Atypical brain network development of infants at elevated likelihood for autism spectrum disorder during the first year of life

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Research highlights

- Infants at elevated likelihood (EL) for autism spectrum disorder (ASD) exhibit hyper-connectivity in the brain compared to infants at typical likelihood (TL) for ASD.
- The modular organization and small-world properties of brain networks are present in infants with and without EL for ASD at 5- and 10-months of age.
- Brain networks of 5-month-old EL infants show higher local and nodal efficiency than 5-month-old TL infants, suggesting an overgrowth local functional network.
- Using a support vector machine (SVM) model, EL versus TL infants could be classified with 77.6% accuracy with network global properties.

Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by behavioural features that appear early in life. Although studies have shown that atypical brain functional and structural connectivity are associated with these behavioural traits, the occurrence and initial alterations of brain networks have not been fully investigated. The current study aimed to map early brain network efficiency and information transferring in infants at elevated likelihood (EL) compared to infants at typical likelihood (TL) for ASD in the first year of life. This study used a resting-state functional near-infrared spectroscopy (fNIRS) approach to obtain the length and strength of functional connections in the frontal and temporal areas in 45 5-month-old and 38 10-month-old infants. Modular organization and small-world properties were detected in both EL and TL infants at 5 and 10 months. In 5-month-old EL infants, local and nodal efficiency were significantly greater than age-matched TL infants, indicating overgrown local connections. Furthermore, we used a support vector machine (SVM) model to classify infants with or without EL based on the obtained global properties of the network, achieving an accuracy of 77.6%. These results suggest that infants with EL for ASD exhibit inefficiencies in the organization of brain networks during the first year of life.

Lay Summary

The brain networks of 5- and 10-month-old infants are able to support efficient communication of information in the brain. Neural networks of 5-month-olds with an elevated likelihood (EL) for autism spectrum disorder (ASD) show an overgrowth in local functional connection, which may not support efficient communication between distant brain regions, while we found no such differences in 10-month-old infants with or without EL for ASD.

Keyword brain network, infant, autism spectrum disorder, functional near-infrared spectroscopy, functional connectivity, neurodevelopmental disorder

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interactions and communication, as well as restricted, repetitive pattern of interests and behaviours (American Psychiatric Association, 2013). Although the neural variations underpinning ASD remain unclear, growing evidence from neuroimaging studies suggests that behavioural characteristics of ASD are often accompanied by atypicalities in brain connectivity (Ecker et al., 2015; Lewis, et al., 2014; McPartland et al., 2021). The current study aimed to explore early developmental changes in brain connectivity in relation to ASD, which has not been fully characterized in infancy.

In recent years, researchers studying brain development in ASD have shifted the perspective from conceptualizing ASD symptoms as a consequence of region-specific dysfunction to their causal relationship with atypical neural circuits. A large number of studies examining the neurobiological basis behind core characteristics of ASD have reported prominent differences in brain networks (Barttfeld et al., 2011; Washington et al., 2014) and atypical functional connectivity among social brain regions (Hull et al., 2017; Vissers et al., 2012), compared to typically developing individuals. In children and adults with ASD, reduced functional connectivity has been found between left-hemisphere posterior superior temporal sulcus and the dopaminergic reward areas (Abrams et al., 2013), in insula and amygdala involving emotional and sensory processing (Ebisch et al., 2011), while increased local functional connectivity has been reported in the middle frontal gyrus and the left praecuneus gyrus (Jiang et al., 2015). Just and his colleagues (2007, 2012) pioneered the ‘underconnectivity theory’ which attributes ASD symptoms to their decreased anatomical and functional connectivity, particularly between frontal and posterior cortical areas. The following ‘disrupted connection theory’ proposed by Kana (2011) is a supplement to the former. It proposes that ‘underconnectivity’ observed in ASD exists primarily in long-distance cortical areas involving complex cognitive and social processing (O’Reilly et al., 2017). On the contrary, ‘overconnectivity’ is often present in adjacent cortical regions involving lower-level sensory and perceptual processing, possibly serving as a compensatory strategy or adaption to the

underconnectivity (Kim et al., 2021).

While the literature on atypical functional connectivity in adults and children with ASD has grown quickly over the past decade, little is known about brain network development during infancy. Given that the socio-communicative features of ASD usually become visible after the child's first birthday (Szatmari et al., 2016), prospective neuroimaging studies of infants at elevated-likelihood (EL) for ASD might be able to identify early postnatal changes in the brain that occur before apparent behavioural atypicalities, and thus bridge the gap between early neural development and later ASD characteristics. Accumulated evidence has indicated that infants with genetic or environmental vulnerabilities are more susceptible to ASD than other infants, such as having an older sibling with ASD (Messinger et al., 2015; Ozonoff et al., 2011), and premature delivery (Agrawal et al., 2018; Laverty et al., 2021; Verhaeghe et al., 2016).

Previous studies have found that EL infants display distinct structural and functional connectivity (Keehn et al., 2013; Swanson et al., 2017). EL Infants at 3 months of age show increased functional connectivity compared to infants at typical-likelihood for ASD (TL) during a trisyllabic sequences language task. This pattern becomes unremarkable at 6 and 9 months, while by 12 months, EL infants exhibit an opposite pattern showing decreased connectivity (Keehn et al., 2013). At 6 to 9 months of age, the brains of EL infants display a U-shaped connectivity pattern when coping with social tasks, with increased connectivity during pre- and post-social periods compared to periods of social interaction with their parents (Bhat et al., 2019). Significant reduced anterior-posterior functional connectivity has been found in 12-month-old EL infants who were later diagnosed with ASD compared to EL infants who were not and to TL infants (Righi et al., 2014). Moreover, atypical anatomical brain development in EL infants between 6 and 12 months, including the cortical surface hyper-expansion (Hazlett et al., 2017) and increased fractional anisotropy of white matter (Wolff et al., 2012), is linked to emergence and severity of ASD symptoms at 24 months. Up to now, most of these prospective studies into early neural correlates of ASD have been performed in younger siblings of children with ASD. A growing number of neuroimaging studies, however, have demonstrated distinct brain networks in preterm infants compared with full-term infants (Lubsen et al., 2011; Wang et al., 2020), as well as underscore the important role of preterm delivery as one of the environmental factors in ASD (Bokobza et al., 2019). In preterm infants, several important brain networks (e.g., the default mode network) develop with different trajectories than term infants and experience rapid neural growth in the third trimester of gestation (Doria et al., 2010). Strong local connectivity has been found in preterm infants with a gestational age of less than 32 weeks, and their inter-hemispheric connections mature by 4 years of age (Lee et al., 2013). As brain development has been disproportionately studied in different groups at elevated-likelihood for ASD, the current study aimed to investigate early development of brain connections in EL infants including both ASD siblings and preterm infants.

