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A Population-based Longitudinal Study of Childhood Neurodevelopmental Disorders, IQ and Subsequent Risk of Psychotic Experiences in Adolescence

Golam M. Khandaker[1,2,3,*], **Jan Stochl**[1,2], **Stanley Zammit**[3,4], **Glyn Lewis**[3,5], and **Peter B Jones**[1,2]

[1]Department of Psychiatry, University of Cambridge, UK

[2]Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

[3]Centre for Mental Health, Addiction and Suicide Research, School of Social and Community Medicine, University of Bristol, UK

[4]Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, UK

[5]Mental Health Sciences Unit, University College London, London, UK

Abstract

Background—Schizophrenia has a neurodevelopmental component to its origin, and may share overlapping pathogenic mechanisms with childhood neurodevelopmental disorders (ND). Yet longitudinal studies of psychotic outcomes among individuals with ND are limited. We report a population-based prospective study of six common childhood ND, subsequent neurocognitive performance and the risk of psychotic experiences (PEs) in early adolescence.

Methods—PEs were assessed by semi-structured interviews at age 13 years. IQ and working memory were measured between ages 9 and 11 years. The presence of six neurodevelopmental disorders (autism spectrum, dyslexia, dyspraxia, dysgraphia, dysorthographia, dyscalculia) was determined from parent-completed questionnaire at age 9 years. Linear regression calculated mean difference in cognitive scores between those with and without ND. The association between ND and PEs was expressed as odds ratio (OR); effects of cognitive deficits were examined. Potential confounders included age, gender, father's social class, ethnicity and maternal education.

Results—Out of 8,220 children, 487 (5.9%) were reported to have ND at age 9 years. Children with, compared with those without ND performed worse on all cognitive measures; adjusted mean difference in total IQ 6.84 (95% CI 5.00- 8.69). The association between total IQ and ND was linear ($p<0.0001$). The risk of PEs was higher in those with, compared with those without ND;

[*]**Address for Correspondence:** Dr Golam Khandaker, Department of Psychiatry, Box 189, Cambridge Biomedical Campus, Cambridge CB2 2QQ, UK. gmk24@medscl.cam.ac.uk.

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adjusted OR for definite PEs 1.76 (95% CI 1.11- 2.79). IQ (but not working memory) deficit partly explained this association.

Conclusion—Higher risk of PEs in early adolescence among individuals with childhood ND is consistent with the neurodevelopmental hypothesis of schizophrenia.

Keywords

Neurodevelopmental Disorder; Dyslexia; Dyspraxia; Autism; Autism Spectrum Disorder; Dyscalculia; Dysgraphia; Dysorthographia; Childhood; Psychotic Experiences; Psychotic Symptoms; IQ; Working Memory; Neurodevelopment; Neurocognitive Performance; Schizophrenia; Psychotic Disorder; Mediation Analysis; Risk; Birth Cohort Study; ALSPAC

Introduction

The neurodevelopmental hypothesis of schizophrenia posits abnormal brain development as a cause of this illness (Murray & Lewis 1987; Weinberger 1987). Empirical support for this hypothesis comes from population-based longitudinal studies demonstrating an association between subtle alterations in motor, cognitive, language and social development in the early life and the risk of adult schizophrenia (Cannon *et al.* 2002; Cannon *et al.* 2000; Crow *et al.* 1995; Jones *et al.* 1994). Common neurodevelopmental disorders of childhood such as autism, dyslexia, dyspraxia share many similarities with schizophrenia (Bassett *et al.* 2010; Owen *et al.* 2011), which typically manifests itself in young adulthood. These conditions are more common in men, associated with cognitive deficits, and neurological soft signs (Owen *et al.* 2011). Genetic studies suggest an overlap of risk between schizophrenia, autism and other neurodevelopmental conditions such as attention deficit hyperactivity disorder (ADHD) (Bassett *et al.* 2010; Kirov *et al.* 2009; Williams *et al.* 2010). Family history of schizophrenia is associated with risk of autism (Sullivan *et al.* 2012). It has been suggested that childhood autism and adult schizophrenia share overlapping pathogenic mechanisms arising from disruptions in brain development (Owen *et al.* 2011).

