TRAJECTORIES IN DEVELOPMENTAL DISABILITIES: INFANCY – CHILDHOOD – ADOLESCENCE

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TRAJECTORIES IN DEVELOPMENTAL DISABILITIES: INFANCY – CHILDHOOD – ADOLESCENCE

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EDITORIAL
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Editorial: Trajectories in Developmental Disabilities: Infancy–Childhood–Adolescence

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Editorial on Research Topic

Trajectories in Developmental Disabilities: Infancy–Childhood–Adolescence

Research into infant and child development is, at its heart, an interdisciplinary and integrative science. Recent theoretical and clinical developments as well as technological advances have allowed us to approach ontogeny from different angles and opened new possibilities to measure and understand progress and regression in typical and atypical development [e.g., (1–6)]. Scientific endeavors aiming to (i) anticipate disorder specific trajectories, (ii) decipher developmental pathways, (iii) reliably predict outcomes and (iv) define determinants of health and disease in developmental disabilities or infants at elevated likelihood for atypical development have substantially increased over the past few decades [e.g., (7–11)]. With this Research Topic we aimed to comply with this trend and addressed researchers focusing on the study of "Trajectories in Developmental Disabilities from Infancy through Childhood to Adolescence". The scope of articles in this compilation reflects the interdisciplinarity in the field of developmental science encompassing basic research, clinical studies, and technological sciences on detection and treatment of individuals with developmental disabilities as well as the impact on the healthcare system.

Various aspects of development in the general population, cohorts at elevated likelihood for atypical neurodevelopment or adverse psychosocial outcome, and late detected developmental disorders are covered in this Research Topic. Van Beek, van der Horst et al.; Van Beek, van de Par et al. report on developmental trajectories in very preterm born infants in an 8-year longitudinal approach. Besides following infants with extremely low birth weight (ELBW) or small for gestational age (SGA), the composition of articles in this issue spans a scope from variability in infants' functional brain networks and its association with behavioral functions (Kelsey et al.) to altered structural and functional brain development in children with intellectual disability [ID; Ma et al.]. Exogenous influences on neurodevelopment were reviewed by Notarbartolo di Villarosa do Amaral et al. studying clinical repercussions of mosquito borne infections (Zika virus). In another section focusing on late detected developmental disorders, Orm et al. report about a 10-year-longitudinal

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project on cooccurring conditions in autism spectrum (ASD) and attention deficit hyperactivity disorder (ADHD). Two further studies on ASD focused on machine learning approaches outlining interventional effects and the role of intellectual capacities on diagnostic procedures respectively (Blanc et al.; Wolff et al.). Studies on the relation of maternal bonding and social competence in preschoolers (Joas and Möhler), the effect of law reforms on coercive measures for young adults with intellectual and developmental disabilities (Geissler et al.), a digital tool to be used for screening of learning disabilities (Xie et al.), and a review on research trends in Down syndrome (Windsperger and Hoehl) add to the complexity of this selected Research Topic. All included articles truly stress the necessity and highlight the impact of longitudinal studies to better understand developmental constraints and potentials and at the same time inherently pointing to the restrictions, we as scientist face, when it comes to implementing longitudinal research paradigms.

Interdisciplinarity is steadily increasing in both research and clinical environments, but we are longing for new innovative frameworks allowing medical sub-specialties, psychological ones, special education, public health, and related fields to meld. Building new grounds in developmental science to reach a deeper understanding of multiple levels of development (molecular, genetic, neuronal, cognitive, behavioral, environmental, etc.), unravel the complexity of its nature, etiology, and trajectories of disorders, is demanding research to liaise on different levels. Scientists, funders, and stakeholders together need to develop structures aiming at bundling resources for multi-discipline and multi-center approaches. There are already a number of such successful undertakings or initiatives, disorder and method focused [e.g., EU-AIMS, EUNETHYDIS (12–14); or funding programs like Collaborative Research Centers, VW-Change of Course, etc.] but also more general ones, such as the German Centers for Child and Adolescent Health, that should serve as point of origin or blueprint to further advance the study of child development, health, and wellbeing. However, we need to be aware, that true interdisciplinary thinking and the more so the establishment of sustainable research structures needs time and cannot be rushed [cf., (15, 16)]. Building common grounds in a complex interdisciplinary field certainly is not trivial and tools for designing and conducting comparable studies but also for evaluating scientific rigor, eligibility, and success are urgently needed. Crossing borders in research disciplines and funding policies will allow developmental science of today become the developmental science of tomorrow.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Aberrant Structural and Functional Developmental Trajectories in Children With Intellectual Disability

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Intellectual disability (ID) is associated with aberrant structural and functional development of the brain, yet how the dynamical developmental changes of the structure and function of ID from childhood to around puberty remains unknown. To explore the abnormal developmental trajectories of structure and function, 40 children with ID aged 6–13 years and 30 sex-, age-, and educational level-matched healthy controls (HC) with age range from 6 to 13 were recruited. The automatic voxel-based morphometry (VBM) and resting-state functional connectivity (FC) analyses were adopted to delineate the structural and functional differences. Significantly decreased total gray matter volume (GMV) and white matter volume (WMV) in children with ID were found, and the developmental trajectories of GMV and WMV in children with ID showed an opposite direction as compared with HC. The voxel-wise VMB analysis further revealed significantly increased GMV in the dorsal medial prefrontal cortex (dmPFC), bilateral orbital part of the inferior frontal gyrus (orb_IFG.L, orb_IFG.R), right cuneus (cuneus.R), and bilateral middle frontal gyrus (MFG.L, MFG.R) in children with ID. The following seed-based whole-brain functional connectivity analyses of the brain areas with changed GMV found decreased FCs between the cuneus.R and left intraparietal sulcus (IPS.L) and between the MFG.R and anterior cingulate cortex (ACC) in children with ID. Moreover, negative correlations between GMV values in the dmPFC, orb_IFG.L, cuneus.R, and intelligence quotient (IQ) scores and positive correlations between the FCs of the cuneus.R with IPS.L and MFG.R with ACC and IQ scores were found in children with ID and HC. Our findings provide evidence for the abnormal structural and functional development in children with ID and highlight the important role of frontoparietal network in the typical development. The abnormal development of GMV and functional couplings found in this study may be the neuropathological bases of children with ID.

Keywords: intellectual disability, gray matter volume, functional connectivity, development, fronto-parietal network

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INTRODUCTION

Intellectual disability (ID) is a generalized developmental disorder and is characterized by deficits in both intelligence and social adaptation with intelligence quotient (IQ) scores <70. ID is a global development delay (GDD) disorder which occurs under 5 years of age and accounts for 0.95–3% of children's disability (1–3). ID is strongly associated with environmental and genetic factors, and it is usually accompanied by brain structural and functional abnormalities and other mental disorders (4, 5). Although conventional magnetic resonance imaging (MRI) is able to detect brain aberrant structural alterations like dysplasia of the corpus callosum, enlarged ventricles, and dysplasia of the cerebral cortex closely associated with intellectual disorder (6, 7), a majority of children with ID appear with invisible structural changes on conventional MRI (6, 8). Moreover, whether/how structural changes lead to abnormal functions and behaviors in ID is elusive. Therefore, quantitative structural MRI analyses could contribute toward the biological determination of morphometric changes in ID.

The development of cognitive functions is closely related to the normal processes of neurogenesis, synaptogenesis, and pruning and myelination, and the abnormal developmental trajectories of gray matter and white matter may result in brain functional impairments (9, 10). Through manually measuring the diameter and cross-sectional area, hypoplastic corpus callosum (11) and enlarged supratentorial CSF spaces (12) were identified in children with ID compared with typical development children. Because of manual bias, a fully automatic voxel-based morphometry (VBM) method (13) was used and reduced total brain gray and white matter volume and increased gray matter volume in ACC in children with ID was found (14), but in this study, the demographic information between groups is unmatched and there is a lack of intelligence level on subjects. By analysis of cortical thickness, Zhang and colleagues found reduced cortical thickness in the bilateral lingual gyrus, fusiform gyrus, parahippocampal gyrus, temporal pole, left inferior temporal gyrus, right lateral orbitofrontal cortex, and right precentral gyrus (15). Using diffusion tensor imaging (DTI), degenerated myelination of the uncinate fasciculus, superior cerebellar peduncle, inferior longitudinal fasciculus, corpus callosum, optic radiation, and corticospinal tract and disrupted network topology properties including global and local efficiency and nodal degree have been revealed (16–19). However, all these studies only include either adult or child participants under 5 years of age, and the sample size is also relatively small. Moreover, during development, the period from childhood to around puberty is important for brain functional integration and segregation, high-order cognitive functions, and individual intelligence maturing (20, 21). Therefore, characterizing the structural and functional differences between atypical ID and typical controls from childhood to around puberty could shed new light on the biological and neural bases of ID. To delineate the structural and functional abnormalities in atypical development ID participants, the voxel-wise VBM and resting-state functional connectivity analyses were adopted in this study to identify the aberrant developmental trajectories of brain structures and functions from childhood to around puberty/early adolescence.

MATERIALS AND METHODS

Participants

Forty children with ID (26 males/14 females, age: 9.70 ± 2.07 years) diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (3) were recruited from the First People's Hospital of Zunyi (from December 2018 to January 2020). Thirty age-, sex-, and education-matched healthy controls (HC, 18 males/12 females, age: 9.51 ± 1.54 years) were also recruited. All participants received MRI examination and intelligent assessment using the Manual for the Wechsler Intelligence Scale for Children-Revised (WISC-R) (22). The inclusion criteria for ID were as follows: (a) deficit in both intelligence and adaptive functions such as reasoning, problem-solving, planning, abstract thinking, academic learning, and social communication and onset during the developmental period; (b) intelligence quotient (IQ) scores <70; (c) no cause of secondary ID, such as tumor, trauma, and tuberous sclerosis in the brain; (d) right-handedness; and (e) aged 6–13 years. The exclusion criteria of ID were as follows: (a) had a contraindication for MRI; (b) fell asleep during rs-fMRI scanning; (c) had a history of neurological disorders other than ID; (d) had focal abnormality with conventional MRI like dysplasia of the corpus callosum, enlarged ventricles, and posterior fossa subarachnoid space; and (e) had abnormal height and weight based on WHO Growth reference data for 5–19 years (23). In the HC group, all the children are right-handed and had IQ scores >90. The written informed consents were given and obtained from all the participants or their guardians. This study was approved by the local ethics committee of the First People's Hospital of Zunyi.

MRI Data Acquisition

MRI data were acquired with a SIEMENS 3.0-T (Magnetom Skyra, Siemens-Healthcare) scanner using a standard head coil at the Department of Radiology, The First People's Hospital of Zunyi. All the subjects were instructed to stay at rest with their eyes closed but keep awake and not think of anything. For each subject, resting-state functional images were acquired using a gradient-recalled echo-planar imaging (EPI) sequence with the following parameters: repetition time = 2,000 ms, echo time = 30 ms, flip angle = 90°, 30 axial slices covering full brain, field of view = 240 × 240 mm^2, slice thickness = 5 mm with no gap, voxel size = 3 × 3 × 5 mm^3, and 210 volumes were obtained. Three-dimensional T1-weighted imaging (3D-T1WI) images were also acquired by using a 3D-T1WI (magnetization prepared rapid gradient echo, MPRAGE) sequence with parameters of field of view = 230 × 230 mm^2, repetition time = 2,200 ms, echo time = 2.48 ms, inversion time = 900 ms, flip angle = 8°, and slice thickness = 1.00 mm, covering 192 axial slices with an in-plane resolution of 0.9 mm × 0.9 mm.

Intelligent Assessments

The participants meeting our inclusion criteria of MRI and physical examinations needed to take an intelligent test (WISC-R). The tests were performed by one of our colleagues

(X.W) who is qualified for clinical children's neuropsychological evaluation. Tests were completed in one quiet room at the Department of Child Health of the First People's Hospital of Zunyi with a professional toolbox. The whole process included items of information, comprehension, arithmetic, similarities, vocabulary, digit span, picture completion, picture arrangement, block design, object assembly, coding, and mazes. According to the manual of WASI-II (Chinese version), during each item, the tester asked questions or gave instructions to the child and scored the child's answers or performance, and finally calculated the intelligence quotient score of the child.

VBM Analysis

High-spatial-resolution T1-weighted MRI data were processed with VBM Toolbox (VBM8; http://dbm.neuro.uni-jena.de/wordpress/vbm/) in statistical parametric mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). First, all images with artifacts were removed. Second, according to default settings in VBM8, images were segmented into gray matter (GM), white matter (WM), and cerebrospinal (CSF) areas and then normalized to Montreal Neurologic Institute (MNI) space and modulated. After checking the segmentation quality, the segmented GM images were smoothed by using an 8-mm full width at half-maximum Gaussian kernel for subsequent group comparisons. The independent two-sample *t*-test with the total brain volume as covariate was used to identify the significant differences in GMV between ID and HC groups. The significant level was determined using the false discovery rate (FDR) method with $p < 0.001$ and minimum cluster size >100 voxels.

Resting-State Functional Connectivity Analysis

The preprocessing of functional images was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF) (24) and statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). To avoid instability of the magnetic field, the first 10 volumes were removed, and the remained volumes were realigned to the first volume to correct the head motion. After realigning, the functional images were normalized to a standard EPI template in the MNI space and resampled to a voxel resolution of $3 \times 3 \times 3$ mm^3. Next, all the volumes were smoothed with 8-mm FWHM Gaussian kernels and detrended. The nuisance covariates containing Friston 24-parameter head motion estimates, averaged time series in white matter, and cerebrospinal fluid were then regressed. Finally, all the fMRI images were filtered with a temporal band path of 0.01–0.1 Hz. To exclude the head motion effects, the subjects were excluded if the head motion exceeds 3 mm of translation or 3° of rotation. Under this criterion, 3 subjects in the ID group and 3 subjects in the HC group were excluded. Moreover, we calculated the frame-wise displacement (FD) value for each volume and censored the bad images (before 2 volumes and after 1 volume) with FD >0.5 (25). The global signal was not regressed to avoid introducing false-negative correlations and eliminate positive correlations (26, 27).

Seed-based whole-brain FC analysis was used to explore the functional differences between ID and HC groups. To calculate FC, the seed areas were first defined by creating spheres with a 6-mm radius based on the peak coordinates yielded by aforementioned group comparisons of GMV. Next, the mean time series of each seed area was calculated, and the Pearson correlation coefficients between the time series of each seed area and the remaining voxels of the rest of the brain were calculated and converted to z scores by Fisher z-transformation. Then, a voxel-wise whole-brain FC map was obtained for each subject. Finally, independent two-sample *t*-tests were used to identify the FC differences in children with ID. The significant level was determined using cluster-level Alphasim correction method with $p < 0.05$ (cluster-forming threshold at voxel-level $p < 0.001$).

Correlation Analysis

Correlation coefficients between IQ scores and the GMV and FC values in brain areas with significant differences between ID and HC groups were performed in all subjects, and the significant level was set at $p < 0.05$ with Bonferroni correction.

RESULTS

Demographics and Clinical Characteristics

Table 1 shows the detailed demographics and clinical characteristics for the used subjects in this study. There

TABLE 1 | Characteristics of ID and HC.

Characteristics	ID ($n = 40$)	HC ($n = 30$)	
	Mean ± SD	Mean ± SD	*P*-value
Sex (male/female)	26/14	18/12	0.67‡
Age, years	9.70 ± 2.07	9.51 ± 1.54	0.67†
Handedness (right/left)	40/0	30/0	–
Education, years	3.43 ± 1.77	3.35 ± 1.70	0.87†
IQ scores	56.00 ± 7.68	107.20 ± 9.81	<0.0001†
FD power	0.28 ± 0.35	0.20 ± 0.14	0.30†

ID, intellectual disability; HC, healthy control; n, number of subjects; SD, standard deviation; IQ, intelligence quotient; FD, framewise displacement. ‡Chi-squared test was used; †Two sample t-test was used.

TABLE 2 | Brain regions showing increased GMV in ID vs. HC.

Brain regions	Peak MNI coordinates			Peak *t*-value	Cluster size
	X	Y	Z		
dmPFC	−9	51	−19.5	5.2083	8069
orb_IFG.L	−51	36	−16.5	5.1772	983
orb_IFG.R	54	36	13.5	4.7254	3588
cuneus	6	−99	18	4.2991	419
MFG.L	−31.5	12	45	4.561	261
MFG.R	46.5	10.5	54	4.2053	129

GMV, gray matter volume; ID, intelligent disability; HC, healthy control; dmPFC, dorsal medial prefrontal cortex; orb_IFG, orbital inferior frontal gyrus; MFG, middle frontal gyrus.

were no significant differences in age ($p = 0.67$), education level ($p = 0.87$), and sex ($p = 0.67$) between the ID and HC groups (**Table 1**). No significant difference in head motion of FD values ($p = 0.30$) was observed between the two groups (**Table 1**).

Between-Group Comparisons of GMV and WMV

First, we compared the total brain GMV and WMV to determine whether ID disorder results in global developmental delay. Between-group comparisons of total GMV and WMV found significantly decreased total GMV ($p = 0.0049$) and WMV ($p = 0.0020$) in children with ID (**Figure 1**). The developmental trajectories of GMV and WMV in healthy controls are U-shaped, whereas the developmental trajectories of GMV and WMV in children with ID are inverted U-shaped (**Figure 1**).

To further determine the specific brain areas with changed GMV, the voxel-wise between-group comparisons of GMV were performed. Significantly increased GMVs in the dorsal medial prefrontal cortex (dmPFC), the bilateral orbital part of inferior frontal gyrus (orb_IFG.L, orb_IFG.R), the bilateral middle frontal gyrus (MFG.L, MFG.R), and the right cuneus (cuneus.R) were found in ID compared to HC (**Figure 2**, **Table 2**).

Between-Group Comparisons of Seed-Based FCs

Whole-brain voxel-wise FC analyses found significantly reduced FC between the cuneus.R and left intraparietal sulcus (IPS.L) [peak t-value $= -4.61$ and MNI coordinates $= [-30, -57, 45]$] (**Figure 3A**) and between the MFG.R and anterior cingulate cortex (ACC) [peak t-value $= -4.26$ and MNI coordinates $= [15, 30, 39]$] in children with ID compared to HC (**Figure 3B**).

Brain–Behavior Associations

To explore the relationship between IQ and GMV, FC, correlation analyses were further applied (**Figure 4**). Significantly negative associations were found between mean GMV of the dmPFC, orb_IFG.L, cuneus.R, and IQ scores. Meanwhile, FCs between the cuneus.R and IPS.L and between the MFG.R and ACC were positively correlated with IQ scores.

DISCUSSION

The voxel-based morphometry and FC analyses were employed to investigate the structural and functional developmental abnormalities in children with ID from childhood to around puberty. Children with ID showed decreased global GMV and

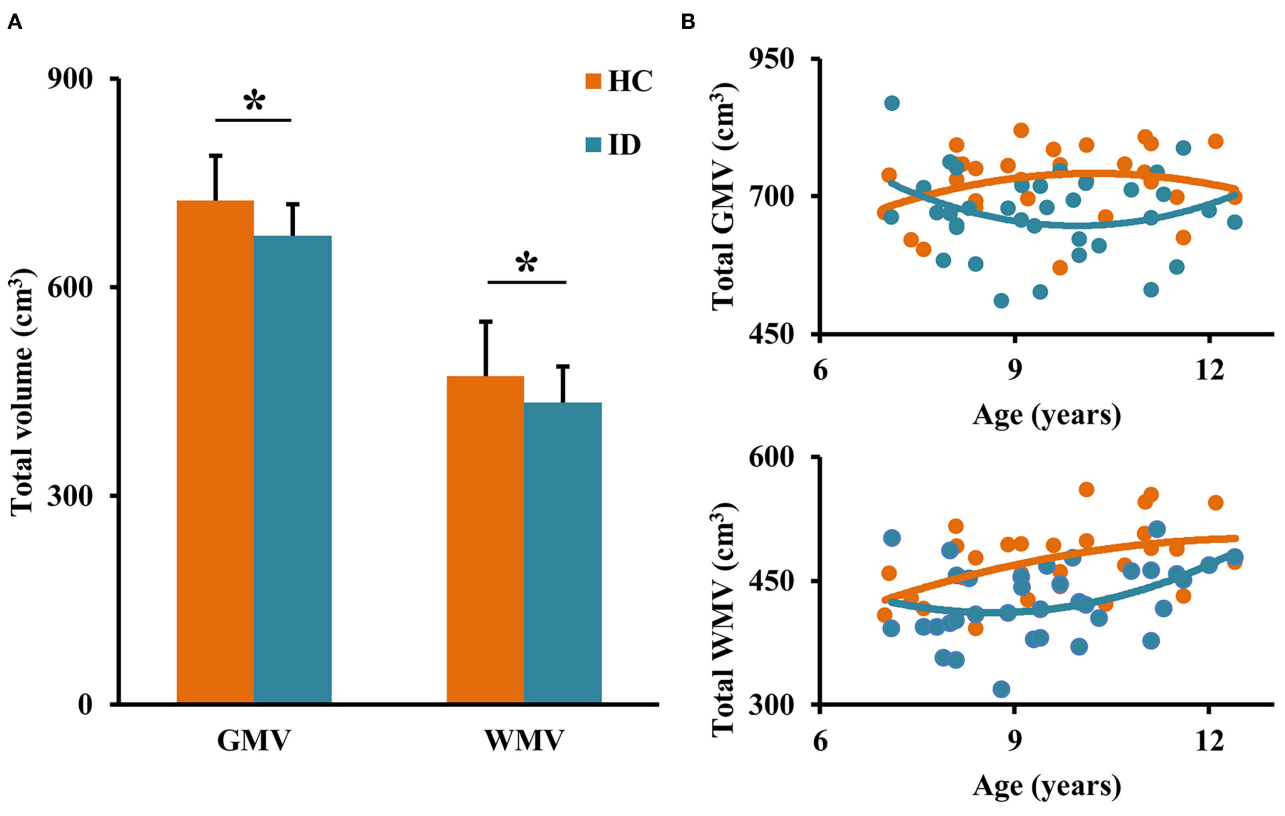

FIGURE 1 | Between-group comparisons of total gray matter volume (GMV) and white matter volume (WMV). **(A)** Decreased total GMV and WMV were detected in children with ID compared to healthy controls (HC). **(B)** Different developmental trajectories of the total brain GMV and WMV were found in ID and HC. *represents significant differences.

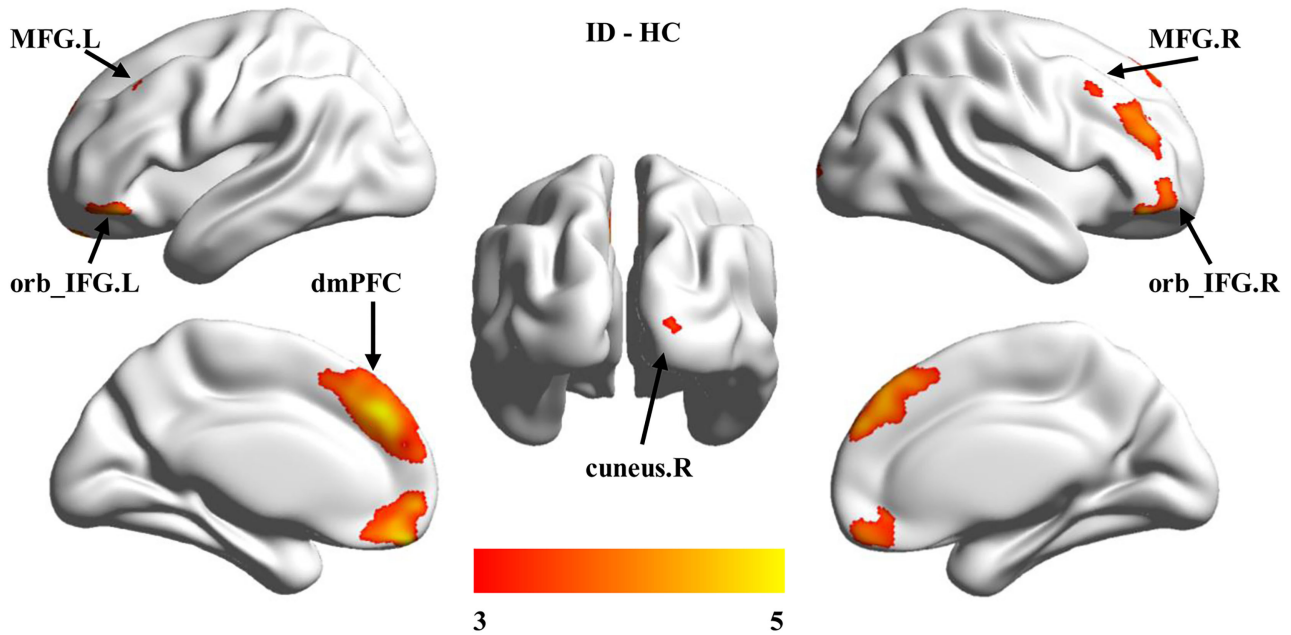

FIGURE 2 | Group differences in gray matter volume (GMV). Voxel-based morphology (VBM) was used to identify voxel-wise changes of GMV in ID participants. Significantly increased GMV was found in the dorsal medial prefrontal cortex (dmPFC), bilateral orbital part of the inferior frontal gyrus (orb_IFG.L, orb_IFG.R), right cuneus (cuneus.R), and bilateral middle frontal gyrus (MFG.L, MFG.R) in ID compared to HC.

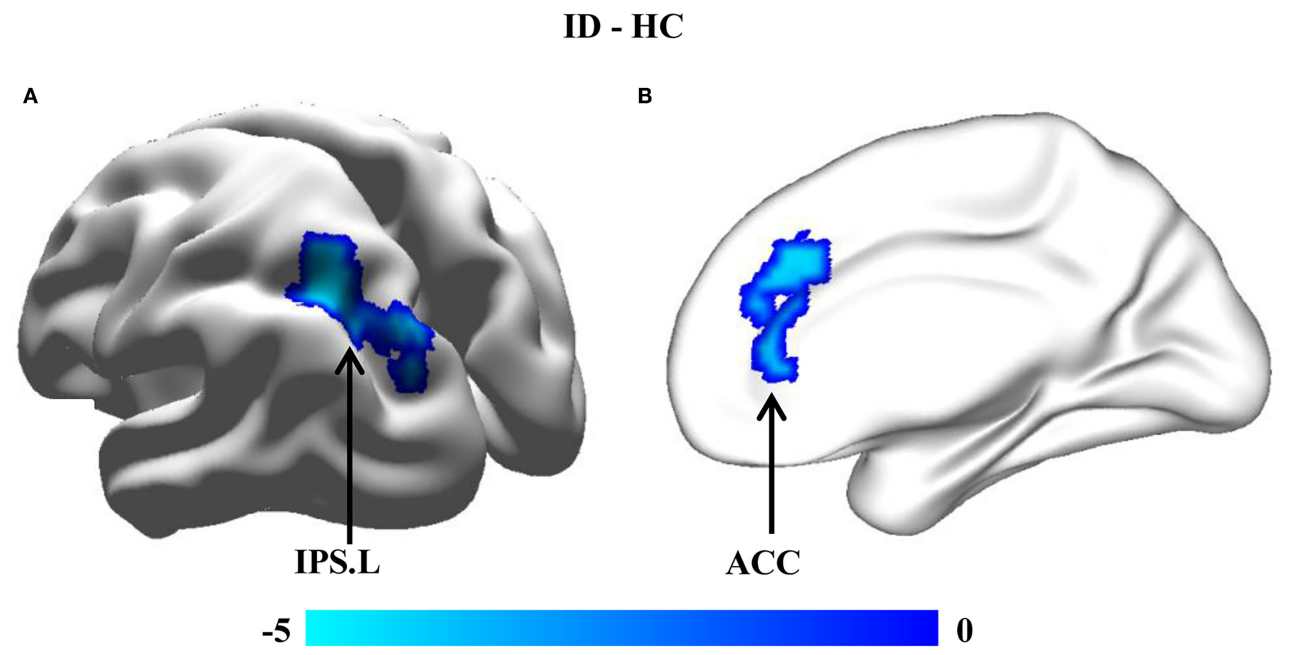

FIGURE 3 | Between-group comparisons of resting-state functional connectivity (FC). Seed-based FC analyses of brain areas showing that changed GMVs were performed to reveal the abnormal functional couplings. Significantly decreased FCs **(A)** between the cuneus.R and left intraparietal sulcus (IPS.L) and **(B)** between the MFG.R and anterior cingulate cortex (ACC) were found in individuals with ID compared to HC.

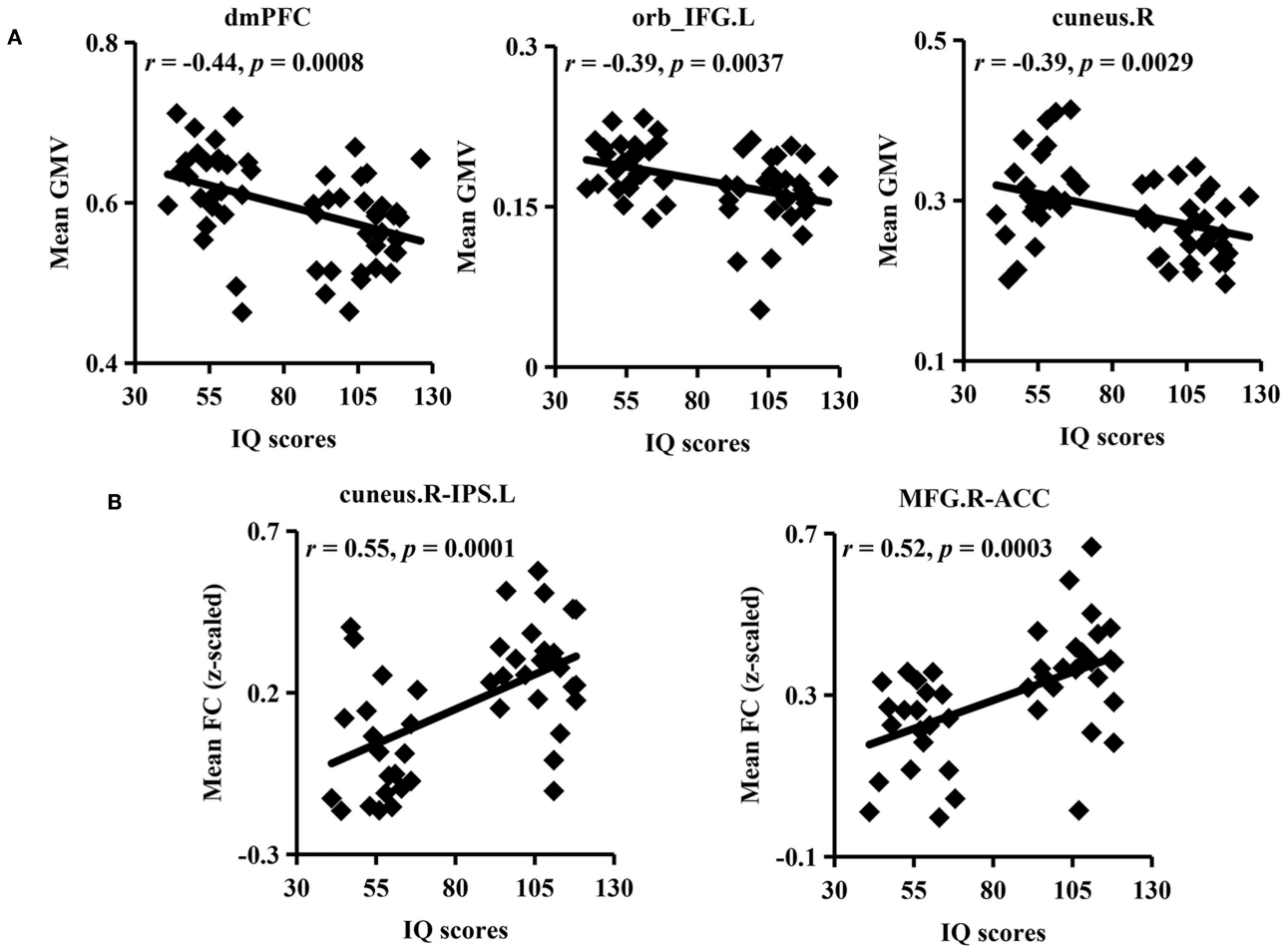

FIGURE 4 | Association analyses. **(A)** Significantly negative correlations were found between intelligence quotient (IQ) scores and mean GMV in the dmPFC, orb_IFG.L, and cuneus.R in ID and HC participants. **(B)** Mean FCs between the cuneus.R and IPS.L and between the MFG.R and ACC were significantly positively correlated with IQ scores.

WMV while increased frontal and occipital GMV. The resting-state FC analyses further revealed decreased functional couplings in attention and executive control networks in ID. The presence of specific structural and functional alterations indicated that children with ID have abnormal developmental trajectory from childhood to around puberty, which may be the neural basis of functional disorders observed in ID.

Altered Maturational Patterns

Our results of significantly decreased total volume of GMV and WMV in ID compared to HC are in accordance with previous findings (14, 20, 28–30). The higher GMV and WMV in HC are mainly related to a larger number of neuron cells and fibers for better computational and communicational ability (31). Although most mature processes of the brain are completed before age 2 years like shape, volume, and fold, and the brain size reaches about 90% of adult size by 5 years of age, it keeps plasticity across the lifespan (32). In our study, we found that the total GMV in HC increases to a peak (about 10–11 years) and then decreases while the WMV keeps increasing. The development trajectories of GMV and WMV in typical children is in line with that found in a previous study (32). During development, the increasing GMV and WMV mainly come from continuous generation of dendrite, axon, and synapse and myelination while decreasing GMV and WMV may result from competitive elimination of redundant synapse. This process serves as the neural substrate of development of the primary system and high-order cognitive functions (10). In the ID group in our study, the developmental courses of total GMV and WMV showed almost opposite directions compared to that in HC, which suggests that delayed development of gray and white matters may be the neuropathology of children with ID.

Different from decreases in global GMV and WMV compared with HC, increased region-specific GMV in the prefrontal and occipital cortices were found in ID. Accumulating evidence supports that the frontal cortex is important to both primary and high-order cognition functions. For example, the prefrontal cortex (PFC) has been demonstrated to be involved in memory

(32), cognitive control, decision-making (33), language (34, 35), and reasoning (36), and the volume of the PFC is closely related to intelligence level (15, 20, 21). Moreover, the increased GMV in ACC is also supported by a previous study of children with ID (12). Additionally, Zhang and colleagues also found decreased cortical thickness in the right lateral orbitofrontal cortex in adults with ID (15). In a word, increased GMV at the prefrontal regions and ACC in children with ID found in our study may be related to the compensatory effect of hypofunctions of high-order cognitive abilities (10, 21).

Altered Functional Couplings in the Attention Network

The dorsal attention network (DAN), which mainly comprises the frontal eye fields (FEF), IPS, and the superior occipital gyrus, is involved in goal-directed attention processes and is associated with working memory and intelligence (34, 37, 38). Moreover, the DAN plays a key role in top-down attention control to guide individuals to filter irrelevant information for better task performance. In our study, we found decreased FC between the IPS.L and cuneus.R, two important nodes of the DAN suggesting impaired attention ability and declined cognitive functions in individuals with ID (39). Our findings further highlight the important role of the DAN in intelligence.

In addition to the top-down control of attention by the DAN, the attention-related process also contains bottom-top competitive stimulation selection by the ventral attention network (VAN), which is strongly associated with social cognition (39). Besides, the MFG is regarded as a converter between the DAN and VAN by sending signals from the DAN to direct VAN focusing on the targets and receiving feedback and environmental information from the VAN to DAN for reorienting attention (37). After receiving the important or interesting target information from the external attention system, the salience network, mainly composed of the ACC and the anterior insula, is enrolled to identify most-concerned or nonsense stimulation for dynamic switching between the default mode network and central executive network to regulate the following behaviors (40, 41). Thus, the decreased FCs within the attention network and between the ACC and MFG indicated relatively lower dynamic interaction within the attention network and lower dynamic modulation by the ACC and MFG in children with ID compared to typically developmental children, which may be the underlying basis of the manifested low intelligence level.

There are several limitations in our study. First, the scanning slice is a little thick, which may contribute to inhomogeneity with the voxel and lead to missing subtle but important findings. Second, the sample size of our study is relatively small, and the findings should be validated in large samples in future studies.

CONCLUSION

Sustaining plasticity of the brain structure and function is crucial for intellectual development. Apart from aberrant gray and white matter volume alterations, decreased functional connections within the attention system and between attention and the execution system was uncovered. Our findings provide biological and neural basis for children with ID and may guide future interventions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the First People's Hospital of Zunyi. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SL and JW contributed to the conception and design, conducted the data analysis, and drafted and approved the final manuscript. XM contributed to the data analysis, drafting, and revision of the manuscript. XW, JT, and YL offered data collection. SL, LJ, and BC contributed to radiological expertise and helped to select and assess cases. PX provided a critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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Developmental Trajectories in Very Preterm Born Children Up to 8 Years: A Longitudinal Cohort Study

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Aim: Long-term outcome data in preterm children is often limited to cross-sectional measurement of neurodevelopmental impairment (NDI) at the corrected age of 24-36 months. However, impairments may only become overt during childhood or resolve with time, and individual trajectories in outcome over time may vary. The primary aim of this study was to describe NDI in very preterm born children at three subsequent ages of 2, 5, and 8 years of age. As a secondary aim, a longitudinal analysis was performed on the individual longitudinal trajectories in NDI from 2 to 8 years of age.

Methods: Single-center prospective cohort study including children born between 1990 and 2011 below 30 weeks' gestation and followed into 2019. The outcome measurement was NDI assessed at 2, 5, and 8 years of age. NDI is a composite score that includes cognitive, neurological, visual, and auditory functions, in which problems were categorized as none, mild, moderate, or severe. Cognitive function measured as total DQ/IQ score was assessed by standardized psychometric tests. Neurological, visual, and auditory functions were assessed by the neonatologist.

Results: In total, 921 children were eligible for follow-up, of whom 726 (79%) children were assessed. No NDI was seen in 54, 54, and 62%, mild NDI was seen in 31, 36, and 30%, and moderate-to-severe NDI was seen in 15, 9.2, and 8.6% of the children at 2, 5, and 8 years, respectively. From 2 to 8 years, 63% of the children remained in the same NDI category, 20% of the children improved to a better NDI category, and 17% deteriorated toward a worse NDI category. No differences were found in baseline characteristics of infants that improved or deteriorated. Extreme prematurity, male gender and low parental education were associated with worse NDI status at all time points. Although we observed considerable individual variation over time in NDI status, the course of the trajectories in NDI were not associated with gestation, gender, and parental education.

Conclusions: Continued follow-up until school life is essential in order to provide optimal and individually focused referrals and care when needed.

Keywords: longitudinal follow-up, neurodevelopmental outcome, very preterm children, trajectories, NDI

INTRODUCTION

The number of preterm deliveries below 30 weeks' gestation has increased over the last decades, with increasing survival rates of preterm children (1, 2). However, improved survival rates still raise the concern of adverse long-term outcome in the increasing number of surviving preterm children. Preterm born children are known to have a higher risk of physical disabilities as well as cognitive problems later in life (3–5). Knowledge on neurodevelopmental outcomes of children born at these early gestational ages (GA) is crucial for clinicians and families as this may influence antenatal counseling, resuscitation polices, and NICU guidelines (6–8).

As the impact of developmental impairment may be different at different stages of development, there is increasing interest in studying development as a dynamic process (9, 10). Currently available outcome data are often limited to cross-sectional measurements in toddlerhood, but longitudinal follow-up of children is important. Early suboptimal functioning may form an important signal for later problems or an indication for early intervention, and impairments may persist over childhood into adolescence and adulthood (11–16). Moreover, there may be considerable variation in individual trajectories that is not detectable in cross-sectional studies (17).

Studies evaluating developmental trajectories in preterm children often have focused on specific components of development, like cognitive, behavioral, or social problems (5, 10, 13, 18–20). However, a composite outcome score combining different domains provides a general insight in the amount and kind of disabilities of preterm born children. As developmental problems can arise over a broad spectrum of outcome measures, evaluation of developmental trajectories using a composite outcome might provide additional information. A frequently used indication of adverse long-term outcome is the composite measure of neurodevelopmental impairment (NDI), a score that takes cognitive, neurological, visual, and auditory function into account (8, 21–24). This outcome measure focuses on severe impairments and provides important prognostic information for clinicians and parents (21).

Since three decades, preterm children born below 30 weeks' gestation are eligible for an extensive follow-up program in our perinatal center. This includes outpatient clinic visits to the neonatologist and psychologist at the corrected age of 2 years and the uncorrected age of 5 and 8 years, making an NDI assessment possible at three subsequent ages. The data collected over a period of more than 20 years provides unique information on the development of very preterm children. Therefore, the primary aim of this study was to describe NDI in very preterm born children who were evaluated at three subsequent ages of 2, 5, and 8 years of age. As a secondary aim, a longitudinal analysis was performed on the individual longitudinal trajectories in NDI from 2 to 8 years of age.

Abbreviations: NICU, neonatal intensive care unit; GA, gestational age; NDI, neurodevelopmental impairment; BOS 2-30, Bayley Scales 2-30 months, Dutch edition; BSID-II, Bayley Scales of Infant and Toddler Development-II; BSID-III, Bayley Scales of Infant and Toddler Development-III; RAKIT, Revised Amsterdam Child Intelligence Test; RAKIT-2, Revised Amsterdam Child Intelligence Test-II; WPPSI-III-NL, Wechsler Preschool and Primary Scale of Intelligence Scale-III Dutch Edition; WISC-III-NL, Wechsler Intelligence Scale for Children-III Dutch edition.

MATERIALS AND METHODS

Patient Population

This cohort study included all children born between 1990 and 2011 and followed into 2019, with a gestational age below 30 weeks, who were admitted within 24 h after birth to the neonatal intensive care unit (NICU) of Máxima Medical Centre (MMC). The NICU of MMC serves a 1.6 million population including antenatal and postnatal transfer from six other hospitals in the region. Children from parents living outside the adherence area of MMC and referrals from other NICUs were excluded. The ethical review board of MMC approved the study in accordance with the Dutch law on medical research with humans (WMO).

Data Collection

Data from the outpatient clinic visits were collected prospectively. Neonatal data were retrieved from the individual medical records. Individual characteristics and medical data included gender (male or female); birth weight in grams; gestational age in days (based on ultrasound findings or on the first day of last menstrual period if ultrasound data was not available); small for gestational age [defined as birth weight below the 10th percentile (25)]; multiplicity (dichotomized as single or multiple birth); mode of delivery (dichotomized as vaginal or by caesarean section); complete course of antenatal corticosteroids (defined as two doses of betamethasone given 24 h apart before the start of labor); Apgar score at 5 min postpartum; inborn or outborn NICU; rate of artificial ventilation $>$ 12 h; days of endotracheal intubation on any mode of ventilation; surgical treatment of a persistent ductus arteriosus; intraventricular hemorrhage grade 3 or 4 based on ultrasound (26); cystic periventricular leukomalacia grade 3 (27); severe brain injury (defined as intraventricular hemorrhage grade 3 or 4 or cystic periventricular leukomalacia grade 3); laparotomy for necrotizing enterocolitis or single intestinal perforation; surgical treatment or laser therapy for retinopathy of prematurity; and total days of NICU admission. Socio-economic status was assessed using scores defined by the Netherlands Institute for Social and Cultural Research (The Hague, Netherlands) based on postal code at birth, with an average score of 0 and a positive score reflecting a higher than average status and a negative score reflecting a lower than average status (28). For children not seen for follow-up, reasons for no show were identified.

Follow-Up

All preterm children below 30 weeks' gestation were eligible for our follow-up program. This consisted of outpatient clinic visits to the neonatologist and psychologist at the corrected age of 2 years and the uncorrected age of 5 and 8 years. The neonatologist assessed the child's health and evaluated the neurological, visual, and auditory functions. Neurological outcome was scored as normal, mildly abnormal, or unilateral/bilateral CP, according to the GMFCS classification

(29). The psychologist evaluated the child's cognitive function, emotional, and behavioral development. At the corrected age of 2 years cognitive development was assessed using the Mental Developmental Index of the Bayley Scales of Infant Development-II (BOS2-30 for children born in 1990-2001 or BSID-II, for children born in 2001-2007) or the Cognitive Composite score of the Bayley-III (for children born in 2007-2011). At the age of 5 years cognitive function was tested using the Total IQ score of the Revised Amsterdam Child Intelligence Test short form (RAKIT, for children born in 1990-2008), the Total IQ score of the Revised Amsterdam Child Intelligence Test-2, short form (RAKIT-2, for children born in 2008-2009) or the Total IQ score of the Dutch version of the Wechsler Preschool and Primary Scale of Intelligence Scale-III (WPPSI-III-NL, for children born after 2009). A strong correlation of 0.76 has been reported between the RAKIT and the WPPSI for total IQ scores (30). At the age of 8 years cognitive function was tested using the Total IQ score of the Revised Amsterdam Child Intelligence Test, short form (RAKIT, for children born in 1990-2005), the Total IQ score of the Revised Amsterdam Child Intelligence Test-2, short form (RAKIT-2, for children born in 2005-2006) or the Total IQ score of the Dutch version of the Wechsler Intelligence Scale for Children-III (WISC-III-NL, for children born after 2006). IQ-scores of the RAKIT and WISC have shown a strong correlation of 0.82 (30). In addition, the psychologist collected information on educational status of the parents, which was classified as low, middle, or high according to the CBS classification (31). This variable was dichotomized describing whether there was a low education or middle-to-high education. If one of the parents was classified as middle-to-high educated, parental education was classified as middle-to-high.

Neurodevelopmental Outcome

The outcome measure was neurodevelopmental impairment (NDI), a composite score based on cognition, neurological assessment, and presence of visual and/or hearing impairment (**Table 1**). NDI was categorized as none, mild, moderate, or severe. NDI was classified as mild if cognitive scores showed a developmental quotient (DQ) or intelligence quotient (IQ) between 70 and 84 (−2 to −1 SD); vision or hearing loss without an aid or with good correction, or abnormal neurological tests in the absence of a neurological syndrome (e.g., posture, coordination, and tone dysregulation disorders). NDI was scored as moderate if cognitive DQ/IQ scores were between 55 and 69 (−3 to −2 SD); limited vision or hearing and the use of aids or the presence of a unilateral cerebral palsy. NDI was scored as severe if cognitive DQ/IQ scores were below 55 (>-3 SD), or blindness, deafness, or bilateral cerebral palsy were present. NDI score was based on the worst determinant in either one of the four categories. If one category was missing, NDI was classified as missing. NDI was determined for examinations at 2, 5, and 8 years of age.

TABLE 1 | Classification of neurodevelopmental impairment.

	Neurology	Vision	Hearing	Cognition
No NDI	Normal	Normal	Normal	>-1 SD
Mild NDI	Abnormal neurological tests but absence of neurological syndrome	Vision loss without an aid or with good correction	Hearing loss without an aid or with good correction	−2 to −1 SD
Moderate NDI	Unilateral cerebral palsy	Limited vision and the use of aids	Limited hearing and the use of aids	−3 to −2 SD
Severe NDI	Bilateral cerebral palsy	Blindness	Deafness	<-3 SD

NDI, neurodevelopmental impairment; SD, standard deviation. Overall NDI score was based on the worst determinant in either one of the four categories.

Statistical Analyses

Children with and without follow-up were compared using the Student's *T*-test or Mann-Whitney *U*-test for continuous variables, depending on distribution of the data, and using the Chi-square test for categorical and dichotomous variable. Parental education was missing for 25% of the children and imputed using the R multivariate imputation by chained equation (MICE) package. A continuation ratio model was used to investigate trajectories in NDI, using an interaction term between age and group to test whether NDI trajectories were different for different groups. These group terms included a dichotomized variable for gestational age [extremely preterm (EP) < 28 weeks vs. very preterm (VP) 28^0-29^6 weeks' gestation], gender (boys vs. girls), and parental education (low education vs. middle-to-high education). First, the effect of being EP was evaluated by adding this group factor to the model. Then, the effect of gender and parental education were examined by adding them separately to the model. A p-value < 0.05 was considered significant. Analyses were performed using R version 3.5.1.

RESULTS

Study Population and Loss-to-follow-Up

Within the study period (1990-2011), 1,107 children born below < 30 weeks' GA were admitted to the NICU. Of these children 186 (17%) died, leaving 921 children eligible for follow-up at the outpatient clinic (**Figure 1**). Of these children, 726 (79%) were seen for follow-up. In total, 693 (75%), 658 (71%), and 579 (63%) children had follow-up at 2, 5, and 8 years, respectively. Reasons for the total group of 195 loss-to-follow-up children are shown in **Table 2**. During a limited period of time, difficulties in availability of staff resulted in a group of 102 relatively low risk children who were not invited for follow-up.

Baseline Characteristics

Table 3 shows the baseline characteristics, separately for children with and without follow-up. Children with follow-up were more immature at birth, compared to children without follow-up. Socio-economic status was higher in children seen for follow-up. Their NICU admission was significantly more often complicated by PDA and ROP, but less often complicated by a laparotomy. The length of NICU stay in children with follow-up was longer, compared to children without follow-up.

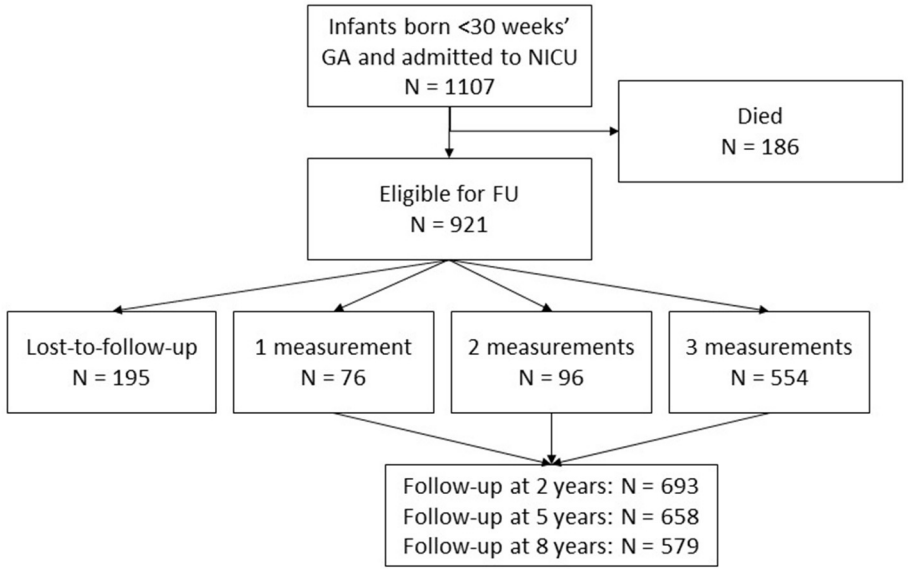

FIGURE 1 | Flowchart of the included children. 921 children were eligible for follow-up at the outpatient clinic. In total, the results are based on 726 participants with data on 1930 follow-up moments, as presented in the gray square.

TABLE 2 | Reasons for no follow-up.

Reason no follow-up	*N* (%)
Logistic reasons	
Not invited for follow-up due to difficulties in staff	102 (52%)
No show (reason unknown)	34 (17%)
Moved or distance too far	9 (4.6%)
Parental reasons	
Parents refused follow-up	11 (5.6%)
No need for follow-up according to parents	6 (3.1%)
Follow-up elsewhere	
Ambulatory or clinic for rehabilitation medicine	15 (7.7%)
Follow-up program at other NICU	18 (9.2%)
Total	**195 (100%)**

NDI Classification

NDI could be calculated for 646, 618, and 560 children at 2, 5, and 8 years, respectively (**Table 4**). No NDI was seen in 54, 54, and 62%, and moderate-to-severe NDI was seen in 15, 9.2, and 8.6% of the children at 2, 5, and 8 years, respectively. Of the 201 infants with mild disabilities at 2 years of age, 25 (12.4%) had a mild disability in two domains. None of the infants had disabilities in more than two domains. Of the 225 infants with mild disabilities at 5 years of age, 49 (21.8%) had a mild disability in two domains, 7 (3.1%) had a mild disability in three domains, and 1 (0.4%) had a mild disability in all domains. Of the 167 infants with mild disabilities at 8 years of age, 29 (17.4%) had a mild disability in two domains, 1 (0.6%) had mild disability in three domains, and 1 (0.6%) had a mild disability in all domains.

When they got older, more children were seen in a clinic for rehabilitation medicine and dropped-out on follow-up. Including these children in the category moderate-to-severe NDI, the percentage at 8 years increased up to 16%. In further analysis, the original data was used categorizing this subgroup as missing. Separate presentation of NDI rates for EP and VP infants showed decreased "no NDI" and increased "mild NDI" rates in EP infants compared to VP infants, but similar moderate-to-severe NDI rates (**Table 4**). In **Appendix 1**, classifications for the separate components of NDI are presented for each follow-up age.

NDI From 2 to 8 Years of Age

In the 554 children with three follow-up contacts, NDI could be calculated at all time points for 495 children. No NDI during the complete trajectory at 2, 5, and 8 years of age was seen for 179 (36%) children and both no-or-mild NDI during the complete trajectory was seen for 427 (81%) children. Moderate-to-severe NDI during the complete trajectory was seen for 21 (4.2%) children. In these 495 children, from 2 to 8 years 314 (63%) children remained in the same NDI category, 101 (20%) children improved toward a better NDI category, and 80 (17%) children deteriorated toward a worse NDI category (**Figure 2**). Of all 293 children with normal NDI at 2 years, 223 (76%) remained in the normal NDI category at 8 years of age. For mild impaired infants 43% (66/152) and for moderate-to-severe impaired infants 50% (25/50) remained in the same NDI category. No differences were found in the characteristics of infants that remained in the same category, improved or deteriorated from 2 to 8 years (**Table 5**).

Individual Longitudinal Trajectories in NDI

In clinical work individuals are more important than (sub)groups. Therefore **Figure 3** presents the horizontal line plot for NDI at 2, 5, and 8 years of age, showing individual patterns

TABLE 3 | Baseline characteristics for children with and without follow-up.

	Children with follow-up *N* = 726	Children without follow-up *N* = 195	*P*-value
Inborn	672 (93)	175 (90)	0.255
Gender (% male)	394 (54)	104 (54)	0.989
Birth weight	1,037 (259)	1,169 (254)	< 0.001*
Gestational age (days)	28.3 [27.9, 29.1]	28.7 [27.9, 29.4]	< 0.001*
Gestational age < 28 weeks	310 (43)	52 (27)	< 0.001*
SGA (<10th percentile)	90 (12)	7 (3.6)	0.001*
Singleton	490 (68)	119 (62)	0.090
Caesarean section	347 (48)	77 (40)	0.061
Antenatal corticosteroids completed	464 (64)	125 (65)	0.231
Apgar 5 min	8 [7, 9]	8 [7, 9]	0.095
Socio-economic status	0.10 (0.82)	−0.07 (0.79)	0.009*
Ventilation > 12 h	495 (68)	125 (65)	0.205
Days ventilation	3 [0, 8]	3 [0, 7]	0.241
Surgically treated PDA	51 (7.0)	6 (3.1)	0.007*
Severe brain injury	38 (5.3)	11 (5.8)	0.925
Laparotomy	18 (2.5)	14 (7.3)	0.003*
Laser therapy for ROP	15 (2.1)	2 (1.0)	0.038*
Length of stay in the NICU (days)	36 [22, 48]	22 [13, 40]	< 0.001*

*N (%), mean (SD) or median [1st quartile, 3rd quartile]. SGA, small for gestational age; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; NICU, neonatal intensive care unit. *Significant on a p-level of 0.05.*

TABLE 4 | NDI at each follow-up age.