Functional near infrared spectroscopy (fNIRS) has been proven to be a useful optical imaging technique for monitoring brain activity through the changes of haemoglobin concentration in certain cortical regions of the human brain (Guo et al., 2013). With reasonable spatial and temporal resolution, fNIRS has been widely used to reveal the neural characteristics underlying cognitive and social processing in infants (Gervain, 2014; Lloyd-Fox et al., 2010), children (Skau et al., 2022) and adults (Quaresima & Ferrari, 2019). In terms of ASD research, there has been a rapid increase in the number of studies exploring the applicability of fNIRS in ASD, aiming to identify 'fNIRS signatures' as biomarkers that support early clinical diagnosis and treatment outcomes (Conti et al., 2022; Rahman et al., 2020; Zhang & Roeyers, 2019). Examination of task-related haemoglobin changes in EL infants and their association with ASD symptoms in early childhood also suggests that fNIRS has the potential to support early screening for ASD (Clairmont et al., 2022; Pecukonis et al., 2022). Resting-state functional connectivity (RSFC) measuring with fNIRS is a feasible approach for exploring functional integration in typical and atypical brain development (Duan et al., 2012; Zhang et al., 2013). The RSFC measurement is based on the hypothesis that even in the absence of a task, spontaneous low-frequency (e.g., ~0.1 Hz) fluctuations in the brain signal exhibit a high degree of temporal synchronization among functionally related brain areas (Fox & Raichle, 2007; Lee et al., 2013). Moreover, the application of the graph theory in neuroscience to examine the properties of complex brain networks has been extensively utilized for collecting key information of brain functional and structural organization (Farahani et al., 2019; Sporns, 2018). Small-worldness, which originated in social networks indicating the local clustering or cliquishness of connections between adjacent nodes, has been used to characterize many complex systems (Bassett & Bullmore, 2017; Humphries & Gurney, 2008). Modular organization and small-world properties have also been found in the human brain network from birth (Huang et al., 2015; Yap et al., 2011) to old (Cai et al., 2018) that support cognitive needs. However, it does not appear to be applicable to individuals with ASD (Hernandez et al., 2015; Rudie et al., 2013) and EL infants (Ciarrusta et al., 2020; Lewis et al., 2017) who exhibit brain network inefficiencies.

As studies investigating the early brain network development in relation to ASD are very scarce, the current study intends to fill this gap by examining the functional brain connection and integration in 5- and 10-month-old EL infants compared to age-matched TL infants. More specifically, the present study aims to (1) explore the functional brain networks in the first postnatal year at two age points, (2) examine the difference in brain functional segregation and integration by using graph theory approach, such as global and local efficiency, between EL and age-mated TL infants, and (3) investigate the relationship between brain network properties in EL infants and their behavioural assessment based on caregiver questionnaire.

Method

Participant characteristics

A total of sixty-five 5-month-old infants (EL_{5M} = 40; TL_{5M} = 25) and fifty-nine 10-month-old infants (EL_{10M} = 39; TL_{10M} = 20) were recruited for the current study. Among the 10-month-old infants, 33.9% (*EL* = 11; *TL* = 9) were enrolled at 5 months. Infants' communication skills were measured by the Caregiver Questionnaire of the Communication and Symbolic Behavior Scales – Developmental Profiles (CSBS-DP, Wetherby & Prizant, 2001), which provides assessments in three domains including social, speech and symbolic representation.

Following the studies from McDonald and Jeste (McDonald & Jeste, 2021) and Szatmari et al., (Szatmari et al., 2016), we included both siblings and premature infants in the EL group. Siblings were recruited if they had at least one older (half) sibling with a clinical diagnosis of ASD. To confirm the elevated likelihood status for ASD, the officially recognized community diagnostic reports of the older sibling(s) with ASD were collected and evaluated, which were based on DSM-IV-TR or DSM-5 criteria (American Psychiatric Association, 2000, 2013) and included comprehensive information such as screening methods, Autism Diagnostic Observation Schedule (ADOS) and/or a (semi-)structured diagnostic interview, developmental testing, as well as extensive behavioural observations in naturalistic settings. Preterm infants were recruited if they had a gestational age of less than 30 weeks. Characteristics of siblings and preterm infants within the EL group are shown in Supplementary Table S1. Children with known disorders that are related to ASD or that could affect brain development (e.g., epilepsy, Tuberous sclerosis, Fragile-X-syndrome) and children with non-corrected hearing or vision problems were excluded from the study. All EL infants in the current study participated in a longitudinal project on the early development of infants with EL for ASD. EL infants were mostly recruited trough centres for developmental disorders, rehabilitation centres, (non-)governmental ASD organizations, well-baby clinics and the website of the longitudinal study. For infants in the TL group, there was no reported family history (first-degree relative) of ASD or other developmental disorders. All TL infants were born after 36 weeks of gestation. TL infants were primarily recruited through day care canters or laboratory social media (e.g., Facebook). Written informed consent was provided by the parents prior to the experiment. The current research protocol was approved by the Ethics Committee of Psychology and Educational Sciences at Ghent University and by the Medical Ethical Committee of the Ghent University Hospital (reference number: 2017/1057).

