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The structural connectome and internalizing and externalizing symptoms at 7 and 13 years in individuals born very preterm and full-term

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Abstract

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Background: Children born very preterm (VP) are at higher risk of emotional and behavioral problems compared with full-term (FT) children. We investigated the neurobiological basis of internalizing and externalizing symptoms in individuals born VP and FT by applying a graph theory approach.

Methods: Structural and diffusion MRI data were combined to generate structural connectomes and calculate measures of network integration and segregation at 7 (VP:72; FT:17) and 13 years (VP:125; FT:44). Internalizing and externalizing were assessed at 7 and 13 years using the Strengths and Difficulties Questionnaire. Linear regression models were used to relate network measures and internalizing and externalizing symptoms concurrently at 7 and 13 years.

Results: Lower network integration (characteristic path length and global efficiency) was associated with higher internalizing symptoms in VP and FT children at 7 years, but not at 13 years. The association between network integration (characteristic path length) and externalizing symptoms at 7 years was weaker, but there was some evidence for differential associations between groups, with lower integration in the VP and higher integration in the FT group associated with higher externalizing symptoms. At 13 years, there was some evidence that associations between network segregation (average clustering coefficient, transitivity, local efficiency) and externalizing differed between the VP and FT groups, with stronger positive associations in the VP group.

Conclusions: This study provides insights into the neurobiological basis of emotional and behavioral problems following preterm birth, highlighting the role of the structural connectome in internalizing and externalizing symptoms in childhood and adolescence.

Keywords

premature birth; connectivity; magnetic resonance imaging; psychopathology; childhood; adolescence

INTRODUCTION

Higher rates of clinically significant mental health problems appear to persist throughout life in those born very preterm (VP) compared with their full-term born counterparts (FT). Using dimensional scales of behavior problems, individuals born VP display more internalizing symptoms such as anxiety, depression and social withdrawal in early childhood (1–3) late childhood(2–4), and beyond (5–7) than individuals born FT. Conversely, rates and progression of externalizing symptoms, including conduct and hyperactivity problems, in this population are less clear. Some studies report elevated externalizing symptoms during early childhood, which decline relative to FT peers across childhood and into adolescence (2, 5) and others report no differences in externalizing problems in early or late childhood compared with FT peers (1, 4).

Socio-environmental factors may contribute to internalizing and externalizing symptoms in the preterm population (8–12), however, it is likely that there is a neurobiological basis for this psychopathology, given the risk of brain injury following VP birth and emerging body of literature linking early brain development with later mental health outcomes (13, 14). White matter injury is the primary neuropathology in preterm infants and is characterized by

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premyelinating oligodendrocyte injury and subsequent impaired oligodendrocyte maturation, as well as microgliosis and astrogliosis (15). Individuals born VP display initial white matter and secondary gray matter volume reductions compared with FT peers in infancy (16) and childhood (17). Altered cingulum and uncinate fasciculi microstructure (18–23) and reduced orbitofrontal cortex (24), amygdalae (25, 26), and hippocampal volumes (26–28) in those born VP suggest a potential neurobiological basis for the psychopathology. However, the role of the global organization of white matter in internalizing and externalizing symptoms in the VP population has not yet been assessed.

Graph theory provides a framework to assess complex white matter organization (29–31), providing insight into disorganization of structural brain networks in various disorders (32). In this context, the brain is modelled as a graph, referred to as a structural connectome, consisting of parcellated gray matter regions (nodes) which are interconnected by white matter tracts (edges). These can be derived from diffusion MRI (dMRI)-guided whole-brain tractography. The strength of connection between each pair of nodes can be quantified in different ways (33–38), and various properties of network topology can be calculated (29, 39–45).

Studies investigating structural connectomes in the wider preterm population suggest a reorganization of network architecture, consistent with preservation of a central core of highly interconnected nodes and modular organization at the expense of peripheral connectivity (46, 47). Features of the adult human connectome, including a rich-club architecture (defined by a central set of highly interconnected hub regions) (44, 45), modularity (division of the brain network into distinct sub-networks of highly interconnected regions) (29), and a small-world topology (simultaneous local specialization in sub-networks of high clustering nodes and global integration for efficient processing) (39) are present at 30 weeks of gestation and appear to be retained in the preterm brain (46, 48–50).

Despite this relative sparing of central connections following preterm birth (46, 48, 50), evidence suggests that the typical developmental course of the structural connectome is affected in those born VP (48, 51, 52). Reduced global efficiency has been reported in preterm-born neonates compared with full-term peers (51), and is consistent with more rapid development of short-range, within-module connections compared with long-range, between-module connections from birth to term-equivalent age in the preterm brain (53). With the basic structural layout of the connectome largely in place by 2 years of age (54), further connectome development is primarily driven by modulations in the strength of connections. Across childhood and adolescence, the connectome appears to follow a trajectory of increasing integration and decreasing segregation (54, 55), likely driven by increases in axon diameter and myelination of long-range connections during this period (54, 56). Such developmental changes in topology support more integrated information processing across the brain to facilitate higher-order cognitive functions (57). We have previously reported higher local efficiency (segregation) and lower global efficiency (integration) in VP children at 7 years of age compared with FT peers (52), which is suggestive of immature white matter organization (54).