Seen for follow-up	Age 2 *N* = 693	Age 5 *N* = 658	Age 8 *N* = 579
NDI status unavailable	*N* = 47	*N* = 40	*N* = 19
Included in analysis on NDI	*N* = 646	*N* = 618	*N* = 560
Age at assessment			
Mean (SD)	2.28 (0.13)	5.08 (0.19)	8.11 (0.22)
Median (IQR)	2.25 [2.22-2.29]	5.03 [5.01-5.21]	8.03 [8.01-8.23]
NDI			
None	351 (54)	336 (54)	345 (62)
Mild	201 (31)	225 (36)	167 (30)
Moderate	46 (7.1)	37 (6.0)	33 (5.9)
Severe	48 (7.4)	20 (3.2)	15 (2.7)
NDI in EP (<28 weeks)			
None	144 (50)	117 (47)	129 (55)
Mild	93 (33)	113 (45)	84 (36)
Moderate	26 (9.1)	14 (5.6)	16 (6.8)
Severe	23 (8.0)	6 (2.4)	6 (2.6)
NDI in VP (28^0-29^6 weeks)			
None	207 (58)	208 (61)	212 (68)
Mild	108 (30)	98 (29)	77 (25)
Moderate	20 (5.6)	21 (6.2)	16 (5.1)
Severe	25 (6.9)	12 (3.5)	8 (2.6)

This table shows NDI rates at 2, 5, and 8 years of age. In the upper half of the table, age at assessment and overall NDI rates are presented for each follow-up age. In the lower half of the table, NDI rates are presented for extremely preterm vs. preterm infants. NDI, neurodevelopmental impairment; SD, standard deviation; IQR, interquartile range; EP, extremely preterm; VP, very preterm; GA, gestational age.

of increasing and decreasing trajectories for all infants including patterns in missing data. Using the continuation ratio model, we found that at all time points very preterm born children had on average a 1.95 (95% CI 1.28-2.96) times higher odds on being in a better NDI category compared to extremely preterm born children. Female children had a 2.00 (95%CI 1.32-3.05) times higher odds compared to male children on being in a better NDI category, and children from parents with middle-to-high education had a 3.37 (95%CI 2.01-5.64) times higher odds compared to children from parents with low education on being in a better NDI category. Studying the trajectories in relation to these characteristics, it was found that EP and VP children showed similar trajectories, as did male and female children and children from parents with low vs. middle-high education.

DISCUSSION

In this study, neurodevelopmental impairment at 2, 5, and 8 years was evaluated in very and extremely preterm children born below 30 weeks gestation. In addition the course of the individual longitudinal trajectories over time was studied. We observed individual variation over time in NDI status in 37% of the children, with 17% showing a change to a more worrisome category, but 20% showing an improvement. However, 63% of the children remained in the same category over time. Longitudinal analysis showed a clear association of gestation, gender, and parental education with the severity of NDI at all time points. No differences were found in the characteristics between children that improved and deteriorated, and the course of the trajectories in NDI was not affected by gestation, gender, and parental education.

Compared to other studies we observed higher rates for children without or with mild NDI. At the age of 5 and 8 years, respectively, 54 and 62% of the surviving children showed a normal neurodevelopment, and 36 and 30% of the surviving children showed a mild neurodevelopmental impairment. In EP children, normal development rates were 47 and 55%, and mild NDI rates were 45 and 36% at 5 and 8 years, respectively. The Swedish EXPRESS study found rates of 36 and 30% for children without and with mild NDI at 6.5 years in children born below 27 weeks' GA (32). The EPICure study from the UK showed a rate of 75% for children with none-to-mild NDI at 6 years and a rate of 53% for children with none-to-mild NDI in 53% at 11 years, in children born below 26 weeks' GA (3, 33). Unfortunately, international comparisons are hampered by differences in age of follow-up, definition of neurodevelopmental impairment and study population (21). For example, the EPICURE and EXPRESS studies included substantially more immature children, born at 22-24 weeks' gestation, whereas in our sample the youngest children were born at 25 weeks' gestation.

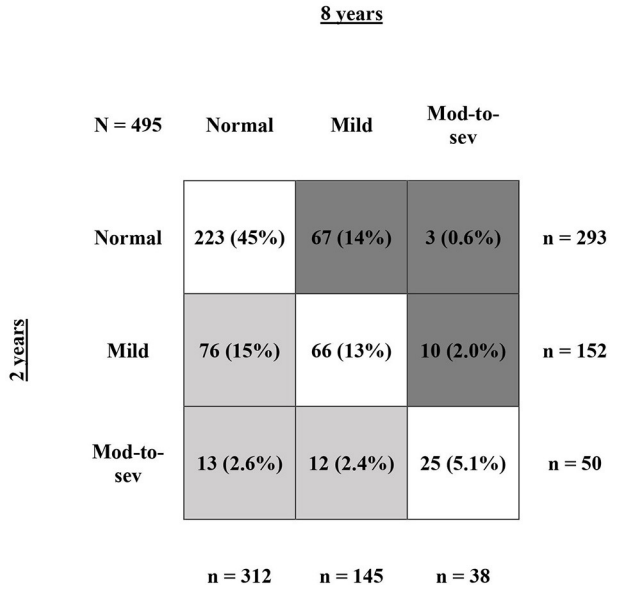

FIGURE 2 | Shifts in NDI from 2 to 8 years of age. This figure shows NDI rate at 2 vs. 8 years of age for infants with NDI calculation at all three follow-up contacts ($N = 495$). The numbers are presented as *N* (%), with the % calculated relatively to the full group of $N = 495$ infants. The row sums show the total number of infants at 2 years of age for normal, mild, and moderate-to-severe NDI. The column sums show the total number of infants at 8 years of age for normal, mild, and moderate-to-severe NDI. The dark gray boxes represent all infants that deteriorated toward a worse NDI category from 2 to 8 years, the light gray boxed represent all infants that improved toward a better NDI category from 2 to 8 years, and the white boxes represent all infants that remained in the same NDI category.

TABLE 5 | Baseline characteristics of children that remained in the same NDI category, improved toward a better NDI category and deteriorated toward a worse NDI category.

	Children that remained in the same NDI category	Children that improved toward a better NDI category	Children that deteriorated toward a worse NDI category	*P*-value
	***N* = 314**	***N* = 101**	***N* = 80**	
Gender (% male)	163 (52)	53 (53)	37 (46)	0.634
Birth weight	1,039 (249)	1,061 (255)	1,005 (282)	0.339
Gestational age (days)	28.4 [27.1, 29.0]	28.3 [27.1, 29.1]	28.0 [26.9, 29.1]	0.788
SGA (<10th percentile)	34 (11)	9 (8.9)	12 (15)	0.418
Low maternal education	37 (14)	13 (17)	11 (17)	0.738
Severe brain injury	15 (4.8)	3 (3.0)	0 (0.0)	0.116
Length of stay in the NICU (days)	34 [22,48]	36 [23, 45]	35 [23, 48]	0.994

N (%), mean (SD) or median [1st quartile, 3rd quartile]. SGA, small for gestational age; NICU, neonatal intensive care unit.

Mild neurodevelopmental problems were seen in 31, 36, and 30% of the infants at 2, 5, and 8 years of age. However, mild deficits in multiple domains might be of the same severity as one moderate-to-severe deficit in a single domain. At 2, 5, and 8 years of age, 12.4, 25.3, and 18.6% of the infants with mild NDI had mild problems in more than one domain. Apparently, at a later age more multiple mild deficits become overt. Multiple deficits across domains may have combined long-term effects, which unfortunately is not reflected by the NDI definition. The significance of milder forms of neurocognitive deficits might need additional research (34).

The moderate-to-severe disability rate in the current study initially appeared to be 8.8% at 8 years of age. However, it was found that 13% of the children lost for follow-up at 8 years of age did not attend follow-up because they were already in treatment in rehabilitation medicine. Including these children as having moderate-to-severe disability resulted in a disability rate of 16%, which is slightly higher than the severe disability rate of 13% reported in both the EPICure and EXPRESS studies (3, 32). On the other hand, children in our study were also lost-to-follow-up because they did not experience any problems. The real moderate-to-severe disability rate probably is somewhere between 8.8 and 16%. This emphasizes the importance of presenting impairment rates in the context of reasons for loss-to-follow-up.

Despite the abundancy of cross-sectional follow-up studies a paucity exists in longitudinal follow-up. This study showed that approximately two third of the children assessed at 2 years of age were classified in the same NDI category at 8 years of age, and that 16% of all children became worse at 8 years of age. Similar results have been reported before in the EXPRESS study, reporting that 47% of all children remained in the similar NDI category and 32% of all children deteriorated toward a worse NDI category from 2 to 6.5 years of age (32). Although overall NDI rates remained comparable over time, these results demonstrate considerable individual variation over time. Indeed this also shows the importance of continuing follow-up until school life for individual and specific referrals and advise.

EP/VP status, gender, and parental education were found to be associated with severity of NDI at all time points. These results were in line with previously published studies, reporting gender-differences in neurodevelopmental outcomes in the favor of girls (35–38). Moreover, these results enhance the formerly reported association between gestational age and neurodevelopmental outcome as well as the association between parental education and neurodevelopmental outcome (11, 36, 38–40).

Although EP/VP status, gender and parental education were found to be associated with NDI, these associations remained stable over time and the course of the trajectories was not affected by these factors. Children with these characteristics therefore seem to have the same developmental growth potential as children without these characteristics (18). Moreover, no differences were found in characteristics between infants that improved or deteriorated from 2 to 8 years. Nevertheless,

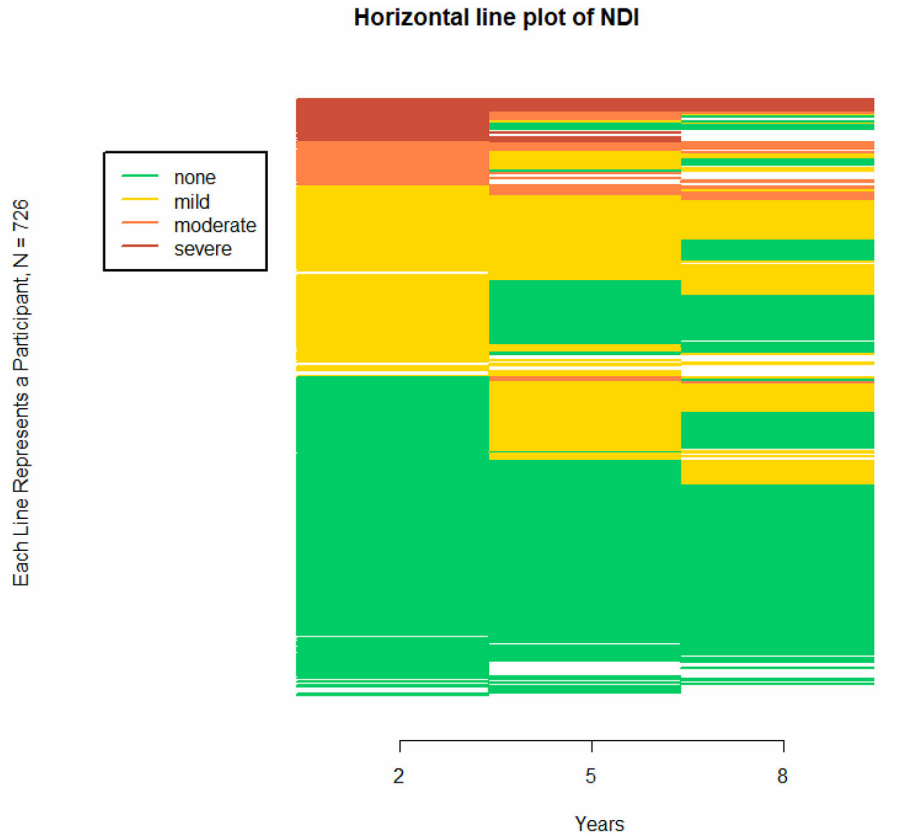

FIGURE 3 | Individual trajectories of neurodevelopmental impairment (NDI) at different ages, presented in a horizontal line plot for all children with follow-up. The horizontal line plot uses colors to differentiate between states on a categorical longitudinal variable for multiple participants. Because categorical data defines a specific state, a trajectory for a categorical variable becomes a sequence of states rather than a continuum. The figure consists of 726 stacked horizontal line, with each horizontal line representing a participant. In this figure, NDI category is presented at 2, 5, and 8 years of age. This figure shows overall patterns of increasing and decreasing trajectories, including patterns in missing data. The blank spaces indicate missing data for that follow-up age.

considerable individual differences were seen in trajectories. This indicates the importance of other factors that might influence development over time, for example early childhood interventions such as an extensive physiotherapy program or special education assistance. Moreover, socio-environmental factors such as the quality of the parent-child relationship are important throughout development (16).

Although extensive evaluation of separate domains is important, the added value of a composite outcome is that it provides an overall impression of the outcomes after very preterm birth. Problems after preterm birth occur in a range of developmental domains and therefore it is important not to focus on single domains of development. Looking separately at the specific domains in this study, the majority of the children did not have any impairment. However, combining the different domains into the NDI composite outcome showed no NDI during the complete trajectory for a minority of 36% of all children. Apparently, the majority of the very preterm children do experience some clear problems at some time during childhood. Moreover, the combined outcome measure used in this study is the longer term outcome most frequently used for comparisons both within and between countries (21). International comparisons can guide clinical decision-making and provide prognostic information for families.

In this study, cognitive scores were corrected for prematurity at age 2, but not at age 5 and 8. The current Dutch national guideline on follow-up and most international guidelines recommends the use of corrected scores for preterm children up to 2–3 years. However, in very preterm children at age 5, a significant difference between corrected and uncorrected IQ was found, with corrected scores of course being higher than uncorrected scores (41). For future research, consistent reporting of cognitive outcome based on corrected scores is recommended (42).

The overall follow-up rate in this study was 79%, which is comparable to follow-up rates of other studies, showing rates varying from 71 to 92% at different ages (3, 5, 32). Moreover, more than 60% of the children completed follow-up at all time points during the longitudinal follow-up program,

which demonstrates a high follow-up rate compared to other longitudinal studies such as the recently published EPICure2 study (follow-up rate 19%) (33). Our results might represent the worst-case scenario as medium risk children have not always been invited for follow-up during the study period because of limited resources as shown in **Table 2**. These children without follow-up were children with an appropriate birth weight, without severe brain injury and with uncomplicated NICU admission. This explains why infants seen for follow-up were more immature at birth and had an increased length of stay in the NICU compared to infants without follow-up. On the other hand, a significant difference was found in socio-economic status between infants with and without follow-up, with a higher SES score in the children that did have follow-up. This finding is similar to findings in previous studies, showing that drop-out was more likely to occur in families with social disadvantages, while preterm children from socially disadvantaged families may have poorer neurodevelopment (3, 32, 43). However, considering the high follow-up rate in this study, limited influence on the presented results is expected.

Strengths and Limitations

Strengths of our paper included the size of the cohort and the high follow-up rate with most children assessed at three ages. Moreover, the longitudinal nature of this study provides important information reading the developmental course of the children. However, this study has several limitations. First, different tests measuring cognitive performance had to be used, both at different ages to be developmentally appropriate, but also over time in order to use the most recent population norms. Use of different tests intending to measure the same constructs at different ages is inevitable when performing long-term longitudinal studies as development continues at high pace and differentiates strongly during infancy and toddlerhood as well as preschool age (5, 19, 44). In addition, tests need to be re-evaluated and updated over time to allow ecologically valid assessments (e.g., think of the appearance and use of phones in the nineties and zero's, causing the need for revision of the images used in cognitive test). As all tests were standardized however, with a mean of 100, results could be compared. Second, defining NDI based on four determinants (cognitive, neurological, auditory, and visual function) has its limitations to delineate a child's development. Additional domains such as behavioral problems could not be taken into account but may also impair children over time. Third, ideally the GMFCS classification would have been used for classifying the severity of problems in the neurological domain. However, this system was not routinely used in 1990. In order to distinguish between moderate and severe neurological problems, uni- and bi-lateral paresis was used as a proxy for GMFCS 1-2 and GMFCS 3-5, respectively. Last, in this retrospective study, no specific information on interventions was available. Improvement during the trajectories could potentially be the result of adequate interventions after detection of NDI at early age, resulting in improved NDI at early age. Future research may elaborate on the effect of interventions on the individual trajectories.

In conclusion, this study evaluated neurodevelopmental impairment at three different ages up to the age of 8 in very preterm children, next to the course of the longitudinal trajectories in these outcomes. A clear association was found of gestation, gender, and parental education with the severity of NDI at all time points. Although we observed considerable individual variation over time in NDI status, the course of the trajectories in NDI were not associated with gestation, gender, and parental education. These results point to the importance of other (unknown) influences on developmental trajectories. Continued follow-up until school life for extremely preterm born children is essential in order to provide optimal individually focused referrals and care when needed.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of privacy regulations according to the General Data Protection Regulation (GDPR). Requests to access the datasets should be directed to Pauline E. van Beek, pauline.van.beek@mmc.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee Máxima MC. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PB, AB, BV, and PA contributed to the conception of the study. PB, IH, JW, and BV organized the database. PB performed the statistical analysis. PB and IH wrote the first draft of the manuscript. PA was responsible for the financial funding of the project and overall supervision. All authors contributed to the interpretation of the results, critically reviewed the manuscript, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.672214/full#supplementary-material

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Variability in Infants' Functional Brain Network Connectivity Is Associated With Differences in Affect and Behavior

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Variability in functional brain network connectivity has been linked to individual differences in cognitive, affective, and behavioral traits in adults. However, little is known about the developmental origins of such brain-behavior correlations. The current study examined functional brain network connectivity and its link to behavioral temperament in typically developing newborn and 1-month-old infants (*M* [age] = 25 days; *N* = 75) using functional near-infrared spectroscopy (fNIRS). Specifically, we measured long-range connectivity between cortical regions approximating fronto-parietal, default mode, and homologous-interhemispheric networks. Our results show that connectivity in these functional brain networks varies across infants and maps onto individual differences in behavioral temperament. Specifically, connectivity in the fronto-parietal network was positively associated with regulation and orienting behaviors, whereas connectivity in the default mode network showed the opposite effect on these behaviors. Our analysis also revealed a significant positive association between the homologous-interhemispheric network and infants' negative affect. The current results suggest that variability in long-range intra-hemispheric and cross-hemispheric functional connectivity between frontal, parietal, and temporal cortex is associated with individual differences in affect and behavior. These findings shed new light on the brain origins of individual differences in early-emerging behavioral traits and thus represent a viable novel approach for investigating developmental trajectories in typical and atypical neurodevelopment.

Keywords: functional near infrared spectroscopy, functional connectivity, default mode network, fronto parietal network, infancy, temperament

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INTRODUCTION

Spontaneous brain activity is characterized by intrinsic dynamics of synchronized low-frequency fluctuations within structurally and functionally connected brain networks (1, 2). Much research has been focused on mapping the human connectome and delineating its anatomical and functional properties (3). Individual variability in functional connectivity profiles can accurately identify specific individuals likened to a fingerprint (4) and is linked to individual differences in cognitive, affective, and behavioral traits in adults (2, 5, 6). More generally, the study of functional brain network connectivity has been argued to be one of the most promising and effective ways in bridging between brain and behavior (7).

From a developmental perspective, functional connectivity within brain networks can be detected from very early in human brain development. A host of studies employing resting-state functional magnetic resonance imaging (rs-fMRI) have mapped and identified functional networks in newborn infants (8–12). In fact, a body of work relying on progress in fetal rs-fMRI suggests that the basic organization and architecture of the functional connectome emerges during the late second trimester of pregnancy (10, 11, 13, 14). In addition, early prenatal and postnatal experiences, such as premature birth, have begun to shape the development of these networks already within the first week of life (15, 16). The existing research with fetuses and infants points to a developmental progression whereby functional connectivity in primary short-range sensory-motor and homologous-interhemispheric networks are already in place at birth, whereas functional connectivity in higher-order cortical networks across longer ranges involving frontal, temporal, and parietal cortex shows more protracted development during infancy (9, 14). For example, there is evidence to suggest that higher-order networks, such as the default mode network (DMN), exist in a rudimentary form even in the fetus and newborn (14, 17); however, functional network integration and synchronization continues to develop during infancy and beyond (18). Other higher-order networks, such as the fronto-parietal network, show an even more protracted development as it is still considered immature by the end of the first year of postnatal life [see (17), for a review]. Moreover, it is these networks with prolonged development, such as the fronto-parietal network, that go on to have the greatest inter-person variability and are considered to be unique identifiers of individuals (4). Taken together, much progress has been made in mapping the functional connectome in early human brain development; however, to date, little is known about whether and how functional brain network connectivity in these networks is linked to early affective, cognitive, and behavioral traits. This is a particularly important question considering that many mental health disorders are: (a) accompanied by alterations in functional connectivity and (b) are argued to have deep developmental origins (2, 19–21).

Infant and child temperament is considered to reflect robust, biologically-based individual differences in affective and behavioral traits (22) linked to adult personality traits and long-term developmental outcomes (23–26). More specifically, profiles of temperament such as high negative emotionality and low levels of regulatory behaviors are considered early indicators of mental health disorders (26–31). To date, a host of studies in the adult literature have shown that high negative emotionality (and specifically high levels of neuroticism), low levels of regulatory functioning, and associated mental health outcomes are characterized by: (1) hypoconnectivity within the fronto-parietal network (FPN; composed of regions in the anterior cingulate cortex, dorsolateral prefrontal cortex, and parietal cortex) implicated in the cognitive control of attention and emotion (2) hyperconnectivity within the default mode network [DMN; composed of regions in the medial prefrontal cortex (mPFC), the precuneus, the posterior and anterior cingulate cortex, the inferior parietal cortex, and the lateral temporal cortex] involved in internally-oriented thought, mind-wandering, social cognition and (3) hypoconnectivity within the homologous-interhemispheric network (HIN; examining cross-hemispheric connections between frontal, temporal, and parietal lobes) involved in emotion regulation (2, 32–36). Considering these alterations in functional connectivity associated with adult personality traits and the possibility that they might have their origins in early human brain development, it is important to examine variability in these brain networks and how this links to individual differences in affective and behavioral traits.

Therefore, the current study followed two major goals. First, we aimed to identify and map individual variability in the three functional brain networks (FPN, DMN, HIN) in young infants using functional near-infrared spectroscopy (fNIRS). FNIRS is a non-invasive, portable, and safe, optical neuroimaging technique for assessing functional connectivity in cortical brain networks during infancy [see the following papers for other examples of functional connectivity analysis using fNIRS with infants (37–39)]. To capture functional connectivity patterns in young infants using fNIRS, we pre-defined the following three long-range brain networks including available channels in specific frontal, temporal, and parietal regions: (1) the FPN was created by measuring functional connectivity between the dorsolateral prefrontal cortex and inferior parietal cortex; (2) the DMN was created by measuring functional connectivity between the lateral temporal cortex and medial prefrontal cortex (note that our probe layout did not allow us to measure activity from superior parietal cortical regions including the precuneus, which is typically included in the DMN); and (3) the HIN was created by measuring functional connectivity between homologous cross-hemispheric connections in frontal, temporal, parietal cortex. In addition, based on previous work measuring functional connectivity using fNIRS in adults (40), we created a so-called control network, computing functional connectivity between left frontal cortex and right temporal cortex and right frontal cortex and left temporal cortex. This served as a non-functional control network, because these regions are not known to have any functional associations and show much lower levels of functional connectivity than established functional brain networks (40). We hypothesized that functional connectivity within the three functional brain networks (FPN, DMN, and HIN) will be significantly greater than in the control network, attesting to the existence of these long-range cortical networks in young infants. In this context, it is important to mention that, to our knowledge, there is no prior work demonstrating long-range functional connectivity in FPN and DMN in newborns and 1-month-old infants (14, 17), whereas functional connectivity in HIN has been shown to exist in the fetal brain (13).

Critically, we also examined whether and how variability in functional brain network connectivity maps onto individual differences in infant temperament, which can be readily and reliably assed through parental report (22). Brain networks assessed during the first few weeks of life have been linked to behavioral temperament 6 months later (41, 42). In addition, previous work with older infants has shown that the networks of interest in the present study appear to be supporting negative emotionality and regulatory functioning already in the first

year of life. For example, a study of 5 to 6-month-old infants found that the DMN (indexed by the medial Prefrontal Cortex response) and FPN (indexed by the dorsolateral Prefrontal Cortex response) are already involved in regulatory functions, such as switching between self- oriented and other-oriented thought (43). Moreover, 6- to 12-month old infants who displayed greater DMN functional connectivity showed greater negative emotionality (44). Finally, a structural fMRI study found that the length of the corpus callosum (thought to underly the homologous-interhemispheric network) was negatively associated with emotional control problems at 4 years of age (45). However, to our knowledge, no prior work has examined the concurrent relation between behavioral temperament and functional brain connectivity in infants younger than 5 months of age. Specifically, we focused our investigation on three critical dimensions of infant temperament (regulation/orienting, negative emotionality, positive emotionality/surgency), which have been previously identified in a factor analysis (46). Based on prior work with adults and with older infants linking functional connectivity in FPN to cognitive control of attention and behavior (2, 33, 34, 47, 48), we hypothesized that infants' regulation/orienting behaviors will be associated with functional connectivity in the FPN with greater connectivity in this network being linked to enhanced regulation and orienting. In contrast, we predicted the opposite pattern of association for the DMN, whereby lower connectivity is hypothesized to be linked to enhanced regulation based on prior work on DMN function with older infants and adults (2, 33, 34, 44, 48). Moreover, we expected that infants' reduced functional connectivity in the HIN will be linked to higher levels of negative emotionality, based on previous findings linking reduced cross-hemispheric connectivity to negative emotionality and related mental health outcomes in infants and adults (33–36, 45). Critically, in our analysis, we expected to see these predicted associations only for the specific functional networks and not for the (non-functional) control network. Finally, considering that there is little work informing how surgency/positive emotionality is linked to network connectivity, we did not have a specific hypothesis regarding this trait, but still included it in our analysis because surgency/positive emotionality has been identified as an important factor in previous work (46). Together, the current study presents a systematic examination of functional connectivity in long-range brain networks and its links to behavioral temperament in a sample of young, healthy, infants.

MATERIALS AND METHODS

Seventy-five newborn and 1-month-old infants (*M* [age] = 25 days; *Median* [age] = 24 days; ranging from 9 days to 56 days; 32 females; 43 males) were included in the final sample used for the present analyses (see **Table 1** for a description of the socio-demographic characteristics for the present sample). Participants were recruited from a local hospital. The diverse sample of infants were representative of the surrounding Mid-Atlantic college town area such that the majority of infants were Caucasian ($n = 50$ Caucasian; $n = 14$ Black; $n = 3$ South Asian; $n = 3$ Pacific Islander; $n = 2$ Asian; $n = 3$ Other), from highly-educated parents ($n = 31$ obtained a Graduate Degree; $n = 19$ Bachelor's Degree; $n = 12$ some College/Associates Degree; $n = 11$ High School Diploma/GED; $n = 2$ some High School), and low to medium-income families ($n = 21$ \$15–45,000; $n = 18$ \$75–110,000; $n = 11$ \$45–75,000; $n = 11$ \$110–175,000; $n = 8$ \$175,000+; $n = 5$ less than \$15,000; $n = 1$ did not respond). All participants were born at term, with normal birth weight (>2,500 g), and did not have any hearing or visual impairments. Thirty-three additional infants were tested but were excluded from the present analyses for the following reasons: $n = 25$ were excluded because they failed to reach our pre-determined inclusion criterion of having at least 100 s of continuous data with non-disruptive behaviors (see below); $n = 4$ were excluded because of inaccurate placement of the cap; $n = 4$ were excluded because more than 33% of the measured fNIRS channels had poor light intensity readings, more specifically, a signal-to-noise ratio of less than 1.5 (37, 50). Note that the current attrition rate (30%) is lower than in previous infant fNIRS studies (51). Moreover, temperament profiles (negative emotionality, regulation/orienting, and surgency/positive emotionality) were compared using independent samples *t*-tests between infants that were included and excluded from the present analyses and no significant differences were found between the two groups (all *p-values* > 0.29). All parents gave informed consent for their infants to participate in accordance with the Declaration of Helsinki and families received a payment for their participation. All procedures were approved by and carried out in accordance with The University of Virginia Institutional Review Board for Health Sciences (Protocol number 20381).

Infant Temperament

Infant temperament was assed using parental reports of the 91-item Infant Behavior Questionnaire Revised Short Form [IBQ-R; (46)]. Parents filled out the questionnaire online using Qualtrics survey platform prior to their appointment. This measure has been widely used and shown to be reliable and valid at the newborn time point [see the following papers for examples of prior work using this measure with newborns (52–54)]. The questionnaire asks parents to report their infant's behavior during the previous 2 weeks and rate the occurrence/frequency of the behavior on a 1 (Never) to 7 (Always) scale. Based on prior work using factor analysis (46), three general temperament dimensions were computed summarizing information from various sub-scales: (1) negative emotionality (contributing sub-scales: fear, distress to limitations, falling reactivity, sadness), (2) regulation/orienting (contributing sub-scales: low intensity pleasure, cuddliness, duration of orienting, soothability), and (3) surgency/positive emotionality (contributing sub-scales: activity level, smiling and laughing, high intensity pleasure, perceptual sensitivity, approach, vocal reactivity) (46). If parents reported the behavior was not applicable at the current time then this item was given a value of 0. Chronbach's alpha coefficients were calculated to determine reliability of the temperament measures and all values were in acceptable ranges for each of the three dimensions: surgency/positive emotionality $\alpha = 0.78$, regulation/orienting $\alpha = 0.78$, and negative emotionality $\alpha =$

TABLE 1 | Socio-demographic information for the present study sample ($N = 75$).

Socio-demographic information		Mean/Count (SD/%)
Infant Age at data collection, days		25.33 (10.10)
Female, *n*		32 (42.7%)
Race, *n*	White	50 (66.7%)
	Black	14 (18.7%)
	South Asian	3 (4.0%)
	Pacific Islander	3 (4.0%)
	Asian	2 (2.7%)
	Other	3 (4.0%)
Birthweight, grams		3459.36 (460.30)
Vaginal Delivery, *n*		56 (74.7%)
Breastfeeding, *n*		56 (90%)
Income, *n*	Less than $15,000	5 (6.8%)
	$15,001 to $30,000	10 (13.5%)
	$30,001 to $45,000	11 (14.9%)
	$45,001 to $60,000	8 (10.8%)
	$60,001 to $75,000	3 (4.1%)
	$75,001 to $90,000	9 (12.2%)
	$90,001 to $110,000	9 (12.2%)
	$110,001 to $125,000	3 (4.1%)
	$125,001 to $175,000	8 (10.8%)
	$175,001 to $225,000	5 (6.8%)
	$225,001 to $275,000	1 (1.3%)
	$275,001+	2 (2.7%)
Maternal Education	Some High School	2 (3%)
	High School Diploma/GED	11 (18.0%)
	Some College/Associates	12 (16.0%)
	Bachelor's Degree	19 (25.3%)
	Graduate Degree	31 (41.3%)
Maternal Depression		10.92 (3.16)

Maternal depression was assessed using the Edinburgh postnatal depression scale (49). Infants whose parent reported breastfeeding at any amount were considered breastfed.

0.91. Finally, correlation analyses between Edinburgh Postnatal Depression Scale scores [assessed at the same time as behavioral temperament; (49)] and behavioral temperament scores were conducted in order to statistically account for any variance in maternal-reported behavioral temperament that may be related to maternal mental health. Here, we did not find any significant associations (all *p-values* > 0.24). Therefore, maternal depression was not used as a covariate in later analyses.

Procedure

The resting state fNIRS task took place in a quiet, dimly-lit testing area. Infants were seated on their parents' lap and placed ∼60 cm from the screen (23-inch monitor). The infants were fitted with a fNIRS fabric cap (EasyCap, Germany) which was secured in place using infant overalls and outside netting. The experimental paradigm was presented using the Presentation software package (Neurobehavioral Systems, USA). A non-social stimulus was created by selecting non-social clips from a popular infant video (Baby Einstein - Kids2 Inc.) that featured videos of toys, stuffed animals, and still images of everyday objects, which was accompanied by classical music (55). Similar screen-saver-like videos have been used in prior work examining functional connectivity using fNIRS [see (38)]. This video was played for a total of 7 min while fNIRS data were being recorded. The clips were segmented into 30 s intervals and the order of presentation was randomized for each infant. Parents were asked to remain quiet throughout the fNIRS recording session. Sessions were video-recorded using a camera mounted above the screen. This allowed for later offline coding of infants' alertness and cap placement.

Data Acquisition

Infants' fNIRS data were recorded using a NIRx Nirscout system and NirStar acquisition software. The fNIRS method quantifies concentration changes of oxygenated hemoglobin (oxyHb) and deoxygenated hemoglobin (deoxyHb) in the cerebral cortex through shining specific frequencies of light that are selectively absorbed by these chromophores [for more information regarding this technique see (56)]. The fNIRS system used contains 16 source-detector pairs (∼2.0 cm apart) resulting in a total of 49 channels positioned over frontal and temporal-parietal regions [see (57–60) for infant work using the identical channel positioning/layout]. The system emits two wavelengths of light in the Near-Infrared spectrum, 760 and 850 nm, and captures both deoxyHb and oxyHb. The diodes have a power of 25 mW/wavelength and data were recorded at a preset default sampling rate of 3.91 Hz.

Behavioral Coding

Infants' behavior during the fNIRS recording session was coded by a trained research assistant using video recordings of the experimental session. Specifically, coders identified timepoints where the parents were talking and where the infants were crying, excessively moving, or looking at the parents. These periods were then removed from the analysis. To assess the reliability of the attentional coding done by the primary coder, an additional trained coder also coded infant behavior from selected subsample of infants (25.3%; $n = 9$). This analysis showed that inter-rater reliability for amount of data included was excellent (Cronbach's $\alpha = 0.94$). In line with previous studies, infants were only included in the present analysis if they had at least 100 s of disruption-free (see aforementioned behaviors) data (37). Moreover, as it takes a minimum of 8 s for the Hemodynamic response function to return to baseline after a stimulus-evoked event, the onset of useable data was delayed for 8 s (37, 38). However, unlike Bulgarelli et al. (37, 38), the time series of fNIRS obtained in the current study was continuous. On average, infants contributed 317.59 s of data ($SD = 115.46$ s; range = 100–420 s). Furthermore, the amount of data included in the current analysis is comparable to other functional connectivity work using fNIRS with older infants (38). In addition, we coded infants' state of alertness on a 1 (Deep Sleep) to 6 (Crying) scale. On average infants were rated as being in an Active Light Sleep to Drowsy State ($M = 2.68$, $SD = 1.27$). Finally, we assessed how infants' behavior throughout the session, specifically the amount

of useable data related to functional network connectivity in each of the networks (see **Supplementary Material**).

Data Analysis

The fNIRS data were analyzed using the functional connectivity program, FC-NIRS (50). First, channels were assessed for light intensity quality and channels were removed if the signal-to-noise ratio was less than 1.5 (50). In order to be included in the present analyses, infants needed to have at least 70% of their channels passing this threshold (37). Next, data were band-pass filtered [using a 0.08 Hz low-pass filter, to remove fast fluctuations related to heart rate, and a high-pass filter of 0.01 Hz, to remove changes that were too slow and related to drift; (37, 61)]. This range of 0.01 to 0.08 Hz was chosen on the basis of prior work (37, 40). This range was also selected because it falls well below the reported range for cardiac fluctuations (greater than 1 Hz), providing us with greater confidence that the measured changes reflect hemodynamic events tied to cortical activity rather than (systemic) cardiovascular system activity [e.g., heart rate (62, 63)]. Finally, concentration changes were calculated using the modified Beer-Lambert law (partial path length factor: 6.0) (64).

For each infant, we obtained a 49 by 49 correlation matrix corresponding to all of the relations between all of the channels measured. Considering that negative values are difficult to interpret in terms of their neurobiological basis, and based on prior work, we first checked data to see if there were any negative values and found out there were none (65, 66). In order to standardize the values, Fisher Z-transformations were performed on all correlation matrices. Networks of interest were created by selecting channels that corresponded to specific regions of interest. Brain networks were composed based on the anatomical information available in Kabdebon et al. (67), a meta-analysis of resting state fMRI (2), a large resting state fMRI functional connectivity analysis of newborn infants (68), and prior work infant and adult work using rs-fNIRS (35, 38, 40, 69). Based on this information four networks were created: (1) The FPN was created by averaging all correlations between three channels in the dorsolateral prefrontal cortex (corresponding with the F3, F4, F5, F6 electrodes) and two channels in the parietal area (corresponding with CP3 and CP4 electrodes); (2) The DMN was created by averaging all correlations between three channels in the medial prefrontal cortex (corresponding with the Fpz electrode) and four channels in the lateral temporal cortex (corresponding with FT7, T7, FT8, T8 electrodes); (3) The HIN was created by averaging all correlations between the 21 channels in the left hemisphere (including frontal, temporal, and parietal cortical regions) with their corresponding (homologous) channels in the right hemisphere; and, (4) a (non-functional) control network was created by averaging all correlations between three channels in the left frontal area (corresponding with the F7 electrode) with three channels in the right temporal area (corresponding with the T8 electrode) and three channels in the right frontal area (corresponding with F8 electrode) with three channels in the left temporal area (corresponding with the T7 electrode; see **Figure 1** for schematic of network configurations). Cortical projections onto a standard MNI newborn (0–2 months old) atlas (70) were created using NIRSite (Nirx) by using 10-20 system references from the cap layout.

All analyses were conducted for both oxyHb and deoxyHb (for deoxyHb results please see **Supplementary Material**). Moreover, statistical outliers—values that were more than 3 SD above the mean—were removed for the subsequent analyses (FPN $n = 2$, negative emotionality $n = 1$).

RESULTS

A series of Spearman's rho correlations were used to identify significant associations between variables of interest and potential socio-demographic factors (for a schematic representation for all associations see **Supplementary Figure 1**). Any demographic variables found to be significantly associated with a study variable of interest were then included in the subsequent models assessing differences in said study variable as a covariate. Negative Emotionality was significantly associated with both infant age (Spearman's rho correlation $r_s = 0.47$, $p < 0.001$) and family income (Spearman's rho correlation $r_s = 0.29$, $p = 0.011$). Regulation/orienting was significantly associated with Education (Spearman's rho correlation $r_s = -0.30$, $p = 0.009$). However, there were no significant associations found between any of the functional connectivity measures and any of the covariates.

Similarly, we tested for associations between alertness levels, amount of usable data collected during the fNIRS testing session, and the study variables of interest. Here, we found that the level of alertness was negatively related to functional connectivity levels in the three networks of interest (HIN $r_s = -0.27$, $p = 0.021$; FPN rs $= -0.38$, $p < 0.001$; DMN $r_s = -0.30$, $p = 0.008$). This analysis also revealed that the amount of data included was positively associated with connectivity for the DMN ($r_s = 0.27$, $p = 0.020$) and negatively associated with behavioral temperament (negative emotionality $r_s = -0.27$, $p = 0.022$; regulation/orienting $r_s = -0.24$, $p = 0.041$). Additional analyses with alertness and amount of data as covariates can be found in the **Supplementary Material**.

Functional Connectivity Across Networks

As a first step, a series of one-sample *t*-tests were conducted to assess whether Fisher-transformed correlation between individual channels within the pre-defined networks of interest differed from zero. As shown in **Figure 2**, this analysis identified significant functional connectivity between individual channels within the pre-defined networks of interest (see **Supplementary Table 1**). Next, we conducted a series of one-sample *t*-tests to assess connectivity at the network level (combining across all channels of interest). Here, all networks (FPN, DMN, HIN, control) were found to be greater than zero [FPN, $t_{(72)} = 9.07$, $p < 0.001$, *q-value* < 0.001; DMN, $t_{(74)} = 6.88$, $p < 0.001$, *q-value* < 0.001; HIN, $t_{(74)} = 9.43$, $p < 0.001$, *q-value* < 0.001; Control, $t_{(74)} = 3.86$, $p < 0.001$, *q-value* < 0.001; see **Figure 3**). To analyze differences in overall connectivity levels across networks an omnibus repeated measures ANOVA with network type (FPN, DMN, HIN, control) as a within-subjects factor was conducted. This analysis revealed a significant

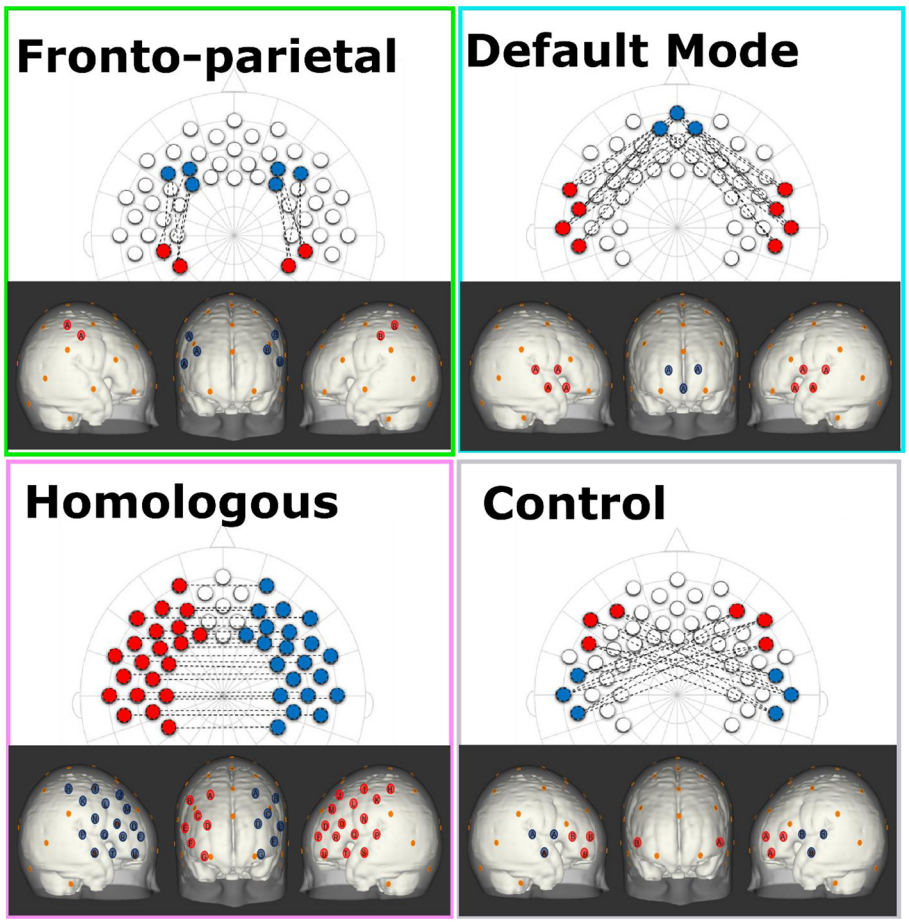

FIGURE 1 | This figure shows the configurations for each of the network patterns in both a 2-dimensional 10-20 system layout and estimated projections onto cortical space of a 0–2 month-old Atlas (70). Each network consists of the average of all of the connections between red and blue channels of the same letter. In addition, the orange dots represent relevant 10-20 landmarks.

within-subjects effect across network types, $F_{(3, 216)} = 18.78$, $p < 0.001$, $\eta^2 = 0.207$. *Post-hoc* analyses with Bonferroni adjustments for multiple comparisons were conducted to assess which networks significantly differed from one another. Importantly, all functional networks of interest had significantly higher connectivity than the (non-functional) control network [$M = 0.05$; $SD = 0.12$; range: −0.20–0.44; HIN vs. Control $t_{(74)} = 5.06$, $p < 0.001$; FPN vs. Control, $t_{(72)} = 6.11$, $p < 0.001$; DMN vs. Control, $t_{(74)} = 4.15$, $p < 0.001$]. In addition, we found that there was significantly greater connectivity in the FPN ($M = 0.21$; $SD = 0.20$; range: −0.16–0.72) compared to both the HIN ($M = 0.13$; $SD = 0.12$; range: −0.12–0.48), $t_{(72)} = 3.63$, $p = 0.003$, and the DMN ($M = 0.13$; $SD = 0.16$; range: −0.28–0.73), $t_{(72)} = 3.63$, $p = 0.010$. However, there was no significant difference found between the level of connectivity for the HIN from the DMN, $p = 1.00$ (see **Figure 3**).

Functional Connectivity and Behavioral Temperament

In order to assess how functional connectivity patterns differentially predicted temperament characteristics, three separate regressions with all four network types (FPN, DMN, HIN, control) predicting each of the three domains of temperament (negative emotionality, regulation/orienting, surgency/positive emotionality) were conducted.

Regulation/Orienting

A multiple linear regression using the entry method was conducted with the socio-demographic covariate (education) and four network types (FPN, DMN, HIN, control) as the predictors and regulation/orienting as the outcome variable. The regression model was statistically significant, $F_{(5, 72)} = 4.84$, $p = 0.001$, $R^2 = 0.27$. More specifically, connectivity in the DMN was negatively associated with regulation/orienting ($B = -1.02$, $SE = 0.42$, $p = 0.018$, *q-value* $= 0.054$); whereas, connectivity in the FPN was positively associated with regulation/orienting ($B = 0.71$, $SE = 0.35$, $p = 0.049$, *q-value* $= 0.074$; see **Figure 4**). Neither the HIN nor the Control network were found to be related to regulation/orienting, all *p-values* > 0.24.

Negative Emotionality

A multiple linear regression using the entry method was conducted with the socio-demographic covariates (age, income) and four network types (FPN, DMN, HIN, control) as the predictors and negative emotionality as the outcome variable. The regression model was statistically significant, $F_{(6, 64)} = 5.50$, $p < 0.001$, $R^2 = 0.34$. More specifically, we found a significant positive relation between HIN connectivity and negative emotionality, ($B = 1.60$, $SE = 0.75$, $p = 0.038$, *q-value* $= 0.114$; See **Figure 5**). However, none of the other networks

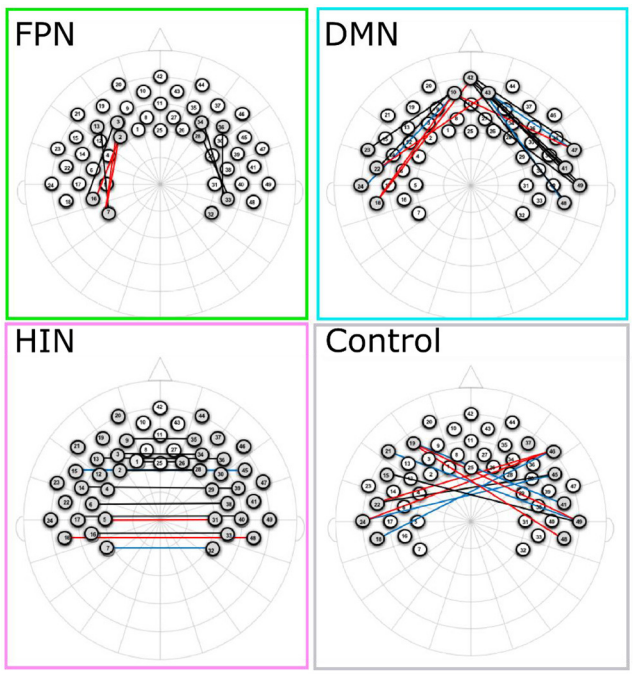

FIGURE 2 | This figure shows the channels that are significantly different than zero for each of the networks. Channels in red, blue, and black represent significant changes for oxyHb, deoxyHb, and both oxy and deoxyHb respectively.

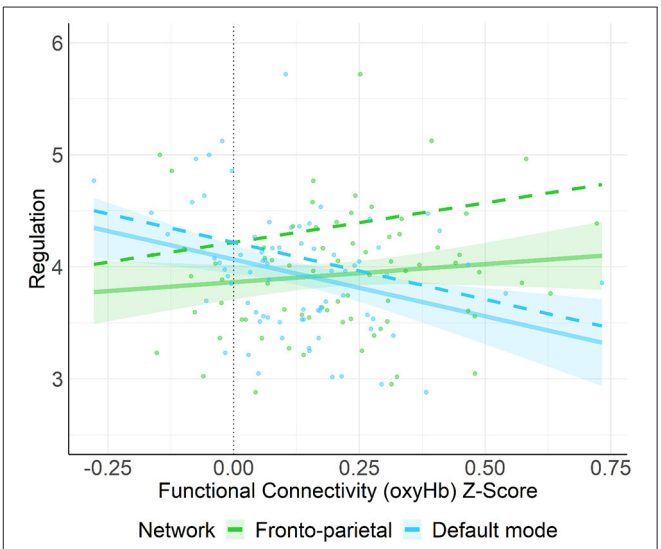

FIGURE 4 | This figure shows the unadjusted (solid line) and adjusted relation (covariates not shown: HIN, Control, maternal education) between functional connectivity (oxyHb) Z-score and regulation/orienting. Here, we found that connectivity in the FPN was positively associated with regulation/orienting ($p = 0.049$) whereas, connectivity in the DMN was negatively associated with regulation/orienting ($p = 0.018$). Shaded regions represent 90% confidence intervals for the raw (unadjusted) data.

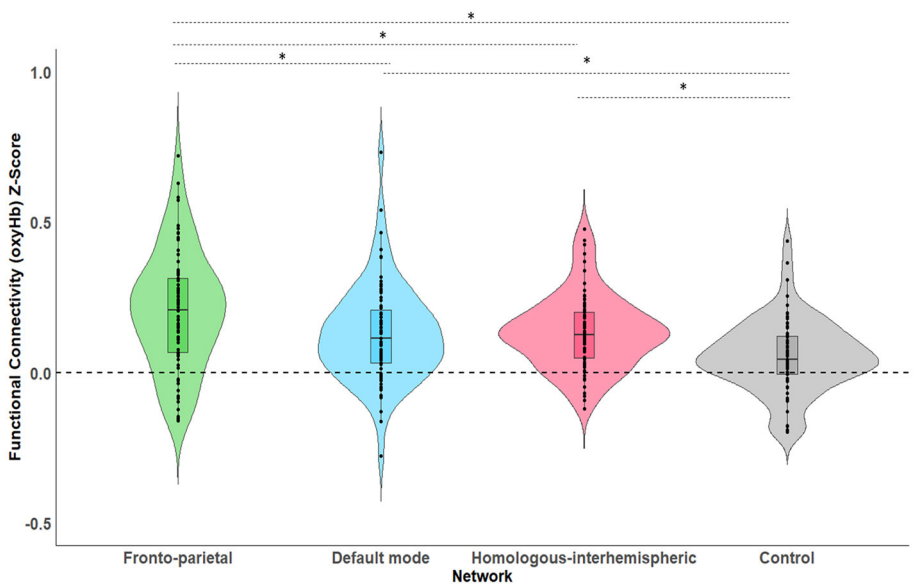

FIGURE 3 | This figure shows the average levels of functional connectivity (oxyHb) and range of variability for each network. The boxplot horizontal lines from bottom to top reflect values for the lower quartile, median, and upper quartile respectively. *$p < 0.05$.

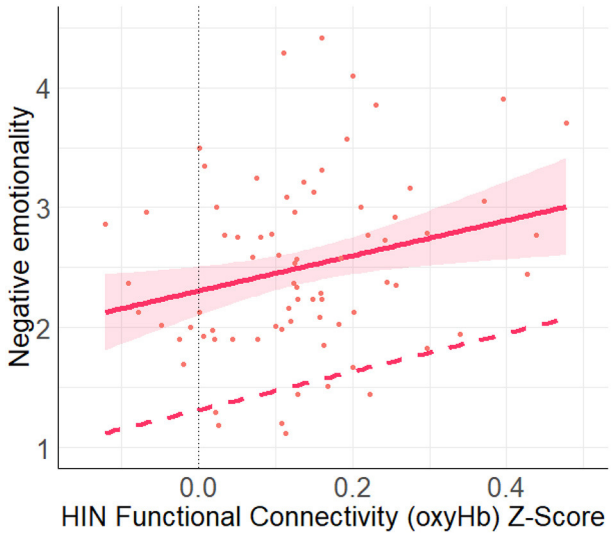

FIGURE 5 | This figure shows the unadjusted (solid line) and adjusted relation (covariates: FPN, DMN, Control, income, age) between HIN functional connectivity (oxyHb) Z-score and negative emotionality. Here, we found a significant positive relation between the HIN and negative emotionality ($p = 0.038$). Shaded regions represent 90% confidence interval for the raw (unadjusted) data.

(functional nor control) were found to be related to Negative Emotionality, all *p-values* > 0.57.

Surgency/Positive Emotionality

A linear regression was conducted with the four network types (FPN, DMN, HIN, control) predicting surgency/positive emotionality using the entry method. Here, the regression model was not statistically significant, $p = 0.39$. Moreover, none of the network types were significantly associated with surgency/positive emotionality (all p's > 0.14).

DISCUSSION

The current study examined functional connectivity in brain networks using fNIRS and behavioral temperament using parental report in young infants. Our results show that functional connectivity in long-range cortical brain networks (FPN, DMN, and HIN) can be identified in very young infants and that functional connectivity in these networks varied considerably among infants. This supports the suitability of fNIRS in assessing functional connectivity and its variability in newborn infants. Importantly, our results also show that such variability in functional brain network connectivity systematically maps onto individual differences in infant behavioral temperament. Overall, the current findings provide novel insights into the brain origins of individual differences in affect and behavior, pointing to the early perinatal foundation of human temperament.

In line with our hypothesis, functional connectivity within the three brain networks (FPN, DMN, and HIN) was significantly greater than in the control network and significantly greater than a zero-value, indicating the existence of these long-range cortical brain networks in young infants. This provides further evidence that functional brain networks exist from early in ontogeny and are detectable in young infants (12, 17, 71). To our knowledge, this is the first study to demonstrate long-range functional connectivity in FPN and DMN in young infants, suggesting a remarkably early emergence of long-range connectivity in higher-order brain networks linked to cognitive control and self-referential processes, respectively. The current findings are noteworthy also in regard to the fact that both networks involve regions in prefrontal cortex, providing new evidence from newborns and 1-month-old infants supporting the view that prefrontal cortex plays a critical role in human brain function from very early in development (14, 72–75).

In addition to the general difference in connectivity between the functional and the (non-functional) control network, we also found that activity in the FPN was significantly greater than in the DMN and HIN (whereas there was no difference in connectivity levels found between the DMN and HIN). One possible interpretation of this finding is that functional connectivity in the FPN might have been enhanced when compared to the other functional networks because, like other resting-state studies with infants, the participants were presented with a video accompanied by music during the fNIRS measurement (37). In other words, the FPN might have been more engaged because infants were attending to external audio-visual stimuli [note that all infants were exposed to the same video (audio-visual) stimulus]. Here, it is important to mention that prior work with adults using fMRI shows that functional connectivity in higher-order cortical resting-state networks can be reliably acquired during the presentation of videos and corresponds to functional connectivity acquired in the absence of any stimulus (4, 76). Nonetheless, based on recent work showing that preterm infants display enhanced functional connectivity in higher-order cognitive networks in response to music (55), we speculate that enhanced functional connectivity in FPN might at least be partly explained by having newborn infants listen to music in the current study. Clearly, future research with infants which systematically compares stimulation protocols is needed to examine whether and how functional connectivity is influenced by the measurement context and the stimulation protocol used. Overall, our functional connectivity analysis supports the notion that intrinsic functional connectivity in cortical brain networks and its variability can be effectively mapped in newborn infants using fNIRS.

Having established functional connectivity in these brain networks as variable and distinct from a (non-functional) control network then allowed for the examination of specific associations between brain network connectivity and infant behavioral temperament. Our results confirmed our hypothesis and showed that infants' regulation/orienting behaviors were associated with functional connectivity in the FPN with greater connectivity in this network being associated with enhanced regulation and orienting. This result is in line with prior work linking functional connectivity in FPN to cognitive control of attention and behavior in adults (2, 48) and more recent work with infants (43). The current results further showed the opposite pattern of association for functional connectivity in DMN, with

greater connectivity associated with reduced regulation and orienting, which is in agreement with our hypothesis based on the DMN previously being linked to self-referential, stimulus-independent thought and mind-wandering in adults (2, 48) and infants (43). To obtain such opposing effects of functional connectivity in FPN and DMN is reminiscent of seminal findings supporting the existence of anti-correlated brain networks in adults (77) and may suggest that similar organizational principles are at play in newborn infants. However, it should be emphasized that functional connectivity in the FPN and DMN in the current study was not anticorrelated as such, but rather had opposing effects on infants' behavioral and attentional regulation.