Although there is substantial inter-individual variation within common childhood neurodevelopmental disorders, there is also a great deal of overlap in their clinical presentation and aetiology (Richardson & Ross 2000). Specific language impairments in autism and dyslexia may be underpinned by the same genetic aberration (Vernes *et al.* 2008). Evidence of neurocognitive deficits such as low IQ or processing speed in autism, dyspraxia and dyscalculia suggest that there is some degree of neurodevelopmental aberrations in these conditions (Butterworth & Reigosa 2007; Matson & Shoemaker 2009; Scalais *et al.* 2005). Therefore, an increased risk of psychotic outcomes in the future among individuals with these disorders in childhood will be consistent with the neurodevelopmental view of schizophrenia. However, longitudinal studies of schizophrenia among individuals with childhood neurodevelopmental disorder are limited (Hutton *et al.* 2008).

It has been suggested that childhood psychotic experiences (PEs) may be important antecedents of adult schizophrenia. These are associated with risk of psychotic illness in adult life as well as a number of risk factors for schizophrenia (Horwood *et al.* 2008; Kelleher & Cannon 2011; Polanczyk *et al.* 2010; Poulton *et al.* 2000; Zammit *et al.* 2013).

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Recently, two studies have reported an increased risk of PEs in early adolescence for autistic traits (speech problem, social problem, rituals) (Bevan Jones *et al.* 2012), or a diagnosis of autism spectrum disorder (ASD) in childhood (Sullivan *et al.* 2013). Similar to the current study, these were based on data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. However, they did not include any other neurodevelopmental disorder as exposure.

Identification of a linear relationship between IQ deficit in the premorbid period and future risk of schizophrenia is a key piece of evidence underpinning a developmental aspect to the disorder (Khandaker *et al.* 2011). IQ deficit is present in different stages of schizophrenia and is one of the most important predictors of functional outcome (Gold *et al.* 2002). Population-based studies have also reported cognitive deficits in childhood among individuals reporting PEs later in childhood or adolescence (Horwood *et al.* 2008; Niarchou *et al.* 2013; Polanczyk *et al.* 2010). Therefore, prospective studies of the effects of IQ and related cognitive factors on the association between childhood neurodevelopmental disorder and later psychotic outcome may help to elucidate the developmental pathways to psychosis.

Using data from the population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, we report associations between six common childhood neurodevelopmental disorders (dyslexia, dyspraxia, dysgraphia, dysorthographia, dyscalculia, and ASD) up to age 9 years, neurocognitive performance assessed as IQ, short term memory, working memory between ages 9 and 11 years, and the risk of PEs at age 13 years. We predicted that neurodevelopmental disorders would increase the risk of PEs, and intermediary neurocognitive deficits would explain this association.

Methods

Description of cohort

The ALSPAC birth cohort is based on all pregnant women resident in the county of Avon, a geographically defined region in the southwest of England, with expected dates of delivery between April 1991 and December 1992 (www.alspac.bris.ac.uk). The initial ALSPAC cohort consisted of 14,062 live births and 13,988 infants still alive at 12 months (Boyd *et al.* 2013; Fraser *et al.* 2013). Avon included both urban and rural areas, and the population was broadly representative of all children in the UK. The parents completed regular postal questionnaires about all aspects of their child's health and development since birth. Since the age of 7 years the children attended an annual assessment clinic during which they participated in a range of face-to-face interviews and physical tests. This study is based on 8,220 individuals with data on neurodevelopmental disorders at age 9 years.