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Based on previous findings indicating that individuals born VP display a less integrated and more segregated topology (48, 51, 52), we have applied connectomics to determine whether aberrant brain organization may relate to concurrent internalizing and externalizing symptoms at 7 and 13 years. We hypothesized that lower integration and small-worldness would be associated with higher internalizing and externalizing symptoms at 7 and 13 years, while higher segregation would be associated with higher internalizing and externalizing symptoms at 7 and 13 years, respectively.

Previous studies have demonstrated that preterm and term children display differential associations between some white matter measures and executive functioning, cognitive functioning and motor outcome (58, 59). Therefore, as an exploratory analysis, we sought to assess whether associations between connectivity metrics and internalizing and externalizing symptoms differed by birth group (VP, FT).

METHODS AND MATERIALS

Participants

227 VP infants (< 30 weeks' gestation and/or birthweight < 1250 g) admitted to the Royal Women's Hospital in Melbourne, Australia between July 2001 and December 2003 were recruited into the Victorian Infant Brain Study (VIBeS; 65% of eligible VP infants admitted during recruitment period). 77 FT individuals (born between 37 and 42 weeks' gestation and birth weight > 2500 g; 45 at birth and 31 at 2 years) were recruited from the Royal Women's Hospital postnatal wards or via response to advertising in maternal and child health centers. Infants with congenital abnormalities likely to affect development were excluded from the study. Participant recruitment and loss at 7- and 13-year time points are presented in Figure 1. Data from 72 VP and 17 FT children at 7 years and 125 VP and 44 FT children at 13 years were included in the current study. The study was approved by the Royal Children's Hospital and Royal Women's Hospital Research Ethics committees and informed consent was obtained from children's parents/legal guardians.

Behavior Problems

During the 7- and 13-year follow-up, parents completed the Strengths and Difficulties Questionnaire (SDQ; (60)) consisting of 25 items scored on a 3-point response scale ('Not true' = 0, 'Somewhat true' = 1, 'Certainly true' = 2). The 5-item emotional symptoms and 5-item peer problems subscales were combined to measure internalizing symptoms. Externalizing symptoms were measured by combining the 5-item conduct problems and 5-item hyperactivity subscales. Higher scores on both internalizing and externalizing scales indicate a greater degree of behavior problems, with each scale demonstrating good convergent validity, discriminant validity and internal consistency (61).

Social Risk

Family disadvantage was assessed at 7 and 13 years using a social risk index (62). Scores (0 – 2) were given for each domain (family structure, education of primary caregiver, primary income earner employment status and occupation, language spoken at home and maternal

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age at birth) and summed to provide an overall risk score (0 – 12). Overall scores ≥2 were categorized as higher social risk, with scores <2 indicating lower social risk (62–64).

MRI Acquisition

At both time points, MRI data were acquired using a 3T Siemens Trio Scanner. Participants were not sedated during scans. At 7 years, T_1-weighted images were acquired using a MP-RAGE sequence (repetition time (TR) = 1900 ms, echo time (TE) = 2.27 ms, voxel size = 0.8 mm isotropic) and dMRI data were acquired using a twice-refocused echo planar imaging sequence (45 gradient directions at $b = 3000$ s/mm^2, six $b = 0$ volumes, TR = 7400 ms, TE = 106 ms, voxel size = 2.3 mm isotropic). At 13 years, T_1-weighted images were acquired using a 3D multi-echo MP-RAGE sequence with prospective motion correction (TR = 2530 ms, TEs = 1.77, 3.51, 5.32, 7.2 ms, voxel size = 0.9 mm isotropic) and dMRI data were acquired using a multiband accelerated echo planar imaging pulse sequence (60 gradient directions at $b = 2800$ s/mm^2, four $b = 0$ volumes, TR = 3200 ms, TE = 110 ms, voxel size = 2.4 mm isotropic, multi-band acceleration factor = 3).

Image Pre-processing

An overview of the structural connectome workflow is presented in Figure S1. Bias-corrected (65) and brain-extracted (66) T_1-weighted images were parcellated into 66 cortical regions based on the Desikan-Killiany atlas (67) and 14 subcortical regions based on the ‘aseg’ subcortical segmentation tool (68) using FreeSurfer version 6.0 (69) to define nodes in the connectome matrices. Intracranial volume (ICV; combined white matter + gray matter + cerebrospinal fluid volumes) used for secondary analysis was obtained with Statistical Parametric Mapping version 12 (http://www.fil.ion.ucl.ac.uk/spm/). All structural image output was visually inspected and participants with severe levels of movement artefact were excluded. Manual editing was performed according to FreeSurfer guidelines as required.

dMRI data were pre-processed predominantly using MRtrix3 (70), MRtrix3Tissue (https://3Tissue.github.io, a fork of MRtrix3), and the FSL package (71). Preprocessing included Gibbs-ringing correction (72), motion (between-volume, within-volume and outlier correction) and distortion correction (73–76) and brain extraction (66). Quality assessment was performed by visual inspection and automatically using the Quality Assessment for dMRI (QUAD) and Study-wise Quality Assessment for dMRI (SQUAD) tools (77). Participants whose diffusion images had severe levels of movement artefact were excluded. Quality control metrics generally did not differ between VP and FT groups (Table S1). 3-tissue response functions were estimated and averaged (78), images were upsampled to 1.5mm isotropic voxels, and Single-Shell 3-tissue Constrained Spherical Deconvolution (SS3T-CSD; (79)), and global intensity normalization and bias field correction (80) were performed.