fNIRS data acquisition

Hemodynamic response was measured using the NIRScout system (NIRx Medizintechnik GmbH, Germany) with two continuous wavelengths of 760 nm and 850 nm at a 3.29 Hz sampling rate. Nineteen source-detector pairs were employed in the fNIRS optode-cap configuration resulting in a total of 57 channels. It covers the prefrontal cortex, bilateral temporal regions, and parts of the parietal lobe, as these regions have been found to play an

important role in developing early cognitive functions (Dehaene-Lambertz & Spelke, 2015) but may develop atypically in EL infants (Ciarrusta et al., 2020). The positioning of the optodes was consistent with the international 10–10 coordinate system (see Figure 1). All infants underwent a 5.5-minute rest state, either sitting in a baby chair or being held by the accompanying parent in a dimly lit quiet room. Before taking NIRS measurements, the head circumference of each baby was measured to select a properly sized elastic cap. During the experiment, the parents were instructed not to engage in any interaction or conversation with their child unless their infant became irritable or started crying. A silent animation was presented on the screen to attract their attention and reduce head movement.

Data pre-processing

Both oxy-haemoglobin (HbO) and deoxy-haemoglobin (Hbb) concentrations were calculated and HbO was used as main dependent variables in the statistical analyses. Raw data quality control was done by visually inspecting the signal-to-noise ratio (SNR) across time for each participant and the frequency spectrograms for each channel by the FC-NIRS tool. The raw data were then converted into optical density (OD). Within each subject, channels with too weak or too strong optical intensity (mean (d) < 0.01 or > 3) as well as channels with a high standard deviation (i.e., the signal d of a given channel changes 15 times greater than the standard deviation over 2 seconds) were not used in the final analyses. A band-pass filtered with cut-off frequencies of 0.01–0.1 Hz was applied to remove slow drifts and high frequency noise as well as other physiological noise such as respiration and cardiac activity. Data samples with a moving SD (MSD) greater than 5 times within a 2-second sliding time window were regarded as artefacts, and were corrected by cubic spline interpolation to reduce motion noise. The linear trend was removed to reduce long-term systemic physiological shifts. The denoised OD signals were then converted into concentration changes using the modified Beer-Lambert law. The continuous 5-min data was extracted from each participant to perform the network analyses. Data processing was performed using the FC-NIRS (Xu et al., 2015) and GRETNA (Wang et al., 2015) based on MATLAB (Mathworks, MA USA).

Network construction and indicators

Functional Connectivity The functional connectivity was first calculated by computing Pearson correlation coefficients for the time series of haemoglobin concentration between each two channels, resulting in a 57×57 correlation matrix for each participant. These correlation coefficients were converted to Z-values via Fisher's transformation.

To better understand the efficiency of the brain network in EL and TL infants, the network global and local efficiency, as well as the nodal efficiency, were calculated separately for each of the constructed networks to characterize the information transformation within a network and the information exchange capacity among nodes of the network. Following previous studies (Bassett et al., 2008; Wang et al., 2017), the correlation matrix was thresholded over a range of

sparsity (1% < s < 50%, stepsize=1%) in order to track the relationship between network topological properties and the thresholding of the inter-region correlation matrix. Each channel was defined as a node and the over-threshold connection between each two nodes were quantified as the edges of a graph.

Global network metrics To explore the global topological organization, four global network properties were calculated (Cai et al., 2018; Latora & Marchiori, 2003; Wang et al., 2015) including the clustering coefficient (C_p), characteristic path length (L_p), global efficiency (E_{glob}), and local efficiency (E_{loc}) of a network. For a network graph G with N nodes (vertices) and K edges (links or connections), the clustering coefficient C_p, representing the degree to which nodes in a graph tend to cluster together, is calculated as shown in the formula below. Where, G_i is the subgraph of neighbours of vertex i, and k_i denotes the number of neighbours of node i,

$$C_p = \frac{1}{N}\sum_{i\in G}\frac{G_i}{k_i(k_i-1)/2}$$

The characteristic path length L_p reflects parallel information transfer and can distinguish an easily negotiable network from an inefficient one. It is defined as the average of the shortest path lengths between two generic vertices, where d_{ij} is the shortest path length between node i and node j.

$$L_p = \frac{1}{N(N-1)}\sum_{i\neq j\in G} d_{ij}$$

To evaluate the global and local level information transformation of the brain network, the global efficiency E_{glob} and local efficiency E_{loc} were calculated. The E_{glob} is the inverse of the average shortest path d_{ij}, while the local efficiency E_{loc} for a given node i is the subgraph efficiency of the nearest neighbours and G_i^{ideal} is the efficiency of the ideal case.

$$E_{glob} = \frac{1}{N(N-1)}\sum_{i\neq j\in G}(d_{ij})^{-1}$$

$$E_{loc} = \frac{1}{N}\sum_{i\in G}\frac{E(G_i)}{E\left(G_i^{ideal}\right)}$$

For more information on these global network properties and equations, see Latora and Marchiori (2003). In addition, we computed these global network properties under random networks. More specifically, the corresponding parameters were averaged from 1000 matched random networks with the same number of node and edge, and degree distribution as the real brain network. To examine the small-world properties, the normalized clustering coefficient $\gamma = \frac{C_p^{real}}{C_p^{rand}}$ and characteristic path length $\lambda = \frac{L_p^{real}}{L_p^{rand}}$ were estimated. A typically small world network should have high local clustering $\gamma > 1$ and short path length ($\lambda \approx 1$).