Ethical approval for the study was obtained from ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

Assessment of neurodevelopmental disorders

The ALSPAC parents completed a questionnaire when the study child was on average 9 years old. A variety of questions were asked about health and development of the child including a specific item on neurodevelopmental disorders. In that item, a lead in, "*Have you*

ever been told that your child has:" was followed by a list of six specific disorders: Dyslexia (developmental reading disorder); Dyspraxia (coordination disorder); Dysgraphia (difficulties in writing); Dysorthographia (difficulties in spelling); Dyscalculia (inability to learn or comprehend arithmetic); Autism, Asperger's syndrome or Autistic Spectrum Disorder. For each disorder the parent ticked 'yes' or 'no'; if 'yes', the child's age at diagnosis. Using this data we created a single binary variable, 'any neurodevelopmental disorder' (ND), which was used as the primary exposure.

Assessment of neurocognitive performance

IQ and short-term memory (average age 9 years)—IQ was measured by the Wechsler Intelligence Scale for Children (WISC III, 3rd UK edition) (Wechsler *et al.* 1992). A shortened version of the test was applied by trained psychologists, whereby only alternate items were used for all subtests with the exception of the coding subtest which was administered in its standard form. Digit span subtest of WISC III was used as a measure of short-term memory.

Working memory (average age 11 years)—The computerised Counting Span Task was used (Case *et al.* 1982), which simultaneously tests information processing and storage abilities. A child's working memory span was calculated automatically by the computer programme. The maximum score a child could achieve was five (i.e. all correct). We used the span score, the main outcome measure for this task.

Assessment of psychotic experiences

Psychotic experiences (PEs) were assessed by the semi-structured Psychosis-like Symptoms interview (PLIKSi) at a mean age of 12.9 years (SD 0.23). The PLIKSi comprised 12 'core' questions derived from the Diagnostic Interview Schedule for Children–IV (DISC–IV) (Shaffer *et al.* 2000), and the Schedules for Clinical Assessment in Neuropsychiatry version 2.0 (SCAN 2.0) (WHO 1994). It included key symptoms covering the three main domains of positive psychotic symptoms: hallucinations (visual and auditory); delusions (delusions of being spied on, persecution, thoughts being read, reference, control, grandiose ability and other unspecified delusions); and experiences of thought interference (thought broadcasting, insertion and withdrawal). This allowed an observer-based rating for the presence of any psychotic experiences in the last six months (further classed as suspected and definite). We used any PEs as the primary outcome, and definite PEs as a secondary outcome. These groups were compared with rest of the cohort. The PLIKSi has good inter-rater reliability (kappa=0.7), and test-retest reliability (kappa=0.5) (Horwood *et al.* 2008). The interview and coding procedure have been reported in detail elsewhere (Horwood *et al.* 2008).

Statistical analysis

Linear regression compared mean scores of IQ and memory tasks between those with and without ND. Mean difference (95% CI) between groups was calculated for each task. Age at the time of testing (in days), gender, father's social class and ethnicity were included as potential confounders. Logistic regression examined the association between total IQ score and ND. Linearity of association between IQ and ND was examined by including a quadratic term (square of IQ score) within the logistic regression model.

Binary logistic regression calculated odds ratio (OR) for PEs in those with, compared with those without ND. Age at the time of assessment of PEs (in weeks), gender, ethnicity, father's social class and maternal education were included as potential confounders. Due to limited number of individuals with PEs, multivariable regression was used to calculate ORs separately only for dyslexia. In addition, we used the likelihood-ratio test to examine whether an alternative approach to defining the exposure variable provided a better fit to the data compared with the null, binary coding (any ND vs. none). The alternative coding of the exposure included five discrete categories (No ND; dyslexia only; dyspraxia only; ASD only; multiple ND).

We examined whether the association between any PEs and ND could be explained by deficit in total IQ (Baron & Kenny 1986). First, separate logistic regression models assessed the associations between: (1) exposure (ND) and outcome (PEs); (2) exposure and mediator (total IQ score); (3) mediator and outcome, controlling for exposure. Finally, exposure-outcome, exposure-mediator, mediator-outcome, all three regression lines were fitted simultaneously in a single model using MPlus. We expected, in the final step, the exposure-outcome relationship would be attenuated (partial mediation), or eliminated (complete mediation). In case of partial mediation, the extent to which the ND-PEs estimate was attenuated after inclusion of total IQ (the mediator) was also calculated. This procedure was repeated using working memory as the potential mediator. Mediating effects of IQ and working memory on the association between dyslexia and PEs were also examined.

