



EEG alpha band functional brain network correlates of cognitive performance in children after perinatal stroke

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ABSTRACT

Mechanisms underlying cognitive impairment after perinatal stroke could be explained through brain network alterations. With aim to explore this connection, we conducted a matched test-control study to find a correlation between functional brain network properties and cognitive functions in children after perinatal stroke. First, we analyzed resting-state functional connectomes in the alpha frequency band from a 64-channel resting state EEG in 24 children with a history of perinatal stroke (12 with neonatal arterial ischemic stroke and 12 with neonatal hemorrhagic stroke) and compared them to the functional connectomes of 24 healthy controls. Next, all participants underwent cognitive evaluation. We analyzed the differences in functional brain network properties and cognitive abilities between groups and studied the correlation between network characteristics and specific cognitive functions. Functional brain networks after perinatal stroke had lower modularity, higher clustering coefficient, higher interhemispheric strength, higher characteristic path length and higher small world index. Modularity correlated positively with the IQ and processing speed, while clustering coefficient correlated negatively with IQ. Graph metrics, reflecting network segregation (clustering coefficient and small world index) correlated positively with a tendency to impulsive decision making, which also correlated positively with graph metrics, reflecting stronger functional connectivity (characteristic path length and interhemispheric strength). Our study suggests that specific cognitive functions correlate with different brain network properties and that functional network characteristics after perinatal stroke reflect poorer cognitive functioning.

Abbreviations

EEG electroencephalography
rs-EEG resting state electroencephalography
ICD international classification of diseases
HIE hypoxic ischemic encephalopathy
SDH subdural hemorrhage
SAH subarachnoid hemorrhage
IVH intraventricular hemorrhage
NAIS neonatal arterial ischemic stroke
NHS neonatal hemorrhagic stroke

db-WPLI debiased weighted phase lag index
IQ intelligence quotient
fMRI functional magnetic resonance imaging
rs-fMRI resting state functional magnetic resonance imaging
ADHD attention deficit hyperactivity disorder
PET positron emission tomography
CPT continuous performance test

1. Introduction

Perinatal stroke has a high morbidity due to permanent motor and

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cognitive disabilities of affected individuals. The term perinatal stroke covers different entities of focal cerebral vascular diseases, occurring from 20 weeks of gestation to 28 days of postnatal age. Subgroups differ by etiology and timing of vascular injury and the classification into 6 subgroups is based on clinical and radiographic features. Individuals with acute symptomatic perinatal stroke (neonatal arterial ischemic stroke, neonatal hemorrhagic stroke and cerebral sinovenous thrombosis) clinically present in the neonatal period, while in presumed perinatal stroke children develop deficits after the neonatal period. Presumed perinatal stroke includes arterial presumed perinatal ischemic stroke, presumed perinatal hemorrhagic stroke and periventricular venous infarction (Dunbar and Kirton, 2018; Kirton et al., 2021; Srivastava and Kirton, 2020). Cognitive outcomes after perinatal stroke are increasingly investigated and addressed but poorly predictable at the time of the diagnosis and professional help is usually given when deficits have already emerged (Dunbar and Kirton, 2018; Lehman and Rivkin, 2014; Wagenaar et al., 2018).

Brain network science or connectomics is a study of brain networks through principles of mathematical graph theory. Functional brain networks or functional connectomes represent connections between synchronously active brain regions. Functional connectivity between brain regions is measured with different neuroimaging or neurophysiologic tools (Park and Friston, 2013). Studies of healthy brain networks showed that human brains are hierarchically organized, arranged in modules and have a small world topology with an optimal balance between segregation and integration, which makes the network as efficient as possible at a still acceptable cost (Sporns, 2013). Studies have shown that functional network organization is related to cognitive performance, especially intelligence (Van Den Heuvel et al., 2009; Stam, 2014; Wu et al., 2013). After establishing the normal brain network properties, focus shifted towards several brain diseases and their influence on network characteristics.