Regional nodal metrics Nodal degree (D_{node}) and efficiency (E_{node}) were evaluated to characterize regional topological of the brain network across groups. A functional hub, which represents the high functional integrity of the network, was estimated as a node with above-average node degree and efficiency (> 1 *SD*). The degree of a given node i can be calculated by the number of the edges linked to the node as stated below, where e_{ij} is the element that sits in the i^{th} row and the j^{th} column of the obtained matrix.

$$D_{node}(G,i) = \sum_{j \neq i \in G} e_{ij}$$

The node efficiency is defined as below, where $d(i,j)$ is the shortest path length between node i and adjacent node j. For more information on the local network properties and equations, see Achard and Bullmore (2007).

$$E_{node}(G,i) = \frac{1}{(N-1)} \sum_{j \neq i \in G} \frac{i}{d(i,j)}$$

Statistical analysis

To characterize the difference in global and nodal topological properties between EL and age-matched TL infants, two-sample t-tests were performed for each global metrics separately. The normalized values were used for further statistical comparisons. The differences in area under the curve (AUC) of all thresholds in each network global property were also calculated to provide a scalar that does not depend on a specific threshold selection. A bootstrap analysis of 95% confidence intervals was conducted. The false discovery rate (FDR) was utilized to correct for multiple comparisons.

To examine differences between groups, the medium gaussian support vector machines (SVM) model (Wang & Su, 2022; Yin et al., 2021) was employed to forecast the groups (EL vs TL) based on the global topological properties. In addition, to further validate whether the network properties we observed could be used to account for the behaviour in the EL infants, we performed partial correlations between each EL infants' network values (both global and nodal indexes) and the four CSBS scores (social, communication, speech and symbolic scores), regressing out age group (a binary variable: 1 for 5 months, 2 for 10 months). All CSBS scores were z-transformed to obtain normalized values with centre 0 and standard deviation of 1. Seven participants (two 5M-EL infants and five 10M-EL infants) were excluded from this analysis because of the missing values in the CSBS scores. Four participants were excluded from this analysis because they provided data for both the 5- and 10-month groups.

Results

Participant Flow

Of the infants enrolled in the study, twenty 5-month-old infants (EL = 14; TL = 6) and twenty-one 10-month-old infants (EL = 16; TL = 5) were excluded from the analyses due to their inability to complete the experiment or excessive movements. One participant in the 10-month EL group was removed from statistical analyses due to an average SNR below 5, while other data samples passed primary data quality control with an average SNR above 5 (ranging from 5 to 50). During data processing, an average of 1.92 channels (EL_{5M} = 0.5, TL_{5M} = 2.9, EL_{10M} = 2.3, TL_{5M} = 2) out of 57 channels were identified as noisy channels and rejected in the detected participants. There was no significant difference in the number of rejected channels among the four groups ($\chi 2$ = 6.94, p = .74).

The final dataset consisted of forty-five infants at 5 months and thirty-eight infants at 10 months (see Table 1 for participant information of the final data sample). Ten infants contributed to the final sample at both 5 and 10 months (EL = 4; TL = 6). There were no significant differences in age (t = -.47, p = .637), head size (t = -.83, p = .411) and gender distribution ($\chi 2$ = 3.00, p = .083) between the EL and TL groups at 5 months. At 10 months, there were no significant differences in head size (t = 1.13, p = .267) and gender distribution ($\chi 2$ = .11, p= .744) between the two groups. A significant difference in age was reported at 10-month groups (t = -2.12, p = .041), but this difference was not clinically relevant (18 days).

Table 1 Participants characteristics

	5 months		10 months	
	EL group	TL group	EL group	TL group
Final data sample (*n*)	26	19	23	15
Age (months)[1]	5.4±0.84	5.5±0.62	10.2±0.87	10.8±0.54
Gender (female: male)	15:11	06:13	15:08	09:06
Head Size (cm)	42.5±1.27	42.8	45.7±2.42	44.88
Sibling/Preterm	12:14		13:10	
CSBS social score[2]	35.2±5.57		44.9±7.19	
CSBS speech score[2]	10.0±2.60		15.6±3.55	
CSBS symbolic score[2]	11.5±2.79		17.8±3.77	
CSBS total score*[2]	56.7±8.4		78.3±12.87	

Note: [1] Corrected age was reported for children born preterm and chronological age was reported for the other children. [2] Raw scores on the Caregiver Questionnaire of the Communication and Symbolic Behavior Scales – Developmental Profiles.

Functional connectivity

The functional connectivity patterns of HbO of each group are shown in Figure 2. Both 5-month-old EL infants (EL_{5M} = .36 ± .16, t =25.09, p < .001) and 10-month-old EL infants (EL_{10M}

= .30 ± .19, t =6.52, p <.001) show greater grand-averaged functional connectivity in terms of HbO during resting-state than age-matched TL infants (TL_{5M} = .19 ± .21, TL_{10M} = .25 ± .21). Functional connectivity in terms of Hbb per group is shown in Supplementary Figure S1. We performed additional analyses to sibling and preterm EL subgroups and found that 5-month-old siblings exhibited lower functional connectivity ($EL\text{-}S_{5M}$ = .34 ± .17, t =9.76, p < .001) than 5-month-old preterm infants ($EL\text{-}P_{5M}$ =.39 ± .17) but with a similar pattern by visual inspection (see Supplementary Figure S2). No differences were found between the EL subgroups at 10 months. We did not further analyse network properties in these EL subgroups due to the small sample size.

Global network properties

Four global parameters (i.e., clustering coefficient, path length, global and local efficiency) for real brain networks and random networks with sparsity ranging from 10% and 50% are shown in the Figure 3. We found that the normalized clustering coefficient γ is greater than 1 and the normalized characteristic path length λ is close to 1 in all groups (see Figure 4 and Supplementary Figure S3). This is consistent with previous findings of early small-world organization in infant brain networks (Huang et al., 2015; Van Den Heuvel et al., 2015). We further examined differences of these properties between EL and TL infants. 5-month-old EL infants exhibited higher normalized C_p *and* E_{loc} values, but lower normalized L_p *and* E_{glob} values compared to 5-month-old TL infants (FDR-adjusted $p < .05$). At 5 months of age, the brain networks of EL infants exhibit greater AUC of clustering coefficient (C_p = .25 ± .004, t = 9.62, p < .001), global efficiency (E_{glob} = .23 ± .005, t = 12.28, p < .001), and local efficiency (E_{loc} = .30 ± .005, t = 11.48, p < .001) but a smaller path length (L_p = .76 ± .033, t = -7.76, p < .001) than those matched parameters in TL infants. These results suggest atypical hyper-efficient brain network organization in EL infants at 5 months of age. We did not observe any significant differences between 10-month-old EL and TL infants.