Sensitivity analyses

In order to examine the association between any neurodevelopmental disorder, IQ and PEs more rigorously, we repeated all analyses after excluding cases of ASD (i.e. any neurodevelopmental disorder included dyslexia, dyspraxia, dyscalculia, dysgraphia, and dysorthographia *but not* ASD). This is because two previous studies from the ALSPAC cohort have reported an association between autism and later PEs (Bevan Jones *et al.* 2012; Sullivan *et al.* 2013).

Results

Frequency of neurodevelopmental disorders at age 9 years and baseline characteristics

Out of total 8,220 children, 487 (5.9%) were reported to have a neurodevelopmental disorder at age 9 years. Out of these, 417 children (5.1%) had only one, whilst 70 (0.9%) had more than one disorder. Dyslexia was the most common (Figure 1); dysgraphia and dysorthographia were reported to be present in the same 24 children. Neurodevelopmental disorders (ND) were more common in boys (Table 1).

Neurodevelopmental disorders at age 9 years and neurocognitive performance between ages 9 and 11 years

Compared with children with no neurodevelopmental disorder, children with neurodevelopmental disorder at age 9 years, as a group, performed worse on all measures of IQ, short-term memory and working memory between ages 9 and 11 years (Table 2). The results were very similar after adjusting for a number of potential confounders.

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We also examined total IQ at age 9 years separately in six specific neurodevelopmental disorders (Table 3). Compared with the rest of the cohort, mean total IQ was lower in all disorders except dysgraphia and dysorthographia.

Distribution of IQ scores in children with and without neurodevelopmental disorders

There was a linear association between IQ and ND, consistent with the left-shift of entire distribution of IQ scores in ND; p<0.0001 (Figure 2). The quadratic term (square of IQ) within the logistic regression model of IQ and ND was not significant (p= 0.22). Similar patterns were observed for individual disorders, dyslexia and ASD.

Neurodevelopmental disorders at age 9 years and risk of psychotic experiences at age 13 years

Data on both ND at age 9 years and PEs at age 13 years were available for 5,830 individuals; out of these 313 (5.4%) had ND. In the group with no ND, 711 (12.9%) developed PEs, of which 285 (5.2%) were definite PEs. However, in the group with ND, 58 (18.5%) developed PEs, of which 26 (8.3%) were definite PEs. Similarly, proportions of PEs were also higher in the group with dyslexia, 17.7% any PEs, 8.3% definite PEs.

The risk of PEs was significantly higher among individuals with, compared with those without any neurodevelopmental disorder (Table 4). Evidence of these effects remained after adjusting for age at the time of assessment of PEs, gender, father's social class, ethnicity and maternal education. Similar increase in risk was also observed for dyslexia and ASD. The likelihood-ratio test for the alternative categorical vs. binary measure of ND was not significant (Chi-squared statistic 0.432; df=4; p=0.97). This provides further evidence that the risk of PEs was not significantly different across discrete categories of ND.

Effects of neurocognitive deficits on the association between neurodevelopmental disorders and psychotic experiences

In bivariate logistic regression, there was a significant association between ND at age 9 years and risk of PEs at age 13 years (effect estimate 0.234, SE 0.085, p= 0.006). Separate regressions showed significant associations between ND and IQ, IQ and PEs after controlling for ND. Finally, ND-PEs, ND-IQ, IQ-PEs, all three regression lines were fitted simultaneously in a single model using MPlus. In this step, the association between ND and PEs was attenuated but still remained significant (effect estimate 0.195, SE 0.085, p= 0.02). The magnitude of attenuation was 17% (95% CI 10- 25%), suggesting partial mediation of the ND-PEs association by IQ. However, there was no evidence of any effect of working memory scores on the association between ND and PEs. Similarly, the dyslexia-PEs association was attenuated by 16% (95% CI 10- 24%) after including IQ as the potential mediator; working memory did not affect this association.