Our results concerning behavioral and attentional regulation and their functional connectivity correlates in infants are principally in line with prior research showing hyperconnectivity in the DMN and hypoconnectivity in the FPN in adults with negative emotionality and related mental health outcomes (33, 34, 48). Moreover, our data show that infants' functional connectivity in the HIN was associated with negative emotionality. Contrary to prior work with adults indicating that hypoconnectivity is associated with negative emotionality and depression (33, 35, 36) and work with infants indicating that corpus callosum length (thought to underly the HIN) is negatively associated with later emotion regulation abilities (45), the current infant data show that greater connectivity between homologous brain regions in both hemispheres was associated with greater negative affect. It is unclear why the direction of the association (positive vs. negative) would differ as a function of age (newborn infants in the current study and preschool aged and adults in previous work), but it is worth noting that the experience and display of negative affect only gradually emerges during infancy and may thus not be fully present in newborn infants (53).

Taken together, the current findings demonstrate specific associations between functional brain network connectivity and behavioral temperament in newborn infants. This suggests a remarkably early emergence of functional networks with behavioral relevance and highlights the importance of evaluating individual differences reflected in intrinsic brain connectivity. Although there are many advantages in the current approach of using fNIRS to examine functional brain connectivity, including its cost-effective and non-confining application, there are some limitations that need to be mentioned. First, because fNIRS is limited in monitoring activity from (superficial) cortical structures (78), our approach did not allow us to measure activity from deeper cortical and subcortical regions and include those in our network analyses. Second, from a developmental perspective, it should be noted that our analysis is limited to only one age group and comprised of very young infants. It is thus critically important to further assess the development of variability in these brain networks and their associations with behavioral temperament over developmental time to determine its long-term effects and the robustness of these associations (69). Third, it is important to note that these associations were assessed in a population of healthy infants, meaning there were no known birth or health complications at the time of the visit. Therefore, given the breadth of work examining how preterm birth and other medical complications (e.g., hypoxia) impact brain development, it will be important to test whether or not these associations generalize to other populations (16, 79, 80).

In conclusion, the current study provides novel insights into the use of fNIRS in identifying neural endophenotypes—variability in functional brain network connectivity—linked to behavioral temperament traits in early human development. The present findings support the notion that functionally distinct neural networks are implicated in regulatory and emotional behaviors already in newborn infants, adding a critical developmental component to efforts directed at mapping how the individual functional connectome links to affective, cognitive, and behavioral traits. The current findings shed light on the brain origins of individual differences in early-emerging behavioral traits and provide the basis for future research examining the genetic and environmental factors contributing to and the long-term developmental consequences of this brain-behavior correlation. More generally, the current study provides early ontogenetic evidence for the idea that studying functional brain network connectivity is an effective way in helping bridge the gap between brain and behavior.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Virginia Institutional Review Board for Health Sciences (Protocol number 20381). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CK and TG contributed to conception and design of the study, and wrote the first draft of the manuscript. CK and KF collected the data. CK performed the statistical analysis. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.685754/full#supplementary-material

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Maternal Bonding in Early Infancy Predicts Childrens' Social Competences in Preschool Age

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Background: There are many studies on mother-child-bonding with little theoretical doubt that better bonding may have a positive effect on further social development. However, there is hardly any empirical evidence. In particular, there is a lack prospective longitudinal studies.

Methods: As part of a longitudinal study, bonding was assessed in a community sample of 97 healthy mothers using the Postpartum Bonding Questionnaire (PBQ) 6 weeks after birth of their child. Social competencies in the offspring were assessed using the Self- and Other-oriented Social Competencies (SOCOMP) at 5.5 years of age. A potential correlation between bonding and social competencies was tested using Spearman Rank Correlation.

Results: Retention rate over 5.5 years was 77.23%. Lower Maternal Bonding Impairment Scores 6 weeks postnatally were positively related to childrens' social competences at 5.5 years of age.

Conclusion: The present data confirm a positive and long-term influence of bonding on social skills and provide further evidence of the importance of parent child bonding for child development in general. This result should give reason to further investigate this relationship in depth, causally and at later points in time.

Keywords: bonding, social competences, social skills, child development, longitudinal study

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INTRODUCTION

Bonding and early social experiences are assumed to be associated with a more healthy social and emotional development, to protect against stress and make children more resilient (1). Bonding is defined in developmental psychology as the emotional connection from parents to their children, in contrast to attachment, which is the emotional connection of the child toward its caregiver. The opportunity for the development of bonding is assumed to have its peak in the 1st min and hours after birth, especially in the close physical contact and the reactions of the helpless infant seeking comfort, protection, warmth and nourishment from the parents' behavior (2–4). This first phase is also postulated to be the "sensitive period" and to equally occur in most mammals (5). Newborns, placed on the mother's abdomen, can instinctively locate and suckle the maternal breast without assistance in their 1st hour of life via their sense of smell/pheromones (6–9).

Undoubtedly, mothers have a large part in establishing social contact with their infant (10), but the newborns are able to interact with her via eye contact, body language and thus in turn elicit linguistic utterances (11). The lack of skin contact with the mother in the first 2 hours after birth

alone causes the infant's body temperature to be lower (12). After 1 year, according to Parent-Child-Early Relational Assessment (PCERA) video analyses, the infants tended to be more dysregulated and irritable, their social interactions with mothers were less substantial (also in terms of reciprocal emotional response) (13).

Mothers and infants with 16 h more physical contact shortly after birth showed more reluctance to leave their baby with another person compared to the control group about 4 weeks later during a standardized interview, a medical examination of the baby and a recorded bottle feeding (14). These mothers watched and mostly stood during the examination, tried to calm their infants more, performed more stroking and expressed significantly more eye contact. There have been numerous studies documenting positive and negative effects of a lack of mother-infant (skin) contact in the infant's 1st h (15). Not only was the body and skin temperature lower in children in cots compared to children with mothers, the glucose content in the blood was also lower and they cried and expended significantly more energy (16, 17). Even 20 min of skin contact was associated with a significant reduction in circulating beta-endorphin (18). After 4 postnatal hours, babies with increased physical contact show a majority of longer sleep, a calmer sleep state, more bending and fewer stretching movements (19). Babies who had a stable very low birth weight even showed improved lung function with direct contact in some cases (20).

Early maternal mind-mindedness ["to treat her infant as an individual with a mind rather than merely as a creature with needs that must be satisfied," (21)] also have been reported to be of influence on the social-cognitive development of her child, affecting the development of empathy skills (22). Social skills in turn, are described to be associated with mental and psychological health (23) as well as—in a negative association—with a wide range of disorders such as anxiety (24), blood pressure (25), substance abuse (26), and problem behaviors such as juvenile delinquency (27). High social skills, on the other hand, have been shown to lead to higher financial and professional success (28). Similar to bonding or also bonding vs. attachment (3) there is a definition and demarcation problem with social competences (e.g., on social skills) (29). According to the literature, studies for attachment and its influence on social competences could be found frequently (30–32), whereas there seems to be a lack of studies regarding bonding and its influence on social skills. It has been described however, that pet bonding of young children, in contrast to simple pet presence, has a positive effect on their social competences and empathy (33). With regard to the methodological problems, the advantages and disadvantages of sociometric or observed recording of social competences in children, we refer e.g., to Foster and Richey (34).

In their review, Alves et al. (35) concluded that a long separation from the mother triggers anxiety and depression—like symptoms in rodents—and is reflected qualitatively and quantitatively in maternal behavior. In a study on foals, separated from their mothers for 1 h, were less socially competent after 1 year, which corresponds to the prepubertal period of these animals. Additionally they were more aggressive and showed withdrawal tendencies (36).

So far however, there has been no study examining the impact of neonatal bonding on childrens' social competences in a prospective longitudinal design. Whether maternal bonding in the neonatal period is related to social competences of children at preschool age in humans is the subject of this study.

MATERIALS AND METHODS

Study Design

In the present study, mothers completed the Postpartum Bonding Questionnaire at 6 weeks after birth. At the age of 5.5 years, the social skills of her child were assessed with a standardized instrument, also based on the mother's assessment.

Participants

The voluntary sample recruited 2002 and 2003 by Möhler et al. (37) consisted of 101 healthy Caucasian mothers with singleton pregnancies. Inclusion criteria were infant weight over 2,500 g, gestational age $>$ 37 weeks, all APGAR scores $>$ 7 and, generally good health of the baby as evidenced by the first 3 postnatal examinations. The mothers were from urban and rural areas and have been recruited from 4 large local maternity units. Exclusion criteria were an inability to speak and read German, an acute psychiatric disorder of the mother, as well as the use of drugs or medication that pose a risk to the fetus, excessive smoking (more than 5 cigarettes/day) and alcohol consumption during pregnancy.

All participants read the participant information sheet and had the opportunity to ask questions. An informed consent form was read, signed and returned by all child custodians. All participants took part in the study voluntarily and could withdraw their participation at any time without giving a reason.

Of the original 101 mothers, 97 filled out the postpartum Bonding Questionnaire 6 weeks postnatally, 78 still responded after 5.5 years which corresponds to a response rate of 77.23%. This sample also had to be adjusted for 1 outlier and another case due a high number (more than 1 missing value) of missing values, so that the final sample is 76. If there was exactly 1 missing value in a questionnaire, the rounded individual subscale mean of the respective test has been used for this. This was necessary in 9 cases. The flow of participants can be found in **Table 1**.

TABLE 1 | Flow of participants.

	N	%
N T0	101	100
n T1	97	96.04
Responded and take part T2	78	77.23
Excluded as an outlier	1	0.99
Excluded due to too many missing values	1	0.99
Sample n T2	76	75.25

T0, prenatal; T1, 6 weeks after birth; T2, 5.5 years after birth.

Measures

The Postpartum Bonding Questionnaire (PBQ) (38) measures disturbances in the mother-child relationship based on self-report by the mother using a six-point Likert scale. The questionnaire, consisting of 25 items and 4 subscales (impaired bonding [12 items], rejection and anger [7 items], anxiety about care of the baby [4 items], risk of child abuse [2 items]) and a total score, has satisfactory interrater reliabilities (*Pearson's r* 0.95, 0.95, 0.93, 0.77), except for the 'risk of child abuse' scale. Similar in terms of sensitivity (0.93, 0.57, 0.43, 0.18, in severe cases sensitivity 1.0, 0.89, 0.56, 0.28). In its validation study (39), these values could be approximately replicated (0.82, 0.68, 0.61, 0.13, in severe cases 0.93, 0.88, 0.64, 0.2).

The Social Competences Inventory SOCOMP (40) captures self- and other-oriented social skills in both its parent/teacher version, which was used because of its low threshold, multidimensionality and suitability for the young children in this study, and its child version. Its 25 items, assignable to the 3 main dimensions of self-oriented social skills, other-oriented social skills and positive peer relationships, are based on already established instruments such as the "Strenghts and Difficulties Questionaire" (scales of prosocial behavior and problems with peers) (SDQ) (41) or "The Social Skills Rating System" (SSRS) (42). Self-oriented competencies, defined as achieving one's own goals and satisfying needs in social interactions, are assessed via 10 items, which can be further divided into the subscales leadership, setting limits and social participation. Other-oriented competences, defined there as the extent to which gratifications and the goals of others are taken into account at the same time, are also surveyed by 10 items and offer the subscales prosocial behavior and cooperative behavior. The remaining 5 items of the positive peer relationships scale measure peer relationship quality. All items are rated using a three-point Likert scale. The internal consistency of the items of the parent version is medium to high (43).

Statistical Analysis

The data were analyzed with IBM SPSS Statistics, version 26. Due to the non-normal distribution of the data (K.-S.-Test: PBQ $p < 0.001$; SOCOMP $p = 0.02$), a Spearman Rank Correlation was calculated. A significance level of 0.05 was used for all statistical tests.

RESULTS

Sample

Characteristics of the sample are presented in **Table 2**. The mothers were aged between 19 and 45 years ($M = 33.58$ years, $SD = 4.07$) at the first time of measurement, non-smokers, did not drink more than an occasional glass of wine or beer during pregnancy and had a term birth. The birth weight of the children ranged from 2,520 g to 4,500 g ($M = 3486.32$, $SD = 421.15$). 57.9% of the children were male, 42.1% female. All mothers were in a stable partnership with the child's father. 19.74% of them had a secondary school leaving certificate, 19.74% had a high school leaving certificate, 60.53% had a university degree and were thus educated above average.

TABLE 2 | Characteristics of sample ($n = 76$).

Characteristic	*M*	*SD*	Min.	Max.
Age of mothers in years T1	33.58	4.07	19	45
Birth weight child in grams	3486.32	421.15	2,520	4,500
Newborn gender	n	%		
Male	44	57.9		
Female	32	42.1		
School graduation (mother)	n	%		
Secondary school	15	19.74		
High school	15	19.74		
University	46	60.53		

T1, 6 weeks after birth.

Descriptive Analysis

Figure 1 shows the distribution of the total PBQ scores (M= 10.42, $SD = 7.01$) of the final sample. The auxiliary lines show that only 4 test persons meet or exceed the cut-off (purple line) of 26 for identifying some type of bonding disorder and no mother reaches the value of a maternal rejection (red line). **Table 3** illustrates that the cut-off was only exceeded in eight cases in the impaired bonding scale.

Distribution of data regarding social competences in preschool age can be seen in **Figure 2**. No child falls below the provisional cut-off value for the total score, the lower limit of which was determined on the basis that each item was agreed to at least proportionally and the upper limit of which reflects the top 10%. Two children lie exactly on the provisional cut-off value ($M = 38.29$, $SD = 4.41$). For the majority of the sample, the social competences are therefore adequate to well-developed. Here, too, it is worth considering the respective subscales (**Table 4**). While almost a quarter (23.68%) of the children have low self-oriented social competences and no child has conspicuously high values in this area, hardly one child (3.95%) has a low level of other-oriented social competences and 44.74% have high values. The results for peer relationships are even more positive. There, only 1 child has a low, but more than half (53.95 %) have satisfactory social competencies.

The mothers' physical and psychological symptoms, assessed at both time points by the Symptom Checklist 90 revised [SCL-90-R; original (44): german version (45)] showed a remarkably low level (Global severity index after 6 weeks: $M = 0.21$, $SD = 0.15$; after 5.5 years: $M = 0.17$, $SD = 0.18$), with regard to global severity index after 6 weeks only two mothers [T60 and T61], after 5.5 years only one mother [T65] scored above the cut off.

Correlation of Maternal Bonding With Social Skills

Even in this socially protected and well-adjusted sample, a Spearman Rank Correlation between the PBQ total scores and the SOCOMP total scores revealed a significant correlation (**Table 5**). High PBQ total scores (high bonding impairment) are therefore negatively related to SOCOMP total scores [$rs(74) = -0.31$, $p = 0.01$]. Less optimal mother-child bonding is shown to predict lower social skills in the child. According to Cohen

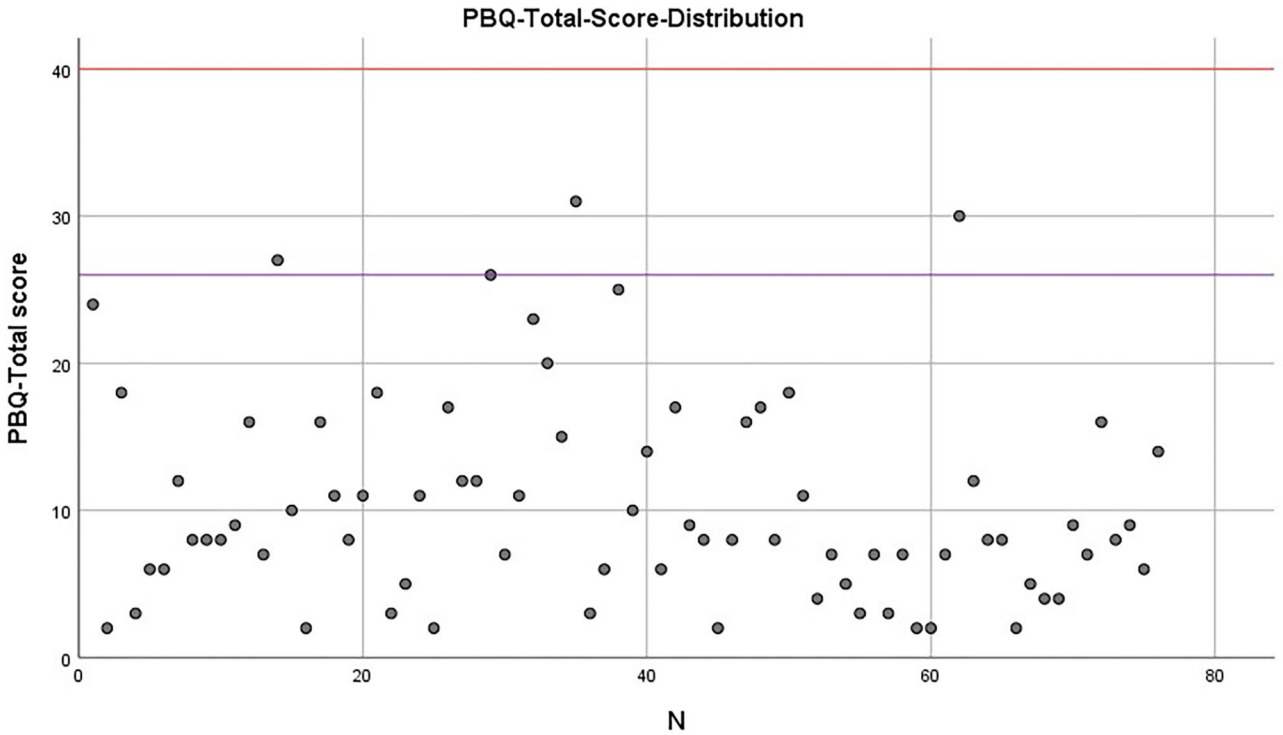

FIGURE 1 | PBQ total score distribution: 4 mothers score above the cut-off of 26 (significant bonding disorder) (purple line), no mother scored above the cut-off of 40 for maternal rejection (red line) ($n = 76$).

TABLE 3 | Descriptive statistics of PBQ results ($n = 76$).

	Total	Impaired bonding	Rejection and anger	anxiety about care of the baby	risk of child abuse
Items	25	12	7	4	2
M	10.42	5.86	2.11	2.33	0.13
SD	7.01	4.10	2.21	1.29	0.38
Minimum	2	0	0	0	0
Maximum	31	17	8	6	2
Cut-off	26 resp. 40	12	17	10	3
n > cut-off	4 resp. 0	8	0	0	0

(46), we are consequently in the range of a moderate correlation ($r = 0.30$).

DISCUSSION

Our data in a healthy community sample indicate an early influence of maternal bonding on childrens' social skills in preschool age. The mechanisms behind this association are presumed to be interactional, however a genetic contribution to this association cannot be excluded. Unfortunately, there are only a few long-term studies with humans, but most of them show positive effects of early maternal bonding (13, 14). Prospective longitudinal studies with humans are difficult, not only from an ethical point of view, but also in general in this area, as there are many influencing variables (e.g., social events, interactions, also with peers, psychopathology, substance abuse). Our sample tried to control these factors with strict inclusion criteria. Long-term studies with animals underline our data showing the negative aspects of a lack of bonding [e.g., on social behavior (36)], even if they are not easily transferable to humans (47).

Defining social competences is difficult. There are also advantages and disadvantages in methodological recording (34). In our case, they were assessed sociometrically and based on mothers' judgements. Self-assessments, which we could have compared, were not yet available in this age group and observations would only have been possible via excerpts. Of course, social skills are not only influenced by bonding, but also by a variety of other factors. Dodge (48) considers social skills as an interaction between biologically determined abilities and environmental factors. On the side of biological factors temperament (49), temperamental surgency and emotion regulation (50) in particular but also malnutrition (51, 52) and genetic influences (53). On the environmental side especially culture (54) and family factors (e.g., involvement, communication, supportive Relationships, enable relationships (55, 56), psychopathology (57), maltreatment (58), single-parent and socioeconomic status (59).

Like social skills, bonding is also influenced by a number of different factors [e.g., parental behavior, nutrition (60),

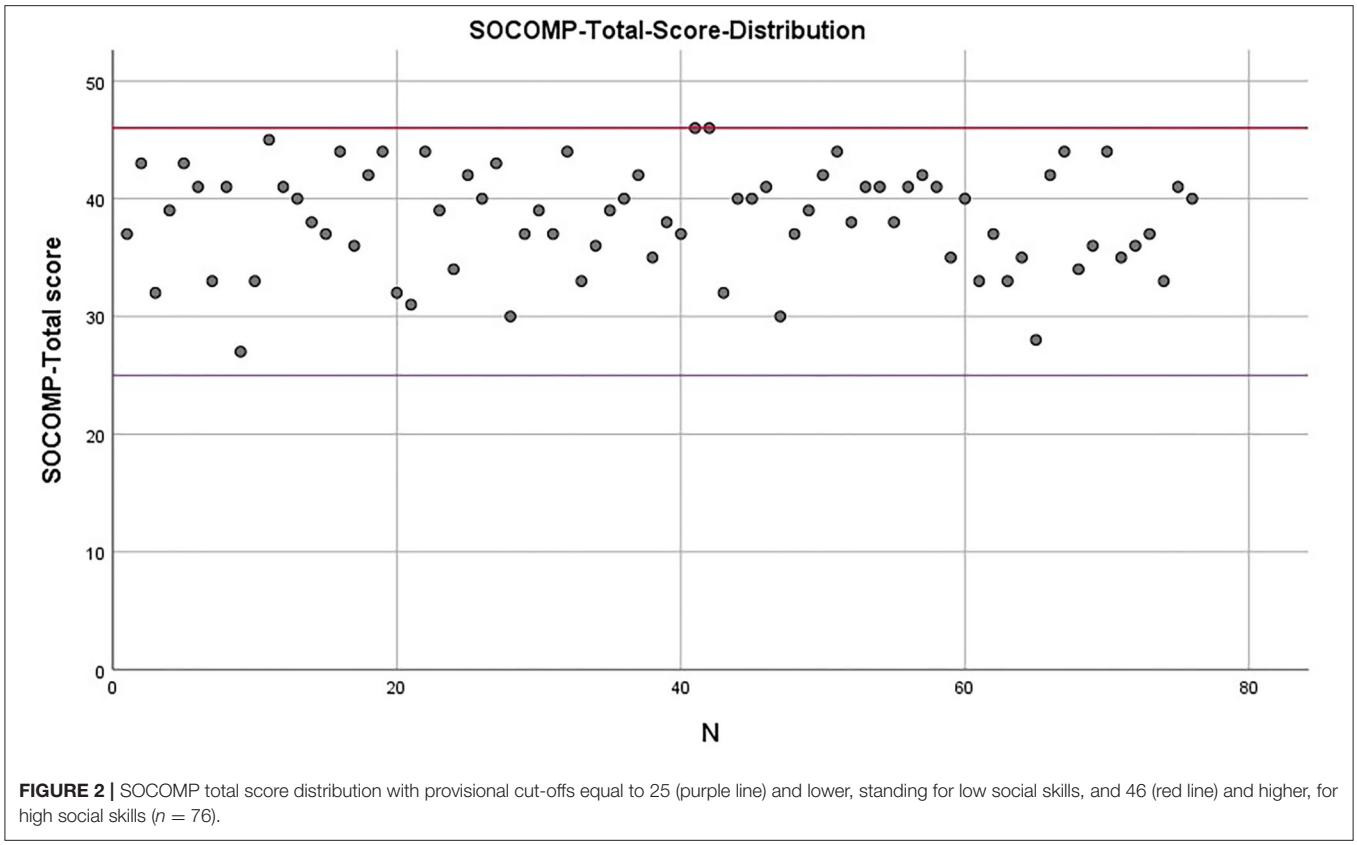

FIGURE 2 | SOCOMP total score distribution with provisional cut-offs equal to 25 (purple line) and lower, standing for low social skills, and 46 (red line) and higher, for high social skills ($n = 76$).

TABLE 4 | Descriptive statistics of SOCOMP-results ($n = 76$).

	Total	Self-oriented social skills	Other-oriented social skills	Positive peer relationships
Items	25	10	10	5
M	38.29	12.47	16.57	9.25
SD	4.41	2.24	2.77	1.10
Minimum	27	8	10	5
Maximum	46	17	20	10
Provisional cut-off	25/46	10/18	10/18	5/10
n </> provisional cut-off	0/2	19/0	3/34	1/41

TABLE 5 | Spearman Rank Correlation of bonding impairment assessed 6 weeks after birth with social competencies assessed at 5.5 years.

Variable	*n*	*M*	*SD*	1	2
1. PBQ-Total score	76	10.42	7.01		−0.31*
2. SOCOMP-Total score	76	38.29	4.41	−0.31*	

*$p < 0.05$.

maternal personality (61)]. As documented earlier, the short-term effects of a lack of bonding are largely negative, but the fact that it can have even a long-term to lifelong influence on a connection with social skills and thus, as we know with regard to the positive function of social skills [ranging from school readiness (62) to academic success (63) and its protective function against developmental psychopathology (64)] seems considerable. This is meaningful because some studies found positive effects of bonding for a short time, e.g., a few days after birth, but which were no longer present weeks later (65) and which may cast doubt on the effectiveness of bonding. Interestingly, correlations with juvenile deliquence can be found for both poor bonding (66) and social skills (27). According to Mak (67) caring mothers who are perceived as warm and understanding are a protective factor against deliquence. In addition, there is evidence that paternal violence, physical abuse and sexual abuse by the father increased adolescents' sexual aggression, whereas bonding to the mother decreased it (68).

The influence of neuropeptides (especially oxytocin (69–76) as one possible mediator of this association, also arginine vasopressin [AVP]), an altered GABAA inhibitory system and steroids (especially oestrogens) in the first social phase on later behavior and emotion regulation has been documented extensively (69–71, 77). Oxytocin arguably stimulates maternal feelings (78), influences maternal behavior (79–83), promotes bonding (84, 85) and at the same time is itself derived from early social interaction (1, 86). Several studies using intranasal oxytocin administration show significant improvements in social skills (87) in the case of rats administered to the central amygdala (88), children and adolescents with autism spectrum disorders (89), others in case of children and adolescents with autism spectrum disorders not (90, 91).

Another mediator of this association might be maternal psychopathology: it has been demonstrated, that psychopathology of the mother can have a negative impact on the quality of bonding with the child [e.g., postnatal anxiety (92), depression at 2 and 6 weeks as well as 4 months (93)]. The study by Galeshi et al. (94) also shows that anxiety, depression and unwanted pregnancy are influencing factors on mother-child bonding and suggests that early diagnosis and treatment of maternal anxiety and depression has a positive effect on bonding. Genetically similar depressive symptoms in children are in turn associated with deficient social skills and problems with peers (95). Conversely, a very high level of prosocial behavior, especially in the case of low social participation, can in contrast promote the development of emotional symptoms (96). Also, as data in our study are based on maternal report only, maternal depression could have lead to maternal perceptive distortions and as such, a more negative perception of bonding and social competences. Furthermore, Bonding has been shown to be related to maternal Psychopathology (93). However, in our psychosocially well-adjusted community sample mothers showed remarkably low levels in terms of psychopathology according to SCL-90-R-cut-off, therefore a distinct relation between bonding and social competences can still be assumed, although this association needs to be elucidated in further studies e.g., on mothers with a significant degree of psychopathology.

The majority of definitions of bonding emphasize the emotional component (3). In the case of babies, therefore, not only the physical satisfaction of needs should be taken into account, more importance should be attached to social interaction. Babies who lack social interaction may do not gain enough weight, become indifferent, listless, withdrawn and develop psychopathology (e.g., depression) (97).

All mothers in our sample were married to the childs' father and had rather good bonding qualities. Children were healthy full term births. It remains to elucidate whether the association demonstrated in this study can also be found in higher risk samples.

There is a lack of studies investigating whether interventions to promote mother-child bonding in early infancy improve the social skills of preschool-aged children.

Strengths and Limitations of the Study

Our results indicate the existence of a -theoretically assumed- relationship between bonding and social skills even in a psychosocially very well-adjusted and healthy community sample. Even in this sample, it is evident that successful bonding seems to increase the social competence of children 5.5 years later. Also, with regard to the multitude of further factors that influence our social competences, the extent of the correlation seems considerable. One major limitation is the fact, that bonding as well as social competences were assessed in maternal judgment. Therefore, a general distortion of maternal perception cannot be excluded. Paternal variables were not assessed. Due to the specificity of the present sample, additional studies (including a clinical sample) are necessary to verify the causality of the relationship. The inclusion of other variables (e.g., ability to regulate emotions, anxiety, temperament, environmental influences, biological factors) would be meaningful in future long-term studies. With regard to the instruments, in order to be able to classify the distribution of the sample with the SOCOMP, provisional cut-off values were assigned, which may influence the results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Heidelberg, Medical School Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

EM recruited participants and collected the data. JJ performed the statistical analysis and wrote the first draft of the manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Furthermore, all authors read, gave feedback, and approved the submitted version.

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frontiers in Psychiatry

SYSTEMATIC REVIEW
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Time to Evaluate the Clinical Repercussions of Zika Virus Vertical Transmission? A Systematic Review

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Background: Vertical transmission of Zika Virus (ZIKV) can be associated with several clinical features in newborn infants. The goal of the present review was to analyze the current state of knowledge regarding clinical repercussions following perinatal exposure to ZIKV in children up to 3 years of age.

Methods: A systematic review of published studies was carried out, without the restriction of language or date of publication, identified in the databases PubMed, Virtual Health Library (BVS), Scopus, and Web of Science and the catalog for CAPES theses and dissertations. According to the proposed flowchart, the bibliographic search resulted in 1,563 papers. Of these, according to the eligibility criteria, 70 were selected for systematic review; all were published between 2016 and 2021.

Results: Regarding clinical findings, 19 papers evaluated clinical imaging alterations, 21 ophthalmic manifestations, and 39 evaluated the central nervous system; of these, 15 analyzed neuro-psychomotor development. The remainder evaluated audiological ($n = 14$), nutritional ($n = 14$), orthopedic ($n = 7$), cardiorespiratory ($n = 5$), genitourinary ($n = 3$) or endocrinological ($n = 1$) manifestations.

Conclusion: It is critical for studies to continue monitoring children with antenatal ZIKV exposure as they grow, given the unknown long-term repercussions of ZIKV and the recognized postnatal complications of this infection during pregnancy. Broader descriptions of observed clinical findings are also important in order to characterize the entire spectrum of disease in children.

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Keywords: zika virus, systematic review, neurological repercussion, clinical repercussion, neurodevelopment

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BACKGROUND

Zika virus (ZIKV) was first reported in East Africa in the 1950 s. In 2007, global attention emerged following an outbreak in Micronesia, and in the following decade, on the island of Yap, in the French Polynesia. The virus spread widely in other Pacific islands over the years, before emerging as a widespread epidemic throughout Latin America (1, 2). In 2015, with the arrival of ZIKV in Brazil, the first studies reported descriptions of women with fever and rash during pregnancy and a possible relationship with congenital microcephaly (3–5). The hypothetical relationship between

ZIKV infection in pregnancy and subsequent abnormal newborn findings arose after a very large increase in microcephaly cases was observed in Brazil a few months after ZIKV circulation was identified in the country. Due to its catastrophic repercussions to newbor infants, the World Health Organization (WHO) declared Zika virus a Public Health Emergency in 2016. Gradually over 2017, ZIKV cases declined consistently across the world, although certain tropical areas of the globe became endemic for ZIKV infection, including Central and South America, the Caribbean, and southern Asia. Outbreaks were reported in 2018 in India and Angola, and in France, a locally acquired infection was reported in 2019. One of the driving forces behind the rapid ZIKV epidemic spread was global warming and population mobility which greatly contributed to an increase in the environmental span of *Aedes sp*. mosquitoes. The possibility of new outbreaks lingers, particularly since arboviral outbreaks are notoriously cyclical. In addition, ZIKV, unlike other arboviral infections, can be transmitted by sexual contact. Therefore, pregnant women may be infected by partners who traveled to endemic areas. Therefore, travel histories should include not only the pregnant patient but their partners as well. Since the virus can persist for extended periods of time in semen, pregnant women could be at risk for infection weeks to months following partner travel to endemic areas.

The fact that ZIKV has a very similar genomic structure to dengue viruses 1–4, has important diagnostic implications. Arboviral flaviviruses in the same family as ZIKV include yellow fever, Japanese encephalitis, and West Nile viruses. Hepatitis C virus, another flavivirus, also shares some genomic similarities with ZIKV, which carries potential antiviral treatment implications. Over time ZIKV evolved from the African lineage to the Asian lineage (there is 90% homology between strains), and potentially acquired higher teratogenic potential during the process. The Asian strain of ZIKV was responsible for the recent pandemic.

Although ZIKV infection is generally asymptomatic, 20% of patients develop mild symptoms. The clinical features resemble that of rubella virus infection. If symptoms occur, they are present 7–10 days following exposure. Most prominent findings are a maculopapular pruritic rash, arthralgia and conjunctival erythema. Fever is rare and, if present, low grade. Rash, pruritus, conjunctival hyperemia, no fever, no petechiae and no anorexia are used as a ZIKV case definition in endemic settings, where dengue and chikungunya are also prevalent. ZIKV infection is typically self-limited with resolution of symptoms within 1 week. Most patients recover without complications, including pregnant women.The absence of clinical symptoms of ZIKV during pregnancy, however, does not indicate no risk of clinical repercussions to infants. Women with asymptomatic disease can deliver infants with microcephaly. Virus load during maternal infection, disease severity and frequency of symptoms, as well as prior dengue immunity have not been predictive of infant outcomes at birth.

The Centers for Disease Control and Prevention (CDC) coined the term Congenital Zika Syndrome (CZS) which refers to infants most severely affected by antenatal ZIKV exposure. Nevertheless, many studies demonstrated a spectrum of clinical manifestations in children ranging from absent findings to severe microcephaly. CZS is defined as a constellation of findings at birth including: (1) severe microcephaly (>3 SD below the mean for gestational age and gender); (2) brain abnormalities (subcortical calcifications, ventriculomegaly, cortical thinning, gyral pattern anomalies, hypoplasia of the cerebellum, or corpus callosum anomalies); (3) ocular findings; (4) congenital contractures, also known as arthrogryposis; and (5) neurologic impairment. Microcephaly rates range from 3 to 7% in prospective studies. Most common abnormalities include cerebral calcifications, cortical developmental malformations (lissencephaly, pachygyria, agyria), ventriculomegaly due to brain atrophy, posterior fossa alterations including brainstem or cerebellar hypoplasia, corpus callosum abnormalities, enlarged extra-axial cerebrospinal fluid spaces, and enlarged cisterna magna. Ophthalmologic and sensorineural hearing loss have been reported in 7 and 12% of infants, respectively, followed since the time of maternal infection. They prevail in children with other CNS findings but can also be an isolated finding. Eye manifestations include abnormalities of the retinal pigment epithelium of the macula, optic nerve hypoplasia, chorioretinal atrophy; other abnormalities are colobomas and microphthalmia. Abnormal visual function is identifiable in early infancy among affected children. Eye abnormalities do not tend to progress. Another interesting observation, which highlights some similarities with congenital rubella syndrome is that 10% of children with *in utero* ZIKV exposure had congenital heart defects in prospective studies. Longer term outcome studies demonstrated that 15% of children may have severe neurodevelopmental problems and sensorineural abnormalities by 3 years of age. Conversely, not all children with abnormalities at birth have later neurodevelopmental repercussions. In the same way, infants found to be normal at birth following maternal infection during pregnancy might have abnormal developmental outcomes years later. Studies demonstrated that close to 1/3 of infants with antenatal ZIKV exposure have below average neurodevelopment or abnormal eye or hearing findings, Secondary microcephaly, which is microcephaly occurring after birth, as well as a higher rate of ASD have been noted in children exposed to antenatal ZIKV, underscoring that long term follow-up is necessary.

ZIKV has been shown to cross the placenta and infect placental macrophages. This disrupts neural progenitor cell evolution, leading to microcephaly in animal models. Maternal infection earlier in pregnancy leads to more severe fetal outcomes. CNS malformations are more common with first and second trimesters infections. Late term fetal demise can occur due to placental vascular involvement with focal necrotic vasculitis and placental failure. In summary, adverse outcomes due to ZIKV infection have been described across all trimesters

Abbreviations: ASD, autism spectrum disorder; BVS, biblioteca virtual em saude – (virtual health library); CAPES, coordenação de aperfeiçoamento de pessoal de nível superior (thesis repository); CNS- central nervous system; CZS, congenital zika syndrome; PRISMA, preferred reporting items for systematic reviews; SD, standard deviation; TORCH, toxoplasmosis, rubella, cytomegalovirus, herpes simplex; ZIKV, zika virus.

of pregnancy. Miscarriages and fetal growth restriction have also been described. The virus can induce CNS calcifications and bone fusion; craniosynostosis may be present in congenital ZIKV infection.

Congenital ZIKV infection has become widely recognized since its original description. Microcephaly is defined as a head circumference of <2 or more standard deviations from the benchmark for gender, age, or gestational age, per the Brazilian Ministry of Health (6). The spectrum of congenital disabilities linked to ZIKV besides microcephaly, such as eye alterations, craniofacial disproportion, and joint and limb deformities, characterize Congenital ZIKV Syndrome (CZS) (7). As previously discussed, clinical alterations and subsequent developmental delays are widely described in babies born without microcephaly, in some cases infants with no stigmata of CZS (8–12). However, there is very little information about future clinical implications of antenatal ZIKV infection in the long term, and this is the target of several studies.

METHODS

A systematic review was undertaken to analyze the current state of knowledge regarding repercussions of vertical exposure to ZIKV on child health. The search for pertinent studies was carried out using databases of the Virtual Health Library (BVS), MEDLINE via PubMed, Web of Science, and Scopus via Capes journals portal, CAPES thesis, and dissertation catalogs.

This comprehensive review was undertaken to address the following question: "*What is the impact of vertical exposure to ZIKV on clinical, nutritional, and neurodevelopmental aspects in children up to 3 years of age?*" This question was formulated per the PICO acronym. The description of this systematic review was based on the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines (13). Thus, the following steps were developed: identification of the research question, literature search, data evaluation, analysis of results, and presentation of the review (**Figure 1**).

The following descriptors were used for the search strategy: "Zika Virus," "Zika Virus Infection" as search terms, along with "Zika Virus Infection/complications" or the specific clinical outcome designations: "neurogenic bladder," "urinary bladder," "Nutritional status," "nutrition," "Anthropometry," "Hearing," "Orthopedics," "arthrogryposis," "vision," "Neurologic disease," "Neurologic Manifestations," "Gastrointestinal Diseases," "Cardiovascular disease," "Cardiovascular Abnormalities," "neurodevelopment." Boolean operators AND, OR, and NOT were used to relate the blocks to each other, to add at least one word from each block. This systematic review was registered and approved by the PROSPERO systematic review protocol registry database under registration number CRD42020205947.

Two independent researchers carried out the search process, which ended in January 2021, with no limits for the period of publication or language restrictions. The bibliographic search resulted in 1,563 papers. Of these, 159 were selected for full-text reading because they evaluated clinical manifestations in cohorts of children with antenatal ZIKV exposure. After extensive selection, 89 papers were excluded because they addressed topics that were not relevant to the present work, leaving 70 studies eligible for this paper, as seen in **Figure 1**. Eligibility criteria for manuscript selection included full text studies that reported clinical findings/outcomes in cohorts of children with documented antenatal ZIKV exposure. As such, incomplete manuscripts/abstracts, review papers, studies in fetuses, animal studies, *in vitro* studies, studies in adults only, and qualitative studies were excluded. In addition, manuscripts referenced in papers selected for this study were also investigated, however no further papers were identified. The selected publications were compared in regards to the following parameters: year of publication, study location, sample size, mean age of participants, design type, eligibility criteria, exposure period, presence of a control group, symptoms, controlled confounders in the analysis, study limitations, and main results.

RESULTS

Seventy papers published from 2016 to 2021 were selected following the search. Of these, most were conducted in Brazil ($n = 58$), followed by Colombia ($n = 4$), the U.S. ($n = 3$), Spain ($n = 2$), French Guiana ($n = 1$), Mexico ($n = 1$), and the French Polynesia ($n = 1$) (**Figure 2**). The sample size ranged from 1 to 5,673 participants. The population studied ranged in age from 0 days to 48 months, with 9 studies not reporting the participant age range (**Table 1**).

Most studies were ($n = 37$) descriptive in design, such as case series or case reports, followed by cross-sectional studies ($n = 17$), cohort studies ($n = 14$), and case-control studies ($n = 2$). Information on study limitations was described in 40 studies; the most prevalent limitation was the limited sample size, lack of a control group, type or lack of laboratory confirmation for ZIKV, loss to follow-up, and use of secondary data for analysis. Details on duration of follow-up, sample size and study design are shown in **Figure 3**.

Concerning clinical findings, 19 papers evaluated clinical imaging alterations, 21 ophthalmic manifestations, 39 the central nervous system, including 15 which evaluated neuro-psychomotor development. Additional studies included audiological ($n = 14$), nutritional ($n = 14$), orthopedic ($n = 7$), cardiorespiratory ($n = 5$), genitourinary ($n = 3$) or endocrinological ($n = 1$) manifestations. It is noteworthy that some articles described more than one organ system and multiple clinical findings (**Table 2**).

The most prevalent clinical imaging abnormalities of the central nervous system included microcephaly, ventriculomegaly, cortical malformations, *mega cisterna magna*, hydrocephalus, cerebellum or brain stem hypoplasia, and cerebral calcifications, especially at the junction between the cortical and subcortical white matter (16, 18, 21, 25, 34, 45, 46, 48, 50, 53, 56, 59–61, 75, 77). One manuscript also reported a decline in head circumference growth (70). Regarding abdominal imaging, there were no characteristic abnormalities identified in ZIKV exposed children that differed from descriptions in the general population.

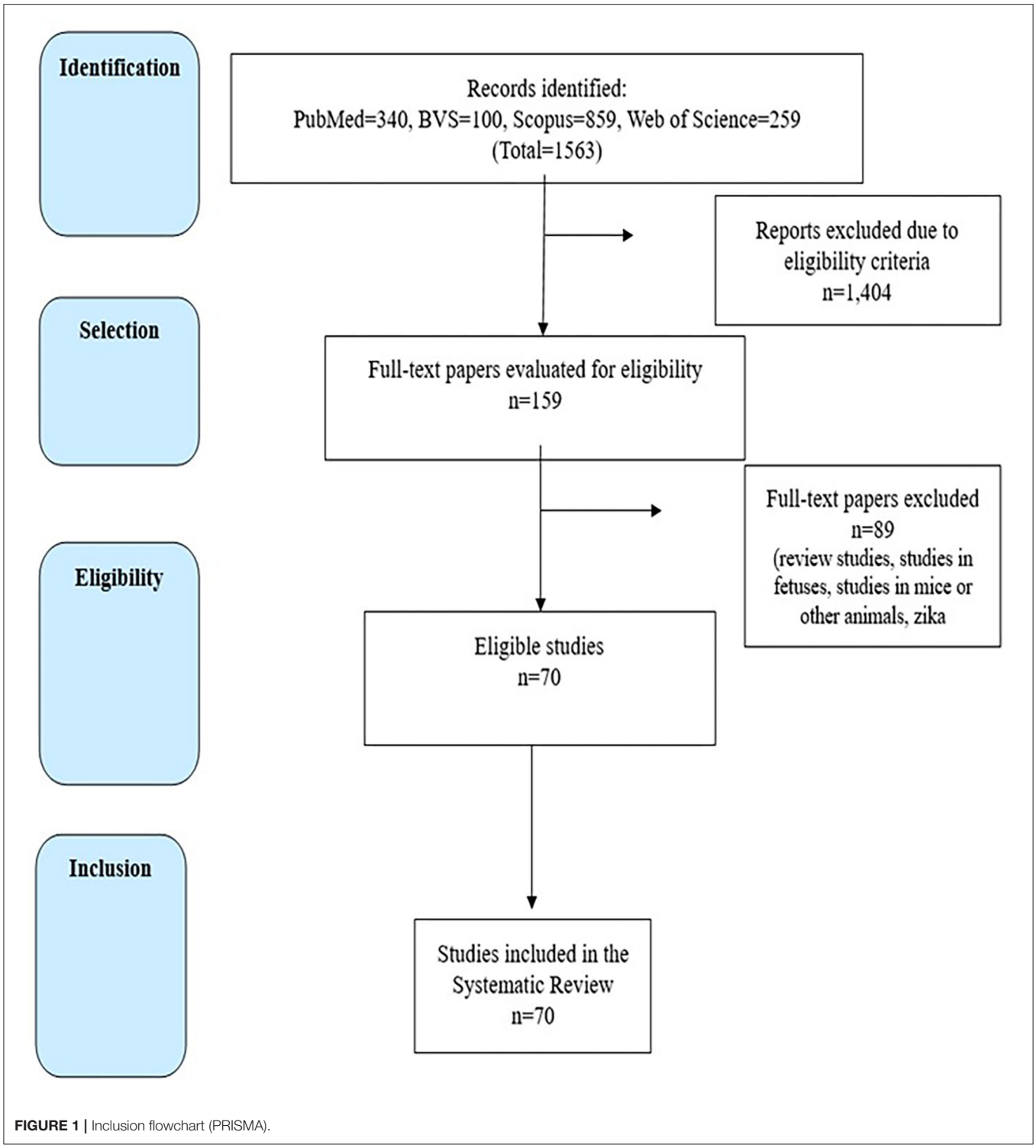

FIGURE 1 | Inclusion flowchart (PRISMA).

Imaging results were normal in 95.3% of 106 children who underwent abdominal ultrasound (55). Of five patients with abnormal abdominal ultrasounds, one (16.6%) had a splenic cyst, one (16.6%) had a diaphragmatic eventration, one (16.6%) had biliary lithiasis, one (16.6%) had multi-cystic dysplastic kidney, and two (33.4%) had a dilated renal pelvis. The prevalence of these alterations was 1.9% for renal pelvis dilatation and 0.9% for other abnormalities (55).

All the papers that evaluated the central nervous system found neurological alterations, and the main ones were seizure, epilepsy, irritability, pyramidal syndrome, sleep disorders, and hyperexcitability (5, 12, 18, 19, 27, 31, 35, 36, 42, 45, 46, 48, 50, 51,

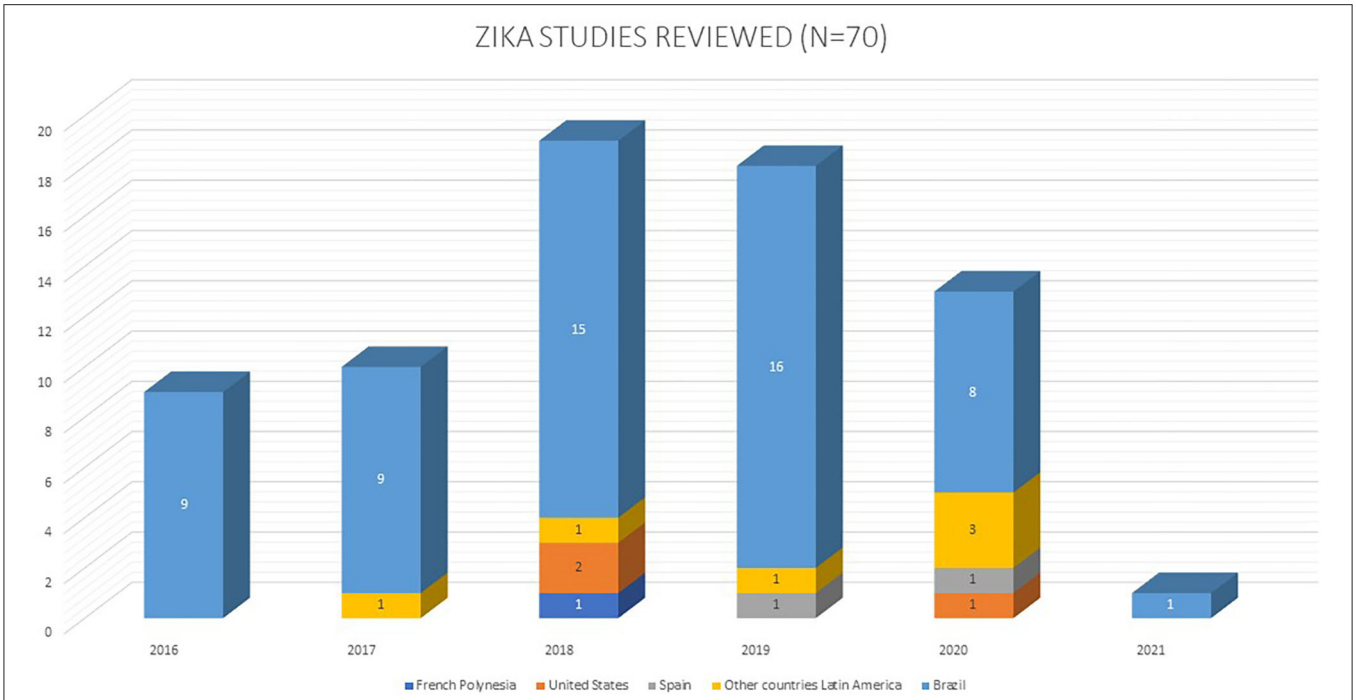

FIGURE 2 | Zika studies reviewed by year of publication and country of origin.

54, 56, 61, 62, 66, 69–71, 74, 77). Regarding neuro-psychomotor development, all 15 papers reported motor, cognitive, or language delay (10, 11, 15, 17, 18, 24, 32, 33, 44, 47, 52, 58, 61, 62, 65). Noteworthy is that, in one paper, the authors reported autism spectrum disorder in three previously healthy children in the second year of life (11).

All studies that performed ophthalmological evaluations exposed some alteration, such as microphthalmia, fundoscopic alterations, macular atrophy, optic nerve abnormalities, strabismus and visual acuity defects (12, 14, 27, 36, 45, 50, 51, 56, 60, 61, 67, 68, 73–79). Twelve of 14 papers that evaluated audiological manifestations in children reported hearing disorders (11, 14, 27, 36, 37, 39, 43, 51, 56, 60, 62, 64) and two did not observe any abnormalities (30, 41).

Two papers reported unilateral diaphragmatic paralysis (45, 57), and another two found echocardiographic abnormalities (49, 61). These abnormalities were characterized by dilatation of the right atrium and the right ventricle, demonstrating an overload of the right heart chambers. In a study of children with Zika-related microcephaly, adenoid hypertrophy and symptoms of respiratory obstruction were reported (40).

Regarding genitourinary characteristics, studies reported neurogenic bladder and cryptorchidism (22, 23, 72). The most common orthopedic alteration was arthrogryposis (12, 16, 21, 36, 42, 46, 57). All papers that evaluated gastrointestinal manifestations reported dysphagia (38, 46, 48, 61). Regarding the nutritional status of children exposed to antenatal ZIKV, nine papers found anthropometric alterations such as low birth weight and growth retardation (14, 20, 21, 28, 29, 33, 48, 50, 63, 66) and one study observed endocrine dysfunctions in children with Zika-related microcephaly (75).

DISCUSSION

In this section we discuss the main results of manuscripts selected for this systematic review to assess the main potential clinical alterations described in antenatally ZIKV-exposed children to date.

Neurologic, Neuroimaging and Neurodevelopmental Findings

Concerning clinical imaging alterations, (16, 34, 53, 59), severe brain damage was reported in CNS imaging studies in most children with antenatal exposure to ZIKV. The most common features identified were brain calcifications at the junction between cortical and subcortical white matter; these were associated with malformations of cortical development, usually with a simplified gyrus pattern and a predominance of pachygyria or polymicrogyria in the frontal lobes. Studies also identified an increased/dilated cisterna magna, corpus callosum abnormalities (which could be either hypoplasia or hypogenesis), ventriculomegaly, delayed myelination, and hypoplasia of the brain stem and/or cerebellum.

Petribu et al. (53) observed an interesting finding in that brain calcifications in children with confirmed or presumed CZS tended to decrease over time. This implies that brain calcifications should not be considered essential for diagnosis of CZS in children who present late to medical attention. Decrease

TABLE 1 | Year of publication, origin, sample size and age of participants of selected studies, 2016–2021.

References	Country	Sample size (*n*)	Age of follow-up
Almeida et al. (14)	Brazil	100	Not provided
Alves et al. (15)	Brazil	24	19.9 (18– 24 months)
Aragao et al. (16)	Brazil	12	135 days
Bertolli et al. (17)	Brazil	120	24 months
Brasil et al. (5)	Brazil	207	Birth
Carvalho et al. (18)	Brazil	82	13, 2 months
Carvalho et al. (19)	Brazil	37	2, 6 (1–5 months)
Carvalho-Sauer et al. (20)	Brazil	393	Birth
Contreras-Capetillo et al. (21)	Mexico	3	Newborns
Costa Monteiro et al. (22)	Brazil	69	13 months
Costa Monteiro et al. (23)	Brazil	22	9 months
Cranston et al. (24)	Brazil	296	0 −48 months
de Fatima Vasco Aragao et al. (25)	Brazil	23	1 month
de Paula Freitas et al. (26)	Brazil	29	1–6 months
de Paula Guimarães et al. (27)	Brazil	69	Not provided
dos Santos et al. (28)	Brazil	21	Not provided
dos Santos et al. (29)	Brazil	65	15 months
Fandiño-Cárdenas et al. (30)	Colombia	66	Exposed: 3.5 months; Control: 3 months
Felix et al. (31)	French Guiana	2	2–4 months
Ferreira et al. (32)	Brazil	34	21 months
França et al. (33)	Brazil	24	20.5 months
Jucá et al. (34)	Brazil	115	Not provided
Kanda et al. (35)	Brazil	23	8.3 months
C Lage et al. (36)	Brazil	102	4.1 months
Leal et al. (37)	Brazil	70	0–10 months
Leal et al. (38)	Brazil	9	4 (2–7 months)
Leal et al. (39)	Brazil	1	Birth−1 month
Leal et al. (40)	Brazil	57	22.9 months
Leite et al. (41)	Brazil	45	10 months
Linden et al. (42)	Brazil	3	7–19 months
Marques Abramov et al. (43)	Brazil	19	Not provided
Melo et al. (44)	Brazil	59	14.7 months
Meneses et al. (45)	Brazil	87	Birth
Lopes Moreira et al. (10)	Brazil	104	2–18 months
Moura da Silva et al. (46)	Brazil	48	1–8 months
Mulkey et al. (47)	Colombia	70	Birth−18 months
Nielsen-Saines et al. (11)	Brazil	216	18 months
Oliveira-Filho et al. (48)	Brazil	27	101 days
Orofino et al. (49)	Brazil	186	97 (1–376 days)
Ospina et al. (50)	Colombia	5,673	Birth
Pacheco et al. (51)	Colombia	60	20–30 months
Peçanha et al. (52)	Brazil	84	1st Moment: 9.7 months 2nd Moment: 15.3 months
Petribu et al. (53)	Brazil	37	1st Moment: 1 to 138 days (median of 11.5 days) 2nd Moment: 105 to 509 days (median of 415 days)
Pinato et al. (54)	Brazil	136	5–24 months
Pone (55)	Brazil	106	Not provided
Pool et al. (56)	Brazil	110	Newborn period
Rajapakse et al. (57)	United States	4	3–10 days of life; 1–86 days
Rice et al. (58)	United States	1,450	≥12 months
Rocha et al. (59)	Brazil	174	9 months

(Continued)

TABLE 1 | Continued

References	Country	Sample size (*n*)	Age of follow-up
Roma et al. (60)	Brazil	20	Newborns
Santana et al. (61)	Brazil	18	21.5 months
Satterfield-Nash et al. (62)	Brazil	19	22 months
Soares et al. (63)	Brazil	115	Birth – 3 months
Soriano-Arandes et al. (64)	Spain	143	1, 4, 9, 12, 18, and 24 months
Subissi et al. (65)	French Polynesia	123	23 months
Sulleiro et al. (66)	Spain	1	24 months
Trigueiro et al. (67)	Brazil	20	Not provided
Tsui et al. (68)	Brazil	224	44 days (12–99 days)
van der Linden et al. (69)	Brazil	21	16–30 months (mean 16 months at the time of the last examination)
van der Linden et al. (70)	Brazil	13	05–12 months
van der Linden et al. (71)	Brazil	7	Not provided
de Vasconcelos et al. (72)	Brazil	22	36 months
Ventura et al. (73)	Brazil	40	2.2 months
Ventura et al. (73)	Brazil	32	5.7 (4–7 months)
Ventura et al. (74)	Brazil	204	Exposed: 8.5 months (6–13 months) Controls: 8.4 months (5–12 months)
Veras Gonçalves et al. (75)	Brazil	30	41 months
Verçosa et al. (76)	Brazil	70	3 months
Walker et al. (77)	United States	95	Newborn period
Zin et al. (12)	Brazil	112	Not provided
Zin et al. (78)	Brazil	173	3–6 months

in brain calcifications over time, however, was not associated with clinical improvement.