The $b = 0$ data were aligned to the T_1-weighted images (intensity inverted to better match the b=0 contrast for the purpose of registration) using the FSL Linear Image Registration Tool (FLIRT) (81) and Advanced Normalization Tool (ANTS) (82). Cortical and subcortical regions were aligned to the dMRI data by applying the inverse of the transformation matrices.

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Whole-brain tractography was performed (83) (iFOD2, step size = 0.75 mm, curvature radius threshold = 1.9 mm [30° per mm;(84)], min streamline length = 10mm) based on white matter fiber orientation distributions from SS3T-CSD. Dynamic seeding within the white matter was performed (85) with cortical and subcortical regions as inclusion regions. A series of anatomical constraints were applied to improve the biological plausibility of reconstructed tracts to ensure streamlines did not enter the cerebrospinal fluid or propagate through and beyond the gray matter. Streamlines were terminated upon reaching the gray matter or exiting the brain mask. Spurious interhemispheric connections between deep gray matter regions were also discarded. Spherical deconvolution Informed Filtering of Tractograms (SIFT2) (85) was performed on the whole brain tractograms.

Connectivity Matrix Construction

Following pre-processing, streamlines were assigned to the relevant nodes. This resulted in an undirected, weighted 80 × 80 connectivity matrix for each subject (ωij) (7 and 13 years separately). In the matrix, each node was represented along rows (i) and columns (j) and each matrix element represented an edge or the connectivity between each node pair (sum of streamline weights). Connectome edge weights were multiplied by the SIFT2 proportionality coefficient for inter-subject normalization (85).

Graph Metrics

The Brain Connectivity toolbox (brain-connectivity-toolbox.net) in MATLAB was used to calculate weighted versions of global efficiency, local efficiency, characteristic path length, average clustering coefficient, transitivity and small-worldness. Descriptions and formulas for each metric used are presented in Table S2 (31, 39, 42, 86–89).

Statistical Analysis

Statistical analysis was conducted using Stata 15.0 (StataCorp, TX). At both 7 and 13 years, associations between connectivity measures and concurrent internalizing and externalizing symptoms were assessed using linear regressions fitted via generalized estimating equations (GEEs) to allow for clustering for multiple births (90). A group-by-connectivity interaction term was included to examine whether associations varied by group; if there was strong evidence that associations varied by group (interaction $p < .05$), associations were presented separately for each group, otherwise the groups were collapsed. All models were adjusted for sex, age at assessment and higher social risk based on the assumed causal diagram showed in Figure S2. Where there was strong evidence of an association, the following secondary analyses were conducted: i) adjusted for ICV to determine if associations were driven by brain size, and ii) excluding participants with an IQ < 70 (n = 9 at 13 years) to determine if findings were driven by a small proportion of children with intellectual impairment. A false discovery rate correction was applied via the Benjamini and Yekutieli method (91) for all analyses to account for multiple comparisons across graph theory metrics.

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RESULTS

Participant characteristics.

Characteristics of participants included in the study are summarized in Table 1. As expected, VP participants at 7 and 13 years were less likely to be a singleton, more likely to have had bronchopulmonary dysplasia or infection, and more likely to have been administered antenatal corticosteroids than FT participants. Groups were similar in all other perinatal characteristics. On average, the VP group displayed slightly higher internalizing symptoms compared with the FT group at 7 and 13 years. VP children also displayed slightly higher externalizing symptoms compared with FT children at 7 years, while externalizing symptoms at 13 years were similar between birth groups. The VP group had smaller ICV and lower IQ at 7 and 13 years than the FT group. A greater number of the VP group had an IQ < 70 than the FT group at 13 years. On average, VP participants included at 7 years were less likely to be a singleton, have had infection or moderate/severe white matter abnormality (WMA) and had lower externalizing symptoms compared with VP children excluded at 7 years because they did not have high quality MRI data available for connectome analysis (Table S3). VP participants included at 13 years also had less infection and moderate/severe WMA than VP children excluded at 13 years (Table S3).

Relationship between the structural connectome and concurrent internalizing symptoms

At 7 years of age, there was strong evidence that lower global efficiency was associated with higher internalizing symptoms (Figure 2a; Table S4) and that higher characteristic path length was associated with higher internalizing symptoms (Figure 2b; Table S4). The evidence for these relationships persisted after adjusting for ICV (Table S4). There was also evidence that lower local efficiency was associated with higher internalizing at 7 years (Figure 2c; Table S4) which further weakened after adjustment for ICV (Table S4). There was little evidence that associations differed by group (group-by-connectivity interaction's $p > 0.466$; Table S4).

At 13 years of age, there was little evidence that structural connectivity metrics were associated with internalizing symptoms or that these relationships varied by birth group (combined $p > 0.242$; group-by-connectivity interaction's $p > 0.179$; Table S5).

Relationship between structural connectome and concurrent externalizing symptoms

At 7 years, there was little evidence that connectivity metrics were associated with externalizing symptoms or that these relationships varied by groups (combined $p > 0.625$; group-by-connectivity interaction's $p > 0.057$; Table S6). The exception was for characteristic path length and externalizing symptoms, whereby there was a weak positive association in the VP group and a weak negative association FT group (group-by-connectivity interaction $p = 0.013$; Figure 3 and Table S6). This finding was similar after adjusting for ICV (Table S6).