Sensitivity analyses

The associations between ND, neurocognitive performance and risk of PEs remained virtually unchanged after excluding cases of ASD (N=96) (see online supplementary material).

Discussion

Our findings demonstrate that children with common neurodevelopmental disorders (ASD, dyslexia, dyspraxia, dysgraphia, dysorthographia and dyscalculia), as a group, show significant deficits in a range of neurocognitive domains. We also found that nearly a fifth of these children developed psychotic experiences at the end of follow up. The group with ND at age 9 years, compared with those without had nearly two-fold increased risk of developing psychotic experiences at age 13 years (both suspected/definite PEs and definite PEs only). Evidence of this remained after adjusting for a number of potential confounders. The risk of PEs did not differ significantly across discrete categories of ND. There was a linear association consistent with the left-shift of the distribution of IQ scores in ND, which partly explained the association between ND and PEs. Neurocognitive deficit and increased risk of PEs among individuals with ND, both may be markers of underlying aberration in brain development. Thus, these findings are consistent with the neurodevelopmental hypothesis of schizophrenia (Murray & Lewis 1987; Weinberger 1987).

These findings are also consistent with the notion that neurodevelopmental disorders that typically manifest in childhood (such as, autism) or in young adulthood (such as, schizophrenia) share overlapping pathogenic mechanisms linked with perturbation in brain development (Owen *et al.* 2011). Cross-sectional studies suggest large proportions of individuals with childhood or adult onset schizophrenia meet criteria for ASD (Rapoport *et al.* 2009; Unenge Hallerback *et al.* 2012). However, longitudinal studies of the risk of adult schizophrenia among individuals with childhood autism or other neurodevelopmental disorders are scarce. We could identify only one study, which reported that out of 135 individuals with childhood ASD no one had developed schizophrenia on follow up (Hutton *et al.* 2008). However, this could be related to the small sample size. Two recent studies from the same cohort as ours have reported an increased risk of PEs in early adolescence for autistic traits (speech problem, social problem, rituals) (Bevan Jones *et al.* 2012), or a diagnosis of ASD in childhood (Sullivan *et al.* 2013). However, the current study is distinct in a number of ways. The previous studies focused only on autism. In contrast, the current study examined six common neurodevelopmental disorders including ASD (dyslexia, dyspraxia, dysgraphia, dysorthographia, dyscalculia, and ASD). We also included a number of neurocognitive measures such as IQ, short-term memory, working memory as outcomes. This is important, as effects of cognitive deficits on the association between ND and PEs may shed light on developmental pathways to psychotic disorders.

It has been suggested that psychotic experiences in childhood or adolescence may provide a valid paradigm (‘symptomatic high risk approach’) for studying the development of adult psychotic disorders (Kelleher & Cannon 2011; Murray & Jones 2012). This is supported by a number of observations. Prospective birth cohort studies have reported increased risk of psychotic disorders in adult life among individuals reporting psychotic symptoms in childhood (Poulton *et al.* 2000; Zammit *et al.* 2013). Childhood psychotic symptoms are familial and heritable (Polanczyk *et al.* 2010). They are associated with a number of risk factors for schizophrenia, such as low birth weight (Thomas *et al.* 2009), cognitive deficits in the premorbid period (Horwood *et al.* 2008; Niarchou *et al.* 2013), pregnancy and birth complications (Zammit *et al.* 2009), and childhood atopic disorders (Khandaker *et al.* 2013

in press). Population-based studies suggest psychotic symptoms in the general population and those observed in psychotic disorders may exist on a continuum (van Os *et al.* 2009). Finally, neurophysiological studies have reported common underlying mechanisms for psychotic symptoms occurring in healthy individuals and in schizophrenia (Howes *et al.* 2013).