Santana et al. (61) reported that all children in their cohort had microcephaly, spasticity, and delayed neurological development. Epilepsy was found in 15 of 18 cases (83%). In a case series, Van Der Linden et al. (70) observed dystonic postures and other frequent and potentially disabling extrapyramidal signs. The study emphasized that early identification of extrapyramidal findings may help recognize neurodevelopmental problems and assist with implementation of rehabilitation, potentially influencing better strategies for rehabilitative interventions.

When analyzing sleep disorders in their cross-sectional study, Pinato et al. (54) showed that the CZS group of children had a shorter total sleep time and night sleep duration than the control group. However, no correlation was found between age and sleep patterns.

In a series of cases that assessed infants exposed to congenital ZIKV who were asymptomatic at birth, neurodevelopmental delay was identified through the use of the Bayley-III scale assessment tool (52). The abnormalities occurred mainly in the language domain during the first two years of life. The Z-score of the head circumference was significantly lower in the group with developmental delay, with the simultaneous presence of neurological abnormalities, which indicates a possible action of ZIKV infection in the developing brain (24).

Nielsen-Saines et al. (11) observed that, among the children evaluated by Bayley-III, 12% scored below two standard deviations (i.e., a score <70; a score of 100 ± 2 SD is the variation) in at least one functional domain; 28% of children scored between -1 and -2 SD in any domain (scores <85–70). Language function was most affected, with 35% of 146 children being below average. The authors described that neurodevelopmental outcomes were improved in female children, term babies, children with normal eye exames, and whose mothers were infected with ZIKV later in pregnancy. Mulkey et al. (47) found that infants with *in utero* ZIKV exposure without features of CZS were also at risk for abnormal neurodevelopment in the first 18 months of life.

Eye Findings

Regarding ophthalmological findings, studies (12, 26, 67, 68, 73, 74, 76, 78–80) found an association between congenital infection due to presumed exposure to ZIKV and macular lesions, macular circumscribed chorio-retinal atrophy, focal-spotted retinal pigment epithelium, optic nerve pallor, early-onset strabismus, nystagmus, and low visual acuity. Also, ocular involvement (macular and eye fundus abnormalities) in babies with presumed congenital ZIKV infection was most frequently observed in babies with a smaller head circumference at the time of birth and whose mothers were infected in the first trimester of pregnancy (73).

Hearing Deficits

Of the papers that assessed audiological function, the main findings were a statistically significant increase in latencies of waves I and III, compared to wave V, absence of otoacoustic emissions, and sensorineural hearing loss (37, 43). In most hearing loss cases associated with congenital infections, damage

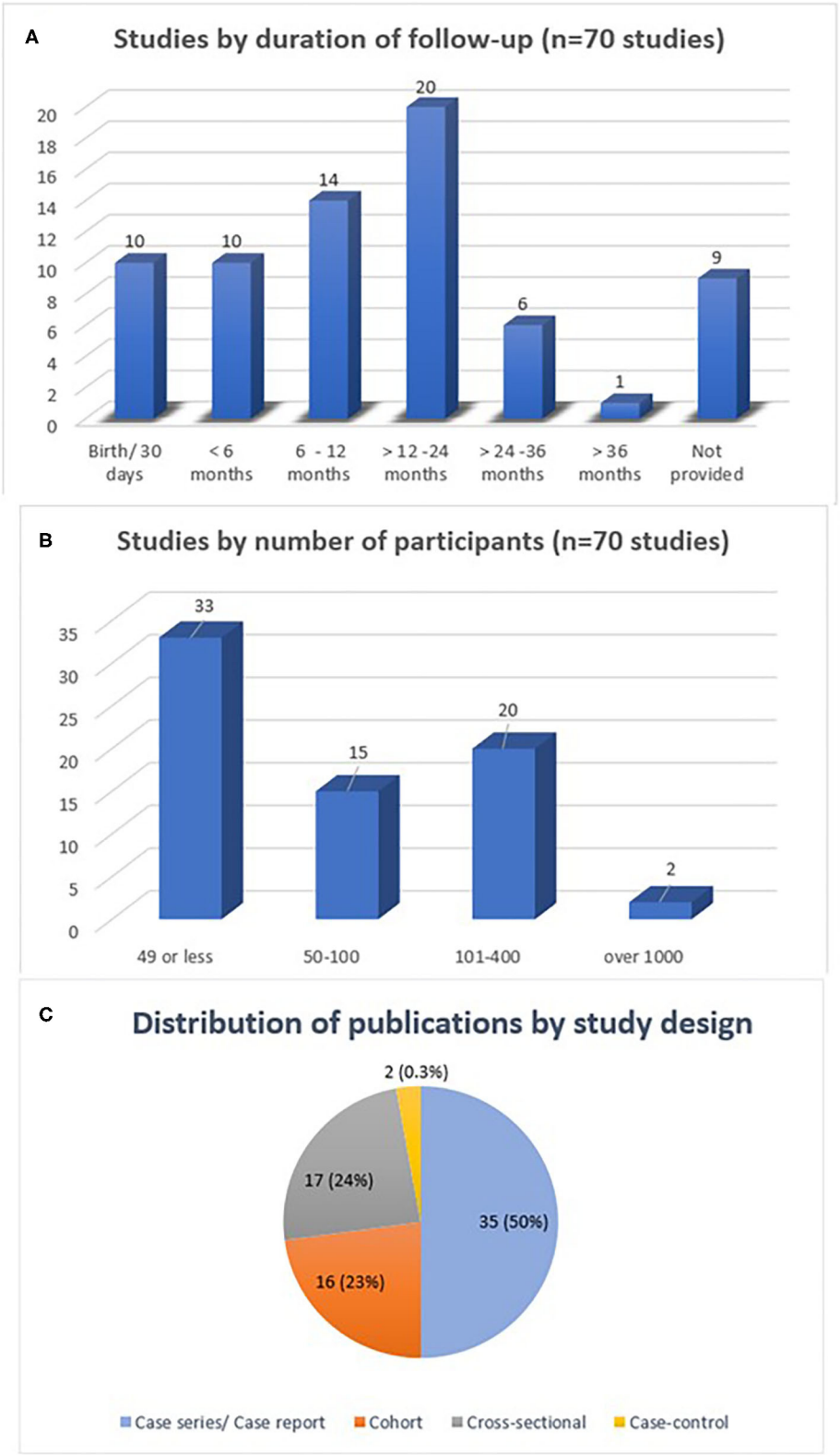

FIGURE 3 | Description of studies reviewed by duration of follow-up **(A)**, number of participants **(B)** and study design **(C)**.

TABLE 2 | Study design, clinical abnormalities and development screening test, 2016–2021.

References	Study design	Clinical abnormalities	Developmental screening test
Almeida et al. (14)	Case series	Hearing abnormalities; Eye abnormalities	–
Alves et al. (15)	Case series	Neurodevelopmental delays	Denver Development Screening Test II
Aragao et al. (16)	Case series	Joint and limb deformities	–
Bertolli et al. (17)	Cohort	Neurodevelopmental delays	ASQ *3*
Brasil et al. (5)	Cohort	Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Carvalho et al. (18)	Case series	Neurological abnormalities; Neurodevelopmental delays; Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Carvalho et al. (19)	Case series	Neurological abnormalities	–
Carvalho-Sauer et al. (20)	Cross-sectional	Growth and nutrition	–
Contreras-Capetillo et al. (21)	Case series	Joint and limb deformities; Growth and nutrition; Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Costa Monteiro et al. (22)	Case series	Genito-urinary abnormalities (Criptorquidia, Neurogenic bladder)	–
Costa Monteiro et al. (23)	Case series	Genito-urinary abnormalities (Criptorquidia, Neurogenic bladder)	–
Cranston et al. (24)	Cohort	Cardiological abnormalities; Hearing abnormalities; Eye abnormalities; Neurological abnormalities; Growth and nutrition; Neurodevelopmental delays	Bayley III
de Fatima Vasco Aragao et al. (25)	Retrospective case series	Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
de Paula Freitas et al. (26)	Case series	Eye abnormalities	–
de Paula Guimarães et al. (27)	Case series	Hearing abnormalities; Eye abnormalities; Neurological abnormalities	–
dos Santos et al. (28)	Descriptive Longitudinal Study	Growth and nutrition	–
dos Santos et al. (29)	Descriptive Longitudinal Study	Growth and nutrition	–
Fandiño-Cárdenas et al. (30)	Cohort	Hearing abnormalities	–
Felix et al. (31)	Case report	Neurological abnormalities	–
Ferreira et al. (32)	Cross-sectional	Neurodevelopmental delays	Common Brief ICF Core Set for CP
França et al. (33)	Cross-sectional	Growth and nutrition; Neurodevelopmental delays	Bayley III
Jucá et al. (34)	Case series	Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Kanda et al. (35)	Cross-sectional	Neurological abnormalities	–
C Lage et al. (36)	Cross-sectional	Joint and limb deformities; Hearing abnormalities; Eye abnormalities; Neurological abnormalities	–
Leal et al. (37)	Case series	Hearing abnormalities	–
Leal et al. (38)	Case series	Gastrointestinal/pulmonary abnormalities	–
Leal et al. (39)	Case report	Hearing abnormalities	–
Leal et al. (40)	Cross-sectional study nested in a cohort	Adenoid hypertroph	–
Leite et al. (41)	Cross-sectional	Hearing abnormalities	–
Linden et al. (42)	Case series	Joint and limb deformities; Neurological abnormalities	–
Marques Abramov et al. (43)	Cross-sectional	Hearing abnormalities	–
Melo et al. (44)	Cross-sectional	Neurodevelopmental delays	Not provided
Meneses et al. (45)	Case series	Eye abnormalities; Neurological abnormalities; Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations); Gastrointestinal/pulmonary abnormalities	–

(Continued)

TABLE 2 | Continued

References	Study design	Clinical abnormalities	Developmental screening test
Lopes Moreira et al. (10)	Cohort	Neurodevelopmental delays	Bayley III
Moura da Silva et al. (46)	Case series	Gastrointestinal/pulmonary abnormalities; Joint and limb deformities; Neurological abnormalities; Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Mulkey et al. (47)	Cohort	Neurodevelopmental delays	Warner Initial Developmental Evaluation of Adaptive and Functio-l Skills (WIDEA) and the Alberta Infant Motor Scale (AIMS)
Nielsen-Saines et al. (11)	Cohort	Hearing abnormalities; Neurodevelopmental delays	Bayley III
Oliveira-Filho et al. (48)	Cohort	Gastrointestinal/pulmonary abnormalities; Neurological abnormalities; Growth and nutrition; Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Orofino et al. (49)	Cross-sectional	Cardiological abnormalities	–
Ospina et al. (50)	Retrospective cohort	Eye abnormalities; Growth and nutrition; Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Pacheco et al. (51)	Descriptive study	Hearing abnormalities; Eye abnormalities; Neurological abnormalities	–
Peçanha et al. (52)	Case series	Neurodevelopmental delays	Bayley III
Petribu et al. (53)	Case series	Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Pinato et al. (54)	Cross-sectional	Neurological abnormalities	–
Pone (55)	Cross-sectional	Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Pool et al. (56)	Retrospective cohort	Hearing abnormalities; Eye abnormalities; Neurological abnormalities; Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Rajapakse et al. (57)	Case series	Joint and limb deformities; Gastrointestinal/pulmonary abnormalities	–
Rice et al. (58)	Descriptive study	Neurodevelopmental delays	Not provided
Rocha et al. (59)	Case-control	Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Roma et al. (60)	Case series	Hearing abnormalities; Eye abnormalities; Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Santana et al. (61)	Case series	Gastrointestinal/pulmonary abnormalities; Cardiological abnormalities; Eye abnormalities; Neurological abnormalities; Neurodevelopmental delays; Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	Not provided
Satterfield-Nash et al. (62)	Case series	Hearing abnormalities; Neurological abnormalities; Neurodevelopmental delays	ASQ 3
Soares et al. (63)	Cohort	Growth and nutrition	–
Soriano-Arandes et al. (64)	Cohort	Hearing abnormalities; Neurological abnormalities	–
Subissi et al. (65)	Case-control	Neurodevelopmental delays	Not provided
Sulleiro et al. (66)	Case report	Neurological abnormalities; Growth and nutrition	–
Trigueiro et al. (67)	Cross-sectional	Eye abnormalities	–
Tsui et al. (68)	Case series	Eye abnormalities	–
van der Linden et al. (69)	Descriptive study	Neurological abnormalities	–

(Continued)

TABLE 2 | Continued

References	Study design	Clinical abnormalities	Developmental screening test
van der Linden et al. (70)	Case series	Neurological abnormalities; Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
van der Linden et al. (71)	Cohort	Neurological abnormalities	–
de Vasconcelos et al. (72)	Case series	Genito-urinary abnormalities (Cryptorchidism/Neurogenic bladder)	–
Ventura et al. (73)	Cross-sectional	Eye abnormalities	–
Ventura et al. (73)	Cross-sectional	Eye abnormalities	–
Ventura et al. (74)	Cross-sectional	Eye abnormalities; Neurological abnormalities	–
Veras Gonçalves et al. (75)	Case series	Eye abnormalities; Endocrine disfunction	–
Verçosa et al. (76)	Case series	Eye abnormalities	–
Walker et al. (77)	Retrospective cohort	Eye abnormalities; Neurological abnormalities; Cerebral abnormalities (Microcephaly, Calcification, Hydrocephaly, Cerebral atrophy, Cerebellar alterations)	–
Zin et al. (12)	Case series	Joint and limb deformities; Eye abnormalities; Neurological abnormalities	–
Zin et al. (78)	Cross-sectional	Hearing abnormalities	–

to the auditory system is due to cochlear involvement (81). Similar injuries are likely to be responsible for hearing loss in children with congenital ZIKV infection, although histological studies need to confirm this (39).

In a cross-sectional study, when evaluating 45 children with a mean age of 10 months, Leite et al. (41) found no association between exposure to ZIKV during pregnancy and audiological alterations. Similarly, when comparing children exposed and not exposed to ZIKV, Fandiño-Cárdenas et al. (30), in their cohort study of 66 exposed children did not observe hearing loss in the first two years of life.

In conclusion, hearing loss due to congenital ZIKV can be sensorineural, neural, conductive, isolated, or mixed. Therefore, a complete hearing assessment should be performed on all ZIKV-infected patients to rule out auditory neuropathy syndrome and sensorineural hearing loss (82).

Cardiac Findings/Congenital Heart Disease

When analyzing the cardiovascular system of ZIKV-exposed children, Santana et al. (61) found echocardiographic abnormalities suggesting tropism of ZIKV to tissue beyond the central nervous system. Corroborating this finding, Orofino et al. (49) found a higher frequency of cardiac alterations in ZIKV-exposed babies than in the general population. However, none of these defects were severe. Therefore, the authors suggested that recommendations for performance of fetal echocardiograms in women with ZIKV infection during pregnancy and recommendations for postnatal infant echocardiogram should follow general infant population guidelines.

Genito-Urinary Findings

All studies concerning genitourinary characteristics were performed in Brazil, two in the state of Rio de Janeiro and one in Pernambuco. Costa Monteiro et al. (22, 23) found that more than 90% of children with microcephaly in their series had neurogenic bladder, a health condition known to cause kidney damage when left untreated. On this theme, de Vasconcelos et al. (72) published a case series describing cryptorchidism in 3-year-old children with ZIKV-related microcephaly.

Nutrition, Gastro-Intestinal Findings and Feeding Difficulties

Regarding the nutritional status of children exposed to ZIKV, nine papers described anthropometric changes such as low birth weight and growth restriction (20, 21, 28, 29, 33, 48, 50, 66).

In a cohort study, Soares et al. (63) found differences in arm and arm muscle circumference and fat-free mass in children from 1 to 3 months of age. Weight and length at 3 months of age were lower in ZIKV-exposed infants. Similarly, Carvalho-Sauer et al. (20) concluded that low birth weight in children with CZS was 4-fold greater as compared to children without CZS. Furthermore, prematurity and cesarean delivery were associated with low birth weight in exposed children. It should also be noted that most children with CZS were born to mothers of African heritage, single, and with less years of education, suggesting CZS disproportionately affected disenfranchised populations (28, 63).

Leal et al. (38) described a delay in the initial pharyngeal phase of swallowing. This combined with significant oral dysfunction, increases the risk of oral aspiration, predominantly with liquid foods. Also, Santana et al. (61) reported that four of 18 patients who had swallowing impairment were fed by gastrostomy.

In addition, Leal et al. (40) in a cross-sectional study nested in a cohort study, found a high prevalence of adenoid hypertrophy in children with Zika-related microcephaly, with consequent upper airway obstruction leading to chronic upper airway obstructive disorder, secretory otitis media and subsequent dysphagia (40). Abdominal imaging studies on the other hand

showed no characteristic findings that were higher than those observed in the general population (55).

Musculo-Skeletal Findings

Regarding orthopedic abnormalities, all seven papers described the presence of arthrogryposis in children with congenital zika, often present in both upper and lower extremities. A study by Aragão et al. (16) found that 75% of children with microcephaly and 100% of those with arthrogryposis had reduced thickness of the thoracic spinal cord. However, the latter group had evidence of narrowing of the entire spinal cord, with severely reduced spinal cord anterior roots. The authors concluded that it is crucial to consider Zika virus infection in the differential diagnosis of congenital diseases of the spinal cord and anterior nerve root if mother-infant pair have any risk factors for ZIKV antenatal exposure. This is especially relevant in mild cases where microcephaly is absent, and the only clinical manifestation is, for example, abnormal joints. On the other hand, health professionals should pay close attention when monitoring children from an epidemic area with mild or no clinical signs of spinal cord and anterior nerve root lesions, as they may have future problems with neuro-psychomotor development.

Endocrinologic Findings

Regarding the endocrine system, the most prevalent and clinically relevant problems were pubertal dysfunctions, thyroid disease, growth faltering and obesity. These conditions require careful monitoring and highlight the need for endocrine evaluations in children with CZS, particularly those with microcephaly. Early diagnosis and referral to appropriate treatment in this situation may often be necessary (75).

Need for Long Term Follow-Up

The repercussions of maternal infection during pregnancy on child development have been extensively described in the literature in regards to classic teratogenic pathogens responsible for TORCH syndromes (26). Fetal infection often triggers a systemic inflammatory response which may persist after birth, compounding further damage to the brain. This is one of the prevailing hypotheses on the pathogenesis of brain injury (26). Lesions associated with deep gray matter injury, vascular compromise and neural progenitor cell dysfunction have also been described (83–85).

Saad et al. (86) made the same recommendation in reviewing the most frequent clinical findings in children born to women with confirmed ZIKV infection during pregnancy. They described a broad spectrum of abnormalities resulting from an inflammatory reaction to the virus or a direct effect of the virus itself, causing damage to the CNS and neurological abnormalities which potentially manifest over time.

These published results describing developmental delay and other neuro-sensory deficits which may manifest later in life point to the need for continued monitoring of children with antenatal ZIKV exposure to assess risks of learning and behavioral disorders in the long term (85).

CONCLUSION

In this systematic review, the most relevant findings were injuries to the infant central nervous system. CZS is a neurotropic disease with several associated abnormalities. Although the majority of published studies were from Brazil, there were no regional differences across the country and also in comparison to other countries in Latin America. Another important finding which the studies underscored is the later delay in development that may subsequently occur in an apparently normal infant at the time of birth. Finally, due to the vulnerability of women and children and the severe repercussions of ZIKV infection in pregnancy, studies should continue to monitor these children as they age. Broader descriptions of clinical findings are also important to further characterize the spectrum of disease in children. Prospective studies evaluating infants and children with antenatal ZIKV exposure may be able to describe the actual prevalence of adverse pregnancy, infant and childhood outcomes in this population. Prompt recognition of clinical abnormalities allows for implementation of early interventions which can improve later neurodevelopmental pathways in children born to mothers with gestational ZIKV infection.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YA, JM, and PGB did the manuscript search, reviewed all the literature and drafted the paper, and approved the final text. PB, KN-S, and MM formulated the research question, performed the analysis and draft of the paper, and approved the final text. All authors contributed to the article and approved the submitted version.

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Declining Trajectories of Co-occurring Psychopathology Symptoms in Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder: A 10-Year Longitudinal Study

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Objective: Our objective was to examine developmental trajectories of co-occurring psychopathology symptoms from childhood to young adulthood in individuals with Attention-Deficit/Hyperactivity Disorder (ADHD), individuals with Autism Spectrum Disorder (ASD), and typically developing (TD) individuals.

Method: We assessed co-occurring psychopathology symptoms in 61 individuals with ADHD, 26 with ASD, and 40 TD individuals at baseline (T1; M_{age} = 11.72, 64% boys), 2-year follow up (T2; M_{age} = 13.77), and 10-year follow up (T3; M_{age} = 21.35). We analyzed trajectories of internalizing behaviors, externalizing behaviors, and total problems with linear mixed models.

Results: From T1 to T3, the ADHD group displayed a small decline in internalizing behaviors ($d = -0.49$) and large declines in externalizing behaviors ($d = -0.78$) and total problems ($d = -0.71$). The ASD group displayed large declines in internalizing behaviors ($d = -0.79$), externalizing behaviors ($d = -0.80$), and total problems ($d = -0.89$). From T1 to T2, the decline in externalizing behaviors and total problems were significantly smaller in the ADHD group compared with the ASD group. The ADHD and the ASD group displayed more co-occurring symptoms compared with the TD group at T3.

Conclusion: Individuals with ADHD and ASD, respectively, displayed declines in co-occurring symptoms from childhood to young adulthood. Individuals with ASD displayed an earlier decline compared with individuals with ADHD. Compared with TD individuals, individuals with ADHD and ASD, respectively, continued to display elevated levels of co-occurring symptoms in young adulthood.

Keywords: attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), psychopathology, longitudinal analyses, externalizing and internalizing behavior, neurodevelopmental disorders, adult outcomes

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) are two major neurodevelopmental disorders (1–3). Despite ADHD and ASD being separate diagnoses, they often co-occur (4–6) and share genetic risk and endophenotypes (7–10). Individuals with ADHD and individuals with ASD experiences high levels of comorbid disorders and co-occurring psychopathology symptoms across the lifespan (11–17).

The co-occurring symptoms may be of particular importance, as these symptoms predict poorer adult outcome, lower occupational functioning, and impaired quality of life in individuals with ADHD and individuals with ASD (18–24). Two broad dimensions of co-occurring symptoms are internalizing (e.g., anxiety and depression symptoms) and externalizing behaviors (e.g., rule-breaking behavior, conduct problems). Several factors contribute to high levels of co-occurring symptoms among individuals with ADHD and individuals with ASD, among them are executive dysfunction, symptom severity, and emotional dysregulation (25–28). However, little is known about the developmental trajectories of co-occurring symptoms in these two clinical populations and how the trajectories compare with each other and with typically developing (TD) individuals (29, 30).

Development of Co-occurring Symptoms in ADHD

High levels of co-occurring symptoms are found across the lifespan in individuals with ADHD (16, 31, 32). In the longitudinal Massachusetts General Hospital Study of individuals with ADHD, the authors found that most comorbid disorders had an early onset in preadolescence years (33–36). In their 16-year follow-up, the authors found high life-time prevalence of comorbid disorders, but in young adulthood the ADHD group only presented with more anxiety disorders compared with the TD group (34). This could suggest that comorbid disorders, and hence co-occurring symptoms, wane over time in individuals with ADHD. In the longitudinal Berkley Girls Study, co-occurring symptoms were examined in childhood, adolescence, and young adulthood (37). The authors found children with ADHD to display more co-occurring symptoms in childhood (mean age 9; $d = 0.94$–1.69) (38), adolescence (mean age 14; $d = 0.87$–1.29) (39), and young adulthood (mean age 19; $d = 0.77$–1.30) (32) compared with TD individuals. These results suggest that individuals with ADHD consistently presents with more co-occurring symptoms from childhood to young adulthood. At the same time, effect sizes could suggest a slightly decline from childhood to young adulthood but no conclusion can be drawn due to the lack of longitudinal analyses of change over time.

A few studies have examined the developmental trajectories of co-occurring symptoms in individuals with ADHD. In a previous study by our research group, declines in internalizing and externalizing behaviors over a 2-year period (mean age 11–13) were found (40). However, in contrast, another longitudinal study following children with ADHD over a 3-year period (mean age 10–13) reported that the majority displayed persistent trajectories of internalizing and externalizing behaviors (61.5 and 93%, respectively) over a 3-year period, with only 10 and 7%, respectively, displaying declining trajectories (41). In a third study, following up children with ADHD 13-years later (mean age 25), the authors found declines in internalizing and externalizing behaviors compared with baseline scores (42). Thus, two studies have suggested declining trajectories of internalizing and externalizing behaviors (40, 42), whereas one study have suggested stable trajectories for the majority of individuals with ADHD (41). Despite a possible decline in co-occurring symptoms over time, the results of Hinshaw et al. (32) and Skogli et al. (40) suggests that individuals with ADHD continue to display high levels of co-occurring symptoms compared with TD individuals.

Some limitations of the aforementioned studies should be mentioned. First, two studies did not examine developmental trajectories but only differences between individuals with ADHD and TD individuals within different assessment waves (35–37). Second, two of three studies examining developmental trajectories only included two assessment waves (40, 42), preventing them from detecting change in the trajectories. Third, two of the three studies examined developmental trajectories over a short time-span (2 or 3 years) (40, 41). Fourth, the only study examining developmental trajectories over a long time-span, from childhood to young adulthood, included relatively few participants with ADHD ($n = 19$) (42). Thus, there is a need for studies examining developmental trajectories over a longer time-span and including several assessment waves and more participants with ADHD.

Development of Co-occurring Symptoms in ASD

High levels of co-occurring symptoms are found across the lifespan in individuals with ASD (5, 13, 29, 43, 44). However, few studies have examined the developmental trajectories of co-occurring symptoms from childhood to adulthood in individuals with ASD (29). In a recent review of longitudinal studies from childhood to adolescence, the authors concluded that the literature suggests a slightly decline in co-occurring symptoms from childhood to adolescence in individuals with ASD, despite persistent higher rates compared with TD individuals (45). This conclusion is in line with previous findings by our research group, showing a decline in parent-reported, but not self-reported, co-occurring symptoms over a 2-year period (25, 43).

A few studies investigating the developmental trajectories of co-occurring symptoms form childhood to young adulthood in individuals with ASD have been conducted. Two studies have found declining trajectories of internalizing and externalizing behaviors from childhood (mean age 8 and 12 years, respectively) to young adulthood (mean age 24 and 23 years, respectively) in individuals with ASD (46, 47). In contrast, another study reported an increase in internalizing behaviors from childhood (age 9) to young adulthood (age 24) in individuals with ASD (48). McCauley et al. (49) identified different trajectories of internalizing behaviors (anxiety and depression symptoms,

respectively) from childhood (mean age 9 years) to young adulthood (mean age 20 years) in individuals with ASD. The authors identified one group with stable low anxiety symptoms and one group with stable high anxiety symptoms. Similarly, the authors identified one group with stable low depressive symptoms and one group with fluctuating but stable high depression symptoms. Thus, two studies have suggested declining trajectories of internalizing and externalizing behaviors (46, 47), one study have suggested stable trajectories of internalizing behaviors (49), and one study have suggested increasing trajectories of internalizing behaviors (48) from childhood to young adulthood among individuals with ASD.

One limitation with the four aforementioned longitudinal studies were the inclusion of individuals with ASD both with and without intellectual disability. In fact, in all four cohorts the majority of participants have been reported to have an intellectual disability (IQ < 70) (46, 48, 50, 51). Thus, there is a need for studies focusing only on individuals with ASD without intellectual disability. This is because higher IQ is associated with different trajectories of co-occurring symptoms (49). For example, McCauley et al. (49) found that higher childhood verbal IQ was associated with greater odds of being in the high/stable trajectory of anxiety symptoms and the high-fluctuating trajectory of depressive symptoms. Further, using the same trajectory measure with individuals with and without intellectual disability cloud the picture, because measures intended for individuals without intellectual disability may be poor measures of co-occurring symptoms among individuals with intellectual disability, and vice versa (49, 52). Another limitation of the aforementioned studies is that none of them included a TD control group for comparison of trajectories. Nonetheless, Gray et al. (46) and Stringer et al. (47) compared co-occurring symptoms in adulthood with a normative sample or clinical norms. They found that, despite a decline in co-occurring symptoms from childhood to adulthood, individuals with ASD still displayed high-levels of co-occurring symptoms when compared with normative data. This is in line with studies finding a relatively high prevalence of co-occurring symptoms among adults with ASD (13, 17, 53, 54). In conclusion, the current literature suggests that individuals with ASD display declines in co-occurring symptoms from childhood to adulthood, but continue to display high levels of co-occurring symptoms in adulthood.

Knowledge Gaps

To our knowledge, no study has previously compared the developmental trajectories of co-occurring symptoms from childhood to young adulthood in individuals with ADHD and individuals with ASD. Further, only one previous study (with few participants) have examined the trajectories of co-occurring symptoms in individuals with ADHD from childhood to young adulthood (42), and no previous study has examined the developmental trajectories of individuals with ASD exclusively without intellectual disability or included a TD comparison group. Thus, a study examining the developmental trajectories of individuals with ADHD and individuals with ASD without intellectual disability, and comparing their trajectories with TD individuals, is warranted. Further, longitudinal studies comparing the developmental trajectories of co-occurring symptoms in individuals with ADHD with individuals with ASD from childhood to young adulthood are needed in order to understand the unique and shared developmental trajectories of these two disorders. Similar developmental trajectories could suggest that communalities in genotype and/or endophenotypes (e.g., executive dysfunction; social cognitive difficulties) contribute to the developmental trajectories of co-occurring symptoms across both groups, whereas differential trajectories could suggest that the two disorders unique factors play an important role.

Study Aims

We aimed to examine and compare the developmental trajectories of co-occurring symptoms among individuals with ADHD, individuals with ASD, and TD individuals from childhood to young adulthood. In line with the majority of previous studies, we hypothesized that individuals with ADHD and individuals with ASD would display declining trajectories of co-occurring symptoms over time (25, 40, 42, 45–47). Further, given that previous studies have suggested that ADHD and ASD are associated with high levels of co-occurring symptoms across the lifespan, we hypothesized that individuals with ADHD and individuals with ASD would continue to display higher levels of co-occurring psychopathology symptoms compared with TD individuals in young adulthood. Since we expected a decline in co-occurring symptoms in both individuals with ADHD and individuals with ASD, and these two groups share endophenotypes assumed to influence co-occurring symptoms, we hypothesized that they would display similar developmental trajectories.

METHODS

Procedure and Participants

This study is part of the Lillehammer Neurodevelopmental Follow-up Study (LINEUP), a longitudinal study currently spanning baseline assessment (T1), 2-year follow-up (T2), and 10-year follow-up (T3). At T1, 85 children with ADHD, 38 children with ASD, and 50 TD children participated. Participants were recruited from child and adolescent psychiatric outpatient clinics at Innlandet Hospital, Norway, upon consecutive referrals. All individuals between 8 and 17 years of age referred for assessment of ADHD or ASD were invited to participate in the study. Those agreeing to participate were assessed for ADHD or ASD and included in the study if they meet diagnostic criteria based on DSM-IV. Thus, age at T1 equals the time of diagnosis in our sample. TD individuals were recruited through local schools and had to attend regular classes. At T1, all TD individuals were screened for mental disorders with the Kiddie-Schedule for Affective Disorders and Schizophrenia/Present and lifetime version (Kiddie-SADS), conducted separately with participants and their parents. Exclusion criteria for all participants were prematurity (<36 weeks), having a disease affecting the central nervous system, or having IQ < 70. An additional exclusion criterion for the ADHD group was no history of stimulant

treatment. Additional criteria for the TD group were no history of psychiatric disorder, dyslexia or head injury with loss of consciousness. Demographic and clinical characteristics of all three groups are presented in **Table 1**. There were no significant differences in age or gender between the groups, but the groups differed on IQ, mothers' education, and ASD/ADHD symptomology.

Diagnostic Assessment

Diagnostic assessment at T1 was based on a semi-structured clinical interview (Kiddie-SADS) (55) conducted separately with participants and their parents, and supplemented with information from the Autism Spectrum Screening Questionnaire (ASSQ) (56) and the ADHD Rating Scale IV [ARS-IV; (69)]. All measures have demonstrated good reliability and validity (55–59). Diagnostic assessment was conducted by experienced clinical psychologists and clinical educational therapist trained to achieve high interrater reliability on diagnostic assessments. Diagnostic decisions were based on comprehensive evaluations of information from the Kiddie-SADS, ASSQ, ARS-IV, and teacher reports on academic and social functioning. The assessments and diagnostic decisions were supervised and independently reviewed by a clinical psychologist specialized in neurodevelopmental disorders (M. Ø.). Disagreements were discussed in order to arrive at a "best estimate" DSM-IV consensus diagnosis. Eight participants meet the criteria for both ADHD and ASD, and were included in the ASD group. In the ADHD group, three participants had comorbid depressive disorder, one had separation anxiety, one had specific phobia, one had social anxiety disorder, three had generalized anxiety disorder, five had Tourette's syndrome, two had conduct disorder, and nine had oppositional defiant disorder. In the ASD group, two had comorbid depressive disorder, one had panic disorder, one had separation anxiety, three had specific phobias, two had social anxiety disorder, one had generalized anxiety disorder, one had obsessive-compulsive disorder, four had Tourette's syndrome, one had conduct disorder, and one had oppositional defiant disorder.

Treatment as Usual

Participants with ADHD and ASD received treatment as usual (TAU) at the child and adolescent psychiatric outpatient clinic after diagnosis. TAU could include psychoeducation for parents, medical treatment, and in some instances unstructured social skills training (for the ASD group). Participants were generally referred for treatment whiteout explicit focus on co-occurring symptoms, and thus, clinical focus may have centered on core symptoms and school performances and less on co-occurring symptoms (43). At T2, 28 participants (35%) in the ADHD group and 15 (41%) in the ASD group had a statement of special needs education, meaning that they received some kind of extra support at school. In the ADHD group, 44 participants (54%) received stimulant medication at T2, and seven participants (12%) received stimulant medication at T3. In the ASD group, four participants (11%) received stimulant medication at T2, and two participants (8%) received stimulant medication at T3.

Sample Retention

Two- and 10-years after baseline assessment, all participants were invited for follow-up assessment. Out of the 173 original participants, 168 participated at T2, giving an overall retention rate of 97.1% (see **Table 1** for retention rates in each group). At T3, 127 of the original participants were re-assessed, giving an overall retention rate of 73.4%. Of the 46 original participants not re-assessed at T3, we were unable to track down nine of them (four from the ADHD group; three from the ASD group; two from the TD group) and 37 declined further participation (20 from the ADHD group; 9 from the ASD group; 8 from the TD group). We examined differences between those who participated at T3 and those dropping-out in baseline (T1) characteristics; age, gender, full scale intelligence quotient, mothers' educational level, symptom severity (ASSQ; ARS-IV), and psychopathology symptoms (Child Behavior Checklist, total problems subscale). We used one-way analysis of variance (ANOVA) and chi-square test of independence with Bonferroni corrected alpha-level ($0.05/7 = 0.007$). There was no statistically significant difference between the two groups in any of the seven baseline characteristics (all $p \geq 0.013$).

Measures

Psychopathology Symptoms

We used the Achenbach System of Empirically Based Assessment (ASEBA) (60, 61) as a primary measure of psychopathology symptoms across all three waves. We chose the ASEBA because it is standardized across all ages, widely used in clinical settings, and includes a validated Norwegian translation (62, 63).

At T1 and T2, we used the ASEBA scale, Child Behavior Checklist (CBCL) (60), a parent reported scale comprising 113 items assessing psychopathology symptoms along eight syndrome scales (anxious/depressed; withdrawn/depressed; somatic complaints; social problems; thought problems; attention problems; rule-breaking behavior; aggressive behavior). In addition, the CBCL includes two broader band scales of internalizing behaviors (comprising anxious/depressed, withdrawn/depressed, and somatic complaints) and externalizing behaviors (comprising rule-breaking and aggressive behavior), as well as a total problems scale (comprising all eight syndrome scales). Raw scores are converted to *T*-scores ($M = 50$, $SD = 10$) based on American norms. Norwegian norms does not exist, but Norwegian children generally seems to obtain lower *T*-scores compared with American children (64). The psychometric properties of the CBCL are good regarding both reliability ($\alpha \geq 0.80$), sensitivity (40–83%), and specificity (70–94%), and confirmatory factor analyses have confirmed the factor structure across different countries (62–65).

At T3, we used the ASEBA scale, Adult Self-Report (ASR) (61), a self-report scale comprising 126 items assessing psychopathology symptoms along eight syndrome scales. These syndrome scales are the same as for the CBCL with one exception, the social problems subscale is replaced by an intrusiveness subscale. As for the CBCL, the syndrome scales are included in two broader band scales of internalizing behaviors (comprising anxious/depressed, withdrawn/depressed, and somatic complaints) and externalizing behaviors (comprising

TABLE 1 | Demographic and clinical characteristics of the three participant groups.

	ADHD[1] $n = 85$		ASD[2] $n = 38$		TD[3] $n = 50$		Group difference	
T1—baseline	***M***	***SD***	***M***	***SD***	***M***	***SD***	***p***	**Bonferroni**
Age	11.61	2.08	12.03	2.34	11.56	1.99	0.532	
% male/female	54/46	84/16	64/36	0.006				
Full scale IQ	94.44	13.75	98.26	17.82	103.78	12.95	**0.002**	1 < 3
Mothers' education in years	12.66	2.15	12.79	2.67	14.58	2.37	**<0.001**	1, 2 < 3
Autism Spectrum Screening Questionnaire	9.68	10.09	21.47	9.27	1.62	1.85	**<0.001**	3 < 1 < 2
ADHD Rating Scale IV	26.62	10.51	21.37	10.28	2.64	2.99	**<0.001**	3 < 2 < 1
CGAS	57.46	8.94	51.61	10.18			**0.002**	
T2—2-year follow-up								
Sample retention (%)	81 (95.3%)	37 (97.4%)	50 (100.0%)					
Age	13.64	2.14	14.22	2.35	13.62	1.95	0.342	
% male/female	53/47	84/16	64/36	0.006				
Autism Spectrum Screening Questionnaire	7.68	7.26	20.56	9.21	1.04	2.78	**<0.001**	3 < 1 < 2
ADHD Rating Scale IV	18.18	10.91	14.44	8.70	2.22	2.70	**<0.001**	3 < 1, 2
T3—10-year follow-up								
Sample retention (%)	61 (71.8%)	26 (68.4%)	40 (80%)					
Age	21.38	2.25	22.15	2.62	20.88	1.88	0.078	
% male/female	56/44	81/19	65/35	0.014				

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; TD, typically developing. The bold values indicate a significant p-value after Bonferroni correction. Superscript values indcates the group number used in the Bonferroni column.

rule-breaking, aggressive, and intrusive behavior), as well as a total problems scale (comprising all syndrome scales). Raw scores are converted to age-adjusted T-scores, making it easy to compare within individual scores over time. The ASR have demonstrated good reliability ($\alpha \geq 0.81$) and validity (66–68).

ADHD Symptomatology

At T1 and T2, the ARS-IV (69) was used as measure of ADHD symptomatology. The ARS-IV is a parent reported scale comprising 25 items assessing ADHD symptoms across the two domains; hyperactivity/impulsivity and inattention. The ARS-IV has demonstrated good psychometric properties with good test-retest reliability of ≥0.77 and internal consistency ($\alpha \geq 0.80$) (58, 70).

ASD Symptomatology

At T1 and T2, the ASSQ (56) was used as measure of ASD symptomatology. The ASSQ is a parent reported scale comprising 27 items assessing ASD symptoms across social interaction problems, communication, and restricted and repetitive behaviors. The ASSQ has demonstrated good psychometric properties with good test-retest reliability of 0.96 and convergent validity with other measures of ASD symptomatology (56).

Statistical Analyses

We used SPSS version 26 for all statistical analyses. We used an alpha-level of 0.05 for statistical significance and used Bonferroni corrected alpha-levels for multiple comparisons. To examine differences in demographic and clinical variables between groups, we used analysis of variance (ANOVA) and chi-square test of independence. Differences between the ADHD, ASD, and TD groups were considered significant if *p*-values were below 0.004 ($0.05/13 = 0.004$).

To examine the developmental trajectories of co-occurring symptoms and relate changes over time to group affiliation, we used Linear Mixed Models (LMM) for longitudinal analyses. The technique includes participants with partial data and is thus more robust in longitudinal studies where missing data is common (71, 72). We estimated the model using restricted maximum likelihood, with piecewise linear splines, with a knot at T2. We fitted separate random intercepts and slopes for the first (T1–T2) and second (T2–T3) time period. Fixed effects of group x time interactions were the parameters of main interest, indicating differences in trajectories between groups. To assess all three group comparisons, we fitted models with all three groups (TD vs. ADHD/ASD) and with only ADHD vs. ASD. We used the Akaike information criteria to assess model fit. We used Pearson's correlation-coefficient, *r*, to examine associations between changes in core symptoms (ADHD and ASD) and changes in co-occurring symptoms from T1 to T2.

To examine group differences in outcome (i.e., psychopathology symptoms at T3), we used multivariate analysis of variance (MANOVA) with the three ASEBA scales internalizing behaviors, externalizing behaviors, and total problems as dependent variables. A significant group effect (Wilks Lambda) was followed-up with ANOVAs for each dependent variable and Bonferroni *post-hoc* tests.

TABLE 2 | Fixed effects of time and group in a Linear Mixed model, with follow-up over 10 years in ASD, ADHD, and TD groups.

ASEBA scale	Internalizing			Externalizing			Total problems		
	Estimate	SE	95% CI	Estimate	SE	95% CI	Estimate	SE	95% CI
Main effect of group									
TD	0 (ref)			0 (ref)			0 (ref)		
ADHD	16.92***	1.80	13.37, 20.48	19.02***	1.75	15.57, 22.46	24.02***	1.56	20.96, 27.07
ASD	23.18***	2.17	18.90, 27.46	18.25***	2.10	14.10, 22.40	26.23***	1.87	22.55, 29.91
ADHD (ref) vs. ASD	6.26**	2.06	2.17, 10.34	−0.77	2.05	−4.83, 3.29	2.21	1.69	−1.12, 5.55
Main effect of time									
T1–T2	−1.25	1.33	−3.88, 1.38	−1.09	1.23	−3.52, 1.34	−1.32	1.23	−3.74, 1.10
T2–T3	4.85*	2.18	0.54, 9.16	3.62	1.98	−0.29, 7.53	7.47***	2.15	3.21, 11.72
Interaction group × time (T1–T2)									
TD	0 (ref)			0 (ref)			0 (ref)		
ADHD	−1.49	1.69	−4.82, 1.85	−3.52*	1.56	−6.59, −0.45	−2.72	1.56	−5.80, 0.35
ASD	−4.38*	2.07	−8.47, −0.29	−7.97***	1.90	−11.73, −4.21	−6.32***	1.91	−10.09, −2.54
ADHD (ref) vs. ASD	−2.89	1.98	−6.82, 1.04	−4.45*	1.89	−8.19, −0.72	−3.58*	1.79	−7.12, −0.05
Interaction group × time (T2–T3)									
TD	0 (ref)			0 (ref)			0 (ref)		
ADHD	−7.65**	2.81	−13.21, −2.09	−7.45**	2.55	−12.49, −2.41	−10.77***	2.15	−16.26, −5.28
ASD	−8.19*	3.54	−15.19, −1.20	−3.91	3.21	−10.23, 2.42	−9.55**	3.49	−16.44, −2.65
ADHD (ref.) vs. ASD	−0.38	3.71	−7.74, 6.98	3.62	3.34	−3.00, 10.24	1.30	3.41	−5.45, 8.05

*Internalizing, externalizing, and total problems = Achenbach System of Empirically Based Assessment; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; TD, typically developing; T1, baseline; T2, 2-year follow-up; T3, 10-year follow-up. *p < 0.05, **p < 0.01, ***p < 0.001.*

RESULTS

Trajectories of Co-occurring Psychopathology Symptoms

Table 2 displays the results from LMM for each symptom trajectory and **Figures 1**–**3** display the trajectories of the three groups across the dependent variables. At baseline (T1), the ADHD and the ASD group displayed significantly higher levels of psychopathology symptoms than the TD group (**Table 2**). The ASD group displayed significantly higher levels of internalizing behaviors compared with the ADHD group, whereas there was no significant difference between the ADHD and the ASD group in externalizing behaviors and total problems. From T1 to T2, the ADHD group displayed a significant decline ($p = 0.025$) in externalizing behaviors relative to the TD group, whereas the ASD group displayed significant declines in both internalizing behaviors ($p = 0.036$), externalizing behaviors ($p < 0.001$), and total problems ($p = 0.001$) relative to the TD group. The declines in externalizing behaviors ($p = 0.020$, −4.5 *T*-scores) and total problems ($p = 0.047$, −3.6 *T*-scores) were significantly larger in the ASD group compared with the ADHD group.

From T2 to T3, the ADHD group displayed significant declines in internalizing behaviors ($p = 0.007$), externalizing behaviors ($p = 0.004$), and total problems ($p < 0.001$) relative to the TD group. The ASD group continued to display declines in internalizing behaviors ($p = 0.022$) and total problems ($p = 0.007$) relative to the TD group, but not externalizing behaviors. In contrast, internalizing behaviors ($p = 0.028$) and total problems ($p = 0.001$) increased significantly in the TD group.

In total from T1 to T3, the ADHD group displayed a small to medium ($d = -0.49$) decline in internalizing behaviors and medium to large declines in externalizing behaviors ($d = -0.79$) and total problems ($d = -0.71$). The ASD group displayed large declines in both internalizing behaviors ($d = -0.79$), externalizing behaviors ($d = -0.80$), and total problems ($d = -0.89$). From T1 to T2, the decline in externalizing behaviors in the ADHD group correlated significantly with a decline in ADHD symptoms ($r = 0.45$, $p < 0.001$) and the declines in internalizing ($r = 0.35$, $p = 0.040$) and externalizing behaviors ($r = 0.51$, $p = 0.002$) in the ASD group correlated significantly with a decline in ASD symptoms. The decline in total problems in the ASD group correlated non-significantly with a decline in ASD symptoms ($r = 0.32$, $p = 0.062$).

Group Differences at T3

A MANOVA with ASEBA scales at T3 as dependent variables showed a significant effect of group [$F_{(6, 236)} = 4.584$, $p < 0.001$, $\eta_p^2 = 0.104$]. Separate ANOVAs for each dependent variable showed a significant group effect in all three domains (see **Table 3**). For internalizing behaviors, *post-hoc* tests showed that the ADHD ($p = 0.004$, $d = 0.69$) and the ASD ($p = 0.002$, $d = 0.98$) group displayed significantly more internalizing behaviors compared with the TD group. For externalizing difficulties, *post-hoc* tests showed that the ADHD group displayed significantly more externalizing behaviors compared with the TD group ($p = 0.001$, $d = 0.80$), whereas the ASD group displayed non-significantly more externalizing behaviors compared with the TD group ($p = 0.051$, $d = 0.64$). For total problems, *post-hoc* tests showed that the ADHD ($p < 0.001$, $d = 0.94$) and the

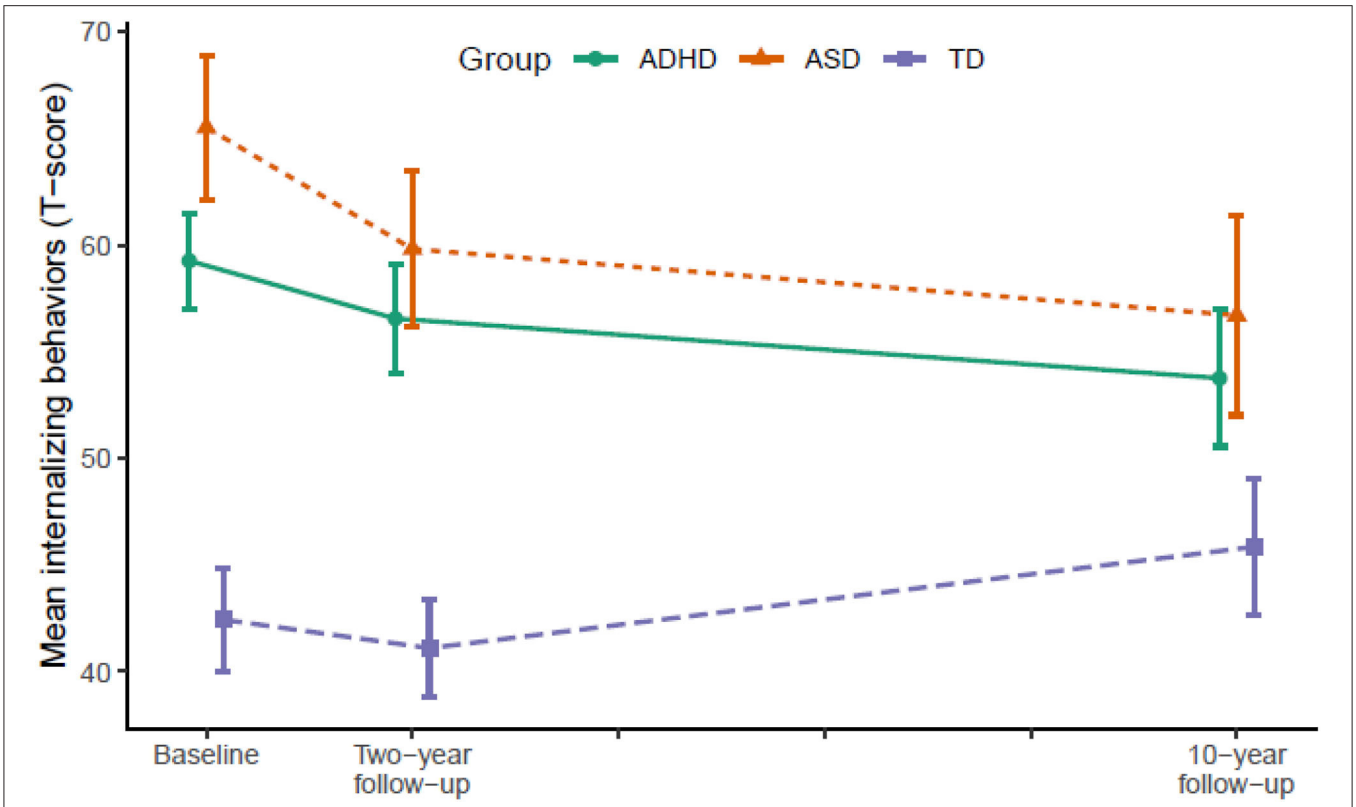

FIGURE 1 | Developmental trajectories of internalizing behavior from baseline (T1) to 10-year follow-up (T3). Vertical error bars indicate 95% CI; Groups are dodged slightly along x-axis to prevent over plotting; Internalizing behaviors = Achenbach System of Empirically Based Assessment; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; TD, typically developing.

ASD ($p = 0.002$, $d = 0.97$) group displayed significantly more total problems compared with the TD group. There were no significant differences between the ADHD and the ASD group.

DISCUSSION

Our findings provide the field with at least three new pieces of knowledge. First, we provide evidence showing declining trajectories of co-occurring symptoms across three assessment waves from childhood to young adulthood (mean age 11–21) in individuals with ADHD. Second, we provide evidence suggesting similar but partially differential trajectories of co-occurring symptoms among individuals with ADHD and individuals with ASD. Third, we found that individuals with ADHD and individuals with ASD continue to display more co-occurring symptoms in young adulthood compared with TD individuals, despite differential developmental trajectories in the three groups (declining vs. increasing). Overall, our findings highlight the persistence of co-occurring symptoms among individuals with ADHD and ASD, respectively, while at the same time providing some optimism regarding the symptom trajectories.

The decline in co-occurring symptoms among individuals with ADHD is in accordance with our hypothesis, previous studies (42), and is consistent with the declining trajectory of ADHD symptomatology observed from childhood to adulthood (73–76). This may indicate that ADHD core symptomatology and co-occurring symptoms follows similar trajectories from childhood to young adulthood. Previous studies have suggested interdependence between ADHD core symptomatology and co-occurring symptoms [e.g., (77, 78)]. Our findings support this interdependence through demonstrating significant associations between changes in core symptomatology and co-occurring symptoms. Thus, it seems that declines in either ADHD symptomatology or co-occurring symptoms associates with declines in the other symptom domain. However, our research group has previously found that declines in ADHD symptoms over a 2-year period were differentially associated with a decline or increase in depressive symptoms in girls vs. boys and based on self-report vs. parent-report (78). Thus, further research examining the relationship between changes in co-occurring symptoms and ADHD symptomatology is needed to understand the interconnected development of these symptom domains. Further, studies examining predictors of change are warranted as this provide knowledge about what factors may be important to target in interventions.

Similar to the ADHD group, and in accordance with our hypothesis, we found declines in co-occurring symptoms across all domains for the ASD group. This is consistent with two of the previous studies of individuals with ASD (46, 47). Our findings suggest that also individuals with ASD without intellectual

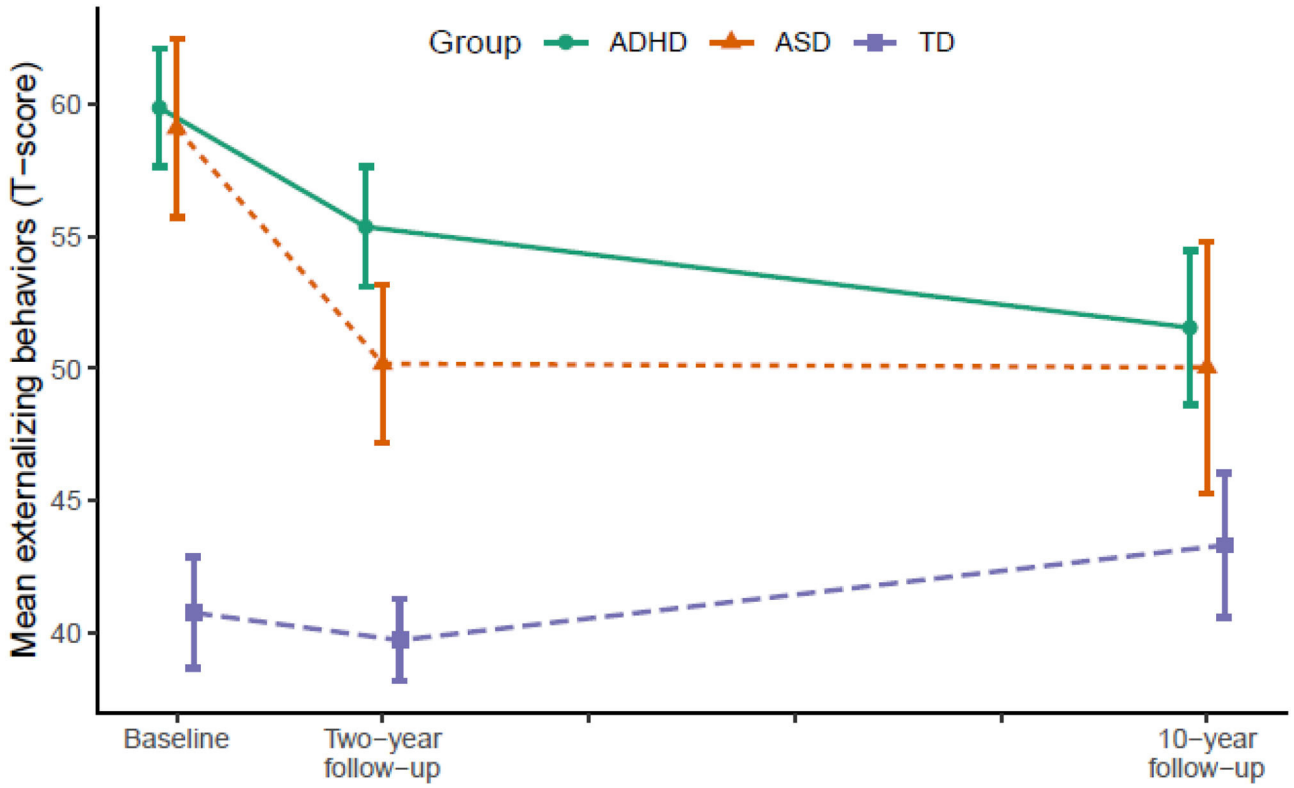

FIGURE 2 | Developmental trajectories of externalizing behavior from baseline (T1) to 10-year follow-up (T3). Vertical error bars indicate 95% CI; Groups are dodged slightly along x-axis to prevent over plotting; Externalizing behaviors = Achenbach System of Empirically Based Assessment; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; TD, typically developing.

disability display declining trajectories of co-occurring symptoms from childhood to young adulthood. There were few differences in the trajectories of co-occurring symptoms from childhood to young adulthood between the ADHD and the ASD group. The ASD group displayed larger declines in externalizing behaviors and total problems from T1 to T2 compared with the ADHD group. Children with ASD without intellectual disability often receives the diagnosis late (around 11–12 years), typically after several years of diagnostic assessment (79). We therefore speculate on whether a late diagnosis of ASD and lack of ASD specific treatment and individual tailoring at school could contribute to this finding. When receiving the diagnosis, co-occurring symptoms among children with ASD are at its most extreme and from there only declines can be observed (i.e., regression toward the mean) (80). In addition, children with ASD may benefit from more individual tailoring at home and school after diagnosis. A diagnosis is often necessary to gain access to social skills training and support staff at school, factors contributing to declines in co-occurring symptoms among children with ASD (81–83). Consequently, considerable declines in co-occurring symptoms are observed after diagnosis.