Graph theory and connectomics are scarcely applied in perinatal stroke research. Craig et al. (2022) published a research of structural network changes after perinatal stroke, where non-lesioned primary motor, somatosensory and supplementary motor areas demonstrated lower betweenness centrality and higher clustering coefficient in stroke groups and clustering coefficient in these areas was inversely associated with motor function. Functional connectivity after perinatal stroke has been studied using only fMRI and the connectivity was not yet used for functional connectome analysis, but rather for exploration of connectivity patterns and strength analysis. Saunders et al. (2019) reported changes in strength and laterality of functional motor network connections after neonatal arterial ischemic stroke. Carlson et al. (2019) showed that inter- and intra-hemispheric connectivity strengths were lower after neonatal arterial ischemic stroke and that this was related to poorer language comprehension. Ilves et al. (2016) found that an increase in default mode network connectivity after perinatal stroke was associated with lower cognitive functions.

Since fMRI has multiple limitations when it comes to applicability in childhood (mainly due to poor compliance), we conducted a study using high-density resting-state EEG. EEG is a highly available diagnostic tool, which can be used repeatedly to follow the trajectory of connectivity changes after a brain injury. EEG analysis in correlation to cognitive functions after adult stroke showed that some parameters, such as relative theta frequency (Schleiger et al., 2017), frontal lobes spectral power irregularities (Hadiyoso et al., 2022) and network properties in the theta band (Lee et al., 2023) predicted post-stroke cognitive impairment.

Since EEG estimated functional brain networks are poorly researched after brain injury in the neonatal period, we conducted a study with aim to find correlates between EEG derived functional network properties and cognitive functions after perinatal stroke.

2. Methods

We designed a matched test-control study to explore functional brain networks and cognitive deficits after perinatal stroke. The study was carried out at the Children's Hospital of University Medical Center Ljubljana, which is the largest national tertiary hospital center in Slovenia. Resting-state functional connectomes from a 64-channel EEG in 24 children with a history of neonatal stroke were analyzed and compared to the functional connectomes of 24 healthy controls. Perinatal stroke group included 12 patients with neonatal arterial ischemic stroke and 12 with neonatal hemorrhagic stroke, 13 were females and 11 were males. 10 patients were affected in the right and 13 in the left hemisphere, one had lesions in both hemispheres. The inclusion criteria for the stroke group were: 1) a history of neonatal stroke—either arterial ischemic stroke or hemorrhagic stroke, 2) birth at term, 3) age 5–18 years, 4) no other co-factors for neurological disfunction. Patients' demographic and clinical characteristics, neuroimaging findings from the neonatal period, and motor outcome can be found in Table S1. The perinatal stroke group selection process is depicted in Fig. 1. The inclusion criteria for the control group were: 1) typically developing children and adolescents, with no history of brain injury or known neurologic or genetic conditions, 2) birth at term, 3) age 5–18 years. We included 15 females and 9 males in the control group. The participants had different social backgrounds, the demographic features of both groups and distribution of features (sex, age and maternal education) are visualized in Fig. 2. Each participant from the perinatal stroke group was matched with multiple controls so they matched in sex and had at most 1 year of difference in their age. Because of this, the distribution of sexes was exactly the same in both groups. There could be slight differences in age between the groups as we did not match these perfectly (we allowed a \pm difference of 1 year in order for us to ease the process of searching for control participants and to be also able to match each stroke participant with several matches from the control group). To investigate possible differences in age between the two groups, we performed an additional Bayesian analysis. Since age is a positive integer in our case, we used a simple Bayesian Poisson model. Our analysis suggests that the probability that the age of the control group is higher than the age of the test group is 49.9 %, meaning that the age distribution between the groups is almost perfectly balanced. There were also differences between the two groups when it comes to the maternal education of participants. The maternal education in the control group seems to be higher than in the perinatal stroke group ($P = 94$ %). However, our regression analysis where age and parent education difference were used as confounding factors showed that this had no impact on our results (see the Statistical analysis section for additional details regarding these analyses).

All participants underwent psychological evaluation to estimate their cognitive functioning and possible deficits. After the data from EEG recordings and psychometric tests were gathered, we first analyzed the correlation between network characteristics and cognitive functions and then compared cognitive test results and network metrics between the two groups to confirm the differences. Our methodology process is visualized in Fig. 3.