At 13 years, there was strong evidence that associations between connectivity metrics (average clustering coefficient and transitivity) and externalizing symptoms differed by group (group-by-connectivity interaction: average clustering coefficient $p = 0.034$;

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transitivity $p = 0.043$). Higher average clustering coefficient and transitivity were related to higher externalizing symptoms in the VP group, but not in the FT group (Figure 4; Table S7). These findings were similar after adjusting for ICV and following exclusion of participants with an IQ < 70 (Table S7). There was weak evidence of a positive association between local efficiency and externalizing symptoms in the VP group and weak evidence of a negative association in the FT group (group-by-connectivity interaction $p = 0.016$; Figure 4; Table S7), however the evidence for this interaction did not persist after adjusting for ICV (Table S7).

DISCUSSION

In a large prospective longitudinal cohort of infants born VP and FT, we found that regardless of birth group, lower network integration was associated with higher concurrent internalizing symptoms at 7 years. However, this relationship was not evident at 13 years. There was also evidence for associations between network integration and externalizing symptoms at 7 years, and between network segregation and concurrent externalizing at 13 years differing by group.

For all children (VP and FT), higher characteristic path length and lower global efficiency were associated with higher internalizing symptoms at 7 years, even after adjusting for brain size. Both measures assess the integration between sub-networks of local, functionally specialized regions and are influenced by long-range connections (31, 54). Maturation of long-range white matter fibers, which include increases in fiber density and myelin thickness, reshape the structural connectome across development, increasing integration between brain regions to support higher order functioning (54). Therefore greater path length between regions and lower global efficiency may reflect weaker, or less mature long-range connections in those with internalizing problems and thus less efficient information transfer across the brain. While VP and FT children displayed similar associations between measures of network integration and internalizing symptoms, poor network integration reported in VP children in the current cohort (52) and in other preterm cohorts (48, 51) may provide a mechanism by which internalizing symptoms are increased in this population. Whether network topology is associated with internalizing symptoms in children in the general population remains to be seen. In adults, one study has found lower network integration in those with generalized anxiety disorder compared to healthy controls (92); however this is not replicated in adults with major depressive disorder (93).

We also report an association between lower local efficiency and higher internalizing symptoms in VP and FT children at 7 years, which may reflect weakened short-range connectivity between local brain regions (42), and is consistent with findings in adults with major depressive disorder (93). However, this relationship weakened following adjustment for brain size and thus should be interpreted with caution.

Despite higher mean symptom scores at 13 years than 7 years in both groups, associations between network integration and internalizing symptoms were not evident at 13 years in VP or FT adolescents. It is possible that in a more mature brain, internalizing symptoms

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may be more strongly associated with the microstructure of specific long-range tracts with protracted maturation, rather than global measures of network integration.

The microstructure of the cingulum and uncinate fasciculus, which continue to mature well into adolescence and are involved in executive control and emotional processing, appear to be altered in individuals born preterm compared with FT peers in adolescence, and thus may provide a more sensitive marker of internalizing problem at this time (21, 23, 94). Alternatively, it is possible that socio-environmental factors may influence the presentation of internalizing symptoms to a greater extent in adolescence compared with childhood. The second follow-up in the current study at 13 years of age occurred during a sensitive period of development marked by major life events, including a transition to secondary education, relationship changes and increased independence from parents. Puberty may also play a role, with studies suggesting a positive relationship between stage of pubertal development and white maturation (95–97). Therefore, future research should investigate the role of white matter organization in psychopathology during adolescence in the context of socio-environmental factors and pubertal status.

At 7 years, there was some evidence that the association between characteristic path length and externalizing symptoms differed by group; high path length (lower integration) was associated with higher externalizing symptoms in the VP group, while lower path length (higher integration) was associated with higher externalizing symptoms in the FT group, although evidence for these relationships were weak. It is important to note that literature investigating links between brain measures and externalizing symptoms in the preterm population is scarce (98). Similar to VP children in the current study, children and adolescents with ADHD display lower network integration than healthy controls (99, 100). Perhaps lower integration and less efficient information transfer across the brain found in preterm cohorts (48, 52), which could reflect delayed or disrupted white matter maturation at a global level (54), is an indicator of shared biological mechanisms involved in internalizing and externalizing problems following VP birth.

At 13 years, increased clustering (average clustering coefficient, transitivity) was associated with higher externalizing symptoms in the VP group. These findings persisted beyond the influence of brain size and after excluding participants with low IQ, suggesting an independent role of network segregation in externalizing symptoms in VP adolescents. Both measures assess connectivity between nearby brain regions, thus VP adolescents with high externalizing symptoms appear to have increased local, short-range connections in the brain. The disparity in findings across the two time points assessed, that is, that lower network integration was associated with higher externalizing symptoms at 7 years, but higher network segregation was associated with higher externalizing symptoms in VP adolescents at 13 years warrants further investigation. Lower integration and higher segregation may be an indication of delayed development of the structural connectome, with the maturation of the human connectome postulated to develop from local to distributed organization across childhood and adolescence (55, 101). Our findings at 7 and 13 years are consistent with studies in clinical populations, with similar increases in clustering and decreases in global efficiency found in youth with ADHD compared with healthy controls in two cohorts aged 8–14 years (99) and 9–17 years (100). There was also evidence that associations

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between local efficiency and externalizing symptoms also differed by group at 13 years and persisted beyond the influence of brain size, however evidence of associations within VP and FT groups was weak. Small-worldness, or the extent to which the brain network reflects a small world topology of highly clustered sub-networks with robust connections linking sub-networks (39), is preserved in the VP brain (48, 52) and was not associated with externalizing or internalizing problems in the current study. Thus, the measure of small-worldness may not be sensitive to the alterations to network integration and segregation observed in the VP brain (48, 52).