In contrast to ASD, we speculate on whether the co-occurring symptoms among children with ADHD may be closer linked to the core symptoms (84) and that children with ADHD may have poorer access and benefit less from individual tailoring at school and psychological treatments such as social skills training (85, 86). Clinical guidelines for treatment of ADHD differs from guidelines for ASD with a greater emphasis on medical treatment and less emphasis on individual tailoring and psychological treatments, despite the fact that many children with ADHD can benefit from the same interventions as children with ASD (87, 88). In our sample, 54% of participants with ADHD received medical treatment at T2, and in accordance with clinical guidelines, all participants shall have received an offer of medical treatment. Thus, almost half of our participants either declined the offer or discontinued medical treatment during the first 2-year period following diagnosis. Since we did not focus on treatment in this study, the reasons for this are unknown, but it is interesting to note that the ADHD group, of which 54% received medical treatment between T1 and T2, had less declines in co-occurring symptoms than the ASD group, which probably received other forms of intervention. However, based on our results we can only speculate to the reasons for this difference, and hence, more research is needed to understand which factors drive the larger declines in co-occurring symptoms from childhood to adolescence in the ASD group compared with the ADHD group. It would be interesting in the future to include variables related to school support and interventions as well as

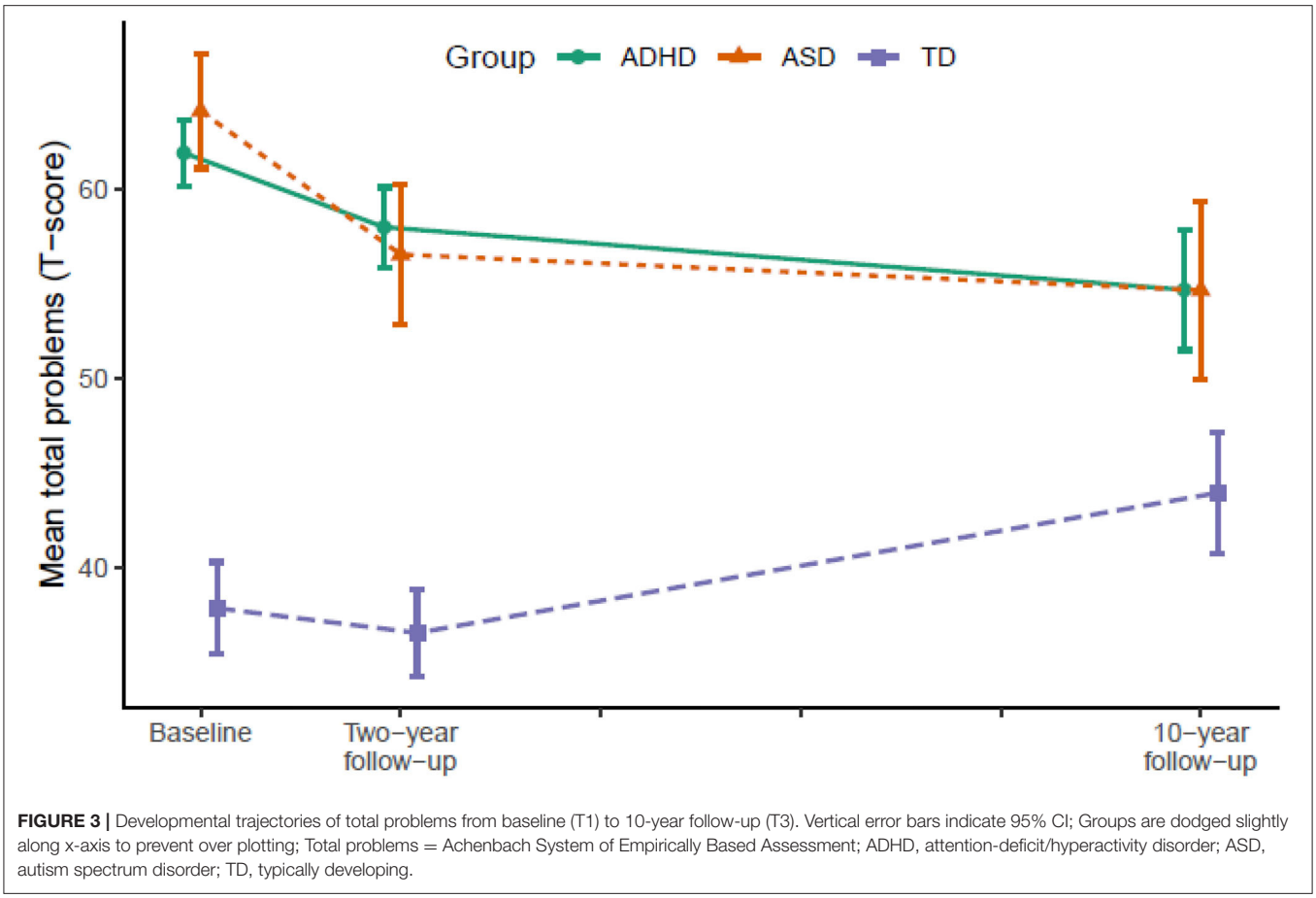

FIGURE 3 | Developmental trajectories of total problems from baseline (T1) to 10-year follow-up (T3). Vertical error bars indicate 95% CI; Groups are dodged slightly along x-axis to prevent over plotting; Total problems = Achenbach System of Empirically Based Assessment; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; TD, typically developing.

TABLE 3 | Group differences across ADHD, ASD, and TD in co-occurring symptoms at 10-year follow up (T3).

ASR	ADHD[1] (*n* = 59)		ASD[2] (*n* = 24)		TD[3] (*n* = 40)				
	M	*SD*	*M*	*SD*	*M*	*SD*	Group comparison		Bonferroni
							F	*p*	
Internalizing[a]	53.76	12.61	56.71	11.72	45.85	10.38	8.038	0.001	1, 2 > 3
Externalizing[a]	51.54	11.44	50.04	11.89	43.33	8.81	7.241	0.001	1 > 3
Total problems[a]	54.69	12.45	54.67	11.74	43.98	10.29	11.417	<0.001	1, 2 > 3

[a]*Adult Self-Report, Achenbach System of Empirically Based Assessment; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; TD, typically developing. Superscript values indcates the group number used in the Bonferroni column.*

parental adaptations at home after receiving the diagnosis to examine whether these factors differentially influence children with ADHD and children with ASD.

A finding that was particularly notable when comparing the developmental trajectories of the ADHD and ASD group with that of the TD group, was that the ADHD and the ASD group displayed declines in co-occurring symptoms from T2 to T3 (mean age 13–21), a period when the TD group displayed increases in internalizing behaviors and total problems. This suggests that while researchers and clinicians have been worrying that individuals with ADHD and ASD may be particularly vulnerable during the transitional periods of adolescence and young adulthood (89, 90), the opposite may be true. Individuals with ADHD or ASD may experience less distress during the periods of adolescence and young adulthood compared with childhood. Perhaps because the transitional periods of adolescence and young adulthood offers opportunities for a new start, greater autonomy in social and academic situations, opportunities to pursue own interests, and a more inclusive environment for instance at high school and university [e.g., (91)]. However, it could also be that these transitional periods provoke other forms of co-occurring symptoms, not measured in the current study, such as substance-abuse, criminal behavior, and personality disorders (42, 92).

Another explanation may be that individuals with ADHD and individuals with ASD have an illusory self-perception (93, 94). Some studies have found that individuals with ADHD or ASD have a tendency to underreport social, emotional, and cognitive difficulties compared with parental reports (93–96). This could suggest that individuals with ADHD and individuals with ASD lack self-awareness about own difficulties, and thus, the decline observed from T2, with the use of parent-report, to T3, with the use of self-report, could be partially attributed to an illusory self-perception causing young adults with ADHD or ASD to underreport their co-occurring symptoms. Indeed, previous studies including both parent- and self-report have observed such discrepancy in young adulthood (37, 97).

Despite considerable declines in co-occurring symptoms from childhood to young adulthood in the ADHD and the ASD group, both groups continued to display elevated levels of co-occurring symptoms relative to the TD group in young adulthood. The ADHD group displayed more co-occurring symptoms across all domains, whereas the ASD group displayed more internalizing behaviors and total problems compared with the TD group. It should be noted that both the ADHD and the ASD group had scores around or only slightly above the normed mean of 50 (*T*-score) at T3, suggesting a low load of co-occurring symptoms relative to the US general population. However, previous studies have suggested that Norway is a low scoring country where the population mean is well below 50 (64). Therefore, the comparison with our TD group provides a more context sensitive comparison of co-occurring symptoms. Thus, the results provide evidence for the persistence of co-occurring symptoms among individuals with ADHD and individuals with ASD, and underscores the importance of early efforts to treat and prevent co-occurring symptoms. Addressing co-occurring symptoms in childhood may improve developmental trajectories, which in turn could benefit adult functioning and quality of life [e.g., (20, 22, 24)].

Strengths and Limitations

The LINEUP study is unique by the inclusion of individuals with different neurodevelopmental disorders (i.e., ASD; ADHD) ascertained after careful diagnostic assessment including clinical interview, self-, parent-, and teacher-report of social, emotional, and academic functioning, and neuropsychological tests (16). To our knowledge, no other longitudinal study spanning childhood to young adulthood (i.e., 10 years) have included several types of neurodevelopmental disorders. Thus, our study is to date the only study allowing comparison of the developmental trajectories of co-occurring symptoms across different neurodevelopmental disorders. Other strengths include a relatively high sample retention and the use of the same measurement system of co-occurring symptoms across all waves (i.e., the ASEBA).

Despite the study's notable strengths, some limitations should be mentioned. One limitation is the use of parent-report at T1 and T2 and self-report at T3. Previous studies of individuals with ADHD or ASD have suggested that young adults may be underreporting externalizing behaviors compared with parental reports (37, 97), which can contribute to the decline observed from T2 to T3. However, whereas externalizing behaviors may be underreported by young adults themselves, internalizing behaviors may be underreported by parents (98, 99), and obtaining valid parental reports can be difficult when young adults are living independently of their parents (97). Thus, an underreporting of externalizing behaviors at T3 is possible, but we think it strengthens the validity of our results that, despite this possible underreporting, we found moderate to large differences in externalizing behaviors when comparing the ADHD and the ASD group to the TD group at T3 ($d = 0.64$–80), and externalizing behaviors showed a similar developmental trajectory as internalizing behaviors and total problems.

A second limitation is that we did not obtain detailed information about possible treatment of co-occurring symptoms and other interventions the participants may have received between assessments. We assume that potential interventions in childhood are largely focused on school performance, activities of daily life, and social skills, rather than co-occurring symptoms *per se* (43). Still, we cannot completely rule out that some participants have received treatment targeting co-occurring symptoms. Further, interventions targeting social skills, school performance, and adaptive functioning may also have beneficial effects on co-occurring symptoms. However, participants in this study only received TAU and it would be ethically questionable to decline participants TAU.

A couple of limitations regarding our sample should also be noted. One limitation is that the sample comprised clinically referred individuals only, and thus, results may not be generalizable to the whole population of individuals with ADHD or ASD. A second limitation is the small proportion of females in the ASD group that, although consistent with the literature (100), prevented us from disentangling sex differences in the development of co-occurring symptoms. Studies have suggested that there may be sex differences in co-occurring symptoms in both individuals with ADHD and ASD [e.g., females displaying more internalizing behaviors than males; see (101, 102) for reviews]. Thus, sex differences in developmental trajectories of co-occurring symptoms should be investigated in future studies.

Clinical Implications

Increased understanding of the developmental trajectories of co-occurring symptoms among individuals with ADHD and individuals with ASD has clinical implications for assessment and intervention. Our findings suggest that clinicians should assess and carefully monitor co-occurring symptoms in individuals with ADHD or ASD to detect clinically significant changes and to target interventions. Standard treatment for individuals with ADHD or ASD should include interventions to prevent and treat co-occurring symptoms and not exclusively focus on core symptoms, school performance, and adaptive functioning. Although these are important skills, and also related to co-occurring symptoms. Given the persistence of co-occurring symptoms among individuals with ADHD or ASD, interventions should be initiated as early as possible, preferably once a child receives the diagnosis (e.g., preventive interventions such as training in emotional control). Since individuals with ADHD seems to have a somewhat slower decline in co-occurring symptoms from childhood to adolescence compared with individuals with ASD, interventions targeting co-occurring

symptoms in children and adolescents with ADHD may be especially important to expedite declining trajectories. It is also important that clinicians, parents, and teachers are aware of the high levels of co-occurring symptoms among these individuals, and the persistence of these symptoms over time. Parents may take comfort in knowing that co-occurring symptoms wane over time, but declining trajectories should not be used by clinicians as an excuse not to provide interventions.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data serving as the basis for the article submitted is stored in a secured repository at Innlandet Hospital Trust (Norway). Due to ethical restrictions on access to the data pursuant to the consent statements participants signed upon collecting the data, the authors are not permitted to upload a data set to sites outside of the repository. Access to the data, however, is available upon request to all serious researchers by contacting the following persons at Innlandet Hospital Trust: Erik Winther Skogli. Requests to access the datasets should be directed to erik.winther.skogli@sykehuset-innlandet.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Committee for Medical Research Ethics in Eastern Norway. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SO contributed to the conceptualization, data curation, formal analysis, and wrote the original draft. MØ contributed to the methodology, investigation, funding acquisition, supervision, and writing—reviewing and editing. IF contributed to investigation and data curation. PA contributed to methodology, investigation, supervision, and writing—reviewing and editing. ES contributed to conceptualization, methodology, investigation, formal analysis, funding acquisition, supervision, project administration, and writing—reviewing and editing. All authors approved the final manuscript for submission.

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The Need for Special Education Among ELBW and SGA Preterm Children: A Cohort Study

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Background: Preterm infants with pre- or postnatal growth restriction may have an additional risk of adverse neurodevelopmental outcome. Whereas reduced cognitive ability and behavioral problems have consistently been associated with prematurity, a more comprehensive evaluation is necessary to identify those preterm infants who are at increased risk for difficulties in school performance. This study evaluated the association between extremely low birth weight (ELBW) and the need for special education and determined if there is an additional risk for the need for special education among small for gestational age (SGA) children.

Methods: This is a single-center cohort study including singleton children born below 30 weeks' gestation between 1990 and 2011 and followed into 2019. ELBW + was defined as a birth weight below 1,000 g, which was compared to ELBW–. Within all ELBW+ children, SGA+ was defined as a birth weight <10th percentile according to Fenton, which was compared to SGA–. The dichotomous outcome measurement was the need for special education at 8 years of age or not, reflecting if the children required a special educational setting designed to accommodate educational, behavioral, and/or medical needs.

Results: In total, 609 children were eligible for follow-up, of whom 390 (64%) children were assessed at 8 years. Of these, 56 (14%) children needed special education, most often determined by cognitive deficiency (43%), behavioral problems (29%), or both (16%). Among the 191 ELBW+ children, 35 (18%) attended special education, compared to 21 (11%) among ELBW– children (*p*-value 0.041). A decreasing risk for the need for special education was found from 25% in ELBW+/SGA+ children to 16% in ELBW+/SGA– children and 11% in ELBW–/SGA– children (*p*-value 0.025). Multivariable logistic regression showed an odds ratio of 2.88 (95% CI 1.20–6.78) for ELBW+/SGA+ children vs. ELBW–/SGA– children for the need for special education.

Conclusions: This study showed that ELBW children are at increased risk for the need for special education compared to non-ELBW children. In addition, children that are both

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ELBW and SGA do have the highest risk for the need for special education. Classifying children as ELBW and SGA can be useful in follow-up for identifying preterm children with an additional risk for adverse long-term outcome.

Keywords: neurodevelopmental outcome, very preterm children, special education, very low birth weight, small for gestational age

INTRODUCTION

Over the last few decades, improvements in perinatal management of very preterm newborns made it necessary to consider the long-term outcome of these infants (1). Very preterm-born children have shown a higher risk for neurosensory disabilities as well as cognitive, motor, behavioral, and academic problems later in life (2–7). Underlying these neurodevelopmental deficits, suboptimal fetal growth is likely to be a key factor (8). A recently published meta-analysis suggested that being small for gestational age (SGA, defined as a birth weight <10th percentile) is associated with an additional risk of adverse neurodevelopmental outcome to that associated with very preterm birth alone (9). The combination of SGA and preterm delivery might additively result in higher rates of perinatal complications and consequently worse long-term neurocognitive outcomes, compared to SGA children delivered at term (10). It has also been shown that, independent of SGA, extremely low birthweight (ELBW, defined as birth weight below 1,000 g) infants are at higher risk for adverse long-term outcome compared to non-low birth weight infants (11).

Whereas, cognitive ability and behavioral problems have consistently been associated with low birth weight, a more comprehensive evaluation is necessary to identify preterm children who are at risk for difficulties in school performance (12). Disorders such as attention deficit hyperactivity disorder, speech-language disorders, and developmental delay are more common among ELBW and SGA children compared to normal birth weight children and do impact school performance (9, 13–16). Due to late recognition of difficulties such as poor concentration and short attention span, sometimes in combination with clumsiness, children might fail in normal schools even in the presence of normal intellectual potential (13, 17).

Therefore, this study aimed to evaluate the association between ELBW and the need for special education and to determine if there is an additional risk for the need for special education among ELBW children that were SGA.

METHODS

Patient Population

This cohort study included all singleton children born between 1990 and 2011 with a gestational age below 30 completed weeks who were admitted to the neonatal intensive care unit (NICU) of Máxima Medical Centre (MMC), Veldhoven, Netherlands. The NICU of MMC serves a 1.6-million population including antenatal and postnatal transfer from six other hospitals in the region. Children from parents living outside the adherence area of MMC, referrals from other NICUs, and children with congenital malformations were excluded. The ethical review board gave approval for the study and waived informed parental consent for participation in this study.

Data Collection

In MMC, all preterm children below 30 weeks' gestation were eligible for a follow-up program at the outpatient clinic up to the age of 8 years, including visits to the neonatologist, physiotherapist, and psychologist. Data from the outpatient clinical visits were collected prospectively. Neonatal data were retrieved from the individual medical records. Individual characteristics and medical data included gender (male or female); birth weight in grams; gestational age in days (based on ultrasound findings or on the first day of last menstrual period if ultrasound data was not available); small for gestational age [defined as birth weight below the 10th percentile (18)]; multiplicity (dichotomized as single or multiple birth); mode of delivery (dichotomized as vaginal or by cesarean section); complete course of antenatal corticosteroids (defined as two doses of betamethasone given 24 h apart before the start of labor); Apgar score at 5 min postpartum; inborn or outborn NICU; rate of artificial ventilation >12 h; days of endotracheal intubation on any mode of ventilation; surgical treatment of a persistent ductus arteriosus; intraventricular hemorrhage grade 3 or 4 based on ultrasound (19); cystic periventricular leukomalacia grade 3 (20); severe brain injury (defined as intraventricular hemorrhage grade 3 or 4 or cystic periventricular leukomalacia grade 3); laparotomy for necrotizing enterocolitis or single intestinal perforation; surgical treatment or laser therapy for retinopathy of prematurity; and total days of NICU admission. Socio-economic status was assessed using scores defined by the Netherlands Institute for Social and Cultural Research (The Hague, Netherlands) based on postal code at birth, with an average score of 0 and a positive score reflecting a higher-than-average status and a negative score reflecting a lower-than-average status (21). Information on educational status of the parents was collected at follow-up visits. This was classified according to the International Standard Classification of Education 2011 (22). The information was dichotomized, describing whether there was a low education (less than post-secondary education) or at least for one of the parents middle-to-high education (post-secondary education or higher).

Abbreviations: NICU, neonatal intensive care unit; GA, gestational age; ELBW, extremely low birth weight; SGA, small for gestational age.

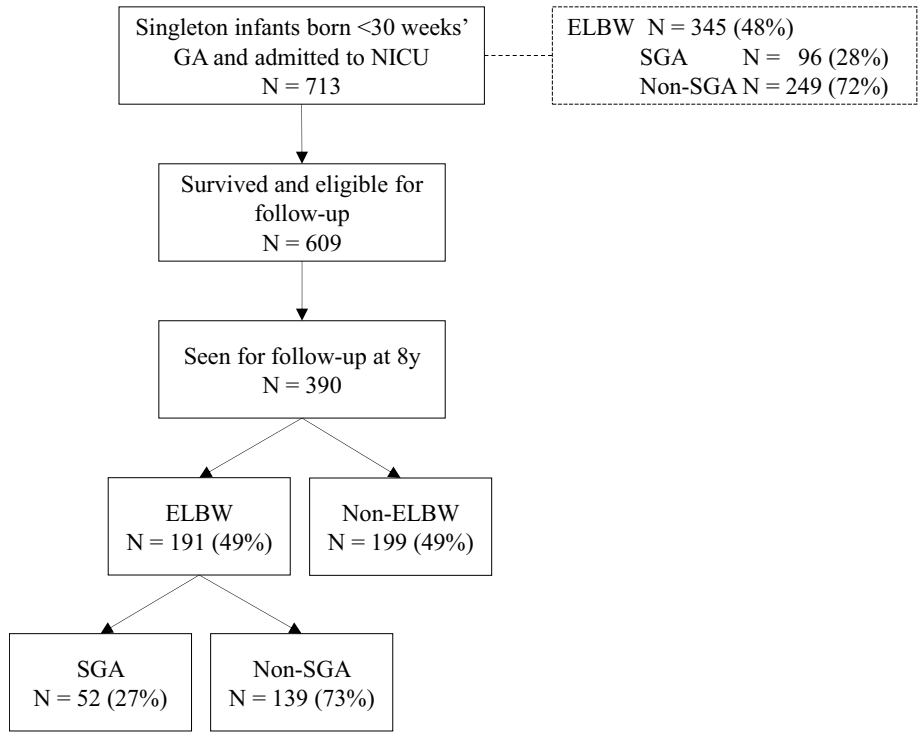

FIGURE 1 | Flowchart of the included children.

Definition of ELBW and SGA

ELBW was defined as birth weight below 1,000 g, which was compared to non-ELBW defined as a birth weight of 1,000 g or higher. Within all ELBW children, SGA was defined as a birth weight <10th percentile for corresponding gestational age and gender according to Fenton (23), which was compared to non-SGA defined as a 10th birth weight percentile or higher.

Outcome Measurement

The primary, dichotomous outcome measurement was of the need for special education at 8 years of age or not, reflecting if the children required an educational setting designed to accommodate educational, behavioral, and/or medical needs that could not be adequately addressed in a regular school environment. For each child attending special education, the reason why a child was placed in special school was determined based on the main issue causing problems in regular school based on the anamnesis with parents.

Statistical Analysis

For this study, ELBW children were compared with non-ELBW children. Within the ELBW children, SGA children were compared with non-SGA children. ELBW vs. non-ELBW and SGA vs. non-SGA children were compared using the Student's *T*-test or Mann–Whitney *U*-test for continuous variables and using the chi-square test for categorical and dichotomous variables. Special education rates were compared between the three groups of ELBW–, ELBW+/SGA–, and ELBW+/SGA+ children using a chi-square test. If significant, additional pair-wise chi-square tests were performed. A logistic regression analysis was performed for the need for special education, including gender, gestational age, parental education, and severe brain injury as parameters in the multivariable model. No data was missing, except for parental education for 25% of the children, which was imputed using the R multivariate imputation by chained equation (MICE) package. A p-value < 0.05 was considered significant. Calculations were performed using R version 3.5.1.

RESULTS

Study Population and Follow-Up Rates

Within the study period, 713 singleton children born below 30 weeks' gestational age (GA) were admitted to the NICU, of whom 345 (48%) children were ELBW, of whom 96 (28%) were SGA (**Figure 1**). Of the 713 admitted children, 609 (85%) children survived and were eligible for follow-up at the outpatient clinic, of whom 390 (64%) children were seen for follow-up at 8 years. Children not seen for follow-up were more mature compared to the children who participated, and their NICU admission lasted significantly shorter (**Supplementary Material**). Among the children seen for follow-up, distribution of ELBW and SGA was similar to children admitted (ELBW 49%, SGA 27%).

Baseline Characteristics

Table 1 shows the baseline characteristics for all 390 children seen for follow-up at 8 years, comparing 191 ELBW+ with 199

TABLE 1 | Baseline characteristics.

				ELBW+			Overall *p*-value
	ELBW+	**ELBW–**	***p*-value**	**SGA+**	**SGA–**	***p*-value**	
	191 (49%)	199 (51%)		52 (27%)	139 (73%)		
Gender (% male)	88 (46)	120 (60)	0.007*	29 (56)	59 (42)	0.139	0.005*
Birth weight	823 (125)	1,243 (183)	<0.001*	701 (102)	867 (101)	<0.001*	<0.001*
Gestational age (days)	27.6 [26.5, 28.8]	28.7 [27.0, 29.3]	<0.001*	28.4 [27.9, 29.3]	27.3 [26.3, 28.4]	<0.001*	<0.001*
Gestational age <28 weeks	106 (56)	53 (27)	<0.001*	15 (29)	91 (66)	<0.001*	<0.001*
Caesarean section [*N* (%)]	130 (68)	77 (39)	<0.001*	51 (98)	79 (57)	<0.001*	<0.001*
Antenatal corticosteroids completed [*N* (%)]	131 (69)	107 (54)	0.004*	31 (60)	100 (72)	0.145	0.003*
Apgar 5 min	8 [6, 9]	8 [7, 9]	0.007*	8 [7, 9]	8 [6, 9]	0.062	0.005*
Inborn [N (%)]	178 (93)	178 (89)	0.258	52 (100)	126 (91)	0.050	0.053
Socio-economic status	0.02 (0.78)	0.11 (0.79)	0.283	−0.03 (0.89)	0.04 (0.73)	0.557	0.475
Low parental education [*N* (%)]	35 (18)	25 (13)	0.151	12 (23)	23 (17)	0.408	0.583
Ventilation >12 h [N (%)]	145 (76)	115 (58)	<0.001*	36 (69)	109 (78)	0.258	<0.001*
Days ventilation	5 [1, 12]	2 [0, 5]	<0.001*	4 [0, 10]	5 [2, 12]	0.229	<0.001*
Surgically treated PDA [*N* (%)]	16 (8.4)	5 (2.5)	0.019*	2 (3.8)	14 (10)	0.276	0.009*
Severe brain injury	10 (5.2)	12 (6.0)	0.904	2 (3.8)	8 (5.8)	0.871	0.829
Laparotomy	6 (3.1)	2 (1.0)	0.258	1 (1.9)	5 (3.6)	0.901	0.254
Laser therapy for ROP	7 (3.7)	1 (0.5)	0.065	4 (7.7)	3 (2.2)	0.168	0.005*
Days NICU	44 [31, 57]	25 [15, 38]	<0.001*	44 [33, 56]	45 [31, 57]	0.749	<0.001*

*Legend: N (%), mean (SD), or median [1st quartile, 3rd quartile]. The left part of the table shows baseline characteristics for ELBW+ vs. ELBW– children. The right part of the table shows the baseline characteristic for all ELBW+ children, separately for SGA+ and SGA– children. The rightmost column shows the p-value comparing baseline characteristics between the three groups ELBW–, ELBW+/SGA+, and ELBW+/SGA– children. ELBW, extremely low birth weight; SGA, small for gestational age; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; NICU, neonatal intensive care unit. *Significant on a p-level of 0.05.*

ELBW– children and 52 SGA+ with 139 SGA– children. ELBW+ and SGA+ children were born with lower birth weights and were more often born by cesarean section, compared to ELBW– and SGA– children. For ELBW+ children, their NICU admissions lasted significantly longer with more complications compared to ELBW– children.

The Need for Special Education

In total, 56 (14%) children needed special education at the age of 8 years. The need for special education was most often determined by cognitive deficiency (43%), behavioral problems (29%), or both (16%) (**Table 2**).

Of the 56 children with the need for special education at the age of 8 years, 21 were ELBW– and 35 were ELBW+, of whom 22 were SGA+ and 13 were SGA–. This resulted in the need for special education among 18% (35/191) ELBW+ children, which was significantly more than the 11% (21/199) among ELBW– children (*p*-value 0.041). A significant decreasing risk for the need for special education was found from 25% in ELBW+/SGA+ children to 16% in ELBW+/SGA– children and 11% in ELBW– children (*p*-value 0.025). A *post-hoc* analysis showed a significant difference between ELBW+/SGA+ and ELBW– children (*p*-value 0.013).

A logistic regression analysis was performed to evaluate the association of being ELBW and SGA with the need for special education, corrected for gender, GA, parental education, and severe brain injury (**Table 3**). The associations found with univariable analysis remained significant when correcting for the aforementioned factors, with an odds ratio of 2.88 (95% CI 1.20–6.78) for ELBW+/SGA+ vs. ELBW– children for the need for special education. Moreover, female gender and higher gestational age were associated with lower odds for attending special education, while the presence of severe brain injury and low parental education were significantly associated with higher odds for the need for special education.

DISCUSSION

In this large cohort of very preterm children, the association between ELBW and of the need for special education was

TABLE 2 | Reasons for attending special education.

Primary reason for attending special education	*N* (%)
Cognitive deficiency	24 (43)
Behavioral problems	16 (29)
Cognitive deficiency and behavioral problems	9 (16)
Cerebral palsy	5 (8.9)
Severely multiply impaired	1 (1.8)
Unclear	1 (1.8)

Cognitive deficiency and behavioral problems were defined as present if there was a deviation of more than one standard deviation.

TABLE 3 | Logistic regression for attendance of special education at 8 years.

	Odds ratio (95% CI)
SGA/ELBW (ref = ELBW–/SGA–)	
ELBW+/SGA–	1.41 (0.65–3.08)
ELBW+/SGA+	2.88 (1.20–6.78)*
Gender (ref = male)	0.23 (0.11–0.45)*
GA (days)	0.96 (0.92–0.99)*
Low parental education	3.55 (1.72–7.23)*
Severe brain injury	6.85 (2.33–19.9)*

*ELBW, extremely low birth weight; SGA, small for gestational age; GA, gestational age. *Significant on a p-level of 0.05.*

evaluated, and it was determined if there is an additional risk for the need for special education among ELBW children that were SGA. This study showed that ELBW+ children are at increased risk for the need for special education compared to ELBW– children and that among ELBW+ children, those that were SGA+ do have the highest risk for the need for special education.

Overall, a special education participation rate of 14% was found among preterm-born children at the age of eight. This is consistent with a former Dutch study, showing a special educational rate of 14% among children born at a gestational age of 26–32 weeks. Also, the EPICure study shows a special education rate of 13% among extremely preterm infants (25, 26). These rates are substantially higher than the 1.9–2.7% of children who are enrolled in special primary education between 4 and 12 years throughout the Netherlands in the past 20 years (27).

At 8 years of age, a significant difference was seen in the special education attendance rate between ELBW+ (18%) and ELBW– (11%) children. Within the ELBW+ children, a distinction could be made between SGA+ and SGA– children. A decreasing risk for participation in special education was found from 25% in ELBW+/SGA+ children to 16% in ELBW+/SGA– children toward 11% in ELBW–/SGA– children. The higher rate among SGA+ children compared to SGA– children is in line with the previous Dutch POPS cohort, a nationwide study cohort of very preterm children born alive in 1983 in the Netherlands, which showed that at 9 years of age more SGA children (16.4%) needed special education compared to AGA children (11.9%) (28). The French EPIPAGE study showed school difficulties at 8 years in 28% of the very preterm children born SGA vs. 18% in very preterm children born AGA, which are similar rates to our study (1). It suggests that the effects of SGA remains important even at very low GAs. In addition to the increased risk of special education among ELBW children, SGA children are at the highest risk for special educational needs.

Logistic regression showed that, after correcting for gender, GA, parental education, and severe brain injury, there was still a significant increase for the need for special education for ELBW+/SGA+ children compared to ELBW–/SGA– children. We found that ELBW SGA children had a more than two times higher odds on in the need for special education compared to ELBW–/SGA– children. Moreover, gender, severe brain injury, and low parental education were important factors associated with the need for special educational. Male gender has often been found to be associated with adverse impaired long-term outcome after preterm birth (24, 29–31). Socioeconomic disadvantage does not only increase the likelihood of adverse school performance but is also a risk factor for low birth weight and preterm birth, placing the infant at dual risk from both biological and environmental factors (25).

It was found that most children participated in special education due to cognitive and/or behavioral problems. Although an underlying general cognitive deficit accounted for much of the educational underachievement observed, IQ scores did not account for all of the learning difficulties found in these children (26). Academic performance and behavioral problems such as attention deficit disorders are therefore useful in developmental follow-up in addition to gross IQ measures (25). Extensive neuropsychological testing might be considered in the high-risk group of ELBW+/SGA+ children. In this study, none of the children participated in special education because of blindness or deafness, as none of the children seen for follow-up at 8 years in our cohort were deaf or blind. Although deafness and blindness seldom occur among preterm children, children with such severe hearing or vision problems often drop-out from follow-up as they are already followed in rehabilitation clinics.

Several differences in baseline characteristics between ELBW+ and ELBW– children were observed. These differences were mainly associated with the immaturity of the ELBW+ group. Obviously, this resulted in a longer length of stay of the ELBW infants in the unfavorable NICU environment, which might interfere with postnatal growth and development (32, 33).

Academic performance is associated with long-term health and life chances (34). A major question for parents of a preterm child is whether their child will be able to follow a regular educational trajectory. This study provides an insight that both ELBW and SGA are useful indicators for higher risk of attending special education. This can be useful in follow-up for identifying preterm children with an additional risk for adverse long-term outcome.

Strengths of our paper included the size of the cohort and the outcome measurement at later age. However, this study has several limitations. Our follow-up rate was 64%, which is comparable to follow-up rates at 8 years of age presented in other studies (1). Several studies have found that children

lost to follow-up are more likely to have a disability. However, our results might present a higher-risk subset of children as medium-risk children have not always been invited for follow-up, resulting in the fact that children not seen for follow-up were more mature at birth compared to children included in this study. The proportion of ELBW and SGA children remained similar in children seen for follow-up, compared to children admitted to the NICU, and socio-economic status was comparable between children seen and not seen for follow-up. Overall, we expect a low risk of bias induced in the associations observed between being ELBW or SGA and the need for special education.

When evaluating long-term adverse outcome in relation to birth weight, the smallest children may be expected to be at greatest risk. This study aimed to evaluate absolute birth weight and birth weight percentile in relation to the need for special education. It showed that ELBW children are at increased risk for the need for special education compared to non-ELBW children and that among ELBW children, those that were SGA do have the highest risk for the need for special education. Classifying children as ELBW or SGA can be useful in follow-up for identifying preterm children with an additional risk for adverse long-term outcome. Extra attention and more extensive follow-up might be required for the very high-risk group of ELBW+/SGA+ children.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of privacy regulations according to the General Data Protection Regulation (GDPR). Requests to access the datasets should be directed to Pauline E. van Beek, pauline.van.beek@mmc.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee Máxima MC. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PB, AB, BV, and PA contributed to the conception of the study. PB, KP, IH, and BV organized the database. PB performed the statistical analysis and wrote the first draft of the manuscript. PA was responsible for the financial funding of the project and overall supervision. All authors contributed to the interpretation of the results, critically reviewed the manuscript, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.719048/full#supplementary-material

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German Law Reform Does Not Reduce the Prevalence of Coercive Measures in Residential Institutions for Children, Adolescents, and Young Adults With Intellectual and Developmental Disabilities

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Background: Approximately 10% of children, adolescents and young adults with an intellectual and developmental disability (IDD) in Bavaria live in residential institutions. 2015 saw media reports raising suspicions about excessive use of coercive measures (cM) in those institutions. Until a law reform at the end of 2017 made permission from family courts mandatory for cM, their use was governed by parental consent. The REDUGIA project conducted a representative survey comparing cM and their relation to challenging behaviour (cB) and employee stress in Bavaria pre and post reform.

Methods: We sent questionnaires to 65 residential institutions for children, adolescents and young adults with IDD in 2017 (pre reform, T1) and 2019 (post reform, T2). To assess changes, we analysed data from all available questionnaire pairs (T1 and T2, $N = 43$). We calculated paired *t*-test and correlative analyses concerning the relationship between cB, cM, and employee stress.

Results: The number of residents overall (T1: $N = 1{,}661$; T2: $N = 1{,}673$) and per institution (T1: $m = 38.6 \pm 32.0$; T2: $m = 38.9 \pm 34.5$, $p = 0.920$) remained stable. We did not see any changes in the *Index cB* ($p = 0.508$) or the proportion of residents per institution displaying various types of challenging behaviour (all ps>0.220). There was no change in the *Index cM* ($p = 0.089$) or any indicator of employee stress, all ps > 0.323. At follow-up, the *Index cB* correlated positively with the *Index cM* ($r = 0.519$ $p < 0.001$). Regarding employee stress, the *Index cB* correlated positively with the frequency of sick leave ($r = 0.322$, $p = 0.037$) and physical attacks on employees ($r = 0.552$, $p < 0.001$). The *Index cM* also correlated positively with the frequency of sick leave ($r = 0.340$, $p = 0.028$) and physical attacks on employees ($r = 0.492$, $p = 0.001$).

Discussion: Coercive measures are not a general phenomenon, but are focused on specialised institutions. The law reform did not lead to changes in the number of children, adolescents and young adults with IDD affected by coercive measures in residential institutions in Bavaria. There were still large discrepancies between institutions in the prevalence of challenging behaviour and coercive measures. Coercive measures were associated with challenging behaviour and employee stress. Taken together, findings from REDUGIA emphasise the need to prevent challenging behaviour and thus coercive measures.

Keywords: intellectual disabilities, developmental disabilities, challenging behaviours, employee stress, coercive measures, residential institutions

INTRODUCTION

Approximately 1% of the population fulfil criteria for an intellectual and developmental disability (IDD; IQ < 70) (1). Youths with IDD are at an increased risk for psychiatric disorders, with 40–50% compared to 10% in the general population in this age group having at least one psychiatric diagnosis (1, 2). At the same time, psychiatric comorbidity is underdiagnosed in this group, because symptoms are a) not reported due to limited communication skills (underreporting), b) primarily attributed to the IDD (diagnostic overshadowing) or c) retrospectively reported as having always been present (baseline exaggeration) (3, 4).

These undiagnosed and untreated psychiatric disorders contribute to the display of challenging behaviour. Around 52% of school-aged children with IDD show challenging behaviour (cB) (5), with self-injury and aggression towards others being the most problematic (6, 7). Challenging behaviour, especially aggressive behaviour, is one of the major issues both professional and family caregivers of people with IDD face, bringing with it a heightened risk to mental health and quality of life (8–12). We recently reported that challenging behaviour is linked to the use of coercive measures (cM) (13). Assuming a direct causal relation, the use of coercive measures may be avoided if the underlying causes of the challenging behaviour were addressed—either by treating relevant psychiatric disorders or by shaping the environment and providing the children with alternative strategies to get their needs met.

In 2011, the Winterbourne View inquiry exposed the inhumane treatment of people with learning disabilities showing challenging behaviour at hospitals run by a private company in the UK. This cast a spotlight on systemic problems leading to a lack of protection for this vulnerable population. A serious case review was commissioned, addressing the causes and laying out preventative measures. In 2015, German media alleged an excessive and inappropriate use of coercive measures in institutions for children, adolescents and young adults with IDD. In response, the Bavarian State Ministry of Labour and Social Welfare, Family Affairs and Women (StMAS) initiated an *ad hoc* examination, which found no indication of systematic abuse of coercive measures (14). An expert commission appointed by the ministry recommended a 10-point plan to improve and ensure quality standards in institutions for children and adolescents (15). The StMAS furthermore funded the SEKiB research consortium (16, 17) comprising three research projects on the reduction of coercive measures. Since there was a lack of data concerning the prevalence of challenging behaviour and coercive measures in institutions for children, adolescents and young adults with IDD, the REDUGIA project (Reducing Coercive Measures on Children and Adolescents with Intellectual and Developmental Disabilities) aimed to assess the magnitude of the issue by conducting a comprehensive survey.

In Germany, §1631b BGB governs the use of coercive measures. In the original version of the law, freedom-restricting measures ('freiheitsentziehende Maßnahmen') were defined as an all-encompassing restriction of a person's freedom of movement (e.g., in a psychiatric clinic or a restricted section in a residential institution). Those measures required permission from the family courts. However, freedom-limiting measures ('freiheitsbeschränkende Maßnahmen') based on §1631b were defined as any measure that is appropriate and common considering the child's age and the circumstances of their residential situation and is within the framework of general duties of education and supervision. Those measures did not require permission from the courts, since they were of shorter duration and limited to the respective situation. They did however require parental permission. Since the only distinction between freedom-restricting and freedom-limiting measures arose from subjective factors such as intensity, duration and child's age, this resulted in a sliding scale.

Since the amendment in October 2017, §1631b BGB defines coercive measures ('freiheitsentziehende Maßnahmen') broadly as any measure that restricts a child's freedom of movement against their will over long periods of time with medication, mechanical or any other means, which they cannot overcome without assistance. The frequency/duration criterion is met when the coercive measure is employed either for more than 24 h, occurs regularly at certain times or in certain situations, or is used repeatedly. For the use of coercive measures, institutions are now required to obtain permission and supervision from the family courts. Certain types of coercive measures (e.g., helmets, protective clothing) are not regulated by the law and still only require parental permission.

It is important to note that when a child's behaviour constitutes a danger to themselves or to others, the emergency use of coercive measure is permitted. Still, institutions must apply for retroactive permission from the court.

To our knowledge, there are no systematic evaluations across larger catchment areas in other countries on the prevalence of coercive measures across (1) residential homes, institutions or facilities for (2) children, adolescents and young adults with (3) intellectual disabilities.

In the following section, we provide a summary of the literature meeting at least two criteria. We only included studies conducted on larger areas, not just from one facility.

We identified three studies on the general use of coercive measures in people with disabilities by either service providers or authorities. Saloviita et al. (18) surveyed all adult residents with intellectual disabilities in a single special care district in Finland. They found high rates of challenging behaviour (72%), with 56% of instances of challenging behaviour being met with a negative intervention (18). Saloviita et al. (19) further conducted a postal survey on the total population of children in Finland aged 5–15 years entitled to the highest disability allowance with their first three diagnoses from the ICD-10 categories F7 (Intellectual disabilities), F8 (Pervasive and specific developmental disorders) or F9 (Behavioural and emotional disorders with onset usually occurring in childhood and adolescence). The authors received a response from 25.9% of families. Of those, 22% ($N = 54$) reported that their child had been restrained, secluded or subjected to aversive procedures by authorities. However, only families where the child was living at home were included (19). Webber et al. (20) attempted to collect population-based date on the use of chemical and mechanical restraint and seclusion 'when a person was in receipt of a disability service' in the State of Victoria, Australia. The mean age of the sample was 36 ± 15.6 years. The authors found that 9% of people with an IDD who received a government-funded disability support service were subject to at least one of those coercive measures. Psychiatric morbidity increased the risk of coercive measures (20).

Regarding the use of coercive measures in residential facilities for people with intellectual disabilities, we found studies from Sweden, Finland and the UK. Emerson et al. (21) investigated the use of physical restraint, mechanical restraint, sedation and seclusion in UK adults with intellectual disabilities receiving various types of residential supports by drawing small samples from village communities, NHS residential campuses and community-based dispersed housing schemes. They found between 3% (mechanical restraint) and 44% (physical restraint) to be affected by coercive measures (21). Lundström et al. (22) found that in a convenience sample of people with ID (16–90 years) living in 118 group homes in one county in northern Sweden, 17.8% of residents had experienced physical restraint, especially those with more behavioural issues or physical impairments. However, in Sweden the use of coercive measures is not permitted, so that number is still high (22). Saloviita et al. (19) cited a study conducted in Finland 'by an official state monitoring agency, Valvira, [which] found only occasional examples of the use of coercive measures in their study of 69 residential organisations for people with intellectual disabilities (23).' However, since the Valvira study is only available in Finnish, we were unable to assess the quality or report specific numbers.

There are several international studies on the use of coercive measures in psychiatric settings for children and adolescents. In their literature review on the prevalence of seclusion and restraint in children and adolescents (<21 years) treated in a psychiatric setting in the last 10 years, De Hert et al. (24) identified 7 studies conducted in the US, Australia and Finland. They reported an overall baseline rate of 26–29% of patients to experience those types of coercive measures. In Finland, Ulla et al. (25) conducted a register study on the use of exclusion and restraint in all adolescents aged 12–17 years who received psychiatric inpatient treatment between 1996 and 2003. The use of restraint/seclusion was very rare (1.71/10,000 per year). The use further decreased after a law reform set even stricter criteria for coercive measures ('acceptable only to stop violent behaviour or prevent imminent violence') (25). Stewart et al. (26) evaluated data collected via a database collecting data on intrusive measures used in a child and youth mental health treatment centre serving a 17-county catchment area in Ontario, Canada. They reported the use of chemical restraint (48.8% of patients) physical restraint (42.3%) or secure isolation (39.3%) during treatment. Developmental disabilities increased the risk for coercive measures (26). Green-Hennessy et al. (27) reported on the use of seclusion/restraint in all US residential treatment centres for children and adolescents via a federally-sponsored survey of mental health services. With a high response rate (88.8%), they found 82% of institutions to use seclusion/restraint. However, no data on the percentage of affected residents was available (27).

To sum up, the use of coercive measures appears to vary greatly on an international level. However, it is difficult to draw international comparisons between rates of coercive measures, since the definition of coercive measures and the regulatory framework varies widely.

REDUGIA assessed the impact of the 2017 law reform in Germany on the prevalence of challenging behaviour, coercive measures and employee stress. This article reports findings from the comparison between 2017 (baseline, pre-reform) and 2019 (follow-up, post-reform) data.

We expected to see a positive relationship of challenging behaviour with coercive measures and with employee stress. We furthermore expected to find a decrease in coercive measures from 2017 to 2019. We formed this hypothesis for two reasons: Firstly, the public focus on the topic due to the amendment of §1631 b might prompt staff and supervisors to re-think the necessity of those types of measures—especially ones that weren't previously classed as coercive measures. And secondly, the paperwork and time required for going through the courts might also prove an obstacle that may have fueled efforts to prevent coercive measures.

And we finally expected an increase in challenging behaviour due to the aforementioned expectation of lower rates of coercive measures in response to challenging behaviour.

METHODS

For the REDUGIA survey, we devised a 48-item questionnaire on structural characteristics of the residential institutions as well as on characteristics of the residents, challenging behaviour, coercive measures and employee stress. All data were self-reported by either management or staff at the participating institutions. We collected pseudonymized information ensuring that the individual institutions or individual residents are not identifiable.

Challenging Behaviour (cB)

Institutions reported data on the number of residents displaying different forms of challenging behaviour as well as the frequency of so-called critical behaviours (aggression towards other residents, self-injurious behaviour, injury of staff members, destructive behaviour) in the last 14 days (for details, see **Table 2**). The *Index cB* describes the proportion of residents with challenging behaviour by dividing the number of residents with cB by the total number of residents.

Coercive Measures (cM)

Institutions reported data on the frequency of different kinds of coercive measures as well as the number of children subjected to each type of coercive measure (for details, see **Table 3**). The *Index cM* represents the proportion of residents subject to coercive measures by dividing the number of residents with cM by the total number of residents.

Employee Stress

We assessed different indicators of employee stress: physical assaults and uses of protective clothing in the last 14 days and instances of sick leave and requests for transferral or quitting the job due to challenging behaviour in the last 12 months.

Some providers operating more than one residential institution reported data for all of their institutions in one questionnaire. We received $N = 43$ questionnaires for the follow-up assessment and only included those with a corresponding baseline questionnaire in the analysis.

The study was approved by the ethics committee of the medical faculty of the University of Würzburg (study number 227/17).

Statistical Analysis

We performed all analyses with IBM SPSS Statistics Version 26. Descriptively, we report frequencies, percentages, sum scores and means with standard deviations. For the analysis of the relationships between challenging behaviour with coercive measures, challenging behaviour with employee stress and coercive measures with employee stress, we calculated regression models or Pearson correlations. Changes between baseline (2017) and follow-up (2019) measurements were assessed with *t*-tests for dependent measures. The significance level was set at $p = 0.05$. We adjusted for multiple testing as follows: for the main pre-post comparisons (*Index cM*, *Index cB* and the 4 indicators of ES), the significance level was set to 0.008. For the correlations (*Index cM* with *Index cB*; *Index cM* and *Index cB* with the 4 indicators of ES), the significance level was set to 0.005. All other exploratory comparisons are uncorrected.

RESULTS

Results From Follow-Up Assessment and Comparison Pre and Post Reform

43 of the 51 institutions (i.e., questionnaires) participating in the baseline evaluation in 2017 also provided data for the follow-up assessment in 2019 (84%). Descriptively, the overall total number of children, adolescents and young adults with IDD

TABLE 1 | Characteristics of occupancy in 2017 und 2019 summarised over all $n = 43$ institutions participating in the follow-up assessment.

	2017				2019				
	Total number	m per institution (sd)	Min	Max	Total number	m per institution (sd)	Min	Max	*p*
Number of groups	255.5	5.9 (5.5)	1	29	215*	5.1 (3.8)	1	15	0.115
Among those: intensive groups (if any)	34	2.13 (1.0)	1	4	25	1.92 (1.1)	1	4	1.000
Among those: regular groups	221.5	5.8 (5.4)	1	27	190*	4.9 (3.7)	1	14	0.923
Number of residents	1,661	38.6 (32.0)	6	131	1,673	38.9 (34.5)	5	144	0.920
Among those: in intensive groups	172.5	11.5 (5.0)	6	24	131	10.1 (5.7)	4	20	0.728
Among those: in regular groups	1488.5	38.2 (32.1)	6	131	1,542	38.6 (33.8)	5	134	0.807
Among those: restricted placements	102	2.4 (6.3)	0	26	50	1.2 (3.6)	0	18	0.128
Permission obtained from family court (§1631b BGB)	146	3.4 (6.7)	0	26	229	5.5 (11.0)	0	56	0.112
Group size									
Size of intensive groups		5.6 (1.6)	1.8	7.0		5.6 (2.3)	2.5	12	1.000
Size of regular groups		7.2 (2.3)	2.2	13.3		7.5 (2.7)	0.87	21	0.416
Full-time position equivalents	1663.2	38.7 (40.6)	6	249.6	1756.4	42.8 (43.0)	7	247	0.119

**One institution reported 49 groups (including 3 intensive groups) for N = 52 residents. This obvious error could not be resolved. We therefore excluded this institution for the calculation of the mean number of groups and counted only the 3 intensive groups of the institution towards the total number of groups overall.*

living in institutions remained stable. 13 institutions had at least one intensive group. The number of regular groups increased, whereas the number of intensive groups decreased. Conversely, the number of residents in intensive groups and under restrictive placements decreased despite a higher number of residents for which permissions for use of coercive measures according to §1631b BGB were obtained from the family court. Overall, groups became smaller while intensive groups had a slightly higher number of inhabitants than in 2017. The mean number of intensive and regular groups per institution remained stable (all *p*s > 0.923). The mean number of residents in total and per regular or intensive group as well as those placed under §1631b also was constant (all *p*s > 0.112). There were no differences in the number of full-time position equivalents ($p = 0.119$; **Table 1**).

TABLE 2 | Mean proportion of residents displaying challenging behaviour in the last 14 days.

Type of challenging behaviour	Proportion of children and adolescents (%)		
	2017	2019	*p*
Any severe challenging behaviour	14.1	9.6	0.771
Stereotyped behaviour	20.3	19.2	0.736
Destructive behaviour	16.9	14.1	0.214
Self-injurious behaviour	15.5	12.6	0.220
Aggression	13.3	15.0	0.390
Motor restlessness	12.7	13.3	0.805
Risk of running away	11.4	9.8	0.449
Excessive screaming	8.8	9.6	0.615
Changes in circadian rhythm	3.7	4.5	0.576
Other	2.2	2.6	0.780

Challenging Behaviour

Institutions did not report any changes in the *Index cB* ($p = 0.446$) or the proportion of children per institution displaying various forms of challenging behaviour (all *p*s > 0.220, see **Table 2**).

Figure 1 displays the relative frequency of critical events per institution per resident within 14 days in 2017 und 2019. Within institutions, there are fluctuations in the number critical events in that time period.

Coercive Measures

Overall, only a comparatively small proportion of children living in residential institutions were subject to coercive measures (**Figure 2**) according to the institutions' self-report. Considering that children with severe challenging behaviour experienced multiple kinds of coercive measures, the true percentage is likely lower.

There was no change in the *Index cM* between baseline and follow-up ($p = 0.241$). Only compulsory medication decreased between measurements ($p = 0.028$). There were trend-level decreases in the number of children sleeping in a Kayser bed ($p = 0.051$) and restraint by holding ($p = 0.070$). All other coercive measures remained at the 2017 level (all *p*s > 0.111) (see **Table 3**).

Figure 3 shows the relative frequency of coercive measure per institution per resident within 14 days in 2017 und 2019.

Employee Stress

Institutions did not report changes in any indicators of employee stress from baseline to follow- up, all *p*s > 0.323. Descriptively, we observed a slight increase in the absolute number of full-time position equivalents and decreases in the total number of physical assaults, the need for protective clothing for employees and the frequency of employees requesting a transfer or quitting the job due to challenging behaviour (**Table 4**).