Regional nodal properties

Comparisons of nodal properties revealed that the brain networks of EL infants at 5 months have a higher nodal degree in bilateral temporal and frontal regions (left hemisphere: channels 10 12 18 19 20 21 23 25 29 30, right hemisphere: channels 35 38 39 40 42 48 53 56). The channel 4, predominantly located in the prefrontal region, showed a lower nodal degree in 5-month-old EL infants than TL infants (see Figure 5). We also observed increased nodal efficiency in a broad range of bilateral regions (p < .05, all corrected by FDR), except a part of prefrontal region (channel 4) and right posterior temporal region (channel 54). We did not find any significant differences in neither node degree or nodal efficiency between 10-month-old EL and TL infants.

Classification: EL vs TL

The medium gaussian SVM model for classifying EL versus TL infants achieved 77.6% accuracy. In terms of model sensitivity, the true positive rate (TPR) was 61.9% in the EL group and 97.1% in the TL group, while the false negative rate (FNR) was 32.7% in the EL group and 3.7% in the TL group. Figure 6 shows the prediction results of the SVM model. The receiver operating characteristic (ROC) curve serves as a visual representation of how well the classification model is working.

Correlation: behaviour and network properties

To estimate whether the association between behavioural assessment and brain network properties is statistically significant, partial correlations regressing out age group were performed. We found that the nodal efficiency of channel 49 showing positive correlation (r = .50, p = .033) with normalized social scores after FDR correction, see Figure 7. Additional analyses including participants who provided data at both age points are shown in the Supplementary Figure S4. We did not observe any significant relationship between other network indices and CSBS scores.

Discussion

This is the first study employing a fNIRS-based brain network approach to investigate the topological organization of functional connection in infants with and without EL for ASD at two age points during the first year of life (i.e., 5 and 10 months). There are several distinct discoveries. First, our study provides evidence that modular organization and small-world properties are present in the infant brain during the first year of life, regardless of whether the infant has EL for ASD. Second, we observed grand-averaged hyper-connectivity (i.e., overconnectivity) in the frontal and temporal regions in EL infants both at 5 and 10 months of age compared to age matched TL infants. Third, several network properties (e.g., local and nodal efficiency) measured based on graph theory were significantly greater in 5-month-old EL infants relative to 5-month-old TL infants, suggesting an overgrowth local network. We did not observe such differences in brain network between 10-month-old EL and TL infants. In addition, it is possible to classify EL versus TL infants using network global attributes.

Our results are consistent with previous research reporting that small-world modular organization exists in brain networks early in life (Huang et al., 2015; Van Den Heuvel et al., 2015) and matures over the course of brain development (Cai et al., 2018). The diffusion magnetic resonance image (dMRI) studies on the brain structural networks have revealed that small-worldness already present in the neonate (Huang et al., 2015; Yap et al., 2011). This small-world regime in terms of functional network organization, at both the global and local levels, has also been reported in previous fMRI studies with infants (Fransson et al., 2011; Mitra et al., 2017). Using a resting-state fNIRS approach, similar to the current study, Cai and colleagues (2018) examined the functional network across early childhood, adolescence and

adulthood, and found relatively steady economical small-world organization across development. Our study further validates that a small-world network organization, especially at the local level including short path lengths with highly local clustering, is presenting at 5- and 10-month-old infants. This means that the brain network is already functionally organized for efficient signal processing and information exchange in combination with a low cost of neuronal wiring in infancy.

There is an ongoing debate in the literature in terms of the alterations of functional connectivity in the brains of individuals with ASD, with findings of hyper- or hypo-connectivity or a combination of both (Hull et al., 2017). The present study reported extensive hyper-connectivity in EL infants at 5 and 10 months of age in comparison to age matched TL infants, indicating the presence of early atypical brain connections in EL infants. We further examine such atypical functional connectivity within the framework of complex networks based on graph theory. The brain networks in 5-month-old EL infants exhibited stronger spatially local connectivity (short-distance) and weaker long-range connection, represented by higher clustering and local efficiency but lower path length, in comparison to the neural network of TL infants. These results are in line with previous MRI studies of EL infants showing network inefficiencies (Ciarrusta et al., 2020; Lewis et al., 2017), although age points and direction of change varied by studies. In typically developing infants, functional integration and segregation of brain networks undergo maturation during the first year of life, generally manifested as increasing connectivity in functionally-relevant regions (Damaraju et al., 2014; Huang et al., 2015). Regional overgrowth connectivity accompanied by weaker remote connections in 5-month-old EL infants can be seen as a proxy for early developmental disconnection (Geschwind & Levitt, 2007). Such networks do not appear to accelerate communication between distant brain regions, nor do they fully conform to the small-world economic properties as shown in TL infants.

Interestingly, unlike 5-month-old EL infants, we did not observe a significant alteration in global or local efficiency of the brain network in 10-month-old EL infants in comparison to TL infants. To some extent, this is consistent with the study of Keehn et al., (2013) which reported increased overall functional connectivity in EL infants at 3 months but not at 6 and 9 months. Together with the finding of decreased connectivity at 12 months, they assumed that EL infants exhibit a decreasing developmental pattern of connectivity from 3 months to 12 months. Newborns with a family history of ASD have been found display higher local connectivity levels than control infants, but showing no differences in long-range function connectivity (Ciarrusta et al., 2020). By 6 months, reductions of global efficiency and nodal local efficiency were reported in the structural network over temporal, parietal and occipital lobes in EL infants who were later diagnosed with ASD, compared to TL infants and EL infants without ASD (Lewis et al., 2017). Despite inconsistent results in 6-month-old EL infants, it appears that EL infants may exhibit an initial local hyper-connectivity pattern after birth (newborns to 5 months), and such overgrowth connectivity decays in the second half of the first year as TL and EL

infants undergo distinct brain developmental pathways. These brain connectivity and network changes may be a consequence of brain development during infancy and the neuropsychological compensation across age (Livingston & Happé, 2017), as microstructural and macrostructural changes occur to reshape the brain's structural network and better accommodate sophisticated functional and cognitive demands. Extensive longitudinal data from young EL infants will help to more precisely determine whether alterations in network efficiency become minimal after 5 months of age and to clarify the underlying physiological mechanism.