We found that the ND-PEs association (also dyslexia-PEs association) could be partly explained by deficit in IQ, but not working memory. This is consistent with current evidence which strongly supports an important role for general cognitive ability as measured by IQ in the pathogenesis and prognosis of schizophrenia. Deficit in IQ, which is present from the premorbid period through to adult life is one of the most consistent findings in schizophrenia epidemiology (Aylward *et al.* 1984; Jones *et al.* 1994; Khandaker *et al.* 2011; Rajji *et al.* 2009). Besides, it has been reported that IQ is a more sensitive and reliable predictor of functional outcome in schizophrenia than measures of specific ability (Gold *et al.* 2002).

An explanation for not detecting a larger mediating effect of IQ could be the outcome studied. Adolescent participants with PEs in our sample are almost certainly a heterogeneous group. In many cases these symptoms are likely to be part of development, whilst in some they may be more pathological (De Loore *et al.* 2011; Rubio *et al.* 2012). Thus, any underlying biological effect (such as mediation by IQ) may have become diluted. Follow-up of these individuals will be helpful to understand the effect of IQ deficit on different trajectories of early-life PEs.

Limitations of this study include the use of parent reported data rather than diagnosis of neurodevelopmental disorders by formal assessments. However, a number of observations suggest that this parent reported data is acceptable. For example, in our sample at age 9 years 1.2% children were reported to have ASD. A recent population based study by Baron-Cohen and colleagues have reported that the prevalence of ASD is 1.5% among 5-9 year old British school children (Baron-Cohen *et al.* 2009). Similarly, in our sample prevalence of dyslexia was 4.4%. The prevalence of dyslexia among school age children in England has been reported to be 4- 8% (Hulme & Snowling 2009). Finally, marked discrepancy between verbal and performance IQ has been reported to be a feature of developmental dyspraxia (Scalais *et al.* 2005). This is reflected in our sample; adjusted mean difference in verbal and performance IQ between children with and without dyspraxia were 4.63 (95% CI 0.94- 8.32) and 12.69 (95% CI 8.90- 16.49), respectively. However, it is difficult to be certain about specific diagnoses from parent reported data. Childhood neurodevelopmental disorders are often comorbid with each other, and there is a great deal of overlap in their presentation and aetiology (Richardson & Ross 2000; Vernes *et al.* 2008). Therefore, we used any neurodevelopmental disorder as the primary exposure, rather than individual disorders.

A third of children with neurodevelopmental disorders (174 out of 487) did not attend the assessment for PEs at age 13 years. If there was an over-representation of individuals with ND who also developed PEs in our sample, this would lead to spurious overestimation of the ND-PEs association. However, there was no reason to believe that this was the case. In our sample, missing data was associated with lower social class and poorer maternal education.

Both of these factors are associated with higher risk of PEs, and over all, poorer health outcomes.

In our sample, neurodevelopmental disorders were relatively more common in children of mothers with better education and in those with higher socioeconomic status. This is consistent with previous studies from both the UK and USA reporting an increased prevalence of autism among individuals with higher socioeconomic status (Thomas *et al.* 2012; Wing 1980). However, it has been suggested that sampling bias and differential access to healthcare may explain the social class effect in autism. A recent population-based study from Sweden that reported an association between lower parental socioeconomic status and ASD in offspring argues that the burden of autism in lower social class groups previously may have been underestimated (Rai *et al.* 2012). In ALSPAC, both lower socioeconomic status and poor maternal education is associated with the risk of PEs. Thus, any bias arising from potential misclassification of autism-exposed children with lower socioeconomic status as unexposed might have led to underestimation of the true ND-PEs association in our study.

In order to reduce the length of assessment so the children were less likely to tire, IQ was measured using a shortened version of the WISC III. Alternate items (always starting with item number 1 in the standard form) were used for all ten subtests, except the coding subtest which was administered in its full form. This approach has been successfully used in the past in other studies (Finch & Chihldress 1975; Stricker *et al.* 1968). We do not have any reliability and validity data for this approach. However, IQ data obtained using this method show robust correlations with other concurrent neurocognitive measures, such as working memory, short-term memory, socio-demographic factors such as social class, age, and subsequent IQ at age 15 years measured by the Wechsler abbreviated scale for intelligence (WASI). Together, they indicate that this may be a time efficient yet reliable way of measuring IQ in large epidemiological studies.