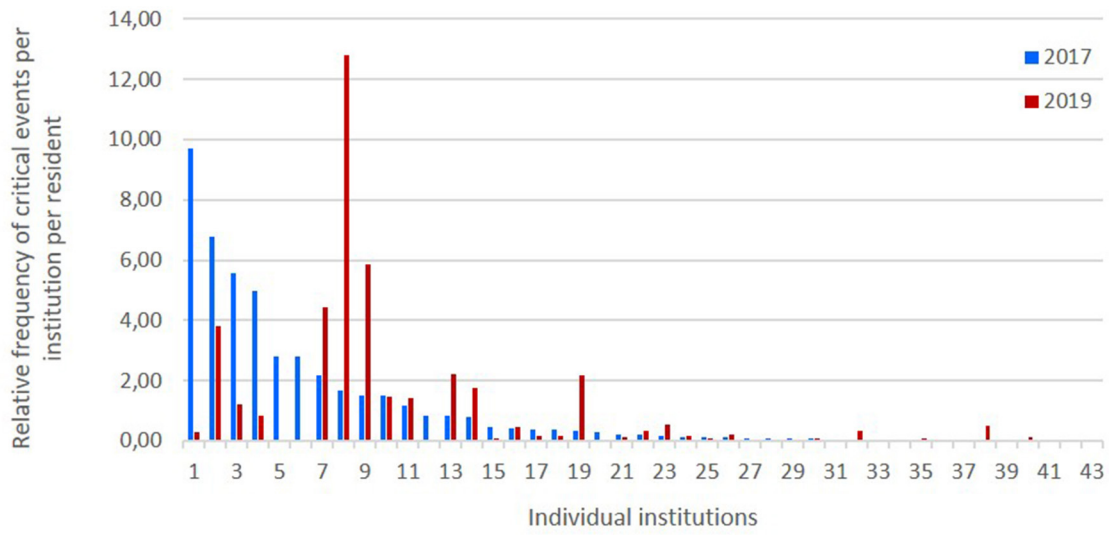

FIGURE 1 | Relative frequency of critical events per institution per resident within 14 days in 2017 und 2019. The x-axis displays the institutions in descending order according to the sum of critical events per resident in 2017 (baseline assessment).

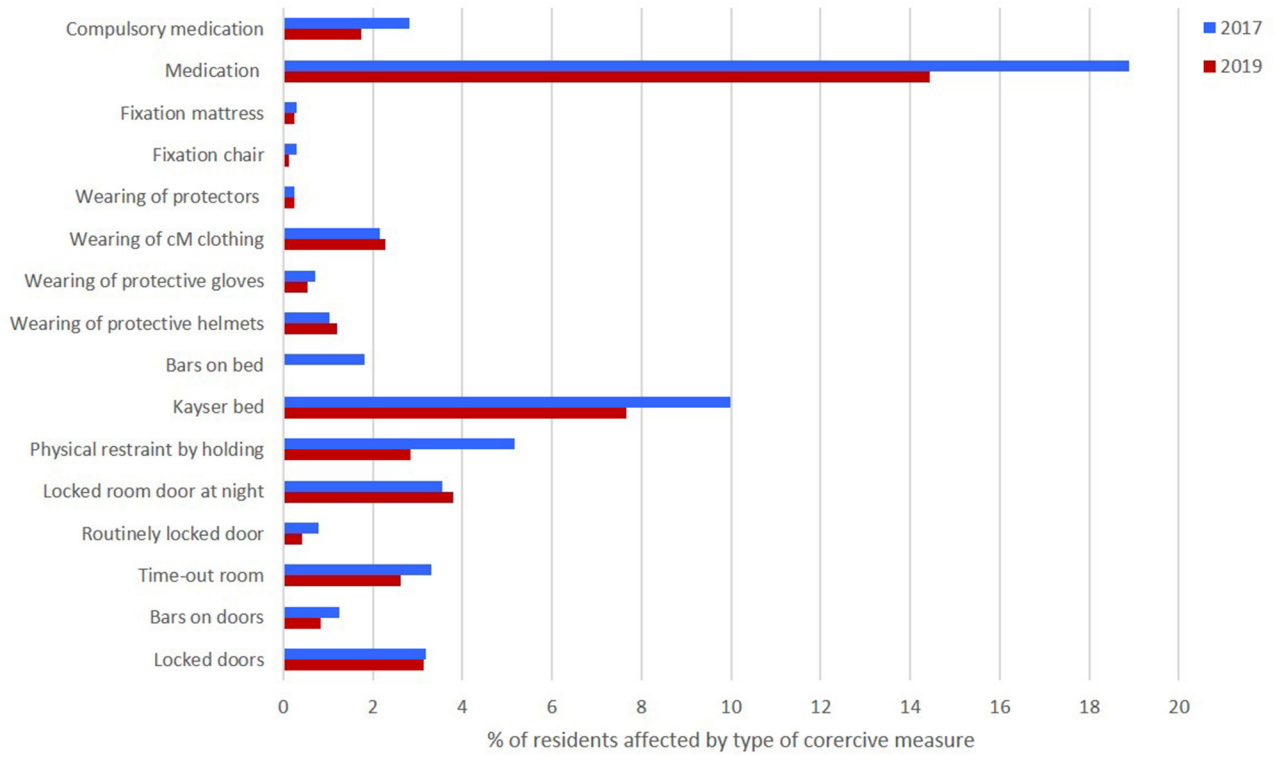

FIGURE 2 | Overall percentage of children affected by any type of coercive measure.

Relationship Between cB, cM and ES

At follow-up, the *Index cB* correlated significantly with the *Index cM* ($r = 0.519$ $p < 0.001$, **Figure 4**). Regarding links to employee stress, the *Index cB* correlated positively with the frequency of sick leave on a trend level ($r = 0.322$, $p = 0.037$) and with physical attacks on employees ($r = 0.552$, $p < 0.001$). The *Index cM* also correlated positively with the frequency of sick leave on a trend level ($r = 0.340$, $p = 0.028$) and with physical attacks on employees ($r = 0.492$, $p = 0.001$).

DISCUSSION

Our study was the first to systematically examine challenging behaviour, coercive measures and employee stress in residential institutions for children, adolescents and young adults with IDD in a German federal state (Bavaria). We furthermore assessed changes in the rates of challenging behaviour, coercive measures and employee stress after the law reform addressing the definition and use of coercive measures in children and adolescents. All data were self-reported by the participating institutions.

In summary, REDUGIA delivered a detailed picture on the topic of coercive measures in institutions for children, adolescents and young adults with IDD. While the findings do not support the worrying accusations of broadly and inadequately applied coercive measures, the data represent a benchmark for future endeavours to further reduce coercive measures. Overall, only a comparatively small proportion of children in residential institutions in Bavaria was affected by coercive measures. With the exception of Kayser beds (10% in 2017, 7.7% in 2019), no coercive measure was employed for more than 5% of the children. Medication for psychiatric disorders (18.9% in 2017, 14.4% in 2019) is not strictly speaking a coercive measure, since it is medically necessary and does not restrict freedom of movement. Considering that children with severe challenging behaviour experienced multiple types of coercive measures, the true percentage of children who are affected by coercive measures at all is likely lower.

Both pre and post reform, coercive measures correlated positively with challenging behaviour, confirming our hypothesis. This points to the primary use of coercive measures as an interventional response towards challenging behaviour, which fits with the existing literature. Nonetheless, challenging behaviour is amenable to interventions other than coercive measures (28). Standardised analyses of behaviour have shown high success rates in identifying and addressing the causes of challenging behaviour (29) and the Triple P Stepping Stones program for parents of children with disabilities is highly effective in reducing challenging behaviour and caregiver stress (30, 31). International guidelines for challenging behaviour in intellectual disability recommend a thorough analysis of living conditions and the function of behaviour for addressing self-injurious behaviour (1, 32).

We could also confirm our hypothesis of a positive correlation between challenging behaviour and employee stress. This finding

TABLE 3 | Mean proportion of children and adolescents per residential institution affected by coercive measures in the last 14 days.

Type of coercive measure	Proportion of children and adolescents (%)		
	2017	2019	*p*
Kayser bed	14.4	10.5	0.051
Physical restraint by holding	7.9	5.4	0.070
Time-out room	3.6	2.8	0.578
Locked room door at night	3.5	3.2	0.734
Locked doors	3.2	3.1	0.904
Wearing of restrictive clothing	2.3	3.6	0.453
Bars on doors	1.4	0.8	0.282
Bars on bed	1.3	0.0	0.111
Compulsory medication*	3.4	1.9	0.028
Wearing of helmets**	1.1	1.5	0.647
Routinely locked door	0.8	0.5	0.169
Wearing of gloves**	0.8	0.6	0.369
Fixation mattress	0.5	0.4	0.530
Fixation chair**	0.4	0.1	0.166
Wearing of protectors**	0.2	0.3	0.991

**only emergency use medication.*

***Coercive measures that were not regulated by §1631b prior to the amendment.*

corresponds with the existing literature reporting a link of challenging behaviour to caregiver stress and quality of life (8). Subjectively, research indicated that staff in institutions for people with IDD rated challenging behaviour as one of the major stressors (9, 10). However, using objective measures of exposure to challenging behaviour, the picture is less clear. Flynn et al. (33) found no association of work-related well-being with the exposure to aggressive challenging behaviour. The authors discussed the influence of different measures of exposure to challenging behaviour and hypothesise that 'emotional exhaustion and positive work motivation are more substantially influenced by working environment than the other variables' (33). In addition to differences in the definition and assessment of challenging behaviour, the definition of ES is also relevant when looking at the link between challenging behaviour and ES. In our study, we focused on physical (physical assault, need for protective clothing) as well as indirect indicators of stress (instances of sick leave, requests for transferral or giving notice due to challenging behaviour). We did not assess the psychological impact of challenging behaviour and coercive measures. Especially for psychological well-being, coping style and personality may be more relevant for the degree of experienced (di)stress. Future research should address this question. Institutions with higher rates of challenging behaviour had a higher staff to patient ratio probably indicative of the higher severity of challenging behaviour in the respective group of children and adolescents. Nevertheless, employee stress was rated higher in those institutions. This may also be due to 3 of the 4 indicators of employee stress—physical assaults, use of protective clothing and instances of sick leave—potentially being direct results of challenging behaviour in the form of aggression. However, it is also possible that the additional staff members did not work in the positions of greatest exposure.

Considering the effects of the law reform, we could not confirm our hypotheses of an increase in challenging behaviour or a decrease in coercive measures. The percentage of children, adolescents and young adults displaying challenging behaviour at follow-up was comparable to baseline. The number of children with severe challenging behaviour was comparatively low both in 2017 (14.1%) and 2019 (9.6%). After the law reform, applications to family courts for permission for the use of coercive measures increased by 57%. However, the percentage of children affected by coercive measures remained roughly the same. This may indicate that even before the requirement of permission from family courts, the institutions had likely carefully examined the necessity of coercive measures before initiating them. However, this does not imply that challenging behaviour necessitates coercive measures *per se*. Employees likely find themselves in situations, in which they have no alternative to using coercive measures to address challenging behaviour, due to e.g., structural conditions or a lack of resources. Creating judicial obstacles such as the law reform cannot address those underlying issues and therefore cannot by itself reduce coercive measures. To meaningfully reduce coercive measures, concomitant changes in pedagogic and therapeutic concepts and the resources at the disposal of the institutions are required. While it is possible that due to the sensitive nature of the topic institutions may have been incentivized to conceal the true frequency of coercive measures, the assured anonymity of the published data and the heterogeneity of reported coercive measures rates between institutions lends credibility to the statements made by the respondents. Furthermore, we have visited 20 institutions for qualitative interviews (data not reported here) that supported the validity of the surveys.

We found a pronounced heterogeneity between institutions in term of the rates of challenging behaviour and coercive measures. Challenging behaviour and coercive measures concentrated in approximately one third of the participating institutions. Around 60% of the institutions reported hardly any or no challenging behaviour or coercive measures. This fits with the observation in our clinical routine that only highly specialised institutions accept residents who display challenging behaviour, especially aggressive behaviour. Furthermore, this pattern confirms that a large proportion of youth with IDD does not display any kind of challenging behaviour. In fact, only 14.1% (T1) and 9.6% (T2) reported any severe challenging behaviour. While this appears low compared to the estimated 52% reported in students attending specialised schools for IDD in Bavaria in the study by Dworschak and colleagues, these numbers fit with population-based estimates of the prevalence of challenging behaviour in people with IDD (34). In the Emerson study, 'informants were instructed to complete these sections if the person showed that form of challenging to the extent that it was considered by them to constitute a serious management problem'. In contrast, Dworschak and colleagues used a composite score

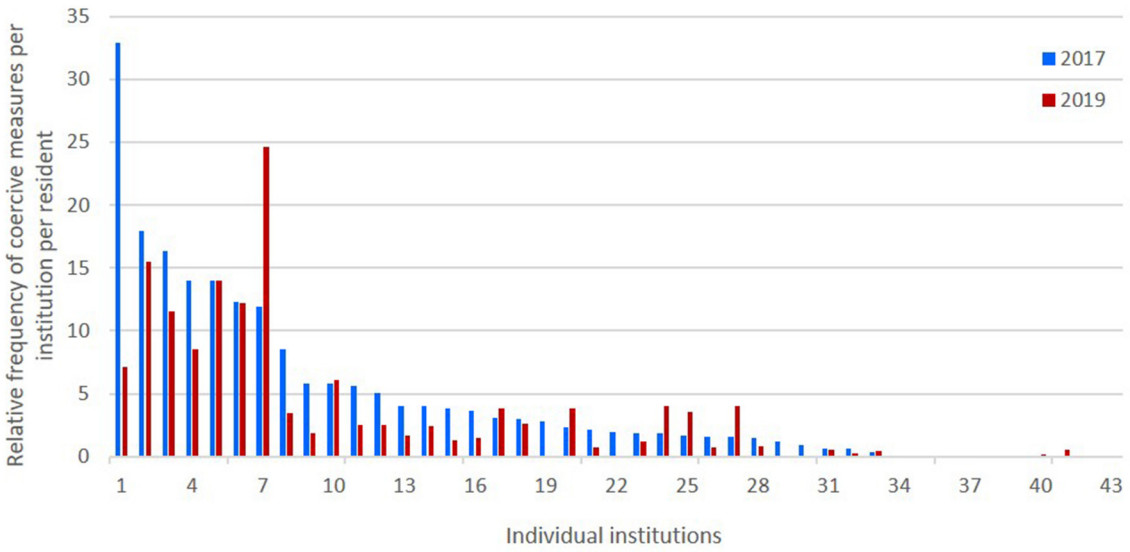

FIGURE 3 | Relative frequency of coercive measures per institution per resident within 14 days in 2017 und 2019. The x-axis displays the institutions in descending order according to the sum of cM per resident in 2017 (baseline assessment).

TABLE 4 | Staff characteristics and employee stress (absolute number of incidents and mean relative frequency per full-time position equivalent) in $n = 43$ institutions participating in the follow-up assessment.

	2017			2019			
	Absolute	**Relative (%)**	**Institutions without N (%)**	**Absolute**	**Relative**	**Institutions without N (%)**	***p***
Full-time position equivalents	1663.2			1756.4			
Physical assault (last 14 days)	617	30.8	17 (39.5)	409	26.5%	16 (37.2)	0.702
Protective clothing for employees (last 14 days)	107	3.2	41 (95.3)	39	0.9%	41 (95.3)	0.323
Sick leave due to cB (last 12 months)	78,5	6.3	21 (48.8)	84	5.2%	21 (51.2)	0.630
Number of employees requesting a transfer or quitting the job due to cB (last 12 months)	31	2.4	27 (62.8)	19	1.5%	29 (67.4)	0.360

from a comprehensive questionnaire inquiring after 33 specific challenging behaviours, whereas REDUGIA asked about more generally about the *number of residents displaying severe challenging behaviour* in addition to inquiring about eight specific types of challenging behaviour. It is likely that caregivers did not consider some of the behaviours scored in the study by Dworschak et al. as severe challenging behaviour. It can however not be ruled out that the institutions without challenging behaviour and coercive measures have a different concept or differing staff qualifications that prevent the occurrence of challenging behaviour and subsequently the need for coercive measures. It would be of great interest to further investigate institutions with low rates of challenging behaviour and coercive measures. We did not collect data on residents' degree of impairment, comorbid diagnoses, staff qualifications and details on quality control measures. While it is possible that those institutions with low challenging behaviour and low coercive measures had less severely afflicted residents, it is also possible that there are e.g., structural or personnel differences that prevent challenging behaviour or allow for an approach to challenging behaviour without coercive measures. Especially considering the small numbers of children in most institutions, it can have a considerable impact on the frequency of critical events and thus freedom-restricting measures if even a few residents with severe challenging behaviour move into or out of an institution. Another factor in the management of challenging behaviour is the level of care for the severely affected residents. One such resident being approved for or stripped of 1:1 care from a designated member of staff can lead to significant changes. Furthermore, our survey only inquired after events of the last 14 days. So even temporary changes such as e.g., a hospital stay, can influence the numbers.

In addition to a general lack of expertise in the field of IDD and of therapeutic options, the dichotomization into 'regular' and 'intensive' institutions leads to an increasing deficit in the availability of suitable care for children, adolescents and young adults with IDD. Given the political and societal measures to encourage the inclusion of individuals with developmental disorders into all societal contexts, the demand for regular institutions is declining compared to more intensive institutions. At the same time, medical advancements ensure

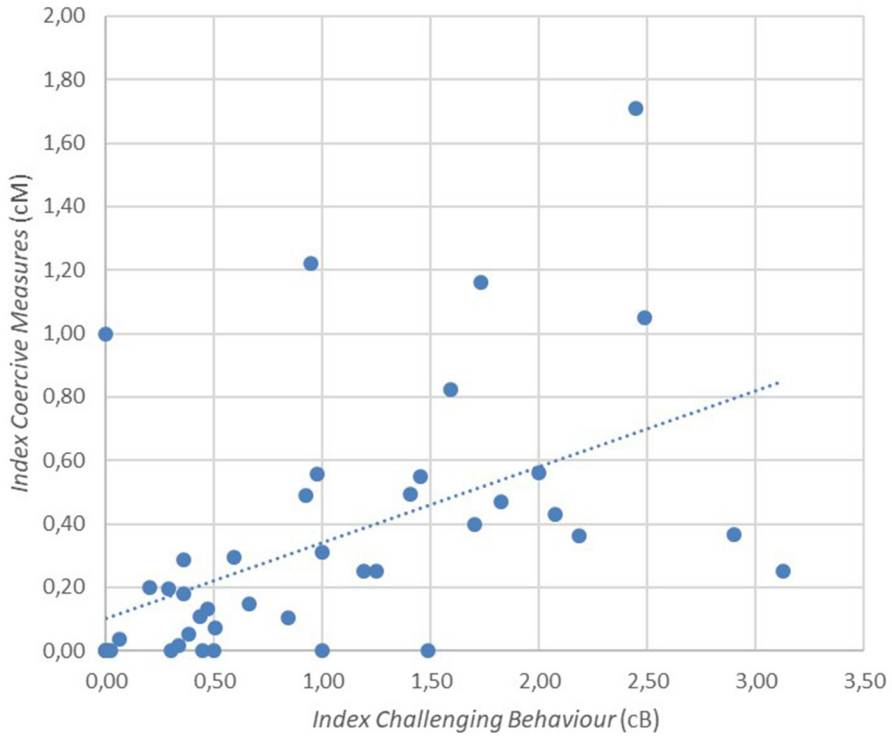

FIGURE 4 | Relationship between the Index cB and the Index cM, $r = 0.519$, $p < 0.001$.

a substantially higher survival rate of children with complex developmental disorders and severe somatic impairments that require specialised care. Hence, 'intensive' institutions have by far more applications than they can actually accept and thus children with the most severe behavioural issues cannot be placed. In fact, those children with the highest needs generally have the longest waiting periods until placement or cannot be placed at all. Often, those children remain in psychiatric clinics and are—upon reaching adulthood—transferred to the adult departments, where in many cases they are hospitalised for many years. Before the reform of §1631b BGB, there were only 102 official restricted placements in Bavaria. The surveyed institutions had obtained permissions from a court for the use of coercive measures for 151 children, adolescents and young adults, indicating that the need for coercive measures potentially exceeds the number of official restricted placements. However, even if permission was obtained, this does not automatically mean that coercive measures were used. Outside of a restricted placement, the use of coercive measures prior to the reform was exclusively regulated via custodial consent. It has frequently been discussed whether the limited number of residential placement options for children, adolescents and young adults with IDD—especially those displaying challenging behaviour—puts pressure on custodians to agree to the use of coercive measures in order to avoid losing the child's placement.

In addition, challenging behaviour and coercive measures lead to the stigmatisation of both the children and their caregivers. Children with challenging behaviour are viewed as hard to adequately take care of. Aggressive behaviour presents a danger to caregivers, who may feel helpless in the face of those behavioural issues—especially if they lack alternatives to coercive measures to address the issues. At the same time, the use of coercive measures is often judged as unjustified and 'the easy way out' by external observers, and this creates additional pressures for caregivers. The higher rate of coercive measures in 'intensive' institutions as a consequence of caring for more severely affected children, adolescents and young adults with higher levels of aggression has repeatedly led to accusations of malpractice against those institutions. Especially children, adolescents and young adults with aggressive behaviour issues require specific conditions to thrive. Institutions require the resources—both structural as well as in terms of staff training and therapeutic-pedagogic concepts—to provide viable alternatives to coercive measures to address and ideally prevent challenging behaviour. While law reforms restricting access to coercive measures are an important first step, only the concurrent development of innovative concepts will lead to reductions in challenging behaviour and coercive measures in the long term. REDUGIA provides extensive data on the status quo. Future research should focus on systematically evaluating preventive measures and interventions.

LIMITATIONS

The reliance on institutions' self-report regarding the use of coercive measures is the most serious limitation of the REDUGIA

project, since such a sensitive topic can lead to socially desirable answers. We tried to address this issue by assuring institutions of anonymity after the follow-up data collection. Still, we cannot rule out the possibility that instances of coercive measures were omitted.

Some providers running multiple residential institutions reported on all of their institutions in one questionnaire. This may have introduced a bias in the data if institutions were very dissimilar.

There are several limitations within the composition of the questionnaire itself. Future surveys should include items assessing a) the number of residents displaying no challenging behaviour, b) the number of residents not affected by coercive measures, c) the frequency of each type of challenging behaviour, d) co-occurring coercive measures after one incident e) the number of persons on staff in addition to the full-time position equivalents, f) psychological employee stress and g) coping strategies and successful strategies for dealing with challenging behaviour without coercive measures.

Lastly, our results pertain to conditions in residential institutions in the state of Bavaria. It is unclear to what extent they can be generalised across the whole of Germany. More research is needed to provide a comprehensive picture.

CONCLUSION

There is a distinct link between coercive measures and challenging behaviour. Addressing the underlying causes of challenging behaviour is therefore key to reducing the need for coercive measures.

Challenging behaviour and the use of coercive measures only occurred in one third of participating institutions. There is reason to believe that this is due to only a minority of institutions admitting residents with known aggressive behaviour. A broader dissemination of specialised knowledge especially regarding aggressive behaviour in people with IDD may create more residential placement options for these complex cases.

The amendment of §1631b BGB mandating permission from family courts for the use of coercive measures did not lead to a decrease in the use of coercive measures. This points to a responsible use of coercive measures by residential institutions for children, adolescents and young adults with IDD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the medical faculty of the University of Würzburg (study number 227/17). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

EW, CR, and MR contributed to conception and design of the study. JG and EW performed the statistical analysis. JG wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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MINI REVIEW
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Development of Down Syndrome Research Over the Last Decades–What Healthcare and Education Professionals Need to Know

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Down syndrome (DS) is the most prevalent neurodevelopmental disorder, with a known genetic cause. Besides facial dysmorphologies and congenital and/or acquired medical conditions, the syndrome is characterized by intellectual disability, accelerated aging, and an increased likelihood of an early onset Alzheimer's disease in adulthood. These common patterns of DS are derived from the long-held standard in the field of DS research, that describes individuals with DS as a homogeneous group and compares phenotypic outcomes with either neurotypical controls or other neurodevelopmental disorders. This traditional view has changed, as modern research pinpoints a broad variability in both the occurrence and severity of symptoms across DS, arguing for DS heterogeneity and against a single "DS profile." Nevertheless, prenatal counseling does not often prioritize the awareness of potential within-group variations of DS, portraying only a vague picture of the developmental outcomes of children with DS to expectant parents. This mini-review provides a concise update on existent information about the heterogeneity of DS from a full-spectrum developmental perspective, within an interdisciplinary context. Knowledge on DS heterogeneity will not only enable professionals to enhance the quality of prenatal counseling, but also help parents to set targeted early interventions, to further optimize daily functions and the quality of life of their children.

Keywords: Down syndrome, trisomy 21, developmental outcome, phenotypic heterogeneity, Alzheimer's disease, medical comorbidities, social environment, prenatal counseling

INTRODUCTION

Down syndrome (DS) is the most common neurodevelopmental disorder with known genetic causes, and an incidence of 1 in 691 live births (1). This suggests that ∼417,000 people with DS live in Europe (2). Currently, an expansive menu of prenatal diagnostic methods for DS is spreading worldwide, advancing the diagnosis of DS from postnatal to prenatal (3). Giving an expectant parent a fetal diagnosis of DS provides them with 2 options: keeping or terminating their pregnancy, following the lack of a cure (4).

Prenatal counseling is crucial for providing parents with an accurate picture of DS so that informed decisions can be made in the context of their own beliefs and values (3). Although studies are still examining the nature of DS, portraying the expected neurodevelopmental outcomes of affected children remains challenging. Indeed, retrospective studies indicate that parents felt that the information received during prenatal counseling was inaccurate, outdated, and unbalanced, and either too negative or too optimistic (5–7). Without appropriate professional training or updated professional development regarding the individual variability in outcomes associated with DS, prenatal counselors might present expectant parents with inaccurate information or impressions. Therefore, expectant parents may not receive the level of information needed. Accordingly, all professionals working with families affected by DS must be aware of the most current scientific research regarding the heterogeneity of phenotypic outcomes (8).

This mini-review closes an existent literature gap by providing a concise update on the available information on within-group variations in the DS phenotype of infants, children, and adolescents for professionals. First, a gross outline of DS research is given, focusing on the significant paradigm shift from a group- to an individual-level approach. Second, the current knowledge on significant within-group variations of DS in cognitive, behavioral, emotional, and olfactory functioning is summarized. Finally, the review concludes by arguing that only an interdisciplinary approach allows for the description of realistic individual DS profiles. The scope of this review is to further increase the awareness on DS heterogeneity concerning developmental outcomes.

A PARADIGM SHIFT IN DS RESEARCH: FROM A GROUP- TO INDIVIDUAL-LEVEL APPROACH

DS research dates back to 1866, when the English physician John Langdon Down systematically described the syndrome for the first time (9, 10). In addition to intellectual disability (ID), he chronicled a distinct physical phenotype of individuals with DS, conjecturing that they were "born to the same family" (page 9) (10, 11). The century following his pioneering work was filled with publications of diverse medical case studies documenting a range of physical traits and medical comorbidities, leading to various etiologies (10, 11).

Almost 100 years later, the French pediatrician and cytogeneticist, Jérôme Lejeune, identified the genetic basis of DS in 1959 as an extra copy of all or part of chromosome 21 (10, 12). The discovery of "trisomy 21" paved the way for further research, to elucidate genotype-phenotype-relationships (13, 14). Since its original description, classical DS research has analyzed the syndrome's phenotypes relative to neurotypicals and/or other neurodevelopmental disorders, hence providing group-level data that have advanced our basic knowledge of DS (8). It is characterized by both typical physical features that make the syndrome "instantly recognizable" (page 8) and ID (11). Common appearance includes craniofacial dysmorphologies, short stature, low muscle tone, and a proportionally large tongue. Additionally, medical comorbidities, such as sleep apnea, visual and/or hearing problems, congenital heart defects, and altered behavioral, hematopoietic, endocrine, gastrointestinal, neurological, and musculoskeletal conditions, are linked to DS (10).

Most of these medical problems are treatable with pharmacotherapy and/or surgical interventions. Therefore, among the key focuses in recent DS research is the widespread field of neurocognition, associating DS with weaknesses in motor ability, auditory processing, verbal short-term memory, and expressive language. However, relative strengths in visuospatial processing, receptive language, and some aspects of social functioning have been reported (15–18). Further, DS is associated with accelerated aging and an increased likelihood of the early onset of Alzheimer's disease (AD) (18).

Although the generalizability of the characteristics of DS has been questioned repeatedly in the history of DS research, the group-level approach is a long-held standard (19, 20). However, this traditional view has changed, following a growing number of studies, which pinpoint significant within-group variations across individuals with DS at many levels of description. Pioneer studies have launched this paradigm shift, from a group to an individual-level approach, by highlighting significant individual differences in genetics, cell biology, brain research, and subsequently, parts of cognitive research on DS [see (8)]. These studies suggest that this heterogeneity may be continued in DS phenotypes (8). The following review aims to supplement the prevailing knowledge about the variability of the developmental outcomes of DS by addressing this issue from an interdisciplinary and applied science perspective, as this practical information may be the most useful for professionals to pass to expectant parents.

INFANTS, CHILDREN, AND ADOLESCENTS WITH DS: VARIABILITY IN DEVELOPMENTAL OUTCOMES

Acquisition of Developmental Milestones

Generally, it was assumed that infants and children with DS reached developmental milestones in the same linear fashion as their non-DS peers, but at later chronological ages. This view is too simplistic, as the age of acquiring milestones among infants and children with DS is reported to vary significantly (21, 22). For example, the mean age at the onset of babbling is ∼15 months, with an interindividual variability of 10 months. Similarly, sphincter control is acquired by DS children at an approximate age of 44 months, with 22 months of interindividual variability (22). Notably, Locatelli et al. suggested that the age at which developmental milestones are reached influences the subsequent development of diverse cognitive domains significantly (21, 22).

Intellectual Disability (ID)

ID, defined by an intelligence quotient (IQ) score of<70, is reported to be universal in the DS population. However, this construct presents in DS with large interindividual variability (23). The majority of individuals with DS fall within the severe

(IQ 20–35) to mild (IQ 50–69) range of ID. However, some cases reach IQ scores equivalent to children without ID (14, 24). Research on the developmental trajectories of cognitive function in neurotypicals shows that IQ is a construct that remains relatively stable and consistent across ages. A slight decline was observed only in older adults (14). Conversely, DS research has identified a linear decline in IQ scores as development progresses, starting in the first year of life (i.e., cognitive gains do not keep pace with chronological age). Notably, single IQ levels and the degree of cognitive decline vary across the DS group (14).

Language

Language is another cognitive domain that generates significant differences among individuals with DS. DS is associated with weaknesses in expressive language and a relative strength in the receptive language (18). The available literature reports developmental delays in both language domains, becoming apparent no later than age five, yet with wide individual differences (25, 26). Regarding vocabulary acquisition and growth, longitudinal studies reported an existing continuum, ranging from non-verbal children to those with a vocabulary close to the normal range (27, 28). Children with DS use gestures as a means of communication, which has been positively associated with the development of spoken vocabulary (29). Nevertheless, significant individual variability in the extent to which this "gestural advantage" is used has been demonstrated by empirical data (30). All within-group differences in language development persist into adulthood (26).

Memory

Memory and learning deficits are universal characteristics of DS and are known to become more pronounced as development progresses (14). In classical DS research, the findings of affected memory domains are mixed, suggesting underlying variability (18). Indeed, scientific data demonstrate that there are individual differences in both implicit and explicit memory (8, 31). Regarding the latter, significant within-group variations are described for short-term verbal and long-term visual memory (8). Individuals with DS often show deficits in processing local detail. Therefore, classical DS literature claims that individuals with DS were "global processors." However, this preference for global over local processing does not always occur in the DS population. Therefore, individuals with DS cannot be simply categorized into one of these processing styles (32).

Executive Function (EF)

EF encompasses a range of cognitive processes involved in goal-oriented behavior, and is a domain in which individuals with DS are shown to have pronounced difficulties (33). The areas of working memory, attention, planning, and inhibition are considered particularly challenging for individuals with DS; emotional control is considered a relative strength (34, 35). However, significant individual differences in EF across the DS group have become evident (33, 36). Within-group variations in auditory attention have been identified *via* electrophysiological measurement among toddlers with DS, data that also predict differences in language abilities as development progresses (37). Patterns of executive dysfunction appear to be relatively consistent across development until adulthood (23, 34).

Adaptive Behavior (AB)

Children and adolescents with DS are known to be severely impaired in AB, which subsumes behavioral skills that enable them to function independently in their everyday life (23, 38). Generally, AB encompasses 4 domains: socialization, communication, daily living, and motor skills (23). Significant within-group variations were apparent for all the 4 domains. For example, DS has been associated with sociability, friendliness, affection, empathy, good competence in forming relationships, and high tendency to smile (39). Yet, children and adolescents with DS are also considered stubborn, to show little accommodation to social partners, and approach strangers inappropriately (40). Some individuals with DS have even deficits in socialization to the extent of a comorbid diagnosis of autism (41).

Maladaptive Behavior (MB) and Psychiatric Comorbidities

MB encompasses a range of behaviors that impede an individual's activities of daily living or the ability to adjust to and participate in particular settings (23). Approximately 1/4 to 1/3 of individuals with DS exhibit clinically significant levels of maladaptive behavioral concerns (42–44). This behavioral construct is another domain that yields significant within-group differences (21, 23, 45). More difficulties with "anxious-depressed" symptoms are observed among adolescents than younger children with DS (23). Children with DS often exhibit externalizing behavior (46). The manifestation of MB is significantly higher when neurobehavioral disorders are concomitant (47–49). According to the available literature, the manifestation of psychiatric features, including autism, depression, and the attention-deficit/hyperactivity disorder, vary significantly, between 6 and >50% (42, 44, 50, 51). Channell et al. underscored within-group differences in the behavioral domain by subtyping a >300-person DS group, hence identifying a separate "behavioral" class as described in **Table 1** (23).

Emotional Functioning

The emotional profiles of individuals with DS have remained underexplored, which could be attributed to the assumed stereotype of high sociability in this population (52, 53). Available literature provides variable data about whether children and adolescents have difficulties in emotional functioning (52). Whereas, some studies negate differences in identifying basic emotion in faces between DS and non-DS groups, other scientific reports indicate that children and adolescents with DS have impairments in this emotional skill [see Roch et al. (52)] (54–57). Deficits in recognizing facial expressions were not generalized to all emotions, but mostly to fear (52, 58). Other studies report impairments in determining feelings, including surprise, anger, and neutral expression (40, 58–61). Some studies pinpoint problems in ascertaining negative emotions (40). Moreover, an inability to distinguish between fear and sadness is another atypical pattern that has been reported among some individuals

TABLE 1 | Characterization of the 3-class model of individuals with DS ($N = 314$; 6–25 years) based on the variability observed in cognitive and behavioral measures, identified by Channell et al. (23) using a latent profile analysis.

	3-class model proposed by Channell et al. (23)		
	Normative class	**Cognitive class**	**Behavioral class**
Number of participants	$N = 153$ (48%)	$N = 109$ (35%)	$N = 52$ (17%)
Strengthens (relative to sample average)	Cognitive skills (IQ, visuospatial abilities), adaptive behavior, executive function	–	Cognitive skills (IQ, visuospatial abilities), adaptive behavior
Weaknesses (relative to sample average)	–	Cognitive skills (IQ, visuospatial abilities), executive function, adaptive behavior, maladaptive behavior (ASD, hyperactivity)	Maladaptive behavior (ASD), executive function

ASD, autism spectrum disorder; IQ, intelligence quotient.

(58). Most of these deficits are identified during infancy and childhood. Therefore, a negative impact on the subsequent development of interpersonal relationships is discussed (52). As previously mentioned, studies have exclusively gathered data at the group level. Moreover, further research should examine whether inconsistencies in findings across studies can be attributed to underlying within-group variations.

Olfactory Functioning

The number of studies on olfactory function among patients with DS is limited and relatively out of date (62–69). Historical studies have described olfactory deficits in the DS population for many years (62, 63, 65, 70). Because rhinologic pathologies have been ruled out by studies showing nasal function in DS as comparable to controls, central-nervous causes are suggested (64). More recently, Cecchini et al. described olfactory function as severely impaired among adults with DS (71). They found a positive correlation between odor identification and cognition (71). To date, the largest study, which included people with DS and under 18 years, described a minimal impairment of olfactory functioning among children and adolescents (9–17 years), which became pronounced in young adulthood (18–29 years) and was the lowest in adulthood (30–50 years) (72). Of the three groups, DS, IQ, and age-matched controls, significant within-group differences were evident only in the DS group (72). However, large and detailed analyses of olfactory function in light of within-group variations among children and adolescents with DS are still lacking. Odor identification deficits are considered a valid non-invasive early marker of AD. Therefore, future research on whether olfactory dysfunction can help to ascertain the subset of children and adolescents with DS that will later develop AD is warranted.

Alzheimer's Disease (AD)

Although the issue of AD appears outside the scope of this review, the following considerations must be made when the heterogeneity of DS is discussed with expectant parents from a full-spectrum developmental perspective. Owing to a shared genetic predisposition, individuals with DS have an increased likelihood of developing early onset AD in adulthood (18). Prevalence rates of dementia among the DS population vary significantly in the literature, from 8 to 100% (18, 73). Recent brain research has identified Alzheimer's plaques among some children with DS, that is, as early as 8 years of age, whereas some DS brains show no plaques until early adulthood (14, 26). Although AD neuropathology occurs in virtually all individuals with DS over the age of 30, only a subset of people develop clinical symptoms of dementia (26, 74, 75). Hence, it is apparent that the widespread interindividual variability, typical for DS, is a pivotal feature not only during development, but also during aging (26). Aging is part of the continuous lifespan development. Accordingly, some authors argue that AD should be considered a disease that occurs during development, rather than aging (76).

EXTRINSIC INFLUENCING FACTORS OF DEVELOPMENTAL OUTCOMES OF INFANTS, CHILDREN, AND ADOLESCENTS WITH DS

Medical Comorbidities

In addition to cognitive limitations, parents must be informed that there is a list of medical comorbidities associated with DS. Some of them, including congenital heart defects (CHD), seizures, visual and/or hearing impairments, autism, and sleep disruptions, are known to moderate cognitive functioning (18). Analogous to neurodevelopmental outcomes, both the occurrence and expression of congenital and/or acquired medical complications are variable (18). For example, 41–56% of infants with DS are born with a CHD, with an atrioventricular septal defect that occurs between 31 and 61% being the most common form (77, 78). Cognition, gross motor skills, and language are significantly worse among infants with DS and CHD, relative to peers without CHD, in some, but not in all related studies (79–81). For example, Alsaied et al. showed that children with DS and CHD, who undergo cardiac surgery during their first year, have no significant differences in neurodevelopmental outcomes at preschool and school age. However, as infants and toddlers, they were prone to poorer outcomes in receptive, expressive, and composite language compared to children with DS without CHD, suggesting that deleterious effects may be dependent on clinical management (82).

Home Environment

Another variable that affects the observed variability of DS phenotypes, which is influenced by the expectant parents, is the home environment. According to Karmiloff-Smith et al., the genetic syndrome changes the family context in terms of parent-child-interactions (8). D'Souza et al. demonstrated that parental depression, a disease linked to difficulties in responding to the child in a sensitive and consistent manner, explained deficits in expressive language development among children between 8 and 48 months of age with DS (83). Similarly, there is evidence that vocabulary development among children with DS is influenced by how parents respond to their children's communication. Deckers et al. argued that mothers with a higher level of education had a better ability to fine-tune their communication with their children with DS (28). Further demographic factors, including socioeconomic status, neighborhood demographics, and the availability of therapeutic resources, modulate the developmental outcomes of DS effectively (84, 85). These data demonstrate that only an interdisciplinary approach that considers psychological, physical, and social parameters will enable professionals to accurately inform expectant parents on how the DS phenotype will be expressed in each individual.

DISCUSSION

Although DS has been examined for a long time, that is 155 years, it is still one of the least understood genetic ID syndromes. The most significant reason for this is the high degree of phenotypic variability observed in the DS population, an issue that professionals are often unaware of when discussing the diagnosis with expectant parents. However, DS research has advanced from a group to an individual-level approach, attempting to acknowledge within-group differences at many levels of basic science (8). To expand on this wealth of data, this mini-review has shed light on the available information on individual variability in the developmental outcomes of infants, children, and adolescents with DS from an applied science perspective, which will enhance the quality of prenatal counseling. Diverse developmental domains, including cognition, behavior, and emotional and olfactory functioning, have been discussed.

The evaluation of developmental outcomes from a full-spectrum perspective, however, must not only address different developmental domains, but also the change of phenotypes over time (86). Outcome variables are not completely intact or impaired uniformly throughout development, but manifest as variations at an early state, that may be magnified with age, ending up as either a strength or a weakness. Therefore, parents should be made aware that early development can be considered a critical window of opportunity to set adequate phenotype-specific interventions before deficits become severely pronounced (87). Thus, the maximization of individual potential is possible. In addition to psychological factors, other influencing variables must be considered by parents when the variability of DS phenotypes is discussed. According to Karmiloff-Smith who states that having a neurodevelopmental disorder changes both the social environment and physical status, only an interdisciplinary research approach can successfully describe valid profiles of individuals with DS (8).

The most convincing argument for emphasizing individual variability among DS groups and discussing them with expectant parents are both an average life expectancy of 60 years combined with an early onset of Alzheimer's disease in the DS population (18). Focusing on individual differences in the development of DS may be the best approach for exploring the risk and protective factors of AD (88, 89).

Modern DS research shows that developmental heterogeneity has become increasingly validated (23). Moving forward, these up-to-date data must be disseminated under the supervision of professionals so that prenatal counseling can be optimized in quality, hence allowing parents to gain realistic expectations about the future of their children. Thus, more targeted treatments and interventions can be set to improve the daily function and quality of life.

AUTHOR CONTRIBUTIONS

KW and SH designed the paper. KW did the literature research and wrote the manuscript. SH provided intellectual input and critically revised the manuscript. Both authors contributed to the article and approved the submitted version.

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Early Intervention in Severe Autism: Positive Outcome Using Exchange and Development Therapy

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Early intervention programs positively affect key behaviors for children with autism spectrum disorder (ASD). However, most of these programs do not target children with severe autistic symptomatology associated with intellectual disability (ID). This study aimed to investigate the psychological and clinical outcomes of children with severe autism and ID enrolled in the Tailored and Inclusive Program for Autism—Tours (TIPA-T). The first step of the TIPA-T is the Exchange and Development Therapy (EDT): an individual neurofunctional intervention consisting of one-to-one exchanges between a child and a therapist taking place in a pared-down environment. It aims to rehabilitate psychophysiological abilities at the roots of social communication through structured sequences of "social play." Cognitive and socio-emotional skills and general development were evaluated with the Social Cognitive Evaluation Battery scale and the Brunet–Lézine Scale—Revised, respectively, before and after 9 months of intervention in 32 children with ASD and ID. Autistic symptomatology was evaluated with the Behavior Summarized Evaluation—Revised scale at five time-points in a subset of 14 children, both in individual and group settings. Statistically significant post-intervention improvements were found in cognitive and socio-emotional skills. All but one child showed improvements in at least one social domain, and 78% of children gained one level in at least four social domains. Twenty-nine children improved in cognitive domains, with 66% of children improving in at least three cognitive domains. Autistic symptomatology evaluated in one-to-one settings significantly decreased with therapy; this reduction was observed in more than 85% of children. In group settings, autistic symptomatology also decreased in more than 60% of children. Global developmental age significantly increased by 3.8 months. The TIPA-T, including EDT in particular, improves socio-emotional skills of most children with ASD and reduces autistic symptomatology, yet with heterogeneous outcomes profiles, in line with the strong heterogeneity of profiles observed in ASD. At the group level, this study highlights the benefits of the TIPA-T for children with severe autism and associated ID. Assessment of autistic core symptoms showed an improvement of social interaction,

both in one-to-one and group evaluations, demonstrating the generalizability of the skills learned during the EDT.

Keywords: autism spectrum disorder, children, assessment, Exchange and Development Therapy, Tailored and Inclusive Program for Autism-Tours

INTRODUCTION

As defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (1), autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communication and social interaction and by restricted, repetitive patterns of behavior, interest, or activities that manifest during the first years of life. ASD is frequently associated with intellectual disability [ID, (2)], with a lower intellectual quotient linked to more severe autism symptoms (3). Most individuals with ASD and/or ID require some level of lifelong support because of the severity of these conditions and the high prevalence of related comorbidities. In addition, ASD is also characterized by an important heterogeneity, notably regarding the severity of autism but also at all levels of clinical examination: biological, genetic, cognitive, neural, and behavioral [e.g., (4, 5)]. Early intervention programs positively affect key behaviors for children with ASD. However, most of these programs do not target children with severe autistic symptomatology associated with intellectual disability. This study aimed to investigate the psychological and clinical outcomes of children with severe autism and intellectual disability enrolled in the Early Phase of the Tailored and Inclusive Program for Autism—Tours (TIPA-T).

Early intervention for children with ASD has been recognized as a health and educational priority (6, 7). Early (i.e., starting before 4 years old) intensive behavioral interventions are recognized as an efficacious approach for improving outcomes for young children with ASD (8–12). Well-known intervention programs based on a naturalistic developmental behavioral approach include the Early Start Denver Model (13), the Joint Attention Symbolic Play Engagement and Regulation (14, 15), Pivotal Response Treatment (16–18), Pediatric Autism Communication Therapy—Generalized (19), Frankfurt Early Intervention Program (20, 21).

Existing intervention programs mostly target children with no or mild intellectual deficiency. The TIPA-T program evaluated in the current study is dedicated to all children, from toddlers to young adults, including those with severe autism and associated intellectual disability.

The TIPA-T is a tailored and global program based on functional, developmental, and multidisciplinary assessments of the children. The program is set up by a multidisciplinary team, including psychiatrists, psychologists, speech therapists, psychomotor therapists, social workers, teachers, and nurses located in the child psychiatry intervention units in the Center of Excellence for Autism in Tours (EXAC-T) (France). The program is tailored to each child's age and needs following an integrative approach to the treatment of ASD and includes both individual and collective sessions. The current paper focuses on the early phase of TIPA-T, dedicated to children between 2 and 6 years old. The weekly program duration is 20 to 25 h following the recommendations of the High Authority for Health in France (HAS, 2012), integrating individual and collective care times [Exchange and Development Therapy (EDT), speech therapy, psychomotor therapy, and educative activities] and school sessions in mainstream kindergarten with individualized support.

Collective interventions, spread on the whole day, comprise speech and psychomotor activities performed by trained professionals, an educative program proposed by nurses and specialized teachers within the child psychiatric unit, alongside group free play aiming at working on socialization, communication, and autonomy. Collective interventions also integrate inclusive school sessions with individual support.

Individual intervention mainly consists of sessions of EDT, an individual neurofunctional therapy based on the experience and practice of a multidisciplinary team (22–24). The EDT aims at reeducating psychophysiological abilities at the roots of social communication, which will, in turn, improve behavior rather than target behavior first. The purpose of the EDT is not the child's performance but its participation in the proposed and shared activities. It focuses on developing, increasing, and enriching social contacts and exchanges with others through adapted means of communication. It is based on the underlying assumption that autistic symptoms are the consequences of the atypical development (25–29) and malfunctioning (25, 30–37) of the cerebral networks underlying change detection and social communication. The neurophysiological principles underlying EDT are cerebral plasticity, physiological curiosity, and free acquisition. It aims to rehabilitate, through structured sequences of "social play" and shared enjoyment, functions subtended by the brain systems of social communication: attention to others, intention, imitation, etc. The EDT consists of a one-to-one exchange between a child and a therapist taking place in a pared-down environment to facilitate mutual adjustments and socio-emotional synchronization between the child and the adult. This rehabilitation therapy is particularly indicated for young children before the age of 4 years, a period of maximum brain plasticity. The EDT is the pivotal element of the therapeutic and educational project built for a child in close relation with their family. Treatment organization is defined at the beginning of the session according to clinical and psychological assessments and behavioral deficits. Activities tailored to each child's needs and interests, evaluated before the therapy, and readjusted according to longitudinal evaluations are selected among a list of predefined activities (e.g., bubbles, motor games, mimed song, etc.).

Abbreviations: ASD, Autism Spectrum disorder; TIPA-T, Tailored and Inclusive Program for Autism—Tours; EDT, Exchange and Development Therapy, SCEB, Socio-Emotional and Cognitive Evaluation Battery; BSE-R, Behavioral Scale Evaluation—Revised.

A growing body of evidence on early interventions for children with ASD highlights a large variability in children's response to treatment [e.g., (38)]. However, so far, it is difficult to identify which children respond to which treatment making it difficult to recommend the intervention better suited to a specific child. Difficulty in assessing outcomes of intervention programs arose from the lack of clinical tools that provide a precise and detailed functional profile of children with autism, specifically oriented toward key symptoms of ASD and sensitive enough to assess subtle changes occurring over a very short period (38). In the current study, we used the Social Cognitive Evaluation Battery [SCEB; (39–42)], a French clinical tool created to assess young children with ASD with autism and associated ID. It explores different functional skills covering cognitive and socio-emotional domains for children with a developmental age (DA) comprised between 4 and 24 months. Complementary to the SCEB, the Behavioral Scale Evaluation—Revised [BSE-R; (32, 43)] evaluates the behavior of children with autism to further assess the severity of autism. Briefly, the BSE-R focuses on several neurophysiological functions, which are believed to contribute to core symptoms of autism in varying degrees (e.g., attention, perception, association, intention, imitation, contact, communication, etc.). The BSE-R provides a behavioral and functional profile of a child and can be used regularly to follow the evolution of a child's particular deficit (24, 32).

This study aimed to describe the evolution of key autistic symptoms and behaviors in some children with severe ASD and concurrent ID following a 9-month early intensive intervention program, the TIPA-T, centered on the EDT. We hypothesized that the TIPA-T would yield progress in socio-emotional skills assessed with the SCEB and a reduction of autistic behaviors with the BSE-R.

METHODS

Subjects

The sample consisted of 32 children (26 males and 6 females) with a diagnosis of ASD, according to International Classification of Diseases 10 (World Health Organization, 1993) and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (1), made by the multidisciplinary team of the Excellence Center for Autism—Tours after full clinical assessment. Mean chronological age was 45 ± [standard error of the mean (SEM)] 8.1 months (range in months [27 60]). All children had severe autism [Childhood Autism Rating Scale (44); mean ± SEM: 38.4 ± 0.51, (33.5 47)] and moderate-to-severe intellectual disability [Psychomotor Developmental Scale of Brunet–Lézine—Revised (45); developmental quotient: mean ± SEM: 39.3 ± 1.8, [15 60]; DA: 17.3 ± 0.7, [7 24]].

Exchange and Development Therapy

The implementation of the EDT is highly structured by visual cues, visually based schedules, and the implementation of routines. EDT sessions take place two or three times a week and last approximately 20 min; sessions are always adapted to the child's attention and concentration skills.

The EDT is based on three general principles: serenity, availability, and reciprocity. The organization of EDT sessions aims at enforcing these general principles. To respect the principle of serenity, the EDT takes place in a bare room, thus creating a very sober space devoid of any distraction and precipitation. Before the session, the therapist prepares the room; that is, they choose furniture that will produce the best environment for inducing interactions with the child (a table and two chairs, or a mat on the floor and poufs) and the toys for the child. The aim is to create an environment that is stable from one session to another. The choice of toys is based on previous experience with the child; toys that have produced high-quality interactions at previous sessions are preferred.

To enforce the availability principle, the toys are offered one by one, in a predefined order, to keep the amount of stimulation to a minimum and focus the child's attention to the play at hand; nonetheless, the organization remains flexible to adapt to the child's envy. To keep the child involved in the sessions, both interactive and relaxing activities are proposed. This allows optimizing exchanges between the child and the therapist.

Perceptual-motor (e.g., mimed songs) and socio-emotional (e.g., itsy bitsy spider) sequences established around free play aimed at progressively increasing the synchronization between the child and the adult to promote reciprocity by fostering sociability. The therapist is continuously attentive to the child's communicative manifestations, however discreet they may be, to adapt the therapy to the child's reaction, and to include the child's initiatives in the sessions. If a child shows no interest in the proposed activity, the therapist tries gently to bring their attention back to the current activity by soliciting them gently. Importantly, they do so without showing disapproval to not reinforce the child's behaviour by a mark of attention. By doing so, the therapist manages to reengage the child and avoid a situation of failure. This permits that the child does not keep in mind a failed interaction. Finally, the adult promotes role-playing games and gradually introduces variations in the proposed scenari, considering the child's progress, so that established routines are not ritualized.

Scoring

The Brunet–Lézine Scale—Revised (45) is an adaptation of Gesell's scales (46), validated in the French population. It allows the evaluation of the psychomotor development of children from 1 to 30 months of age. The Brunet–Lézine—Revised allows, in addition to the estimation of global developmental age (GDA) the assessment of developmental ages in four different areas: posture, oculo-manual coordination, language, and sociability (SDA).

Cognitive and socio-emotional skills were assessed with the Social Cognitive Evaluation Battery (40–42). Based on Piaget's, Bruner's, and Fisher's theories of psychological development (47), the SCEB assesses both cognitive and socio-emotional areas of development at four developmental levels (level 1 = from 4 to 8 months, level 2 = from 8 to 12 months, level 3 = from 12 to 18 months, and level 4 = from 18 to 24 months). The cognitive area comprised seven domains: self-image, symbolic play, object-relation schemata, operational causality, means–ends, spatial relations, and object permanence. The

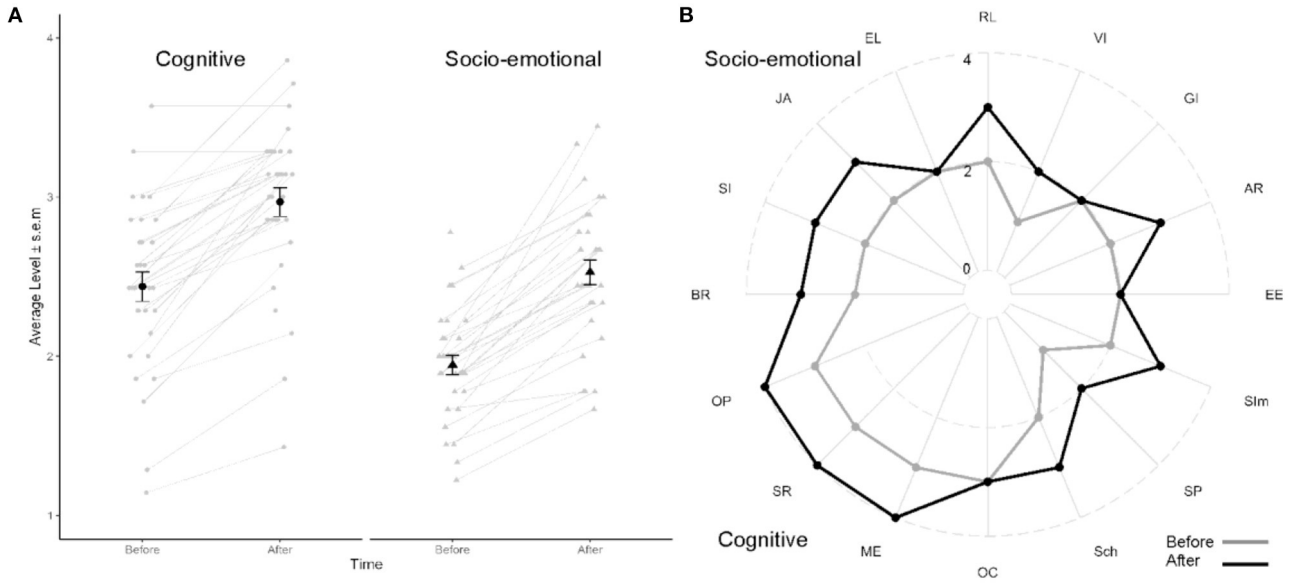

FIGURE 1 | Cognitive and socio-emotional assessment. **(A)** Average level across all cognitive and all socio-emotional domains before and after 9 months of therapy. Each individual is plotted as a gray line. Black dots represent group mean ± standard error of mean. Note that participant 28 was the participant producing the lowest scores; however, a progression was also observed with therapy. **(B)** Radar plot of statistical mode for each domain assessed with SCEB. Socio-emotional are presented on top and cognitive domains on bottom of image. Grayline, before therapy; black line, after therapy. Socio-emotional domains: BR, behavior regulation; SI, social interaction; JA, joint attention; EL, expressive language; RL, receptive language; VI, vocal imitation; GI, gestural imitation; AR, affective relation; EE, emotional expression. Cognitive domains: SIm, self-image; SP, symbolic play; Sch, object-relation schemata; OC, operational causality; ME, means–ends; SR, spatial relations; OP, object permanence.

socio-emotional area includes nine domains: behavior regulation, social interaction, joint attention, expressive language, receptive language, vocal imitation, gestural imitation, affective relation, and emotional expression.