A major strength of our study is the use of a large prospective longitudinal cohort of VP and FT-born individuals, which enabled investigation into the role of the structural connectome in psychopathology in childhood and early adolescence. However, the FT group in the current study was relatively small, which may have affected statistical power to find group differences in associations. Longitudinal structural connectome analyses (such as group × time interactions) were not performed in the current study due to updated dMRI sequences over time; future work incorporating identical sequences over time or scan harmonization techniques may be beneficial to improve understanding of longitudinal changes in the structural connectome. Currently, there is no consensus on the optimal brain parcellation scheme, however studies have indicated that the parcellation scheme used may influence connectome findings (102, 103) and thus should be considered when comparing connectome findings across studies. Subject motion is an inherent challenge in pediatric neuroimaging studies, however we minimized this through quality control procedures, which reduced the sample size particularly at 7 years. Our finding that VP children excluded at 7 years (due to poor quality or no MRI data available) had greater externalizing symptoms compared with VP children included in the current study at 7 years reflects the challenges of scanning this subset of children at a young age and may have limited our ability to fully characterize relationships with externalizing symptoms at 7 years. Finally, in addition to the parent-report of the SDQ, future studies should include the self-report version in adolescence to gain greater insight into an individual's emotional state. It would be interesting to continue to explore associations between connectivity measures and self-reported internalizing symptoms in adolescence.

CONCLUSION

In the current study, we applied a graph theory approach to provide novel insights into the neurobiological basis of psychopathology in childhood and adolescence. We found that lower network integration, potentially reflecting weaker long-range connections and less efficient information transfer across the brain, was associated with higher internalizing symptoms at 7 years, but not at 13 years. There was also disparity in associations with externalizing symptoms at 7 and 13 years. Integration again appeared to be the most strongly associated with externalizing symptoms at 7 years, however there was little evidence for associations within either birth group. At 13 years, high clustering was associated with higher externalizing symptoms, but only in the VP group, suggesting a distinct biological basis of externalizing problems in this group. Future studies incorporating stratification techniques and assessment of socio-environmental factors may help to clarify the extent to which variability in degree of compromise and/or socio-environmental factors

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may contribute to the likely multifactorial relationship between brain connectivity and psychopathology in individuals born VP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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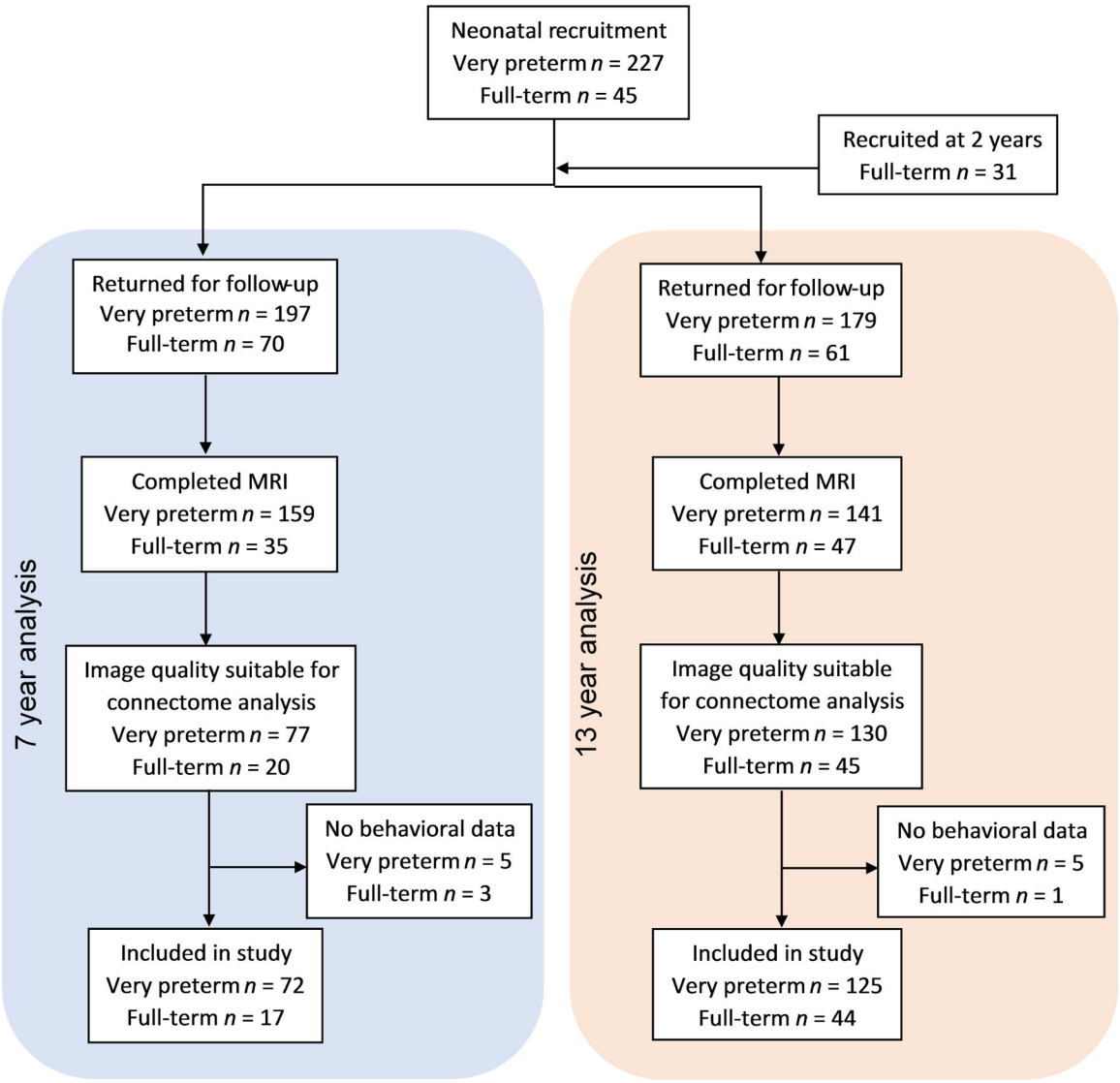