The current study also showed that, using a medium gaussian SVM model, it is possible to classify infants with EL versus TL using obtained network global properties. In a resting-state fMRI study, using the SVM approach, brain network information was sufficient to characterize infants at 6 versus 12 months of age, but failed to accurately classify EL versus TL for ASD (Pruett et al., 2015). In our study, the four global network properties drove a relatively accurate SVM classification of infants with or without EL for ASD. This encourages our future work to differentiate infants who are later diagnosed with ASD from those who do not meet the diagnostic criteria, thereby supporting early detection of ASD. In addition, the regional network properties in EL infants were found correlated with their social behaviour. Strong regional connectivity in the temporal lobe appears to positively correlate with social competence in EL infants: the greater the efficiency of the right temporal region (channel 49), the fewer social-emotional skills (e.g., emotion and gaze). This is consistent with findings of diminished social neural processing in 5-month-old EL infants, where the right posterior temporal cortex did not show a significant response to social stimuli as TL infants (Braukmann et al., 2017). It is possible that a highly locally connected temporal lobe itself may hinder the transfer of information to other spatially remote regions, such as to the frontal lobe involved in higher-level functioning, and thus cannot support sophisticated social processing. Further measurements of a whole-brain design are needed to support this assumption.

In the present study, the sample sizes of the sibling and preterm subgroups of EL infants were relatively small, making it difficult to draw concrete statistical inferences for each subgroup. However, the observation of the present study regarding greater functional connectivity in 5-month-old infants with ASD siblings, than in preterm infants of the same age, is inspiring for our future work to expand the sample size of the subgroups and distinguish the brain network characteristics of infants exposed to different genetic or environmental vulnerabilities. Although all older siblings had an official community diagnosis of ASD, we did not confirm their diagnosis at the time of the study with a standardized instrument but based ourselves on well-documented diagnostic reports. This can be considered to be a limitation of the present study. Another limitation is the lack of measurements of behaviour in the TL group, making further comparisons on the behavioural level difficult.

Despite these limitations, the current study has implications for clinical practice as it suggests that: (1) brain network properties in 5-month-old EL infants may be important target

biomarkers for early detection, whereas searching for such features in 10-month-old EL infants can be difficult. (2) we may be able to benefit from machine learning approach like support vector machine for auxiliary diagnosis of ASD in the future. However, we also acknowledge that the clinical application of fNIRS and machine learning still faces some challenges such as the lack of 'ideal' biomarkers and standardized data-processing. The ongoing pursuit of reliability and reproducibility within the fNIRS community has in part enhanced the potential of fNIRS in clinical usage to support early detection and intervention in ASD and other neurodevelopmental disorders (Yücel et al., 2021). In addition, future work is needed to use brain network features observed in 5- and 10-month-old EL infants to predict behavioural performance (e.g., social and communication) at 14 and 24 months, and to further explore potential neural signals for early detection of ASD.

Overall, this study used resting-state fNIRS and graph theory to investigate brain network development in the first year of infants with and without EL for ASD. We found that both EL and TL infants exhibit small-world traits at 5 and 10 months of age, whereas 5-month-old EL infants exhibit marked overgrown spatial clustering, which may provide adequate processing regionally but is insufficient to support overall network information transfer. Our study demonstrates that EL infants undergo remarkable neural network alteration during the first year of infancy.

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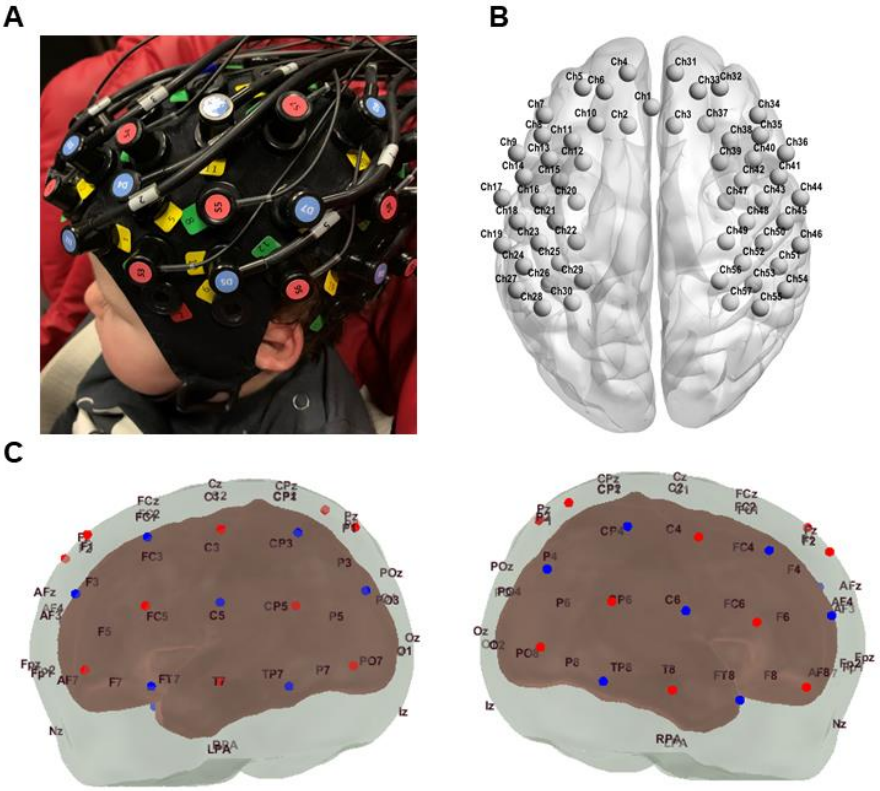

Figure 1 fNIRS optodes placement. (A) During the experiment, the fNIRS headband was placed on the infant's head while they sat in a baby chair. (B) Fifty-seven channel positions on a head template. (C) The underlying regions of the cerebral cortex according to the 10-10 system were labelled on a 5-month-old infant's head template. The fNIRS source is marked in red and the detector is marked in blue.