Autistic symptomatology was assessed using the BSE-R scale (32, 43). The BSE-R assesses 29 behaviors scored from 1 to 5 according to the frequency of occurrence (1 = never, 2 = sometimes, 3 = often, 4 = very often, and 5 = always). These 29 behaviors can be grouped into two factors: interaction deficits (factor 1) and modulation deficits (factor 2). Here, the data of each factor were analyzed. The BSE-R scale is a recognized tool used in observational and intervention evaluation studies (48).

Organization of Assessments

Scorings of the Brunet–Lezine scale and the SCEB were performed at the beginning of therapy and after 9 months by psychologists experienced with these tools. The initial evaluation necessary to work out a tailored therapy program constitutes the baseline. The BSE-R scale was evaluated both in a one-to-one therapy session, through recordings of EDT sessions, and in collective settings to study a generalization of acquired skills at months 1, 3, 5, 7, and 9 of therapy.

Data Analysis

Statistical analysis and figures were made with R [version 4.0.2; (49)] within Rstudio [version 1.3.1056; (50)] environment using the following packages: lmerTest (51), rstatix (52), ggplot2 (53), tidyverse (54), readr (55), readxl (56), ggpubr (57), ggiraphExtra (58), and ggradar (59).

SCEB scores averaged across all social and all non-social domains (**Figure 1A**) were analyzed with a two-way repeated measure analysis of variance (ANOVA) with time (before/after therapy) and domains (socio-emotional/cognitive) as within-subject factors. Previous to the ANOVA, assumptions were verified, and participant 28 (**Figure 2**) was identified as an extreme outlier {outside the range [Q1 – 3 * interquartile range (IQR) Q3 + 3 * IQR]; in cognitive domains after therapy} using the IQR method: his averaged SCEB scores were all outside the range (Q1 - 1.5 * IQR Q3 + 1.5 * IQR) (lowest values on **Figure 1A**). Shapiro–Wilk tests performed on each factor combination from the 31 remaining participants highlights that the data did not differ from a normal distribution ($p > 0.09$); before removing participant 28, data in the cognitive domain after therapy did not follow a normal distribution ($p = 0.01$).

For each factor of the BSE-R, longitudinal scores were fitted with a linear mixed model with two fixed-effects parameters, intercept and slope, of the linear trend over time (e.g., month of therapy) for the population and two random effects for each subject. Random effects for a particular subject were the deviations in intercept and slope of that subject's time trend from the population. The model allowed for the correlation of random effects for the same subject due to the relationship between intercept and slope (**Figure 3**). The model was fit as: scores $\sim 1 + \text{time} + (1 + \text{time} \mid \text{subject})$. *T*-tests for fixed

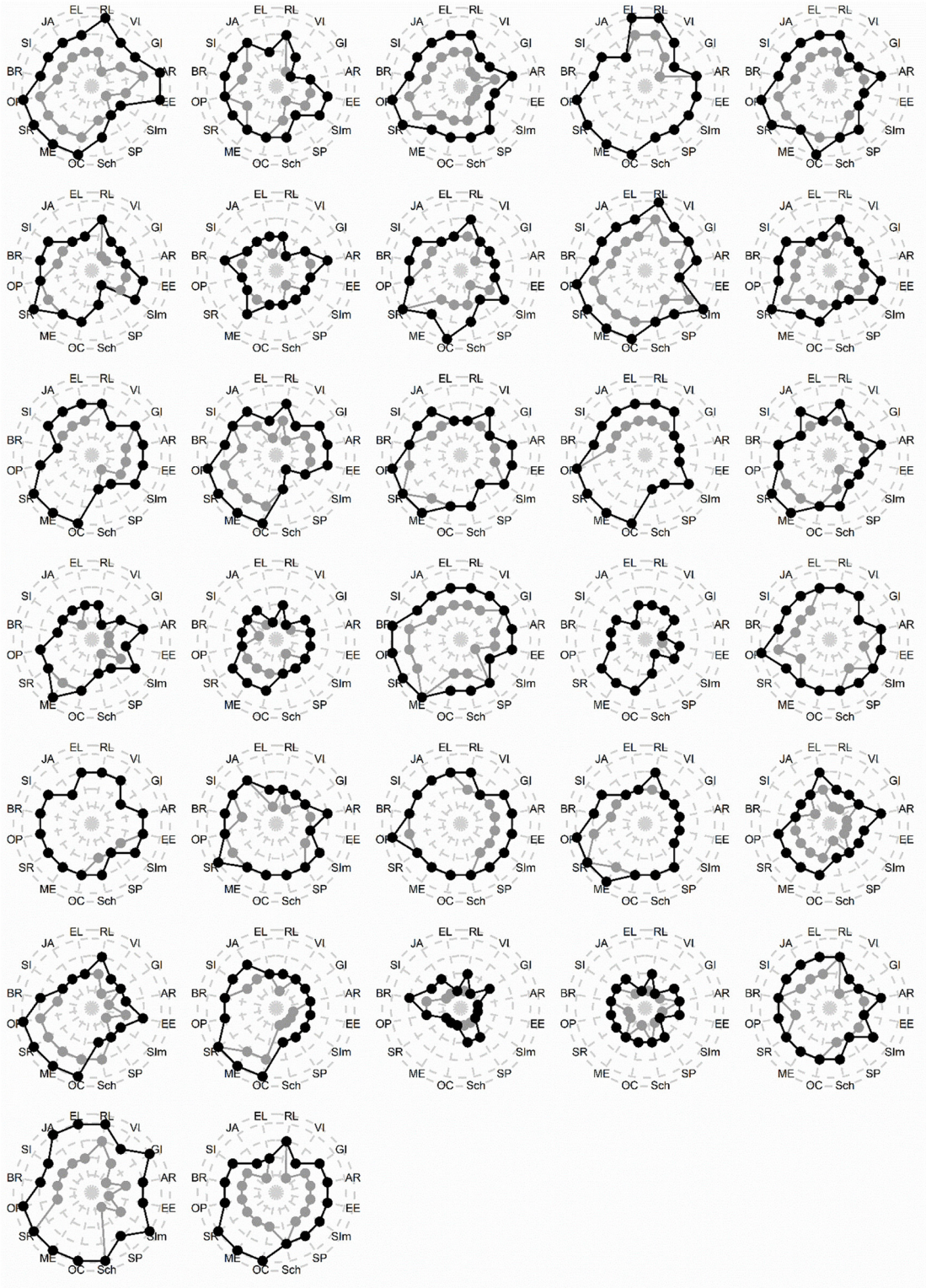

FIGURE 2 | Individual data ($N = 32$) for cognitive and socio-emotional assessment. Each radar plot represents a child enrolled in TIPA-T. Grayline: before therapy; black line: after therapy. Note that Subject 28 (before last line, middle column) was an extreme outlier and was removed from statistical analysis. Socio-emotional domains (top): BR, behavior regulation; SI, social interaction; JA, joint attention; EL, expressive language; RL, receptive language; VI, vocal imitation; GI, gestural imitation; AR, affective relation; EE, emotional expression. Cognitive domains (bottom): SIm, self-image; SP, symbolic play; Sch, object-relation schemata; OC, operational causality; ME, means–ends; SR, spatial relations; OP, object permanence).

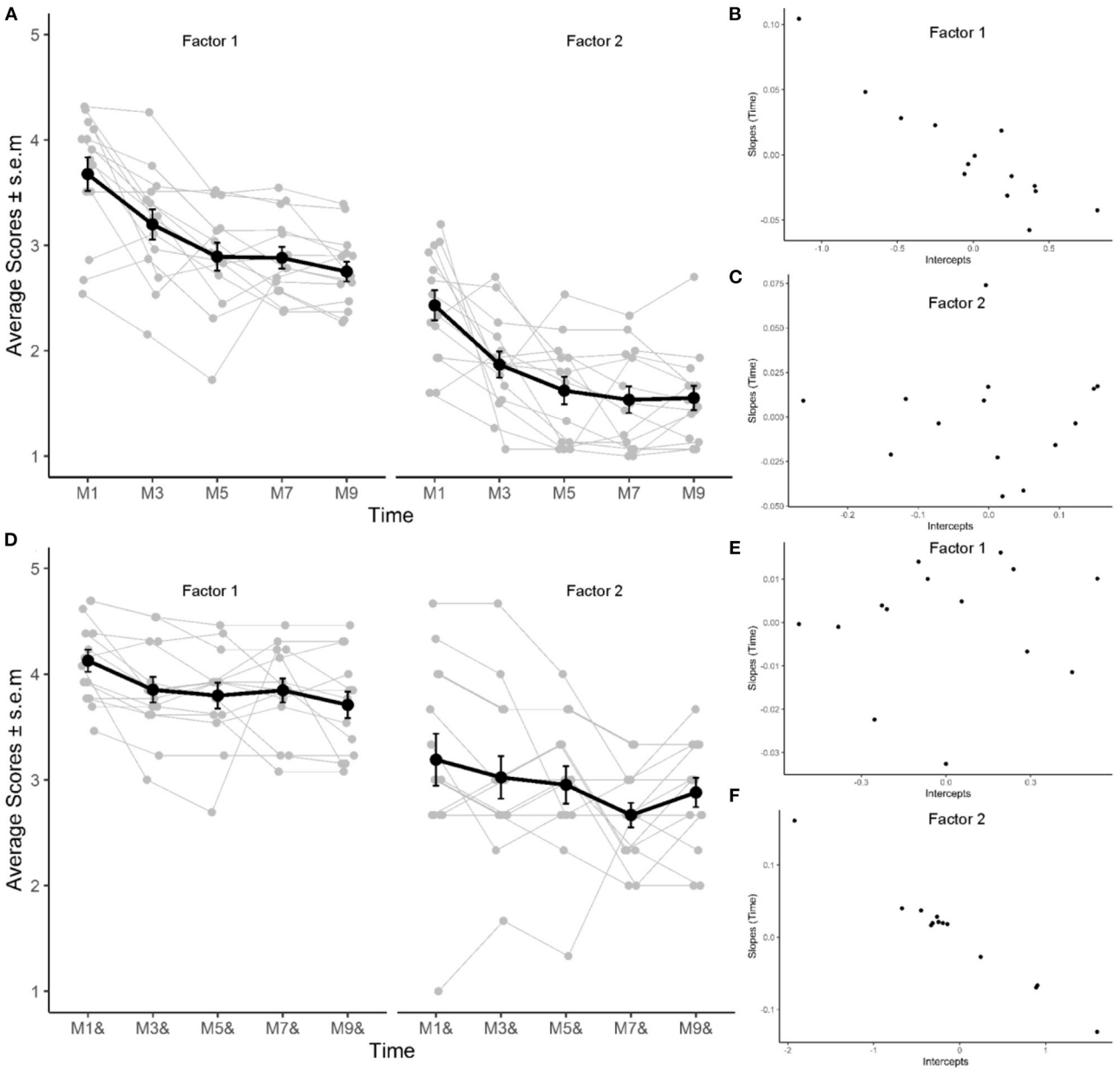

FIGURE 3 | Evolution of factors 1 and 2 of BSE-R during therapy. **(A–C)** Evaluation performed after one-to-one exchanges. **(D–F)** Evaluation performed in group therapy. **(A,D)** Average (black) and individual (gray; $N = 14$) scores assessed at months 1, 3, 5, 7, and 9 of therapy. **(B,E)** Correlation of within-subjects random intercept and slopes for factor 1 in individual and group therapy session, respectively. **(C,F)** Correlation of within-subjects random intercept and slopes for factor 2 in individual and group therapy session, respectively.

effects parameters use the Satterthwaite's method for the degree of freedom calculation as in lmerTest (51).

Developmental assessments using Brunet–Lézine data were analyzed at the beginning and at the end of therapy. GDA was analyzed using a paired Student *T*-test after removing one extreme outlier (participant 31 who showed an overall improvement of 13 months); effect size was computed as Cohen's d. DAs for each area were analyzed with Wilcoxon signed-ranked test on paired data. Participant 32 was identified as an extreme outlier in SDA, showing an improvement of 19 months, and was therefore removed for SDA analysis.

RESULTS

Cognitive and Socio-Emotional Assessment

A repeated measure ANOVA with time and domain as within-subject factor revealed main effects of time

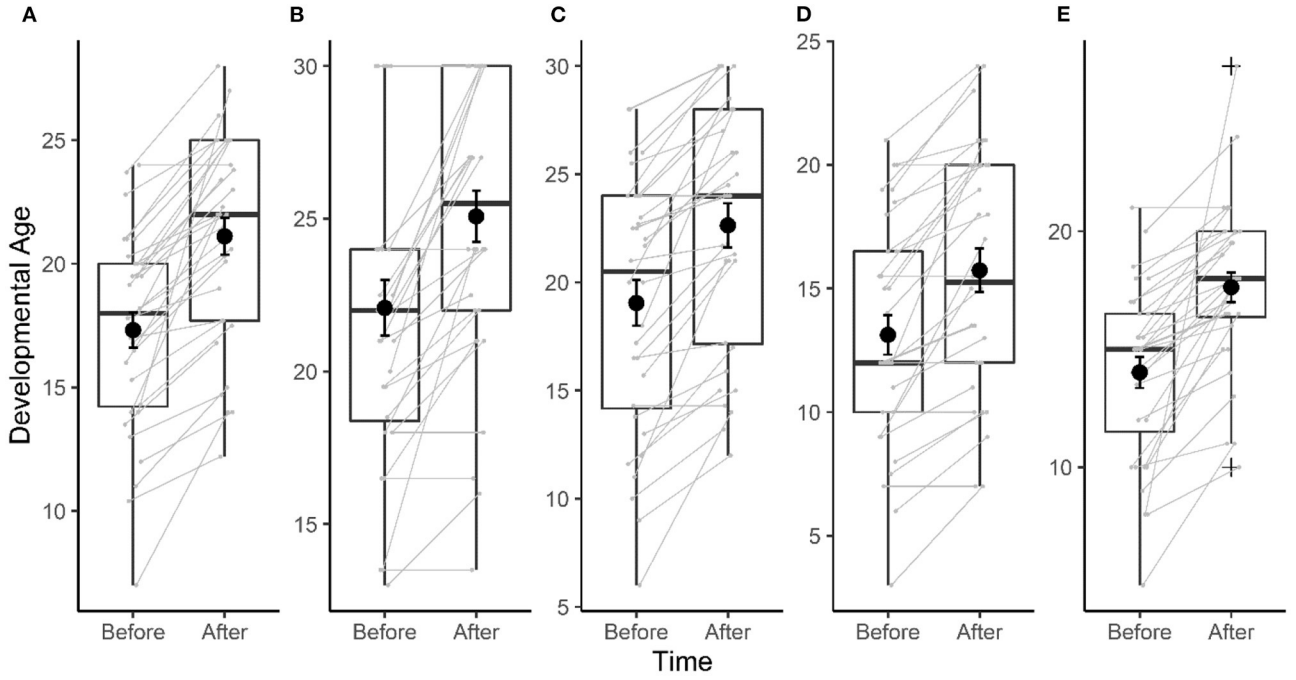

FIGURE 4 | Evolution of developmental age assessed with Brunet–Lézine before and after 9 months of therapy. **(A)** Global developmental age (GDA). **(B)** Postural developmental age (PDA). **(C)** Oculo-manual coordination developmental age (CDA). **(D)** Language developmental age (LDA). **(E)** Sociability developmental age (SDA). Black dot and error bar represent mean and SEM. Gray dot and connecting lines represent individual data.

[$F_{(1,30)} = 125.89$, $p < 0.001$, $\eta^{2[g]} = 0.32$] and domains [$F_{(1,30)} = 97.18$, $p < 0.001$, $\eta^{2[g]} = 0.26$] on the average levels of the SCEB but no interaction [$F_{(1,30)} = 0.85$, $p = 0.36$, $\eta^{2[g]} < 0.001$; **Figure 1A**]. Average levels were higher for cognitive than socio-emotional domains and were higher after 9 months of therapy. For information, an ANOVA with all participants yielded similar results, with effects of time [$F_{(1,31)} = 129.24$, $p < 0.001$, $\eta^{2[g]} = 0.27$], area [$F_{(1,31)} = 80.86$, $p < 0.001$, $\eta^{2[g]} = 0.21$], and no interaction.

At the beginning of therapy, the developmental level was low for both socio-emotional [mean level across the different domains: 1.94 ± 0.06; (1.2 2.8)] and cognitive domains [2.44 ± 0.09; (1.1 3.6)]. After 9 months of therapy, mean levels had increased by approximately 0.5 for both social [2.53 ± 0.08; (1.7 3.4)] and cognitive [2.97 ± 0.09; (1.4 3.9)] domains (**Figure 1A**). To have a more precise comprehension of the evolution of children's profiles with therapy, descriptive statistics using statistical mode were used (**Figure 1B**). The statistical mode, corresponding to the level shown by most children, increased by one level with therapy for all cognitive domains but operational causality. For skills in the social domains, a one-level increment was observed for behavioral regulation, social interaction, joint attention, receptive language, vocal imitation, and affective relation.

Exploration of individual data (**Figure 2**) revealed a majority of children gained at least one level in all the socio-emotional domains: behavioral regulation, social interaction, joint attention, receptive language, vocal imitation, affective relation, and emotional expression (**Figure 2**). In cognitive domains, a majority of children improved in self-image, symbolic play, spatial relation, and object permanence.

All but one child showed improvements in at least one social domain, and 78% of children gained one level in at least four social domains. Twenty-nine children improved in cognitive domains, with 66% of children improving in at least three cognitive domains.

Behavioral Assessment

Exploration of the interaction and modulation deficits assessed with the BSE-R in individual EDT session revealed an average reduction of symptoms of 0.92 and 0.88, respectively. Attenuation of interaction deficits was observed in 93% of children, and modulation deficits decreased in 86% of children.

For the interaction deficits factor, estimated fixed parameters (β) for time, across the population, were significant for both intercepts {β [95% confidence interval (CI)]: 3.6 [3.3 3.9]; $T_{(14)} = 22.3$; $p < 0.0001$} and slope [β (95%CI):−0.11 (-0.15−0.07); $T_{(14)} = -5.8$; $p < 0.0001$], highlighting that interaction deficits before therapy were high but decreased by approximately 0.1 point (on a five-point scale) per month of therapy (**Figure 3A**). The standard deviation of random effects for intercept and slope were 0.54 and 0.05, respectively, suggesting that in a typical population, expected factor 1 scores would vary between 2.55 and 4.65 and that the expected decrease due to therapy would vary between−0.2 and−0.002. In addition, a high within-subject correlation between random effects for intercept and

slope (−0.87; **Figure 3B**) for factor 1 was observed, highlighting a strong relationship between severity of interaction deficits at the start of therapy and decrease in autistic symptomatology in the population: the larger the deficits at the start of therapy, the larger was the improvement brought on by the therapy.

For the modulation deficits, estimated fixed parameters for time were significant for intercept [β (95%CI): 2.3 (2.1 2.6); $T_{(14)} = 20.2$; $p < 0.0001$] and for slope [β (95%CI):−0.1 (-0.15−0.06); $T_{(14)} = -4.95$; $p = 0.0002$; **Figure 3A**], revealing that typical modulation deficits (F2) in the population were less high than interaction deficits at the start of therapy (2.3) but still decreased by approximately 0.1 point per month of therapy. The standard deviation of random effects for intercept and slope were 0.21 and 0.04, respectively, suggesting that in a typical population, expected factor 2 scores would vary between 1.92 and 2.75 and that the expected decrease due to therapy would vary between−0.18 and−0.03; random effects for slope and intercept were less correlated (correlation coefficient: −0.45; **Figure 3C**).

Exploration of the interaction and modulation deficits assessed with the BSE-R in group sessions revealed an average reduction of symptoms of 0.42 and 0.31, respectively. Attenuation of interaction deficits was observed in 86% of children, and modulation deficits decreased in 64% of children.

For BSE-R evaluated in group therapy, effect of time was significant for both intercept [β (95%CI): 4.1 (3.8 4.3); $T_{(14)} = 37.2$; $p < 0.0001$] and slope [β (95%CI):−0.04 (-0.07−0.01); $T_{(14)} = -3.3$; $p = 0.0057$] for factor 1 (**Figure 3D**), highlighting a decrease of interaction deficits of approximately 0.04 per month of therapy. Correlation coefficient for within-subjects' random effects of intercept and slope was−0.19 (**Figure 3E**). Effect of time for factor 2 (**Figure 3D**) evaluated in group therapy sessions was significant for intercept [β (95%CI): 3.2 (2.7 3.7); $T_{(14)} = 12.8$; $p < 0.0001$] but not for slope [β (95%CI):−0.05 (-0.1 0.003); $T_{(14)} = -1.98$; $p = 0.07$]. Correlation coefficient for within-subjects' random effects of intercept and slope was high (-0.98; **Figure 3F**).

Developmental Assessment

GDA assessed with the Brunet–Lézine scale significantly increased by an average of 3.8 months with therapy [GDA, $T_{(30)} = 10.15$, $p < 0.001$, Cohen's d = 1.5; **Figure 4A**]. Of the 32 children included in the study, only one child showed no increase in their GDA.

An improvement of approximately 3 months was also found in each area assessed with the Brunet–Lezine with large effect sizes ($r > 0.7$): postural developmental age ($V = 210$, $p < 0.001$, $n = 32$, $r = 0.77$; **Figure 4B**), oculo-manual developmental age ($V = 465$, $p < 0.001$, $n = 32$, $r = 0.87$; **Figure 4C**), language developmental age ($V = 300$, $p < 0.001$, $n = 32$, $r = 0.82$; **Figure 4D**), and SDA ($V = 465$, $p < 0.001$, $n = 31$, $r = 0.87$; **Figure 4E**). A large majority of children showed an improvement of their DA over the 9 months of therapy in each area, with the smallest proportion observed for the postural developmental age (62.5% of children).

Keeping outliers in the statistical analysis does not change observed effects: GDA: $T_{(31)} = 8.49$, $p < 0.001$, Cohen's d = 1.5, SDA: $V = 465$, $p < 0.001$, $n = 32$, $r = 0.87$.

DISCUSSION

Using clinical tools tailored for ASD and sensible to subtle changes occurring over a short amount of time (the SCEB and the BSE-R), positive outcomes were observed in children with severe ASD and concurrent ID following a 9-month early intensive intervention program, the TIPA-T centered on the EDT in a specialized medical center. The TIPA-T, including its pivotal first step, the EDT, allowed for a general improvement for both cognitive and socio-emotional domains and a reduction in the severity of autistic symptomatology. In addition, assessment of autistic core symptoms with the BSE-R showed a decrease of interaction deficits, in particular, both in one-to-one and in group evaluations. The latter demonstrates the generalizability of the skills learned during the EDT.

Children's developmental trajectories were positive, but their evolution was atypical and characterized by uneven progress. Large individual variations in outcomes were observed in this study, consistent with the findings from previous research (10, 20, 21, 24, 60) and in line with the strong heterogeneity of profiles observed in ASD. However, general improvement for each cognitive and socio-emotional domain was seen during therapy (e.g., joint attention, imitation, social interaction, etc.). Moreover, autistic behaviors tended to decrease (reduction in the degree of severity of the deficits in interaction and modulation), particularly in one-to-one exchanges. Although we cannot be certain that these results do not reflect the natural maturation of children, we believe this is unlikely because we observed progress in key domains of autistic symptomatology, specifically targeted by the EDT. Moreover, poor outcomes were observed in some children suggesting that natural maturation alone is unlikely to improve performance. Finally, in the current study, no children showed a worsening of their condition within the 9 months of the therapy, whereas a 9% worsening rate could have been expected based on natural maturation only (61).

Results of this study are consistent with other follow-up studies showing that early and intensive intervention program over a relatively short period yields positive outcomes for children with autism. Dawson and collaborators (13) showed the efficacy of an intensive intervention program designed for toddlers with ASD as young as 18 months: the Early Start Denver Model (ESDM). After 2 years of intervention, children provided with the ESDM showed significant improvements in IQ, adaptive behavior, and diagnostic status. More recently, it was shown that low-intensity ESDM is of some benefit to children with ASD in imitation, engagement, and intentional vocalizations (62). The results of a 1-year study on a developmentally based social pragmatic approach, the Frankfurt Early Intervention program, which starts on average at 66 months, showed improvements in autistic symptoms and cognitive development (20, 21). Pivotal Response Treatment, in children aged 64 months on average, results in increases in self-initiations and has positive effects on interaction and verbal communication, play skills, and maladaptive behavior for a number of children (17, 18). In line with these studies, the developmental and behavioral progress of children included in the TIPA-T program, which are generally more retarded, were important for a short period. Although the

current study measures improvements following EDT in slightly older children than the ESDM, the EDT is also designed for younger children and children with ASD and severe ID, and the program can be started before age 2 years. The EDT relies on a functional baseline, which not only allows characterizing the changes brought on by the therapy but also helps to target and prioritize specific functions, making it an essential therapeutic tool for children with ASD and with specific needs. Consistently, the EDT benefits severe more to children with severe autistic symptomatology, for whom the progression was larger. Taking together these studies demonstrate that when therapy is provided systematically for children with ASD within the framework of highly structured and intensive therapy, contact behaviors, exchange, and communication deficits are reduced both in the short and long terms (23, 31, 63–67). Improvements also affect both "primary" behavioral disturbances such as disorders of perception and association and "secondary" symptoms such as social withdrawal (22).

Difficulties in assessing the benefits of intervention programs arose from the lack of clinical tools dedicated to assessing subtle changes occurring over a small period (38). Here, we used the SCEB (39–42), which allows assessing a range of cognitive and socio-emotional skills for young children with ASD associated with a moderate-to-severe intellectual disability. The BSER-R (32, 43) provides additional information regarding the severity of autistic symptomatology, focusing on key behaviors contributing to core symptoms of ASD in varying degrees (e.g., attention, perception, association, intention, imitation, contact, communication, etc.). The use of these scales, which allows measurement of subtle changes, revealed progress in different cognitive and socio-emotional domains and a reduction in autistic symptomatology, even over a period as short as 9 months. Moreover, the BSE-R can be evaluated in one-to-one and in group sessions, allowing the demonstration of generalization of the skills learned during the EDT, in particular regarding interaction deficits. Finally, using these scales helped identify the functions that were the first to respond to therapy and the resistant ones, providing orientations for therapy prevention and early intervention (11, 20, 24, 35). Combining autistic behaviors, cognitive and socio-emotional abilities assessments provide the basis for a richer dialogue with families to improve educational and therapeutic synergy around the child. It also meets specific needs to specify and individualize the contents of psycho-educational and therapeutic actions, making them essential batteries for child psychiatric teams in daily practice.

Using these assessments complemented the findings obtained with a classical tool such as the Brunet–Lézine—Revised scale. Results from the Brunet–Lézine—Revised scale showed a general improvement in DA, as well as domain-specific improvement. On average, the 9-month therapy yielded a 3-month gain in DA, and importantly, this increase in DA was observed in a large majority of children. This highlights the benefit of the TIPA-T, including specifically the EDT for the cognitive development of children considering that children with low IQ tend to maintain their IQ over time (61), consistent with previous observations that intellectual disability in children with ASD who have benefited from early intensive care can be improved (9, 13, 68, 69). However, the Brunet–Lezine scale is a non-specific clinical tool that, despite allowing only for assessing the evolution of DAs and quotients, can be used to monitor children with ASD. The results of the current study showed that with more specialized and precise tools such as the SCEB and BSE-R, the child could be understood as a whole, and clinicians can obtain subtler and more precise information regarding the effects of treatment in children with ASD (38).

There are several important clinical implications for these data. When diagnosing young children with ASD, it is important to assess cognitive skills and social-reciprocal interaction deficits and abilities using standardized tests. Both measures are strongly related to outcomes and are correlated with each other. These measures can help clinicians to assess responsiveness to intervention and treatment planning. In addition, early social-interaction abilities may be a pivotal skill that should be addressed in intervention programs. The study also emphasizes the effectiveness of the intervention at a very early age across the autistic symptomatology severity range. A therapy such as the EDT might also benefit from being developed in at-home settings by providing support and teaching parents the functional basis and the implementation of EDT at home.

CONCLUSIONS

The TIPA-T, including specifically EDT, improves cognitive and social skills and core symptoms of autism of most children with severe ASD and associated ID. Assessment of autistic core symptoms with the BSE-R showed a decrease of interaction disorder in particular, both in one-to-one and group evaluations. Importantly, this demonstrates the generalizability of the skills learned during the EDT. However, as for other intervention programs in autism, large individual variations were seen in the outcomes, in line with the strong heterogeneity of profiles observed in ASD. Data acquired in the current study do not allow understanding the reasons for the therapy being extremely successful in some children and less in others. Future studies should aim at identifying predictive factors of success to potentiate positive outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CHRU Tours. Written informed consent to participate in this study was provided by the participant's legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CB, J-LA, and RB contributed to conception and design of the study. RB, MG, JM, PD, and AR contributed to data collection.

SR organized the database. ML performed statistical analyses. RB, ML, JM, FB-B, and J-LA wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Abilities and Disabilities—Applying Machine Learning to Disentangle the Role of Intelligence in Diagnosing Autism Spectrum Disorders

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Objective: Although autism spectrum disorder (ASD) is a relatively common, well-known but heterogeneous neuropsychiatric disorder, specific knowledge about characteristics of this heterogeneity is scarce. There is consensus that IQ contributes to this heterogeneity as well as complicates diagnostics and treatment planning. In this study, we assessed the accuracy of the Autism Diagnostic Observation Schedule (ADOS/2) in the whole and IQ-defined subsamples, and analyzed if the ADOS/2 accuracy may be increased by the application of machine learning (ML) algorithms that processed additional information including the IQ level.

Methods: The study included 1,084 individuals: 440 individuals with ASD (with a mean IQ level of 3.3 ± 1.5) and 644 individuals without ASD (with a mean IQ level of 3.2 ± 1.2). We applied and analyzed Random Forest (RF) and Decision Tree (DT) to the ADOS/2 data, compared their accuracy to ADOS/2 cutoff algorithms, and examined most relevant items to distinguish between ASD and Non-ASD. In sum, we included 49 individual features, independently of the applied ADOS module.

Results: In DT analyses, we observed that for the decision ASD/Non-ASD, solely one to four items are sufficient to differentiate between groups with high accuracy. In addition, in sub-cohorts of individuals with (a) below (IQ level ≥4)/ID and (b) above average intelligence (IQ level ≤ 2), the ADOS/2 cutoff showed reduced accuracy. This reduced accuracy results in (a) a three times higher risk of false-positive diagnoses or (b) a 1.7 higher risk for false-negative diagnoses; both errors could be significantly decreased by the application of the alternative ML algorithms.

Conclusions: Using ML algorithms showed that a small set of ADOS/2 items could help clinicians to more accurately detect ASD in clinical practice across all IQ levels and to increase diagnostic accuracy especially in individuals with below and above average IQ level.

Keywords: autism spectrum disorders, IQ, intellectual disability, ADOS, machine learning, diagnostic, intelligence

INTRODUCTION

Public awareness about autism spectrum disorder (ASD) is steadily increasing (1, 2). This is also reflected by the growing number of children, adolescents, and adults who use diagnostic services in outpatient clinics for ASD. Although, in the eyes of the public, the term autism is often associated with special talents and abilities (3), creating a somewhat distorted picture of the disorder, the larger part of the group of autistic people shows intellectual abilities below the average of the general population. Fombone (4) reviewed 20 epidemiological studies of ASD published from 1966 to 2001 and summarized that the median percentage of individuals with ASD and cognitive impairment was 70% (range 40–100%). More recent epidemiological studies reported that about 56% of people with ASD have an IQ < 70 (5) or 31% of children with ASD are classified in the range of an intellectual disability (ID), 25% in the borderline range (IQ 71–85), and 44% have IQ scores in the average to above average range (i.e., IQ > 85) (6). This heterogeneity of data about IQ in ASD is in line with statements that IQ might be *the* source of heterogeneity of ASD as a heterogeneous (group of) disorder(s) (7–9).

The IQ is associated with the individual level of functioning and—particularly in ASD—with the ability to acquire and apply specific skills in order to handle typical everyday situations, to plan and act with foresight and to be flexible and adaptive to changing environmental conditions (9, 10). Knowledge regarding the individual IQ is thus important to gain more knowledge about the functionality of the person with ASD. This, in turn, is relevant for both diagnostic accuracy and the treatment planning and success.

It has been observed that ASD symptom measures such as the Autism Diagnostic Observation Schedule (ADOS), the Autism Diagnostic Interview Revised (ADI-R), and Social Responsiveness Scale (SRS) capture much more than just the pure symptoms of ASD: increased scores may reflect rather additional impairments than ASD-related social communicative deficits and repetitive behaviors alone (11). IQ-related particularities increase the risk for drawing incorrect conclusions about etiological and phenotypic relationships (11). Such incorrect conclusions may result in false-negative or false-positive decisions in ASD diagnosis.

Within the so-called gold standard clinical diagnostics for ASD, a standardized interview conducted with the caregiver of the individual (ADI-R), a standardized behavioral observation of the individual itself (ADOS/2), a differential diagnostic examination, and an IQ testing are included. Based on all this information, individuals are categorized according to the psychiatric multiaxial schema (12, 13). Within this schema, individuals will be categorized in six axes: (1) psychiatric syndromes; (2) circumscribed developmental delay; (3) intellectual level or mental retardation; (4) somatic symptomatology; (5) associated current abnormal psychosocial circumstances; and (6) global assessment of psychosocial stressors and adaptive functioning. With respect to axis 3, the intellectual level, a rough categorization based on the tested or estimated IQ is made: level 1: IQ > 129, level 2: IQ = 115–129, level 3: IQ = 85–114, level 4: IQ = 70–84, level 5: IQ = 50–69, level 6: IQ = 25–49, level 7: IQ = 20–34, and level 8: IQ < 20 (13).

Although the ADOS/2 offers good sensitivity and specificity values (14, 15), there are frequent cases in which the diagnosis is either missed (false negative) or given incorrectly (false positive)—false particularly in the retrospective consideration of changes in phenomenology and thus diagnoses during development over several years (16). There are several potential reasons facilitating false-positive or false-negative cases, like under-resourced familial or educational environment, presence of only subtle ASD symptoms, and presence or absence of coexisting or differential diagnoses [e.g., anxiety disorder (17), ADHD (18), or psychosis (19)]. In addition, high intelligence enabling a partial compensation of ASD-related social and communicative difficulties may be an influencing factor (20). Although individuals with ASD may benefit from high intelligence by potentially higher compensation abilities, it was also observed that individuals with ASD with above average IQ perform low in domains of facial and emotional identification, visual pattern recognition, and verbal working memory (7). Thus, individuals with ASD with above average IQ also show impairments, which may be targeted in clinical assessment and treatment. Individuals with low intelligence are also susceptible to ASD misidentification—either because an intellectual disability (ID) diagnosis overshadows ASD symptoms or because cognitive impairments are falsely interpreted as ASD (21–23). As the accuracy of psychiatric diagnoses affects both the preferred therapy choice and the respective outcome (24), and implications from obtaining a lifelong diagnosis such as ASD can be severe, the diagnostic accuracy should be as high as possible. Therefore, clinicians should be aware of specific individual characteristics, which are concomitant with different levels of IQ and which may lead to increased or decreased ADOS/2 scores (16).

The present study aimed to (1) analyze the accuracy of the ADOS/2 algorithm by comparing the reaching and exceeding of the ADOS/2 cutoffs with the BEC ASD diagnosis also for sub-cohorts defined by different IQ levels. (2) In addition, we investigated whether these accuracies can be increased by applying data-driven machine learning (ML) approaches that processed additional features including the IQ level. Finally, (3) with the help of ML approaches, we aimed to identify which of the considered features are most important to discriminate accurately between participants with and without a BEC ASD diagnosis to focus clinicians' attention on features that best distinguish between ASD and Non-ASD, so that the most accurate, economical, and comprehensive classification of each individual is achieved.

MATERIALS AND METHODS

Participants

Data from participants originate from a large German research consortium called ASD-Net (25) and were obtained from four specialized centers in Germany. All included participants of our data received the BEC diagnosis or did follow the

ASD diagnostic gold standard procedure that was applied by specialized clinicians in all centers. Data from more than 2,500 patients were collected retrospectively from medical records (retrospective chart review) and analyzed anonymously, with approval from the local ethics committee (Az. 92/20). Due to the retrospective nature of data collection and analysis based on anonymized data, there was no need for further informed consent. All methods were applied in accordance with relevant institutional and international research guidelines and regulations. From the ASD-Net database, all participants with available information about their IQ level and ADOS data were selected ($N = 1{,}084$; 40.6% with ASD, 5.5% with ID). Data of the applied IQ tests were not available for all included individuals; for some individuals, IQ levels were only present in terms of clinical impressions. IQ level 8 was not assigned within the sample. Sample characteristics are given in **Table 1**.

Measures

Information regarding the IQ level of the individuals was recorded with respect to the psychiatric multiaxial schema, in which axis 3 describes the level of intelligence. Hence, intelligence can be either measured psychometrically or assessed clinically. Please note that although individuals from IQ level 5 to 8, i.e., IQ $\leq$ 70, fulfill the diagnostic criteria of ID according to the psychiatric multiaxial system, the diagnosis ID was assigned to only 28.9% of the cases in clinical practice. Therefore, presence or absence of an ID was included in all analyses as a separate factor in addition to IQ level. The four modules (the toddler module has not been included) of the ADOS (26) consist of 29, 27, 28, or 31 items, respectively. The ADOS items (hereafter abbreviated to "items") are rated by a trained psychologist from zero (inconspicuous) to three (conspicuous) or, in a few cases, with seven or eight (indicating a conspicuous behavior, which is not to be evaluated in the sense of autism or indicating the impossibility to rate this item, e.g., because the individual shows too few vocalizations for intonation to be judged). Individuals with more than four missing items in their respective module's protocol were discarded from analyses. The final BEC diagnosis was coded as 0 for Non-ASD and 1 for ASD and will be the dependent variable in all following analyses.

ADOS/2 Algorithm

To apply the ADOS/2 algorithm, the item-rating three is converted to two; similarly, seven and eight are converted to zero. Depending on the applied module, 11 to 16 items are summed up for each individual participant. If module-specific cutoffs are exceeded, the diagnosis of ASD is suggested by the ADOS/2 algorithm. However, according to the ASD diagnostic gold standard procedure, the BEC diagnosis that is given by the trained expert is also based on the clinical impression and can differ from the result of a very well-established diagnostic instrument as the ADOS/2. The ADOS/2 algorithm's accuracy is obtained by comparing the ADOS/2 cutoff with the BEC ASD diagnosis.

Data-Driven Machine Learning Approaches

In contrast to the ADOS/2 algorithm, the estimated ML algorithms are not module-specific. Therefore, the recoded data from all ADOS modules have been combined to one data set before being processed by the ML algorithms. The intention was to increase robustness of the model estimation by increasing the number of samples available for training a single model. Hence, a single model is trained on the whole data instead of training four module-specific models on the modules' respective data only.

In order to be able to process all individuals congruently, similar labeled (and thus assumingly corresponding) items from different modules have been identified and were arranged accordingly; missing items were filled with−5. This value was chosen, as it is clearly out of range, allowing the algorithms to use the information whether data were collected or not. In the present paper, the naming of the items used is listed in module order, i.e., module 1/module 2/module 3/module 4. Furthermore, the naming refers to the ADOS convention: indication of initial letters (A–D) for the respective dimension plus a number (indicating the temporal sequence of the item). There are items that occur in all four modules ($N = 17$), items that occur in three modules (modules 2–4, $N = 3$), and items that occur in two modules (modules 1 and 2, $N = 6$; modules 3 and 4, $N = 7$). If items do not appear in all modules, they are marked with a "-" in the appropriate place to indicate that they do not appear in that module.

To offer two examples: (a) item "B3/B2/B2/B2" indicates the item "socially directed facial expression," which is item B3 in module 1 and item B2 in modules 2 to 4. In addition, it is also visible that this item is included in all four modules. In contrast, (b) item "-/-/B6/B7" indicates the item "social insight," which is part of modules 3 (B6) and 4 (B7). In modules 1 and 2, however, this item does not occur and is therefore coded as−5 for all participants of these modules.

Besides the items, all potentially relevant additional information that is collected during standard diagnostic procedure was provided to the ML algorithms, i.e., the applied ADOS module, IQ level, age of the individual, sex of the individual, and presence or absence of an ID. In total, the number of features processed by the ML algorithms summed up to 49 for each subject, independently of the applied ADOS module. All individual features can be identified in **Figure 4** in the Results section.

These features were processed by decision trees (DT) with the aim to discriminate subjects with a BEC ASD diagnosis from subjects without as accurate as possible. DTs are simple models that are inherently interpretable due to their flowchart-like structure where nodes are representing categorical tests that are applied to individual features.

DTs are grown node by node, always aiming to find a condition and a factor that split the data in homogeneous groups of individuals with ASD and individuals without ASD. The inhomogeneity (or impurity) of a group can be measured, e.g., with the entropy or the gini-index of the depended variable, i.e., the diagnosis variable. The reduction of the impurity measure (or impurity decrease) is used during training for choosing

TABLE 1 | Sample characteristics.

	Non-ASD		ASD		Non-ID		ID	
	N	M (SD)	*N*	M (SD)	*N*	M (SD)	*N*	M (SD)
Age	644	13.4 (±9.7)	440	14.9 (±11.1)	1,024	14.1 (±10.4)	60	12.9 (±8.9)
IQ	545	99.3 (±21.1)	370	101.2 (±26.0)	892	101.2 (±22.4)	23	57.3 (±9.6)
IQ level	644	3.2 (±1.2)	440	3.3 (±1.5)	1,024	3.1 (±1.2)	60	5.5 (±0.7)

Total number of participants is N = 1,084. Patients were chosen based on the presence of information about their IQ level.

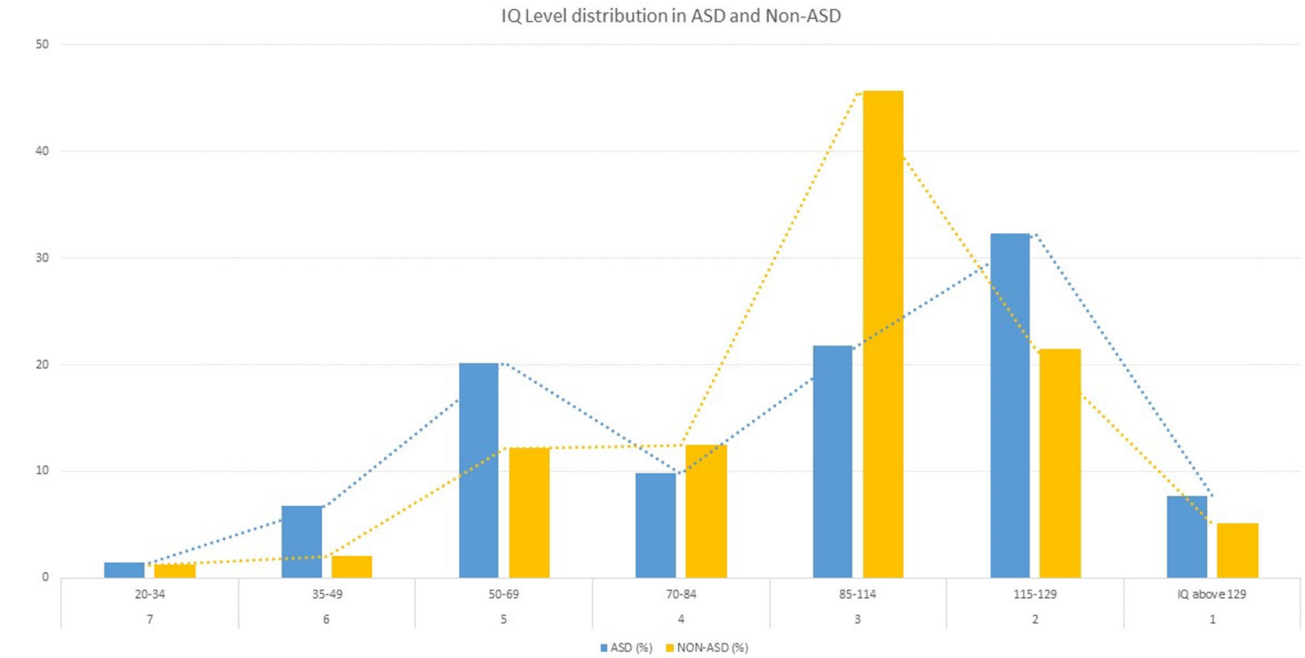

FIGURE 1 | IQ level distribution (from IQ level 7-1 in %) of ASD (n = 440) and non-ASD (n = 644) group in a German sample referred to specialized ASD clinics.

appropriate features and conditions for each node (27). Here, the reduction of the impurity measure is defined as the difference of the impurity before the split and the average impurity of the two samples after the split, weighted with their respective number of samples in the training data.

While DTs are natively interpretable, they can be sensitive to minor changes in input data and often suffer from suboptimal classification performance (27). To overcome these limitations, outputs from multiple DTs can be combined, forming an RF. Usually, each tree is trained on randomly sampled subsets of the original data. While RFs are more powerful and typically superior in terms of stability and accuracy, their complexity comes at the cost of reduced interpretability of their decision process.

ML Stage 1: Parameter Selection

The available data were randomly split in 80% training and 20% test data. The relative frequencies of IQ level were preserved in both data sets. In order to determine optimal (in terms of predicting the BEC diagnosis) model parameters for the DT, a fourfold stratified cross-validated grid search was performed on the training data. For this procedure, all possible combinations of predefined parameter sets are compared. The best parameters were chosen based on the cross-validated out-of-bag accuracy on the training data only. Afterwards, multiple trees with optimized parameters were combined to an RF. Each tree in the ensemble was trained on a different set of samples, drawn randomly with replacement from the training set. This procedure is called bootstrap. The optimal number of estimators used for the RF as well as the number of randomly drawn samples for each bootstrap is again determined in a fourfold stratified cross-validated grid search on the training data.

ML Stage 2: Performance Estimate on Unseen Data

In order to estimate the performance of the optimally parameterized models on unseen data, they were subsequently trained on the whole training data and tested on the 20% held-out test set.

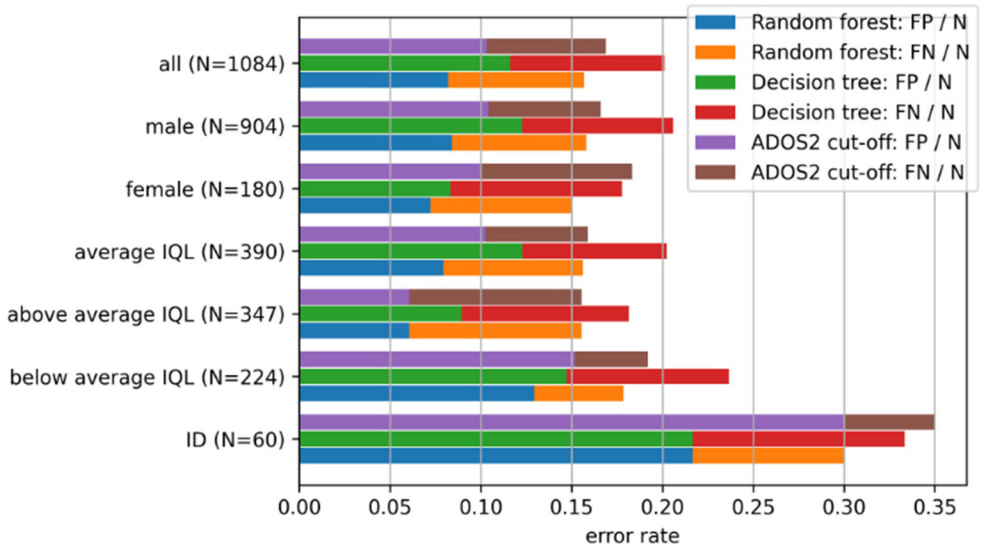

FIGURE 2 | Comparison of error rates and their composition of false negatives (FN) and false positives (FP) by several sub-cohorts (e.g. sex-specific). For the calculation of the error rates of the respective algorithm [random forest (RF), decision tree (DT), ADOS/2] per sub-cohort, FN and FP are divided through the respective sample size N of the sub-cohort. IQL, IQ level.

ML Stage 3: Performance Estimate on Unseen Data

To obtain out-of-sample classifications for the whole available data set, a fivefold stratified cross-validation was used. The classifiers were trained on four splits and evaluated on the fifth. Subsequently, the predictions of the five test splits were combined.

Identification of Best Discriminating Features

Finally, for the identification of discriminating features by the aid of ML algorithms (aim 2), the algorithms were parameterized according to the previously determined optimal parameters (aim 1, Stage 1). In order to allow all available samples to contribute to this analysis, the whole data set was used for training. Subsequently, based on the trained models, the relevance of the individual features in regard of the discrimination between participants with and without finally diagnosed ASD according to ASD gold standard procedure was analyzed.

For the DT, the decision paths are visualized and discussed. Together with the distribution of the data, the discriminating power of individual features can be determined intuitively in this structure.

An RF constitutes of up to hundreds of DTs, which all contribute to the final decision. Therefore, an explicit description of the decision rules of a RF would be too complex to obtain an intuition about relevance of individual features. Hence, the importance of features for the trained RF will be considered only statistically.

There are numerous methods for estimating importance of input variables for RF or ML algorithms in general (28). Here, the reduction of the impurity measure is used, averaged over all training samples as well as all nodes of the RF that are associated with the respective factor.

Data analysis and visualization were implemented in python, using the packages scikit-learn (29), pandas (30), matplotlib (31), and scipy (32). The used code is available under URL (https://github.com/MatthiasEb/ASD-IQ). As the original data that were used for the presented results cannot be published as they contain clinical information, sample data are provided.

RESULTS

IQ Level Distribution

Of the 440 individuals with ASD, 38.2% had a below average IQ level (IQ level ≥ 4, IQ < 70), while 8.2% had moderate to severe intellectual disability (IQ level ≥ 6, IQ < 50); 21.8% had average intelligence (IQ level $= 3$, $114 >$ IQ > 85) while 40% had an above average IQ level (IQ level ≤ 2, IQ > 115) (see **Figure 1**). In contrast to the 644 individuals without ASD, 27.7% had a below average IQ level (IQ level ≥ 4, IQ < 70), while 3.2% had moderate to severe intellectual disability (IQ level ≥ 6, IQ < 50); 45.7% had average intelligence (IQ level $= 3$, $114 >$ IQ > 85) while 26.5% have an above average IQ level (IQ level ≤ 2, IQ $>$ 115). Differences between individuals with ASD and Non-ASD are significant $\chi^2 = 85.93$, $df = 6$, $p < 0.001$.

Although 38.2% of the individuals with ASD had a below average IQ level (IQ level ≥ 4, IQ < 70) and therefore fulfill the diagnostic criteria of ID according to the psychiatric multiaxial system, the diagnosis ID was given only in 28.9% of the cases.

ADOS/2 Algorithm Accuracy (Aim 1) and Comparison to ML Approaches (Aim 2)

For all participants, the cutoffs according to the ADOS/2 algorithm match the final BEC ASD diagnosis in 83.87% across all IQ levels. The sub-cohort-specific error rates and their respective

TABLE 2 | Parameters considered for grid search.

	Parameter	Values
Decision Tree	Maximal depth	2, 3, 4, 5*, 7, 10, 15
	Complexity parameter for Minimal-Complexity pruning	0*, .1, .5, 1, 5, 10
	Splitting criterion	Gini index, Entropy*
	Minimum number of samples for split	2*, 3, 4, 5, 10
	Minimum number of samples per leaf	1, 2, 4, 8*, 16
Random Forest	Number of estimators	2, 4, 8, 16*, 32, 64, 128, 256
	Number of samples drawn for the training of the individual trees, in proportion to the number of samples in the train set	0.3, 0.5, 0.7, 0.8, 1*

*Parameters that were found to be optimal to predict the final BEC ASD diagnosis.

composition of false positives and false negatives are shown in **Figure 2**.

The results of the individual stages of the application of DTs and RFs described in the previous section are given in the following:

ML Stage 1

The investigated parameters, their respectively considered values, as well as the optimal choices are given in **Table 2**. The mean accuracy to predict the final BEC ASD diagnosis of the four cross-validation runs with optimally parameterized DTs was 80.74%. Analogously for the RF, the highest observed cross-validated accuracy for all grid-search runs was 84.08%.

ML Stage 2

In order to estimate the accuracy of the optimally parameterized models on unseen data, both were subsequently trained on the whole training data and tested on the held-out test set. A test accuracy of 83.87 and 86.16% was achieved for the DT and the RF, respectively.

ML Stage 3

On the whole data set, the accuracies to predict the final BEC ASD diagnosis are 84.08% for a single DT classifier and 86.16% for the RF, respectively. The sub-cohort-specific error rates and their respective composition of false positives (FP) and false negatives (FN) as well as the comparison to the ADOS/2 algorithm performances are shown in **Figure 2**. Differences in FPs and FNs of the ADOS/2 algorithm between the listed cohorts are tested by paired *t*-tests. For the ADOS/2 algorithm, the relative number of FPs of patients with ID is increased by a factor of approximately three compared to patients with average IQ level ($T = -33.13$, $df = 199$, $p < 0.001$). Even for individuals without a diagnosis of ID but with a below average IQ level (IQ $\leq$ 84), the number of FPs is increased by a factor of 1.5 ($T = -12.88$, $df = 199$, $p < 0.001$). For individuals with an above average IQ level (IQ $\geq$ 115), the relative number of FNs is increased by a factor of 1.7 compared to patients with an average IQ level ($T = -21.84$, $df = 199$, $p < 0.001$).

In order to estimate the confidence of an increase in performance between RF and ADOS/2 cutoff, 200 bootstraps with $N = 900$ were sampled from the original data. Sampling was performed with replacement. Out-of-sample predictions of the RF as well as for the ADOS/2 cutoff were calculated on the remaining data. Subsequently, the performances of the RF classifiers and the ADOS/2 cutoffs were compared for these 200 sets. An average increase in accuracy of 1.86 $\pm$ 1.17% was observed for the RF, the probability of the RF performing equally or worse than the cutoff could be estimated to 8%.

Identification of Discriminating Features (Aim 3)

One DT parameterized optimally to predict the final BEC ASD diagnosis (according to aim 1, stage 1), trained on all available data, is shown in **Figure 3**.

We observed that solely the item B3/B2/B2/B2 ("Socially directed facial expression") could be sufficient to suggest that the participant has presumably no ASD. In more detail, if B3/B2/B2/B2 is rated as inconspicuous (value 0), the likelihood to diagnose ASD is only 11.5% (see **Figure 3**). If additionally the item "quality of social responses" (-/B10/B9/B11) is rated as inconspicuous (value 0) or no data were collected (value−5), the likelihood to diagnose ASD is only 4.7% ($N = 344$). As -/B10/B9/B11 is not part of module 1, it is therefore−5 for all participants from this module. As a consequence, the DT classifies all participants from module 1 with inconspicuous rating for B3/B2/B2/B2 as Non-ASD ($N = 22$, 9% received ASD diagnosis).

In contrast, if B3/B2/B2/B2 is conspicuous (value 1–3), the likelihood to diagnose ASD is 63% (37% receive no ASD diagnosis). If additionally the items B12/B8/B7/B9 ("quality of social approach") and A5/A4/A4/A4 ("stereotypical/idiosyncratic language use") are conspicuous (value 1–3) as well, 86.3% of the analyzed cases ($N = 190$) receive an ASD diagnosis. This suggests that, depending on the outcome of the before-mentioned items, very few (i.e., 1–3) items can be sufficient to obtain an accurate estimate of the likelihood of an ASD diagnosis.

The mean reduction of the entropy of an RF parameterized as indicated in **Table 2** and trained on all available data is shown in **Figure 4**. We observed that most features that are rated as relevant for the RF also appear in the DT: All of the six most descriptive features across the four modules (B3/B2/B2/B2, B12/B8/B7/B9, A8/A7/A9/A9, B1/B1/B1/B1, -/B10/B9/B11, and A5/A4/A4/A4) for the RF also appear in the presented DT. Additionally, as each of their position is relatively close to the root node, these items can be further considered highly relevant for the tree as well. Furthermore, it can be observed that the additional features provided to the algorithm contribute, if at all, only moderately to the decisions (i.e., age and IQ level, see **Figure 4**).