2.1. EEG recording

We recorded a resting state 64-channel EEG (BrainAmp DC, Brain Products GmbH) in all participants from the perinatal stroke and the control group. The participants' head circumference was measured for the selection of the appropriate EEG cap (EASYCAP, Standard 64Ch actiCAP Electrode Cap). The 64-channel EEG was recorded in a resting state with a sampling rate of 1000 Hz. The recording reference was positioned at the vertex (Cz). The recordings were saved using the BrainVision Recorder program. Participants were seated in a dark experimental room 130 cm away from a 24-inch monitor (53.1 \times 29.9 cm). They were instructed to remain as still and as quiet as possible and

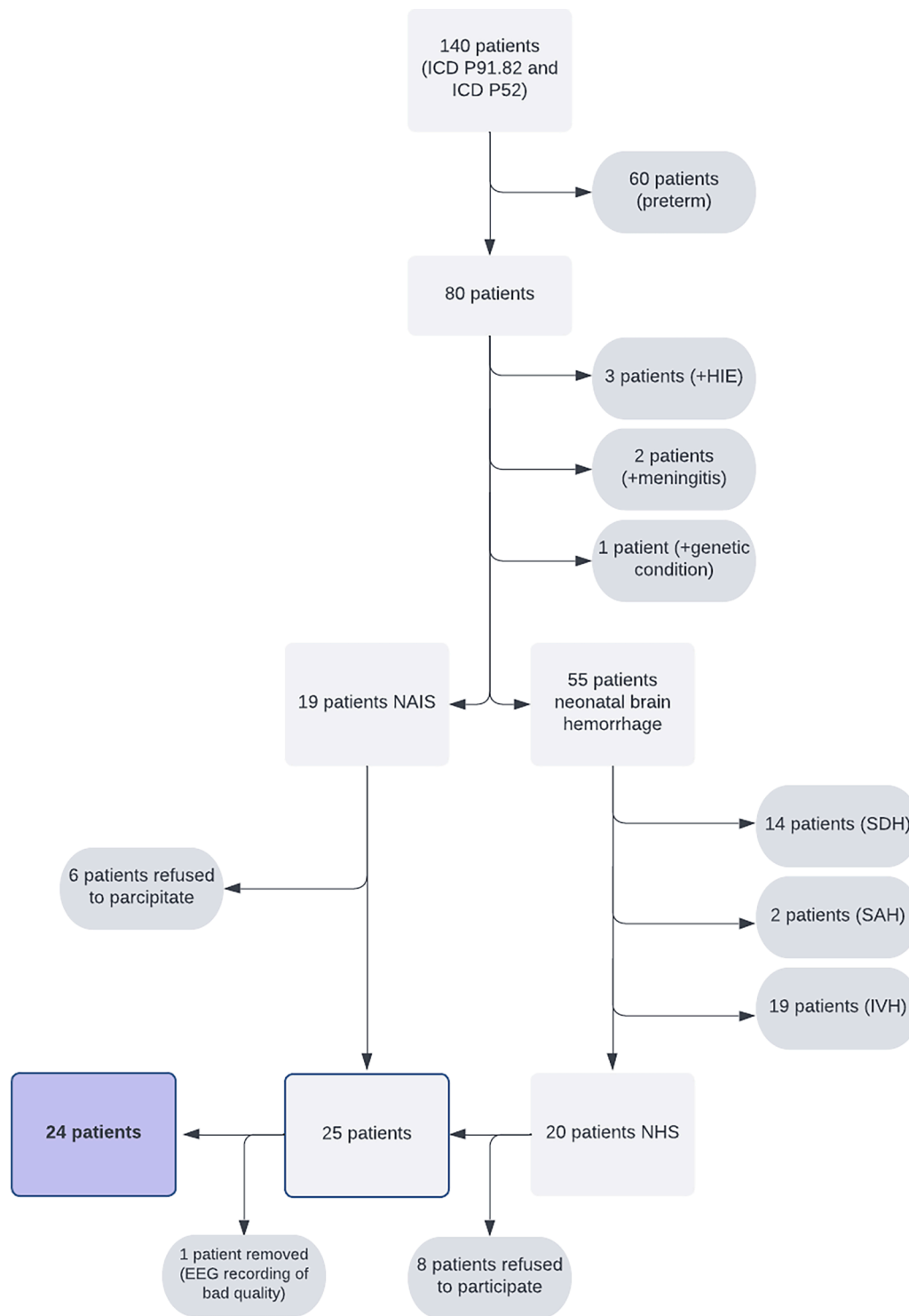


Fig. 1. The perinatal stroke group participant selection process. A total of 140 patients with ICD P91.82 (neonatal cerebral infarction) or ICD P52 (intracranial nontraumatic hemorrhage of newborn) were detected in our patient database from 2003 to 2017. 60 patients were excluded due to additional prematurity, 3 due to additional HIE, 2 due to additional meningitis, 1 due to a confirmed co-existing genetic syndrome, causing developmental delay. In patients with brain hemorrhage, 14 had SDH, 2 had SAH and 19 had IVH. Finally, there were 19 patients left with isolated NAIS and 20 patients with NHS. In both groups a total of 14 patients refused to participate and one patient was removed due to poor EEG recording quality, which resulted in a final number of 24 participants.