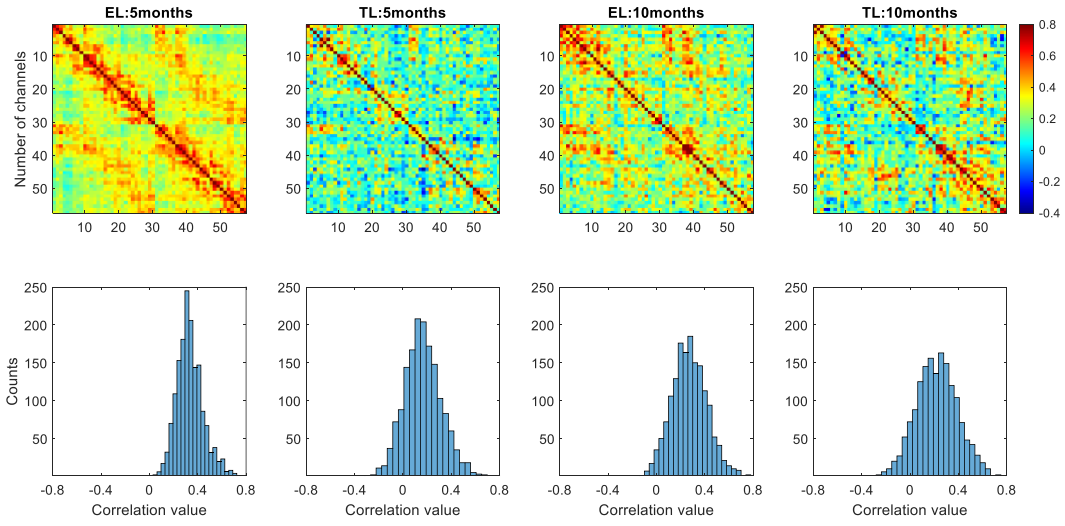

Figure 2. The functional connectivity of HbO in each group. The upper figures exhibit the averaged correlation matrices among all the channels in each group separately. The color scale represents *r*-values ranging from -.2 to .8 The lower figures show the corresponding distribution of the r-values.

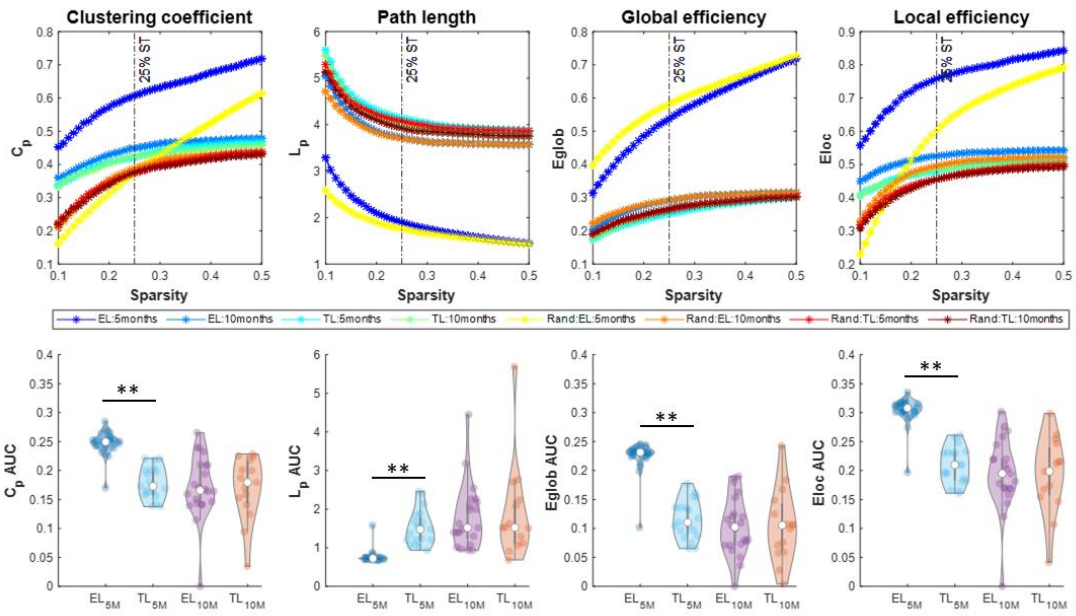

Figure 3. The global network metrics at 1%-50% sparsity thresholds. The upper panel shows the global prosperities of the network in each group at different sparsity thresholds compared to the matched random network, including clustering coefficient C_p, path length L_p, global efficiency E_{glob} *and* local efficiency E_{loc}.. The lower panel represent the violin distribution of the area under curve (AUC) of each network global parameter per group. ST: sparsity thresholds, $^{**}p < .01$.

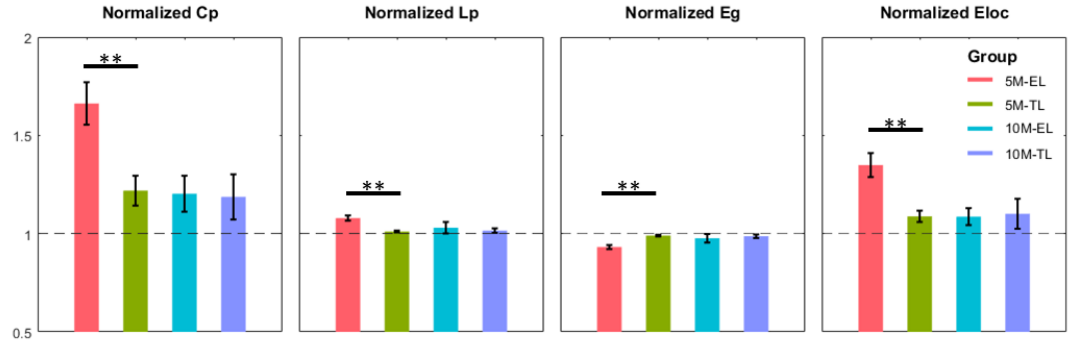

Figure 4. The normalized global network properties in each group. Bars represent the normalized values in four groups separately, and error bars represent standard errors across participants within each group.**p < 0.01.