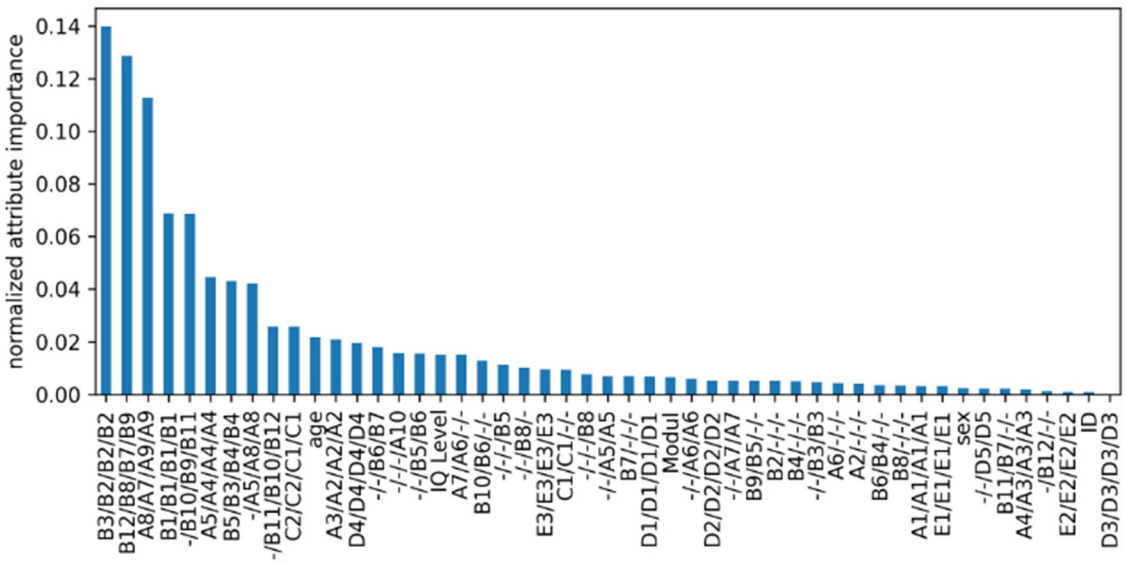

FIGURE 3 | Decision tree with optimal parameters, trained on the full dataset. Its in-sample accuracy (i.e. on the training data/the full dataset) is 84.08%. Samples are passing the tree from top to bottom. If the conditional test associated with a node is passed, the left child-node will be visited, else the right node. Furthermore, the number of samples, proportion of ASD samples in the training set are given as well as the estimated class. The color codes the "purity" of the sample: From blue (100 % ASD) over white (50% ASD) to orange (0% ASD). For the ADOS-items, the names of corresponding items in all four different modules are given, separated by "/". If no corresponding item for a given module could be found, they are marked as "-".

DISCUSSION

Within this study, we aimed to clarify whether the existing ADOS/2 algorithms are accurately discriminating between individuals with/without ASD with different IQ levels (aim 1). Furthermore, we compared the accuracy of ADOS/2 algorithms with ML algorithms that processed additional information, namely, the ADOS module, IQ level, age of the individual, sex of the individual, and presence or absence of an ID (aim 2). Finally, we examined discriminating features for distinguishing between ASD and Non-ASD based on these ML algorithms (aim 3).

To analyze the accuracy of the ADOS in different IQ levels, we initially looked at the IQ distribution of our sample and observed that solely 8.6% of the individuals with ASD have a co-existing diagnosis of ID, which is considerably low in comparison to former studies. For example, Baio et al. (6) reported 31% of children with ASD to be classified in the range of an ID. However, 28.4% of the individuals with ASD of our sample had an IQ < 70, which is closer to the reported values of the epidemiological study by Baio et al. (6). In addition, we observed that 40% of our sample of individuals with ASD had an IQ level above average (IQ $>$ 115), which is higher than in former studies (6, 33). For example, the latter reported that 3% of the children and adolescents with ASD had an above average IQ.

ADOS/2 Algorithm Accuracy (Aim 1) and Comparison to ML Approaches (Aim 2)

Overall, we observed that the accuracies of 86.16% (RF), 84.08% (DT), and 83.87% (ADOS/2) are comparable across the ML (RT and DT) and the ADOS/2 algorithm (see also **Figure 2**). These accuracies are generally in line with recent studies from our groups and others (34, 35). Also, higher accuracies have been reported [e.g., Stroth et al. (36), who even observed an accuracy of 98.27% and 98.66% in ADOS Modules 2 and 3], probably due to module-specific analyses resulting in more homogeneity of the analyzed sample. Only a minor increase in total accuracy of 1.21% could be observed for RFs compared to the ADOS/2 cutoff.

Sub-cohorts—Influence of IQ

All three algorithms (DT, RF, and ADOS/2 cutoff) are coherent in their performance in patient sub-cohorts with different IQ levels. Especially for individuals with an average IQ level (IQ: 85–114), no significant differences in performance could be observed. For individuals with below average IQ and ID, as compared to individuals with average IQ, false-positive diagnoses were significantly increased by the factor 2–3, when the ADOS/2 cutoff is applied. This confirms our hypothesis as well as the clinical impression (namely: the ADOS/2 algorithm is potentially overestimating ASD symptoms in sub-cohorts with very low cognitive abilities) and negatively influences the validity of the final BEC. This higher rate of false-positive diagnoses is alarming, given that 38% of our sample of individuals with ASD have a below average IQ. Previously, a false-positive diagnosis in individuals with a below average IQ has been suggested to be less devastating than a false-negative diagnosis of individuals with ASD (37). However, Kamp-Becker et al. were rather critical of this statement, arguing that a cutoff resulting in a false-positive ASD diagnosis in individuals with developmental delay is

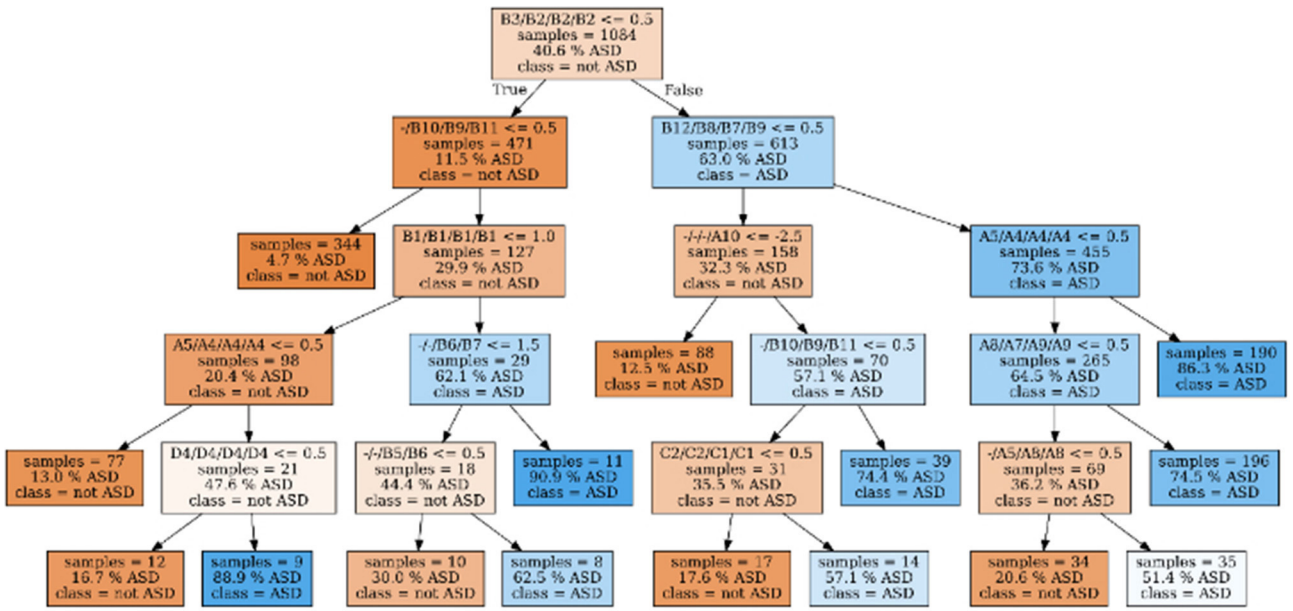

FIGURE 4 | Feature importance for the trained random forest classifier. Features' importance have been normalized so that they sum to 1. All features used in this study are shown. The features corresponding to ADOS items are reported in the order M1/M2/M3/M4 according to their content. Features that do not appear in all modules are marked with a "-" to indicate that they do not appear in the respective module.

rather confusing in clinical practice, affecting both the individual with ASD and his social environment. As an alternative, the authors advocated the introduction of two cutoffs: a higher threshold for "higher specificity" and a lower threshold for "higher sensitivity" (38). Somewhat in line with the potential benefit of two ADOS/2 cutoffs, we observed that the false-positive rate in both individuals with below average IQ and with below average IQ plus ID can be reduced by applying alternatives to the ADOS/2 cutoff, as shown here with DTs or RFs. However, this increase in specificity comes at the cost of a lower sensitivity, i.e., an increase in the false-negative rate (which was not statistically significant).

In addition to the described high rate of false-positive diagnoses in individuals with below average IQ levels and with below average IQ plus ID, we detected a significantly increased number of false negatives (i.e., individuals with ASD, who did not reach ADOS/2 cutoff but have the BEC diagnosis ASD) for individuals with above average IQ levels (IQ $\geq$ 115) as compared to individuals with average IQ levels. This amount of false negative diagnoses is also concerning, given the finding that 40% of our ASD sample have an above average IQ level. However, the amount of individuals with an above average IQ level differs with respect to age and applied module. While, for example, within M4, 65.3% of individuals with ASD and a mean age of 26.07 years $\pm$ 12.28 have an above average IQ, in M3, this is true for 44.6% (mean age of 10.06 years $\pm$ 2.52). Within M2, solely 9.8% of individuals with ASD have an above average IQ (mean age of 8.15 years $\pm$ 4.03), and within M1, 1.5% (mean age of 6.33 years $\pm$ 3.27). Thus, especially for individuals who were diagnosed later in life (about 10 years and older), this observation may be explained by better adaptive performance during the diagnostic assessment and more efficient as well as compensatory strategies, like camouflaging, to mask or hide social difficulties (39–41). However, this is a *post-hoc* assumption and should be investigated in further studies.

Nevertheless, the increase in false positives for individuals with below average IQ levels as well as the increase in false negatives for individuals with above average IQ levels was independent of the algorithm applied in the present study but strongest in the ADOS/2 algorithm. As the BEC diagnosis of ASD is dependent not only on ADOS/2 results but also on the clinical impression as well as on further diagnostics, individuals with similar ADOS/2 results can receive different diagnoses. From this point of view, conspicuous behaviors during ADOS/2 assessment situations are seemingly not sufficiently specific for distinguishing between individuals with below average IQ plus ID and individuals with ASD, which is in line with recent research (42). However, further studies are needed to confirm this hypothesis.

Identification of Relevant Discriminating Features (Aim 3)

With respect to DT analyses, we observed that for the differentiation between BEC diagnosis of ASD yes vs. no, (a) very few items are relevant, and (b) for most of these items, it is sufficient to know that the behavior is inconspicuous [0]; further gradations (1–3) are not necessary.

The starting item within the DT is B3 "Socially directed facial expression," which was observed to be sufficient to suggest that the individual has presumably no ASD. The relevance of this item within M1 was previously confirmed (34), but also somewhat contradicts findings from our group and another group (36, 43). Moreover, for M2–4, the likelihood to exclude ASD is even higher, by adding the Item "quality of social responses" (-/B10/B9/B11). The high relevance of that item was previously confirmed for all three Modules (2, 3, 5) by others (34, 44) and our group (35, 36).

These insights from data-driven ML models are consistent with the features that contribute to the calculation of the ADOS/2 cutoff: The four features with the highest average impurity decrease are relevant for the calculation of the ADOS/2 cutoff in all modules. Furthermore, all nine top-rated RF features contribute to the ADOS/2 cutoff in two or more modules.

Nevertheless, ADOS/2 cutoff relevant items differ between the four modules. Offering *post-hoc* suggestions to optimize the performance of module-specific cutoff calculation is thus difficult, since we could not analyze the data within their respective module. In this regard, a cautious indication, still requiring more testing, could be that the items B10 (Quality of social responses) and A5 (Conversation) are possibly underestimated within M2 and might be considered to be additionally included in the cutoff calculation. The same is true for item B4 (shared enjoyment of interaction) within M4 (compare **Figure 3**).

On the other hand, there are items included in the ADOS/2 cutoff that ML rated as less relevant. For some items that only occur in one or two modules, relevance is likely underestimated in the ML models for statistical reasons. In contrast, it is evident that "D" items in particular (which would have the necessary power due to their cross-module occurrence) seem to be less relevant for the differentiation between ASD and Non-ASD, at least as listed within the RF results. Only D4 ("unusual repetitive interests or stereotyped behaviors") appears relevant within the DT. If this item (in the drawn DT path sequence) is conspicuous, the calculated likelihood for ASD is 88.9% instead of 16.7% when the item is inconspicuous.

Importantly, features like age and IQ level also rank in the upper third of the most important features, suggesting a more direct influence on ASD diagnostic than it was apparent up to now. Although age is included in the ADOS/2 cutoff algorithm of M2, this focus is missing for the remaining modules. Moreover, IQ level is not taken into account in any of the four modules. In sum, especially with respect to the high amount of false positives (in case of individuals with below average IQ and ID) or else of false negatives (in case of individuals with above average IQ), we recommend clinicians to be aware of these potential confounding features in the diagnostic process. Based on the present data, it can be suggested that going through the short DT pathways, to reinsure the decision for or against ASD, may decrease the risk of false positives and false negatives in individuals with below and above average IQ levels remarkably. However, it is relevant to keep in mind that, in addition to or in interaction with IQ, further factors may influence the complex diagnostic process, including other differential or comorbid diagnoses (17, 18, 36, 45), female gender (46), parental psychiatric diagnoses (47), aspects of healthcare supply (48, 49), and experience of the diagnostician (50). Further, since IQ and language are observed to account for the heterogeneity in ASD and the variability in diagnostic and therapeutically outcomes, it appears relevant to consider also developmental trajectories of autistic symptom severity and adaptive functioning (51). For example, within analyses of the longitudinal EU-AIMS project, it was observed that higher age, lower IQ, and increased severity in (parent rated) social communication symptoms were predictive for lower adaptive functioning (52). Thus, the interplay between IQ, age, and symptom expression as well as their possible trajectories may be considered as well, if risks for false negatives or positives during ASD diagnostics were attempted to be reduced. However it was also concluded that individualized interventions need to focus on both aspects (symptom severity and adaptive functioning), since improvement in one domain does not ensure improvement in the other (51). In addition, even severely impaired children may improve substantially, so that they may enter adolescence with severity scores that are comparable to high functioning children. Prerequisite for this developmental trajectory is not to have an ID and to have a more educated, non-minority mother (53). In summary, the present and recent findings (7, 52) underline the high relevance of taking the IQ into account for the assessment of ASD symptomatology as well as for statements about course/prognosis and thus individual developmental trajectories and opportunities (54).

Limitations

DTs are known to be very sensitive to changes in the training data: Minor modifications in the data provided for training can result in different trees. Therefore, in general, care has to be taken when drawing conclusions about the importance of attributes from DT. However, considering that the RF consists of DTs trained on randomly sub-sampled data, the impurity decrease measure can be regarded as a more robust measure of item importance. As the relevant features derived from the impurity decrease in the RF (**Figure 3**) are widely consistent with the relevant features obtained from the DT shown in **Figure 2**, the latter can be considered representative for similar data sets. As our analyses were applied in a cross-ADOS-module approach, further research is necessary to confirm the data as well as the drawn pathway within individual ADOS modules. A further limitation is that the ADOS/2 was part of the state-of-the-art diagnostic approach. Thus, the coincidence of ASD diagnosis and the ADOS/2 cutoff exceedance is possibly circular, confounding the results.

CONCLUSIONS

In general, accuracies to predict BEC diagnosis of ASD yes vs. no between ADOS/2 cutoff and ML models are comparable. However, within sub-cohort analyses, i.e., individuals with below and above average IQ levels, the ADOS/2 algorithm was less accurate, resulting in 3 times higher risk for a false-positive ASD diagnosis in individuals with ID as well as 1.7 times higher risk for a false-negative ASD diagnosis in individuals with an

above average IQ. This may be circumvented or decreased to the accuracy of individuals with average IQs by following the presented DT pathways, which could serve as a brief screening and as a solid decision-making basis for a subsequent all-encompassing diagnosis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Department of Psychiatry, Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin, Berlin, Germany (Az. 92/20). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

NW and ME executed the study idea, prepared and analyzed the data, wrote the first draft of the paper, and incorporated the comments and remarks from the co-authors. SS, IK-B, SR, and LP reviewed the paper, added comments, and rewrote parts of the paper. VR collaborated in all stages of the editing process of the final manuscript, added comments, and reviewed the paper from the first to the final draft. All authors contributed to the article and approved the submitted version.

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Establishing Normative Data for the Number Cancelation Test Among Children in Kindergartens and Primary Schools in China

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This study aimed to suggest an attention assessment tool using a Digital Pen for measuring the temporal-spatial parameters during the Number Cancelation Test (NCT), and then to establish the normative data for the NCT among children in kindergartens and primary schools in China by recruiting a total of 989 children (496 males). Four measures, i.e., selective attention (SA), speed of cognitive processing (SpC), averaged time of circlings (ATC), and averaged circumference of circled curves (ACCC), were proposed to evaluate the NCT performance. They basically have a development trend with fast speed in the beginning before Grade 1 or 2 of primary schools, and then enter an extremely slow development period (with ceiling or floor effect). SA and SpC have gender and grade main effects, while ATC and ACCC have the grade main effect, only. In particular, females have higher SA scores than males in middle class of kindergarten, and Grade 2–Grade 5 of primary school, but no gender differences in other grades; females have higher SpC scores than males in middle class of kindergarten, and Grade 3–4 of primary school, but no gender differences in other grades. More importantly, in clinical practice, if SA or SpC measure of a child is below than the 5th centile (i.e., p5 level) of his/her grade-specific normative data, then this child may be predicted to have a high-risk of learning disabilities. Findings suggest that the proposed method can be used for early screening of learning disabilities by setting appropriate cut-off values.

Keywords: Number Cancellation Test, attention, visual-motor integration, learning disabilities, attention deficit/hyperactivity disorder

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INTRODUCTION

Attention is the basic of complex functions involving several different cognitive and emotional processes and abilities (1, 2). Although there are several definitions and subdivisions of attention capacity, selectivity is arguably the central defining quality of attention and is largely dependent on the frontal lobe (1, 2). The presence of attentional deficits may have a long-lasting impact on daily learning and living. Hence, it is significant to develop precise and accurate attention assessment tools for early detection of attentional deficits (1, 2).

Cancelation tests (3–16) are widely used for measuring individuals' ability to simultaneously search and scan all stimuli of a certain type (targets) while ignoring stimuli of all other types (distractors). Their clinical utility has been reported in the evaluation of visual attention, associated

with a wide range of neurological and psychiatric disorders, such as attention deficit/hyperactivity disorder (ADHD) (3, 4), learning disabilities (LDs) (5), visuospatial neglect syndrome (6, 7), stroke (8), Alzheimer's disease (9), mild cognitive impairment (10), Parkinson's disease (11), epilepsy (12), depression (13), and traumatic brain injury (14). Thus far, previous results have basically focused on adults, but only a few studies have been conducted specifically to children (7).

On the other hand, dependent on the traditional paper-and-pencil test, the cancelation tests may have some disadvantages and limitations in performance measures and scoring processes. First, typical performance measures of the cancelation tests include the number of omissions, the number of correct responses, the total number of cancelations, and completion time, but cannot consider the temporal-spatial features from the perspective of handwriting kinematics, such as pre-movement time (initiating), movement time (moving pen to a stimulus), drawing time (completing a cancelation), circumference of a drawn curve, real-time spatial positions (trajectory) of drawing, and the time sequence of drawings. Second, the manual counting method is utilized in the scoring processes of the cancelation tests and thereby, is inconvenient in clinical applications.

Taken together, the current study aimed to suggest an attention assessment tool using a Digital Pen (with an embedded smart mini-camera) for measuring the temporal-spatial features during the Number Cancelation Test (NCT) (15, 16). According to China's school system, kindergartens are divided into three grades, and primary schools are divided into six grades. A total of 989 children in kindergartens and primary schools were recruited to establish normative data for the NCT among children in kindergartens and primary schools in China. To our knowledge, this is the first time to report normative data (e.g., percentiles for each grade group) of the NTC for such a wide range of children (especially for Chinese children). By setting appropriate cut-off values for these normative data of the NTC, the suggested method had the potential capability for early screening of LDs. This study also investigated if and how the gender and grade influence these temporal-spatial features during the NCT. The internal consistency, test-retest reliability, and validity of the suggested method were discussed as well.

MATERIALS AND METHODS

Participants

The current study was conducted in Nanjing, Jiangsu Province, China, between September 2020 and March 2021, and selected participants with a multistage stratified random sampling. According to the districts' rankings of GDP per person in 2019, the districts of Nanjing were divided into three levels, i.e., Strong (>130,000 RMB), Medium (100,000–130,000 RMB), Weak (<100,000 RMB). By a random-number generator *via* Matlab Statistic Toolbox (R2012b), we conducted a sequence of random operations as follows. First, we selected randomly three districts (corresponding to Strong, Medium, and Weak level, respectively), and two primary schools and one kindergarten for each district. Then, we chose randomly one class from a grade of each primary school, and three classes from a grade of each kindergarten. Furthermore, we selected randomly ten males and ten females from a class of each primary school or kindergarten. By steps above, we recruited a total of 720 children from primary schools and 540 children from kindergartens. We excluded 38 children with a history of previous neurological or psychiatric disorders, or children who had repeated a grade. We further excluded 233 children, who cannot submit their experimental data due to loss of data or refusal to attend the experiments. Hence, 989 children (496 males) were finally considered in the current study.

All study procedures and research methods were carried out in accordance with the Declaration of Helsinki (17) by the World Medical Association concerning human experimentation, and were approved by the Research Ethics Committee at Southeast University. Informed consent was obtained from all parents of participating children and oral consent was obtained from all participating children. Each child received an age-appropriate toy after completing the study.

Procedure

We suggested a newly developed tool using a Digital Pen for recording the temporal-spatial features during the NCT, and obtained the NCT measures for attention assessment. More importantly, we aimed to establish the normative data for the NCT measures from 989 children in kindergartens and primary schools. In addition, it was hypothesized that by setting appropriate cut-off values for these normative data, the NCT measures can be used for early screening of LDs. To test this hypothesis, we suggested using the Pupil Rating Scale Revised (PRS) questionnaire (18–21), which has been widely used for the screening of LDs and is assumed to be a golden standard of LDs in this study, to investigate the validity of screening using the NCT measures.

Participating children were instructed to complete the NCT task. The teachers of participants from primary schools were required to complete the PRS questionnaire. The participants took the tests at school in a quiet room.

Number Cancelation Test Task

The examiner sat in front of a participant and presented the participant with a standard B5-size paper showing a series of numbers arranged in organized arrays with 26 rows and 40 columns, and the participant hold the Digital Pen with an embedded smart mini-camera correctly. The test instruction given to participants was that "Honey, there are many numbers below. You should find the number "3" (the targeted number) and draw a circle on it, but ignore all other numbers (distractors), as quickly as possible within 2 min." A laptop linked to the Digital Pen with Bluetooth wireless technology, and recorded the data generated and transferred from the Digital Pen. The technical advantage of the Digital Pen was the usage of a smart mini-camera (being embedded in the Digital Pen), designed to measure the temporal-spatial parameters during the NCT. In the current study, four parameters were suggested as the scores to measure individuals' performance during the NCT, including:

(1) Speed of cognitive processing (SpC) was defined as:

$$SpC = M \sum_{i=1}^{N} R_i \quad (1)$$

where M was the amount of numbers in one row (here $M = 40$); N was the total number of rows to be circled; $R_i = 1$ represented the case if any number in the i-th row has been circled; and $R_i = 0$ represented the case if no number in the i-th row has been circled.

(2) Selective Attention (SA) was defined as:

$$SA = \frac{1}{T}\frac{m-\omega}{m+o} \times \mathrm{SpC} \quad (2)$$

where o was the amount of omitted targets; ω was the number of distractors being circled; and m was the total amount of targets that should be circled; T was the task time (here $T = 120$); SpC was defined by Eq. 1.

(3) Averaged time of circlings (ATC) was defined as:

$$ATC = \frac{1}{n} \times \sum_{i=1}^{n} t_i \quad (3)$$

where n was the amount of numbers being circled; and t_i was the time to circle the i-th number.

(4) Averaged circumference of circled curves (ACCC) was defined as:

$$ACCC = \frac{1}{n} \times \sum_{i=1}^{n} C_i \quad (4)$$

where n was the amount of numbers being circled; and C_i was the circumference of the curve circling the i-th number.

An example (see **Figure 1**) illustrated a case that a participant completed only 6 rows in 2 min, where "3" was the targeted number and all other numbers were distractors. It is easy to see from **Figure 1** that the whole task lasted 2 min (i.e., $T = 120$); the total amount of numbers being circled was 14 (i.e., $n = 14$); the number of omitted targets was 12 (i.e., $o = 12$), where the amount of omitted targets in the 1st, 2nd, 3rd, 4th, 5th, and 6th row was 2, 1, 3, 3, 2, and 1, respectively; three distractors (i.e., "8" in this case showing in **Figure 1**) in the 1st, 4th, and 5th row were circled (i.e., $\omega = 3$); the total number of targets that should be circled was 22 (i.e., $m = 22$); the amount of numbers in one row was 40 (i.e., $M = 40$); $R_1 = R_2 = R_4 = R_5 = R_6 = 1$ because there were at least one number (being circled) in the 1st, 2nd, 4th, 5th, and 6th row; and $R_3 = 0$ because no numbers were circled in the 3rd row. Therefore, $SpC = 40 * (R_1 + R_2 + R_4 + R_5 + R_6) = 200$; $SA = \frac{1}{120}\frac{22-3}{22+1} \times 200 = 0.43$. The parameter ATC can be easily calculated by averaging the time of circling each number. While, the parameter ACCC can be simply calculated by averaging the curve circumference of each circling.

Pupil Rating Scale Revised Questionnaire

The PRS questionnaire (18–21) has been widely used for the screening of LDs and is assumed to be a golden standard of LDs in this study. It consists of 24 items rated on a 5-point Likert scale, and is comprised of five subscales (including auditory comprehension and memory, spoken language, orientation, motor coordination, and personal-social behavior). The score of each item ranges from 1 ("the lowest") to 5 ("the highest"). Hence, the total score of the PRS questionnaire ranges from 24 (minimum) to 120 (maximum). Higher score means better learning ability.

The PRS questionnaire includes verbal and non-verbal measures, where verbal and non-verbal measures contain the items from two subscales (i.e., spoken language, and auditory comprehension and memory) and from other three subscales (i.e., orientation, motor coordination, and personal-social behavior), respectively. Therefore, the total score of the verbal measure ranges from 9 (minimum) to 45 (maximum); while the total score of the non-verbal measure ranges from 15 (minimum) to 75 (maximum). It has been verified (18–21) that LDs can be screened by the rule that the participants with verbal measure below than 20, with non-verbal measure below than 40, and with total score below than 65 were suspected to be verbal LD, non-verbal LD, and general LD, respectively. Findings of a large sample research ($n = 3991$) verified (20) that the PRS questionnaire had a high reliability for Chinese children (its reliability coefficients being higher than 0.84 for all subscales).

The teachers of participants from primary schools were instructed to complete the PRS questionnaire and evaluate participants' risk of LDs.

Centile Curves

Centile curves of the NCT measures were computed using the LMS method (22–24), which obtains normalized growth centile standards by optimizing three curves representing the skewness (L), median (M), and coefficient of variation (S). The resulting L, M, and S curves contain the information to draw any centile by the following formula (22–24):

$$C_{100\alpha}(t) = M(t)\left[1 + L(t)\,S(t)\,Z_\alpha\right]^{1/L(t)} \quad (5)$$

where Z_α is the normal equivalent deviate of size α. For participants, the 5th, 10th, 15th, 25th, 50th, 75th, and 90th centiles were chosen as age-specific reference values. Centile curves, shown in Eq. 5, were calculated with R language (version 4.0.2).

Cut-Off Values for Screening of Learning Disabilities

Participants were suspected to be LD if their PRS measures meet one of the following conditions: (i) The score of verbal measure is below than 20; (ii) The score of non-verbal measure is below than 40; (iii) The total score is below than 65. It is hypothesized that a participant is suspected to be LD, if the following condition can be satisfied

$$NCT^{(j)} < \beta_{pi}^{(j)} \quad (6)$$

where $NCT^{(j)}$ is the j-th measure of NCT; $\beta_{pi}^{(j)}$ is the cut-off value of $NCT^{(j)}$ with the pi-th centile.

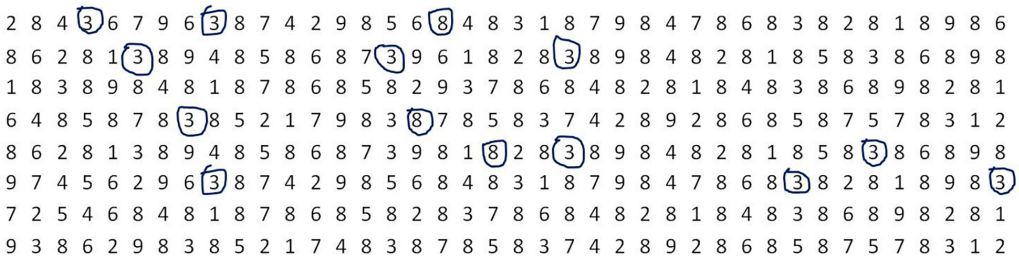

FIGURE 1 | An example illustrated a case that a participant completed only 6 rows in 2 min, where "3" is the targeted number and all other numbers are distractors. In this example, 14 numbers were circled, where the amount number of "3" was 11 and that of "8" was 3. In addition, the amount number of omitted "3" was 12, where the number of omitted "3" in the 1st, 2nd, 3rd, 4th, 5th, and 6th row was 2, 1, 3, 3, 2, and 1, respectively.

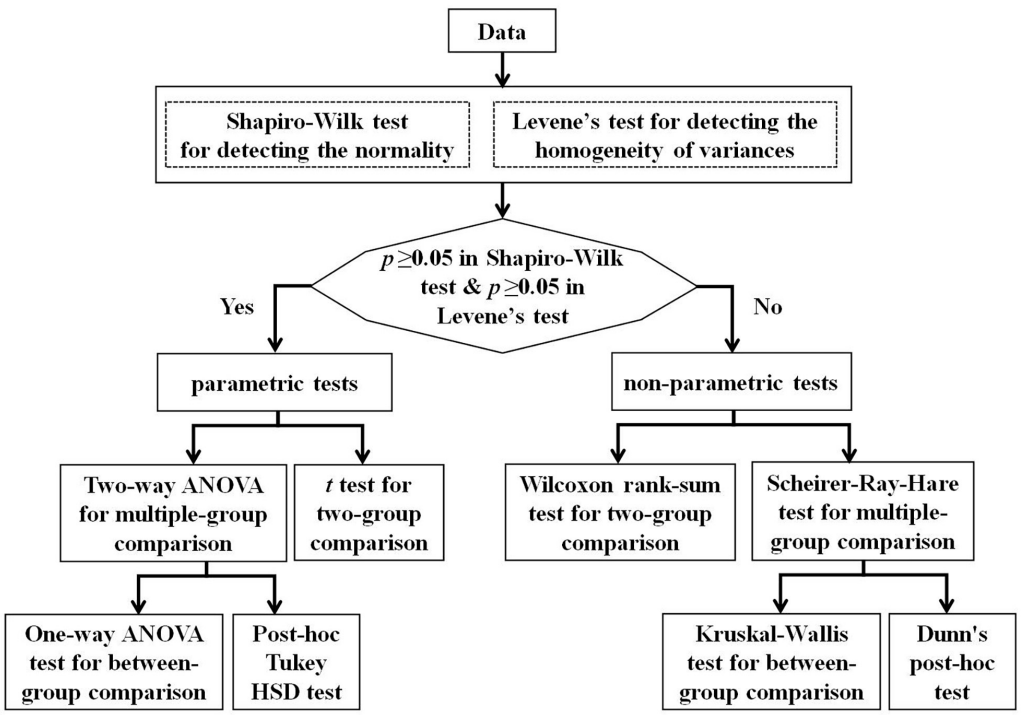

FIGURE 2 | The flowchart of statistical analysis.

The screening of LD by PRS measures is assumed to be a golden standard in this study. By this way, one can investigate the screening performance based on the NCT measures. In particular, this study revealed that how the screening accuracy of LD is influenced by the cut-off values $\beta_{pi}^{(j)}$.

Statistical Analysis

We aimed to investigate how the gender and grade influence the measures (i.e., SpC, SA, ATC, ACCC) quantifying the NCT performance of participants. Hence, we conducted a series of two-way ANOVA for these measures, according to the flowchart (see **Figure 2**). We verified that our data (i.e., the NCT measures) failed to pass both normality test and variance homogeneity test, so we conducted a series of non-parametric two-way ANOVA procedures (i.e., Scheirer–Ray–Hare tests) for the NCT measures. In addition, we used the Kruskal Wallis method and Dunn's *post-hoc* test for multiple comparisons with Benjamini-Hochberg procedure to control the false discovery rate. All statistical analysis above was conducted with R language (version 4.0.2).

RESULTS

General Information of Participants

The current study actually investigated a total of 989 children, including 496 males and 493 females. The ratio of males to females was 1.006:1 and the participants were distributed in 9 grade groups, ranging from GR1 (corresponding to junior class of kindergartens) to GR9 (corresponding to Grade 6 of primary

schools), see **Table 1** for detailed information. It has verified that there was no significant gender difference ($\chi^2 = 10.43$, $p = 0.24$).

Main Effects of Age and Gender

In this study, we aimed to investigate how the gender and grade (age) influence the four parameters (i.e., SpC, SA, ATC, ACCC). According to the statistical flowchart shown in **Figure 2**, we verified that our data (i.e., the NCT measures) failed to pass both normality test and variance homogeneity test (p's ≥ 0.05). Hence, we conducted a series of non-parametric two-way ANOVA procedures (i.e., Scheirer–Ray–Hare tests) to reveal the gender and grade main effects as well as for their interaction. Our findings showed that: (i) The main effect of grade is significant for ATC and ACCC (Gender: p's > 0.05; Grade: p's $< 1 \times 10^{-4}$; Gender * Grade: p's > 0.05); and (ii) The main effects of gender and grade were significant (but there was no interaction effect) for SpC and SA (Gender: p's < 0.01; Grade: p's $< 1 \times 10^{-4}$; Gender * Grade: p's > 0.05).

According to the statistical flowchart shown in **Figure 2**, we further utilized the Kruskal Wallis method and Dunn's *post hoc* for multiple comparisons with Benjamini-Hochberg procedure to control the false discovery rate. **Figures 3–5** summarized our results and verified that:

(i) For ATC (see **Figure 3**): Children in GR1-GR4 had higher scores than other grades (p's < 0.05, adjusted), but there was no significant difference between children in GR1 and GR2 ($p > 0.05$, adjusted); there were no significant differences among GR7-GR12 (corresponding to Grades 3–6) (p's > 0.05, adjusted).

(ii) For ACCC (see **Figure 3**): Children in GR1-GR3 had higher scores than other grades (p's < 0.05, adjusted), but there was no significant difference between children in GR1 and GR2 ($p > 0.05$, adjusted); there were no significant differences between children in Grades 1–3 and between Grades 2–6 (p's > 0.05, adjusted).

(iii) For SpC (see **Figure 4**): Females had higher scores than males in GR2, GR6 and GR7 (p's < 0.05), but no significant differences had been found in other grades (p's > 0.05).

(iv) For SA (see **Figure 5**): Females had higher scores than males in GR2, GR5-GR8 (p's < 0.05), but no significant differences had been found in other grades (p's > 0.05).

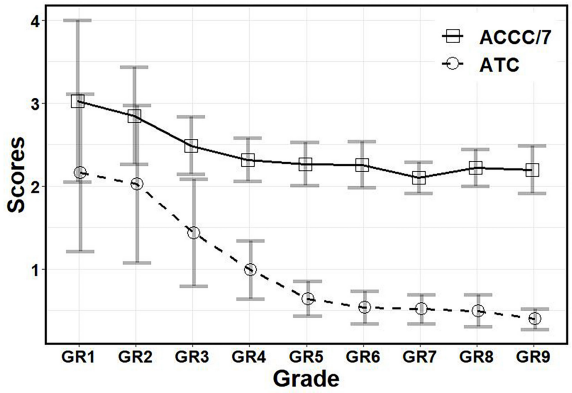

FIGURE 3 | The scores of ATC and ACCC in different grades. ATC, Averaged time of circlings; ACCC, Averaged circumference of circled curves; GR1, Junior Class of kindergarten; GR2, Middle Class of kindergarten; GR3, Senior Class of kindergarten; GR4, Grade 1 of primary school; GR5, Grade 2 of primary school; GR6, Grade 3 of primary school; GR7, Grade 4 of primary school; GR8, Grade 5 of primary school; GR9, Grade 6 of primary school.

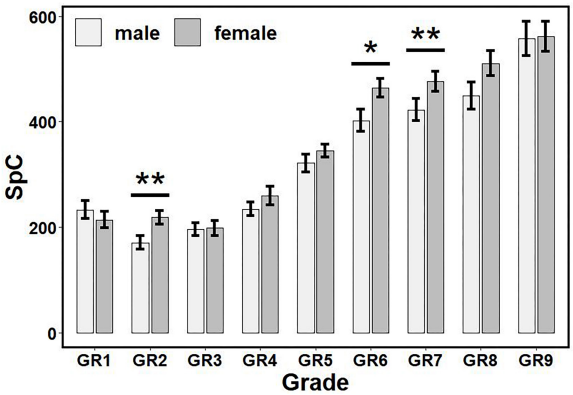

FIGURE 4 | The influence of gender and grade on SpC scores. There are gender differences in GR2, GR6, and GR7. * $p < 0.05$, ** $p < 0.01$. SpC, speed of cognitive processing; GR1, Junior Class of kindergarten; GR2, Middle Class of kindergarten; GR3, Senior Class of kindergarten; GR4, Grade 1 of primary school; GR5, Grade 2 of primary school; GR6, Grade 3 of primary school; GR7, Grade 4 of primary school; GR8, Grade 5 of primary school; GR9, Grade 6 of primary school.

TABLE 1 | Demographic characteristics of participants.

Grade groups	Males (*N*, %)	Total (*N*)	Age (years)
GR1 (Junior Class of kindergarten)	73 (49.7)	147	3.91 ± 0.27
GR2 (Middle Class of kindergarten)	84 (45.65)	184	4.85 ± 0.27
GR3 (Senior Class of kindergarten)	89 (53.61)	166	5.91 ± 0.29
GR4 (Grade 1 of primary school)	59 (61.46)	96	6.84 ± 0.31
GR5 (Grade 2 of primary school)	49 (49.49)	99	7.84 ± 0.30
GR6 (Grade 3 of primary school)	49 (50)	98	8.76 ± 0.28
GR7 (Grade 4 of primary school)	42 (53.16)	79	9.82 ± 0.34
GR8 (Grade 5 of primary school)	34 (43.59)	78	10.80 ± 0.30
GR9 (Grade 6 of primary school)	17 (40.48)	42	11.80 ± 0.27
Total	496 (50.15)	989	N/A

Internal Consistency and Test-Retest Reliability

The internal consistency of these four temporal-spatial indexes was detected by the linear correlation analysis. **Table 2** summarized our results and showed that there were high correlation coefficiencies (thus high internal consistency) among these four indexes. In addition, we also verified that the consistency among experimenters was 0.997, implying that the operation of all experimenters was highly consistent.

To assess the test-retest reliability by calculating intraclass correlation coefficients (ICCs) for all parameters, 117 participants were asked to undergo a second NCT test, where time between two assessments was 14 days. It was very encouraging that ICCs

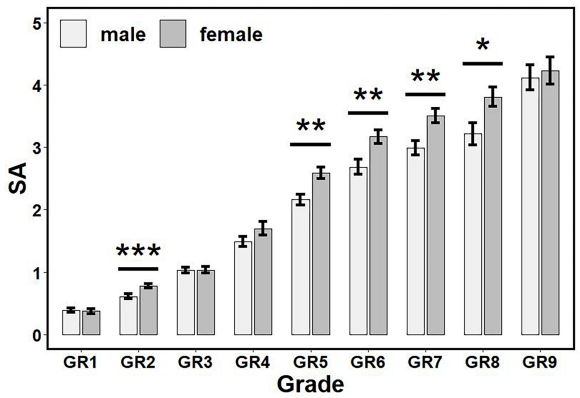

FIGURE 5 | The influence of gender and grade on SA scores. There are gender differences in GR2, GR5–GR8. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. SA, Selective Attention; GR1, Junior Class of kindergarten; GR2, Middle Class of kindergarten; GR3, Senior Class of kindergarten; GR4, Grade 1 of primary school; GR5, Grade 2 of primary school; GR6, Grade 3 of primary school; GR7, Grade 4 of primary school; GR8, Grade 5 of primary school; GR9, Grade 6 of primary school.

of SA, ATC, SpC, and ACCC are 0.81, 0.81, 0.655, and 0.62, respectively. This implies that according to Fleiss's rule, the test-retest reliability of SA and ATC are excellent (ICCs > 0.8), while the test-retest reliability of SpC and ACCC are good (ICCs > 0.6).

To summarize, the internal consistency, the consistency among experimenters, and the test-retest reliability are acceptable.

Test Validity

The PRS questionnaire has been widely used in evaluating the risk of learning disabilities in children. Findings revealed (see **Table 3**) that SpC, SA and ACCC scores were correlative with the indexes of PRS questionnaire (p's < 0.05).

Normative Data

The normative data is naively a simple reference range. Clearly, in our case that the measures are strongly dependent on grade, the reference ranges change with grade and lead to inconvenience in practice. Fortunately, centile curves (22–24) overcome the drawback of the grade-related reference ranges, and provide a visualizing outline to present the normative data. Centile curves were calculated according to Eq. 5 for SA, ATC, ACCC, and SpC measures. Any percentile can be evaluated for each grade group by the formula shown in Eq. 5. In this study, the 5th, 10th, 15th, 25th, 50th, 75th, and 90th centiles were chosen as grade-specific reference values. **Tables 4–7** summarizes our results, and showed the 5th, 10th, 15th, 25th, 50th, 75th, and 90th centiles for SA, ATC, ACCC, and SpC measures for each grade group.

TABLE 2 | Internal consistency of the NCT.

	SpC	SA	ATC	ACCC
SpC	–			
SA	0.81↑	–		
ATC	–0.53↑	-0.68↑	–	
ACCC	–0.25↑	–0.43↑	0.61↑	–

↑ $p < 0.0001$.
NCT, Number Cancelation Test; SpC, Speed of cognitive processing; SA, Selective Attention; ATC, Averaged time of circlings; ACCC, Averaged circumference of circled curves.

Cut-Off Values for Screening of Learning Disabilities

It was interesting to detect whether these measures (i.e., SpC, SA, ATC, and ACCC) can be used to screen LDs, according to

TABLE 3 | Correlation between the NCT indexes and the PRS scores.

	SpC	SA	ATC	ACCC
Auditory comprehension and memory	0.08*	0.14**	-0.006	-0.11*
Spoken language	0.10*	0.16***	-0.01	-0.10*
Orientation	0.11*	0.17***	-0.019	-0.11*
Motor coordination	0.14**	0.19***	-0.006	-0.13**
Personal-social behavior	0.11*	0.19***	-0.056	-0.15**
Verbal measure	0.09*	0.17***	-0.0097	-0.11*
Non-verbal measure	0.12*	0.20***	-0.05	-0.14**
Total score	0.12*	0.19***	-0.035	-0.13**

*$p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.*
NCT, Number Cancelation Test; PRS, Pupil Rating Scale Revised; LD, learning disability; SpC, Speed of cognitive processing; SA, Selective Attention; ATC, Averaged time of circlings; ACCC, Averaged circumference of circled curves.

TABLE 4 | The 5th, 10th, 15th, 25th, 50th, 75th, and 90th centiles for Selective Attention (SA) measure for different grade groups.

Grade groups	P5	P10	P15	P25	P50	P75	P90
GR1 (Junior Class of kindergarten)	0.02	0.06	0.08	0.14	0.30	0.53	0.74
GR2 (Middle Class of kindergarten)	0.11	0.25	0.33	0.46	0.67	0.90	1.16
GR3 (Senior Class of kindergarten)	0.33	0.46	0.58	0.79	0.97	1.31	1.60
GR4 (Grade 1 of primary school)	0.51	0.79	1.02	1.24	1.55	2.14	2.43
GR5 (Grade 2 of primary school)	1.50	1.62	1.69	2.01	2.51	2.94	3.30
GR6 (Grade 3 of primary school)	1.71	2.21	2.33	2.63	2.95	3.48	4.13
GR7 (Grade 4 of primary school)	2.12	2.25	2.38	2.59	3.28	3.80	4.16
GR8 (Grade 5 of primary school)	2.07	2.24	2.37	2.69	3.40	4.25	5.07
GR9 (Grade 6 of primary school)	2.59	2.85	3.09	3.66	4.17	4.83	5.22

TABLE 5 | The 5th, 10th, 15th, 25th, 50th, 75th, and 90th centiles for Speed of cognitive processing (SpC) measure for different grade groups.

Grade groups	P5	P10	P15	P25	P50	P75	P90
GR1 (Junior Class of kindergarten)	80	80	80	120	200	280	440
GR2 (Middle Class of kindergarten)	40	80	80	120	160	240	360
GR3 (Senior Class of kindergarten)	80	80	120	120	160	240	360
GR4 (Grade 1 of primary school)	120	120	160	200	240	320	372
GR5 (Grade 2 of primary school)	200	240	240	280	360	400	480
GR6 (Grade 3 of primary school)	280	320	330	360	440	480	640
GR7 (Grade 4 of primary school)	280	320	360	360	440	510	560
GR8 (Grade 5 of primary school)	280	304	320	360	480	560	720
GR9 (Grade 6 of primary school)	346	360	400	480	560	640	708

Eq. 6. **Tables 8**, **9** summarized our results and showed that SA and SpC measures could be used to screen LDs with high accuracy (bigger than 0.73) by setting appropriate cut-off values, but ATC and ACCC measures were inconsistent for all grades and failed to screen LDs (not shown). In addition, we suggest from **Tables 8**, **9** that the 5th centile (i.e., p5 level) can be considered as the optimal cut-off value of SA and SpC measures because the screening accuracy reaches its highest accuracy for all grade groups. This implies that if SA or SpC measure of a child is below than the 5th centile (i.e., p5 level) of his/her grade-specific normative data, then this child may be predicted to have a high-risk of LDs.

DISCUSSION

This study aimed to suggest an attention assessment tool using a Digital Pen with an embedded smart mini-camera for recording the temporal-spatial features during the NCT. The advantages of the suggested method are twofold. First, it considers not only the traditional static features (e.g., the number of omissions, the number of correct responses, the total number of cancelations), but also the dynamic features, such as drawing time (completing a cancelation), circumference of circled curves, drawing speed, real-time spatial trajectory of drawings, and the time sequence of drawings. Second, the suggested method has an automated scoring process, thus provides a more sensitive and accurate measure of process and outcome of attention, motor, and visuospatial performance than traditional administration.

TABLE 6 | The 5th, 10th, 15th, 25th, 50th, 75th, and 90th centiles for Averaged time of circlings (ATC) measure for different grade groups.

Grade groups	P5	P10	P15	P25	P50	P75	P90
GR1 (Junior Class of kindergarten)	0.77	1.04	1.23	1.52	2.00	2.85	3.43
GR2 (Middle Class of kindergarten)	0.94	1.06	1.18	1.42	1.81	2.39	3.27
GR3 (Senior Class of kindergarten)	0.65	0.85	0.92	1.03	1.30	1.80	2.09
GR4 (Grade 1 of primary school)	0.48	0.49	0.60	0.68	0.90	1.17	1.41
GR5 (Grade 2 of primary school)	0.36	0.38	0.41	0.47	0.57	0.68	0.83
GR6 (Grade 3 of primary school)	0.32	0.35	0.36	0.37	0.46	0.57	0.70
GR7 (Grade 4 of primary school)	0.28	0.33	0.35	0.38	0.50	0.62	0.74
GR8 (Grade 5 of primary school)	0.27	0.29	0.32	0.37	0.45	0.59	0.78
GR9 (Grade 6 of primary school)	0.22	0.27	0.28	0.32	0.38	0.43	0.55

TABLE 7 | The 5th, 10th, 15th, 25th, 50th, 75th, and 90th centiles for Averaged circumference of circled curves (ACCC) measure for different grade groups.

Grade groups	P5	P10	P15	P25	P50	P75	P90
GR1 (Junior Class of kindergarten)	7.70	14.19	15.59	17.20	20.98	24.72	29.65
GR2 (Middle Class of kindergarten)	14.19	15.80	16.83	17.74	19.21	21.61	24.56
GR3 (Senior Class of kindergarten)	13.34	14.64	15.50	16.13	17.49	18.75	19.99
GR4 (Grade 1 of primary school)	13.39	13.86	14.14	14.91	16.19	17.10	17.16
GR5 (Grade 2 of primary school)	13.05	13.62	13.70	14.30	15.67	17.05	17.94
GR6 (Grade 3 of primary school)	12.74	13.45	14.00	14.45	15.36	16.76	18.02
GR7 (Grade 4 of primary school)	12.36	13.07	13.30	13.99	14.64	15.47	16.09
GR8 (Grade 5 of primary school)	13.32	13.78	13.93	14.55	15.49	16.37	17.42
GR9 (Grade 6 of primary school)	12.87	13.36	13.46	13.89	15.15	16.33	17.33

TABLE 8 | Screening accuracy of learning disabilities (LDs) based on Selective Attention (SA) measure by setting cut-off values ranging from 5th (p5) to 90th (p90) centiles for different grade groups.

Grade groups	P5	P10	P15	P25	P50	P75	P90
GR4 (Grade 1 of primary school)	0.85	0.84	0.82	0.76	0.53	0.37	0.26
GR5 (Grade 2 of primary school)	0.85	0.83	0.81	0.75	0.49	0.33	0.20
GR6 (Grade 3 of primary school)	0.82	0.79	0.79	0.73	0.51	0.35	0.23
GR7 (Grade 4 of primary school)	0.73	0.71	0.73	0.71	0.64	0.42	0.35
GR8 (Grade 5 of primary school)	0.78	0.78	0.73	0.68	0.53	0.42	0.30
GR9 (Grade 6 of primary school)	0.87	0.85	0.81	0.72	0.54	0.33	0.19

It is clear that the 5th centiles (p5) obtain the highest accuracy for all grade groups.

TABLE 9 | Screening accuracy of learning disabilities (LDs) based on Speed of cognitive processing (SpC) measure by setting cut-off values ranging from 5th (p5) to 90th (p90) centiles for different grade groups.

Grade groups	P5	P10	P15	P25	P50	P75	P90
GR4 (Grade 1 of primary school)	0.87	0.87	0.78	0.56	0.44	0.31	0.23
GR5 (Grade 2 of primary school)	0.82	0.81	0.81	0.67	0.33	0.24	0.11
GR6 (Grade 3 of primary school)	0.81	0.77	0.77	0.64	0.38	0.30	0.14
GR7 (Grade 4 of primary school)	0.74	0.73	0.67	0.67	0.55	0.45	0.36
GR8 (Grade 5 of primary school)	0.78	0.78	0.71	0.67	0.53	0.40	0.27
GR9 (Grade 6 of primary school)	0.83	0.83	0.78	0.63	0.52	0.24	0.22

It is clear that the 5th centiles (p5) obtain the highest accuracy for all grade groups.

A total of 989 children (496 males) in kindergartens and primary schools were recruited to establish the normative data for the NCT among children in kindergartens and primary schools. **Tables 4–7** showed the 5th, 10th, 15th, 25th, 50th, 75th, and 90th centiles of the NCT measures for each grade group. Remarkably, SA, ATC, ACCC, and SpC measures basically have a developmental trend (i.e., increased or decreased continuously with grade), especially after GR2 (Middle Class of kindergarten). To our knowledge, this is the first time to report normative data of the NTC for such a wide range of children (especially in China).

It was verified (see **Tables 8**, **9**) that by setting appropriate cut-off values (e.g., the 5th centile), SA and SpC measures can be used for early screening of LDs with high accuracy (bigger than 0.7). This is consistent with the fact that the prevalence of LDs, as reported by the DSM-5 [APA (25)], is between 5 and 15% in the school population.

The findings showed that SpC and SA measures have gender and grade main effects but no interaction effect, while ATC and ACCC measures have the grade main effect, only. In addition, it was very encouraging (see **Figures 3–5**) that all measures have a development trend with fast speed in the beginning before Grade 1 or 2 of primary schools, and then enter an extremely slow development period (with ceiling or floor effect). Remarkably, females have higher SpC scores than males in GR2, GR6, and GR7, but no gender differences in other grades; females have higher SA scores than males in GR2, GR5–GR8, but no gender differences in other grades.

It is well established that females have a faster cognitive and social development up to the end of adolescence than males of the same age. Previous research has also shown that gender

difference plays a significant role in the evaluation of neurological and psychiatric disorders, and the literature associated with LDs and ADHD supports a higher prevalence in males (26–29). Remarkably, our findings (shown in **Figures 3–5**) verified that: (i) Females have higher SpC scores than males in GR2, GR6, and GR7, but no gender differences in other grades; and (ii) Females have higher SA scores than males in GR2, GR5–GR8, but no gender differences in other grades. Hence, our findings about the gender difference are consistent with previous studies. However, our results also showed that there were no gender differences of SpC or SA after Grade 5 or 6 of primary schools. These results here might provide some new insights into understanding the gender difference in the evaluation of neurological and psychiatric disorders (26–29). First, it deserves to test whether there are gender differences across the lifespan (especially after Grade 6 of primary schools). Second, the apparent gender differences of LDs or ADHD might be caused by the gender difference of cognitive level at some age period. Third, the diagnostic criteria for LDs or ADHD might be biased or poorly specified for one gender and/or grade group.

Children with LDs may suffer from the deficits of skills in selective and sustained attention, motor inhibition, visuospatial search, planning, organizing, psychomotor speed, intact visual-perception abilities, fine motor coordination, and sensory motor integration. These skills may basically be measured and interpreted by the suggested method measuring temporal-spatial features during the NCT. Hence, it is not surprising that these temporal-spatial features are highly correlative with the scores of the PRS questionnaire. More importantly, it has been revealed that by setting appropriate cut-off values (e.g., the 5th centile), SA and SpC measures can be used for early screening of LDs with high accuracy (bigger than 0.7). In particular, if SA or SpC measure of a child is below than the 5th centile (i.e., p5 level) of his/her grade-specific normative data, then this child may be predicted to have a high-risk of LDs. These findings suggest that our method, in combination with classification using machine learning tools and considering more temporal-spatial features, has the potential for early screening of LDs, and will be investigated in a future research.

CONCLUSION

This study aimed to suggest an attention assessment tool measuring temporal-spatial features during the NCT, and then to establish normative data (i.e., percentiles for each grade group) for the NCT among children in kindergartens and primary schools in China. The influence of the gender and grade (age) on the NCT measures have been investigated as well. In clinical practice, if SA or SpC measure of a child is below than the 5th centile (i.e., p5 level) of his/her grade-specific normative data, then this child may be predicted to have a high-risk of learning disabilities. Findings verified that the suggested method has the potential for early screening of LDs by setting appropriate cut-off values, thus allowing for better diagnosis and intervention. Future research is warranted to develop effective personalized programs for remediation and rehabilitation, dependent on an individual's attention measure scores.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee at Southeast University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XC and DY developed the idea for the study. YX, YC, FL, MY, LZ, PL, and QH collected the data. YX, YC, HW, XC, and DY did the analyses. DY wrote the manuscript. All authors contributed to the article and approved the submitted version.

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