To our knowledge, this is one of the first longitudinal studies of common childhood neurodevelopmental disorders, subsequent neurodevelopment, and the risk of psychotic outcomes. Our findings suggest that future studies of neuropsychological outcomes among individuals with ND should also include psychotic experiences. In the future, birth cohort based neuroimaging studies will be useful to elucidate specific neural networks that underlie the associations between childhood neurodevelopmental disorder, cognitive performance and subsequent psychotic symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
IQ	Intelligence Quotient
PEs	Psychotic Experiences
ASD	Autistic Spectrum Disorder
OR	Odds Ratio
CI	Confidence Interval
SD	Standard deviation

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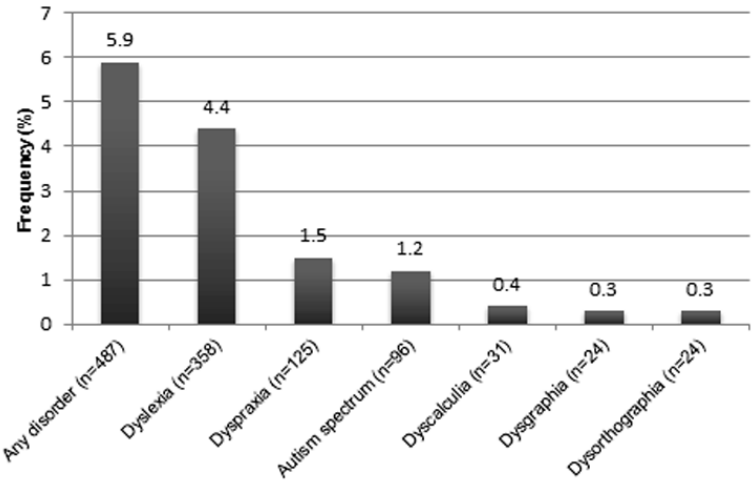

Figure 1. Frequency of parent-reported neurodevelopmental disorders at age 9 years in the ALSPAC birth cohort

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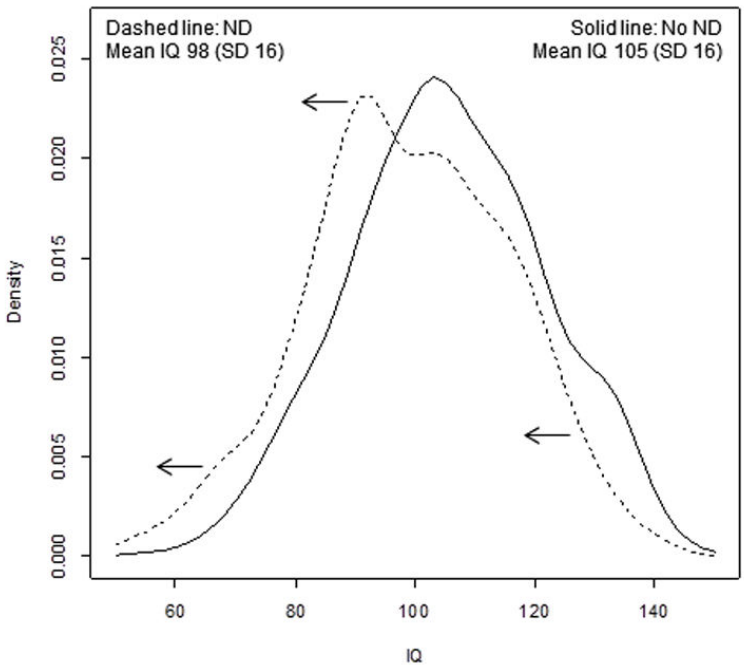

Figure 2. Distribution of total IQ scores in children with and without neurodevelopmental disorders (ND) at age 9 years

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Table 1

Baseline characteristics of individuals with and without neurodevelopmental disorders in ALSPAC