Figure 1. Flow chart of participant recruitment and loss at 7- and 13-year time points.

89% of those initially recruited returned for 7-year follow up and 80% of those initially recruited returned for 13-year follow-up. Reasons for attrition included families moving out of state/internationally, withdrawing from the study or loss of contact. Imaging data that was not of sufficient quality were excluded primarily due to incomplete or incorrect acquisitions, non-uniform diffusion gradient directions (7-year only) or movement artefacts.

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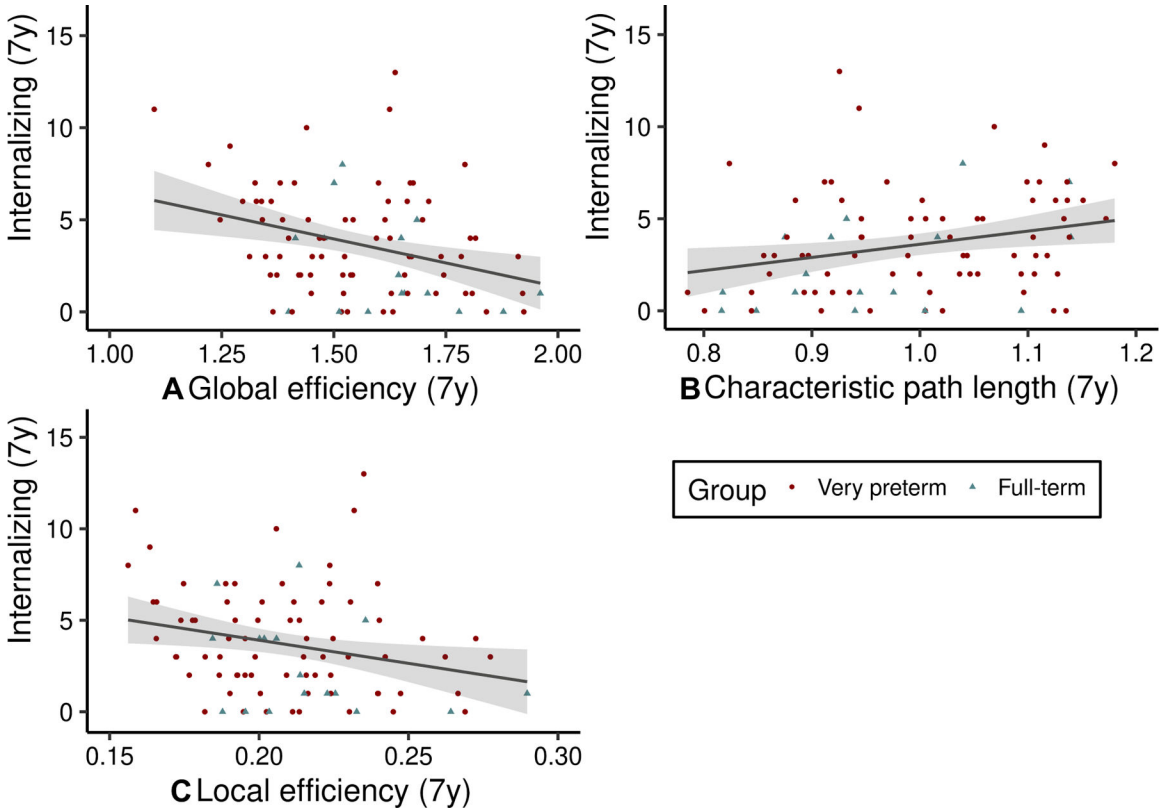

Figure 2. Relationship between (a) global efficiency, (b) characteristic path length and (c) local efficiency and internalizing symptoms in very preterm and full-term groups combined at 7 years.

There was little evidence that associations differed between very preterm and full-term groups, therefore combined group associations are presented. Adjusted for sex, age at assessment and higher social risk at 7 years. Shading represents 95% confidence intervals.