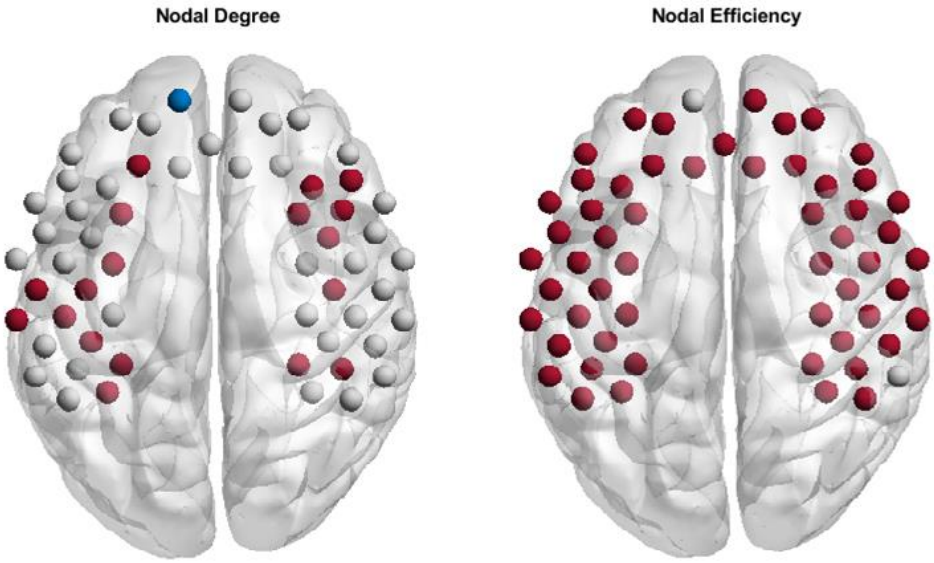

Figure 5. Differences of the network regional properties at 5 months of age. The differences of nodal degree and efficiency were found between the 5-month-old EL infants and the age-matched TL infants. Red circles represent channels with greater nodal degree or efficiency in the 5-month-old EL group compared to TL infants, while the blue circle indicates the channel with lower nodal degree ($p < .05$, corrected by FDR).

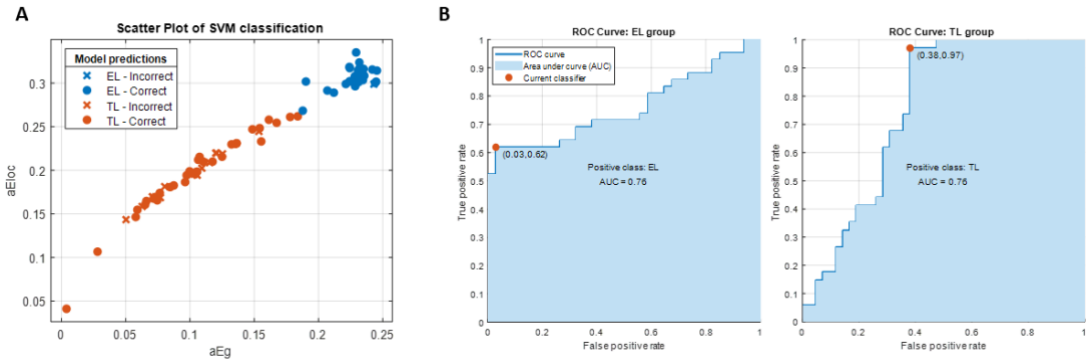

Figure 6. The performance of the medium gaussian SVM model to predict EL versus TL infants by global network properties. (A) The graph on the left shows the correctness of the prediction. (B)The graph on the right shows the receiver operating characteristic (ROC) curve for the SVM classifier in EL and TL group separately.

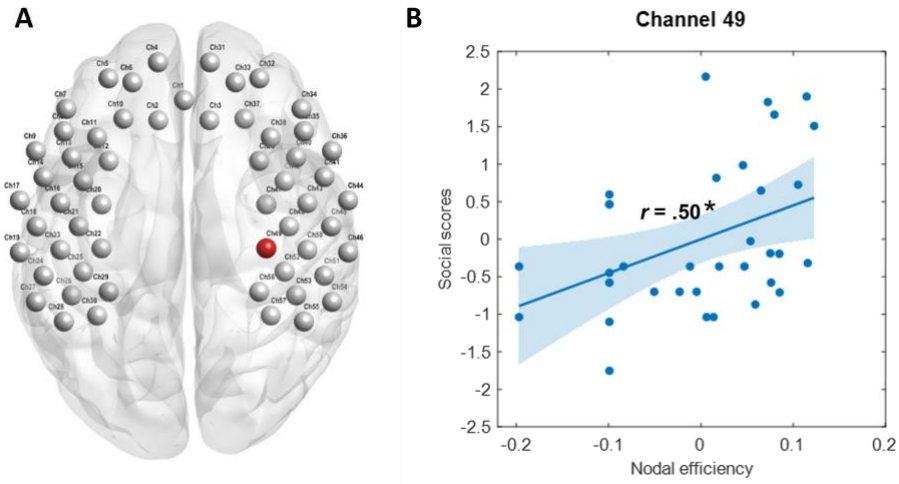

Figure 7. The behaviour-brain relation in 5- and 10-month-old infants with EL for ASD. **(**A) The topographic map and channel layout. The red circle indicates that nodal efficiency of channel 49 positively correlated with social scores. (B) Scatter plot of the correlation between node properties and CSBS scores. * $p < .05$ corrected by FDR.