Group/ characteristics	Neurodevelopmental disorder	No neurodevelopmental disorder
Total number	487	7,733
Age at PE, mean (SD) in years	12.90 (0.26)	12.87 (0.21)
Male (%)	65.9	49.6
British White (%)	98.9	98.3
Father's Social class (%)		
I	14.6	12.8
II	42.7	35.8
III non manual	10.3	11.8
III manual	23.3	28.6
IV	6.2	8.3
V	2.9	2.5
Armed forces	0.0	0.2
Maternal education (%)		
Secondary school	9.8	14.2
Vocational	7.0	8.7
O level	36.5	35.3
A level	28.2	25.6
Degree	18.4	16.2

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Table 2

Neurocognitive performance in children with and without neurodevelopmental disorders in ALSPAC

Cognitive ability and average age of testing	Neurodevelopmental disorder		No neurodevelopmental disorder			
	n	Mean (SD)	n	Mean (SD)	Mean difference (95% CI)	Adjusted mean difference (95% CI)†
Age 9 years						
Total IQ	340	98.80 (16.99)	5919	105.36 (16.20)	6.55 (4.78- 8.33)	6.84 (5.00- 8.69)
Verbal IQ	345	101.99 (17.51)	5941	108.24 (16.54)	6.25 (4.45- 8.05)	6.82 (4.95- 8.70)
Performance IQ	343	94.78 (18.19)	5934	100.65 (16.79)	5.87 (4.04- 7.71)	5.68 (3.75- 7.61)
Short-term memory	333	9.01 (2.95)	5804	10.52 (3.06)	1.51 (1.17- 1.84)	1.47 (1.12- 1.84)
Age 11 years						
Working memory	317	3.18 (0.81)	5685	3.44 (0.84)	0.26 (0.16- 0.36)	0.28 (0.18- 0.39)

†Adjusted analyses included age at the time of testing, gender, ethnicity, and father's social class as potential confounders

Table 3

Total IQ at age 9 years in children with specific vs. no neurodevelopmental disorder in ALSPAC

Specific disorder	Present		Not present		Mean difference (95% CI)	Adjusted mean difference (95% CI)†
	n	Mean (SD)	n	Mean (SD)		
Dyslexia	277	99.94 (15.62)	5982	105.24 (16.30)	5.29 (3.33- 7.25)	5.36 (3.32- 7.41)
Dyspraxia	83	97.36 (19.86)	6177	105.10 (16.25)	7.74 (4.20- 11.27)	8.62 (4.98- 12.28)
Autism spectrum	48	98.62 (18.02)	6212	105.05 (16.30)	6.42 (1.17- 11.67)	7.55 (2.80- 12.30)
Dyscalculia	27	103.25 (14.47)	6233	105.06 (16.33)	1.74 (−4.42- 7.92)	2.50 (−4.11- 9.13)
Dysgraphia and dysorthographia‡	21	106.19 (13.08)	6239	104.99 (16.33)	−1.19 (−8.19- 5.80)	−0.70 (−8.24- 6.83)

† Adjusted analyses included age at the time of testing, gender, ethnicity, and father's social class as potential confounders.

‡ Dysgraphia and dysorthographia both were reported to be present in these 21 children.

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Table 4

Risk of psychotic experiences (PEs) at age 13 years among individuals with neurodevelopmental disorders (ND) at age 9 years

ND and adjustment for confounding	N	Odds ratio (95% CI)	
		Any PEs	Definite PEs
Any ND			
Unadjusted	5830	1.53 (1.14- 2.06)	1.66 (1.10- 2.53)
Age and sex	5830	1.55 (1.15- 2.08)	1.70 (1.12- 2.60)
Age, sex, social class, ethnicity, maternal education	5019	1.52 (1.10- 2.12)	1.76 (1.11- 2.79)
Dyslexia			
Unadjusted	5830	1.44 (1.04-2.01)	1.64 (1.03-2.61)
Age and sex	5830	1.44 (1.03- 2.01)	1.66 (1.05- 2.64)
Age, sex, social class, ethnicity, maternal education	5019	1.45 (1.00- 2.09)	1.90 (1.16- 3.11)