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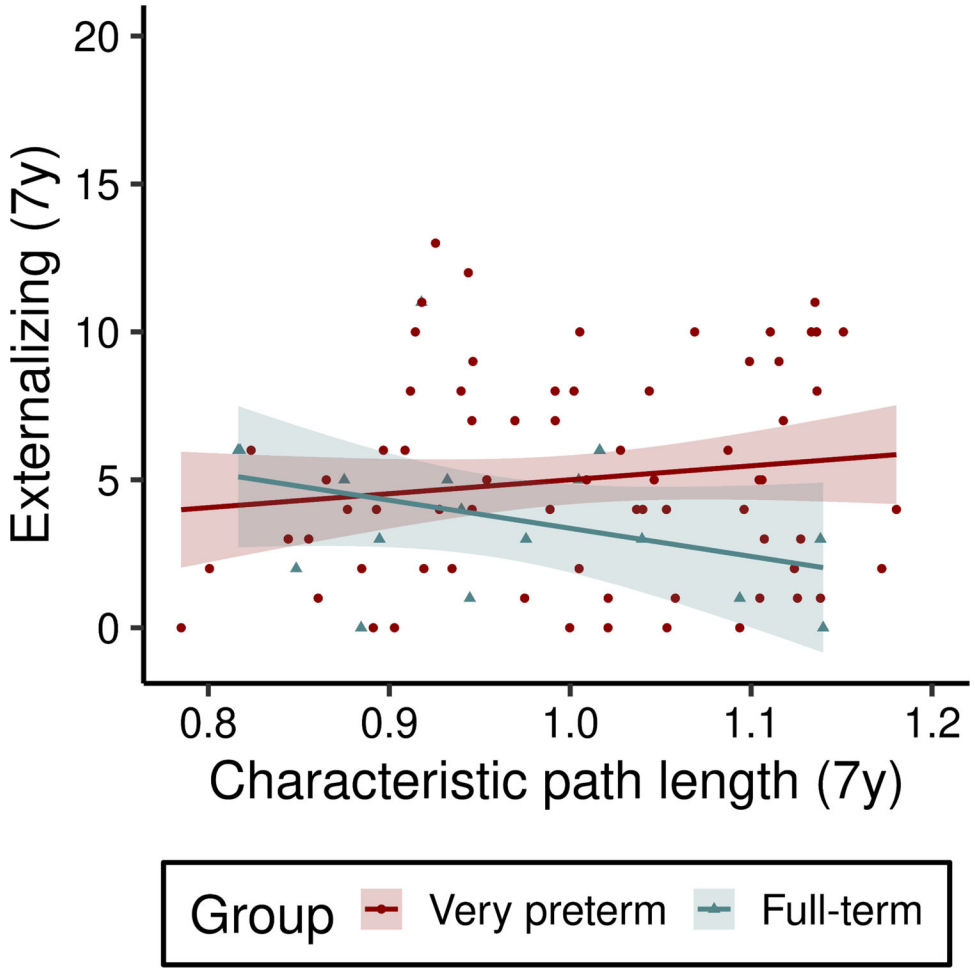

Figure 3. Relationship between characteristic path length and externalizing symptoms in very preterm and full-term children at 7 years.

There was evidence that the association differed between very preterm and full-term groups, therefore associations are presented separately. Adjusted for sex, age at assessment and higher social risk at 7 years. Shading represents 95% confidence intervals.

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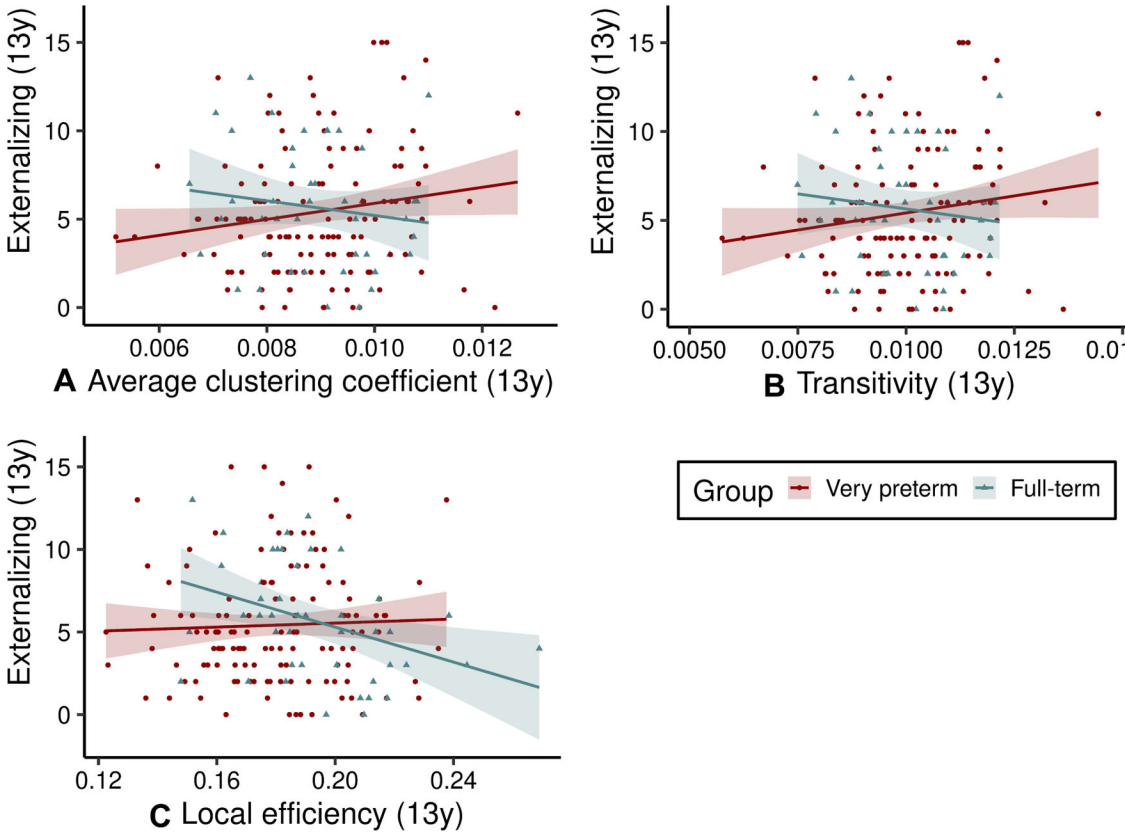

