; Level 2: cohort clustering). Given that some NDDs have different prevalence rates in males and females[52,53,54], we meta-analysed studies that provided sex-specific estimates in separate models to minimize sample heterogeneity across studies and report separate grand estimates for combined, male-only, and female-only samples.

Data reporting

We report transdiagnostic grand estimates across all disorders and for broad NDD categories, comprising all studies that investigated the aetiology of a disorder either using diagnoses, categorical or quantitative measures. For example, the broad ADHD phenotype includes studies that have measured ADHD using diagnoses, clinical cut-offs, and continuous measures of ADHD traits, such as checklists and questionnaires. The only exception is intellectual disability. We did not consider quantitative measures of general intelligence as indexing a continuum of intellectual disability given that intellectual disability, as described in the DSM-5 is a complex disorder, not only characterized by impairments in intellectual performance, but also in adaptive functioning and communication[3,44]. Finally, we considered specific manifestations of NDDs, for example, beyond ADHD, we also consider the hyperactive/impulsive and inattentive sub-types separately. Results for all sub-categories of NDDs and for their co-occurrence with other disorders are reported in Supplementary Note 2, Supplementary Figures 2 and 3 and Supplementary Tables 2, 4 and 6.

Aggregation of non-independent effects

Multilevel meta-analytic models allow to account for non-independence of estimates derived from partly or completely overlapping samples (i.e., estimates obtained from multiple studies that have used the same cohort of participants). To further account for the non-independence of sampling variance (i.e., when sampling errors correlate because data from partly the same individuals is used to estimate multiple effect sizes), we also aggregated multiple estimates within each individual study (e.g., estimates at multiple timepoints derived from the same study). Aggregation of dependent effects sizes was performed at the level of each study using the R package Meta-Analysis with Mean Differences[96,91] (MAd), applying a default correlation between estimates of 0.5. We conducted several sensitivity analyses, comparing different

aggregation methods, i.e., aggregating at the level of the study, cohort, and country, and varying the assumed correlation between dependent effect sizes (0.5, 0.3 and 0.9). Results of these additional checks are presented in Supplementary Figure 30 and discussed in Supplementary Note 15. Since differences in aggregation strategy did not result in significant differences in meta-analytic effects, we report results obtained when the correlation between dependent effect sizes was set to 0.5.

Bias and heterogeneity assessment

The potential for publication bias was explored using funnel plots and Egger's linear regression[97].
The proportion of heterogeneity across estimates was estimated using the I^2 statistics, which calculates the fraction of variance across studies that can be attributed to heterogeneity, rather than chance . The I^2 statistics was computed as a proportion of true variance of true effects to variance of the observed effects, in line with the following formula :

$$I^2 = \frac{V_{TRUE}}{V_{OBS}}$$

where V_{TRUE} is the variation of true effects and V_{OBS} is the variation due to sampling error. In other words, I^2 can be interpreted as the dispersion of observed effects as compared to the dispersion that would be predicted just from sampling error . The I^2 statistics also provides insight into the degree to which confidence intervals from individual studies are independent . We also conducted outlier cases identification analysis, followed by re-calculation of I^2 estimates after removing studies considered to be outliers[101]. Studies having a substantial impact on the grand estimates and heterogeneity were identified using influential cases identification analysis[101]. Heterogeneity assessment analyses were conducted using the metafor[49], meta[102] and dmetar[103] packages in R[91].

Certainty assessment

We evaluated our confidence in the body of work included in the present meta-analysis, based on the outcomes of study quality assessment and analyses of publication bias. This is described in Supplementary Note 16.

Limitations of the review process

Supplementary Note 17 includes a discussion of the potential limitations that applied to the review process and the design of the current meta-analysis.

Moderation analyses

We tested for the effect of several moderators. Selection of moderator terms was determined based on available data, considering completeness of reported moderator variables. We implemented a >50% rule of thumb, i.e., if 50% or more studies reported data on the moderating variable, we included this moderator in our analyses. For example, less than 50% of studies reported the percentage of participants of Asian ancestry in the sample, hence we did not include the percentage of Asian participants in moderation analyses. We considered the following 11 moderators: age group, design, type of model, rater, measurement, percentage of individuals who identified as White, number of covariates included in the analysis, measure adopted,

country, and specific phenotype measured, each moderator is described in greater detail in Supplementary Note 3. Moderation analyses were conducted using a two-step procedure. First, only studies that reported data on the level of the moderator were selected (for example, only studies reporting estimates for adolescents). Second, analyses stratified by levels of the moderator were run using a multilevel random-effects meta-analysis in metafor for R , i.e., a grand estimate was derived for adolescents and subsequently compared with estimates for other developmental stages (i.e., childhood and middle childhood) using the same procedure. We report unstratified estimates (Supplementary Tables 1, 3 & 5) and estimates stratified by specific phenotype measured (Supplementary Tables 2, 4 & 6), age category (Supplementary Tables 19-21), country (Supplementary Tables 22-24), and ancestry (Supplementary Tables 25-27) in the main text, whereas estimates stratified by all other moderators are reported in Supplementary tables 37-50.

Data availability statement

The data that support the findings, including master extraction tables, is available at https://github.com/CoDEresearchlab/Meta_analysis_NDDs_DICCs.

Code availability statement

The code for all analyses is available at https://github.com/CoDEresearchlab/Meta_analysis_NDDs_DICCs.

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Author contributions

Conceived and designed the study: AG, MM, YIA. Conducted literature search and study screening: AG, LYL, MD, FP and ED. Extracted and analysed the data: AG. Wrote the paper: AG and MM with helpful contributions from YIA, GM, AGA, JAB, FP, AR, and KR. All authors contributed to the interpretation of data, provided critical feedback on manuscript drafts, and approved the final draft.

Competing interests

Authors of this meta-analysis declare no competing interests.

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