Figure 4. Relationship between (a) average clustering coefficient, (b) transitivity and (c) local efficiency and externalizing symptoms in very preterm and full-term adolescents at 13 years.

There was evidence that the association differed between very preterm and full-term groups, therefore associations are presented separately. Adjusted for sex, age at assessment and high social risk at 13 years. Shading represents 95% confidence intervals.

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Table 1.

Sample Characteristics

	7 years		13 years	
	VP *n* = 72	**FT *n* = 17**	**VP *n* = 125**	**FT *n* = 44**
GA at birth (weeks), *M (SD), range*	27.5 (1.7) 24–31	39 (1.2) 38–40	27.4 (1.9) 22–32	39 (1.4) 37–42
Birthweight (g), *M (SD), range*	1004 (209) 560–1390	3292 (539) 2482–4140	964 (232) 414–1425	3296 (542) 2220–4290
Male, *n* (%)	33 (46)	8 (47)	67 (54)	21 (48)
SGA,[a] *n* (%)	4 (6)	1 (6)	11 (9)	0[b]
Singleton, *n* (%)	32 (44)	15 (88)	65 (52)	40 (91)
BPD,[c] *n* (%)	19 (26)	0	40 (32)	0[b]
Antenatal corticosteroids,[d] *n* (%)	65 (90)	0	113 (90)	0[b]
Postnatal corticosteroids,[e] *n* (%)	2 (3)[f]	0	10 (8)[g]	0[b]
Infection,[h] *n* (%)	17 (25)[i]	0	40 (33)[j]	0[b]
Cystic PVL, *n* (%)	2 (3)	0	4 (3)	0[b]
Grade III/IV IVH,[k] *n* (%)	2 (3)	0	6 (5)	0[b]
Moderate/severe WMA,[l] *n* (%)	6 (9)[i]	0	16 (13)	0[b]
Age at assessment (years),[m] *M (SD)*	7.6 (.2)	7.6 (.2)	13.2 (.38)	13.2 (.46)
ICV (cm^3), *M (SD)*	1350.8 (114)	1438.8 (110.9)	1443.7 (131.8)	1523.7 (157.8)
Internalizing score,[n] *M (SD)*	3.9 (3)	2.5 (2.6)	5.0 (3.4)	4.3 (2.6)
Externalizing score,[o] *M (SD)*	5.1 (3.5)	3.8 (2.8)	5.4 (3.6)	5.7 (3.4)
IQ,[p] *M (SD)*	99.9 (12.7)	110.4 (10.2)	99.5 (18.2)	110.1 (12.4)
IQ < 70,[p] *n* (%)	0	0	9 (7)	0
Higher social risk,[q] *n* (%)	38 (53)	4 (23.5)	77 (62)	16 (36.4)

Note:

[a] Birthweight more than two standard deviations below the mean.

[b] *n* = 24.

[c] Oxygen requirement at 36 weeks.

[d] Typical regime: Betamethasone Chronodose, 11.4 mg intramuscularly, full course: two doses 24 hours apart; part course: single dose.

[e] Postnatal dexamethasone, usual dose 0.15 mg/kg per day for 3 days, reducing over 10 days: total dose 0.89 mg/kg.

[f] *n* = 71.

[g] *n* = 124.

[h] Proven necrotizing enterocolitis and/or sepsis.

[i] *n* = 68.

[j] *n* = 121.

[k] Graded according to Papile et al.

[l] Scored using Kidokoro system.

[m] Corrected for prematurity.

[n] Calculated using the Strengths and Difficulties Questionnaire (SDQ; emotional symptoms + peer problems subscales).

[o] Calculated using the SDQ (hyperactivity + conduct problems subscales).

[p] Wechsler Abbreviated Scale of Intelligence (WASI) full scale IQ score administered at 7 years, Kaufman Brief Intelligence Test, 2nd Edition (K-BIT 2) composite standard score administered at 13 years (M = 100, SD =15).

[q] Family social risk score ≥ 2.

BPD: bronchopulmonary dysplasia; FT: full-term; GA: gestational age; ICV: intracranial volume; IQ: intelligence quotient; M: mean; PVL: periventricular leukomalacia; SGA: small for gestational age; SD: standard deviation; VP: very preterm; WMA: white matter abnormality.

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