to follow the instructions on the screen. The stimuli were presented via the PsychoPy2 program (Peirce, 2007). The participants were instructed to close their eyes for 5 min. Participants older than 10 years performed recordings sitting alone in the room, while younger participants were accompanied by their parents or a research assistant.

2.2. EEG data analysis

First, we preprocessed the raw EEG recordings, and then computed functional connectomes for each participant. Programs MATLAB (Mathworks, 2021) and EEGLAB (Delorme and Makeig, 2004) were used to preprocess EEG recordings. Preprocessing was executed in

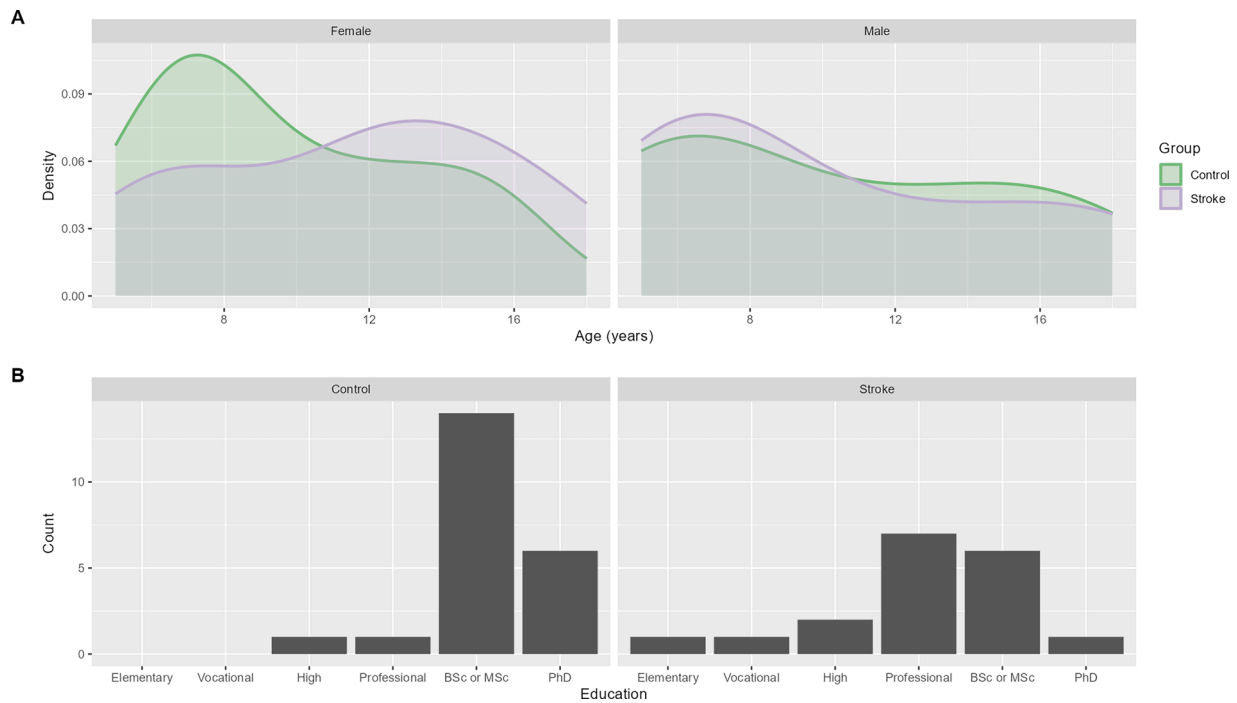


Fig. 2. Comparison of demographics between the control and the stroke group. Panel A compares the female and male age distribution in both groups. Panel B visualizes the maternal education in perinatal stroke and control groups. Data regarding maternal education were not available in two control group participants and in 5 perinatal stroke group participants.

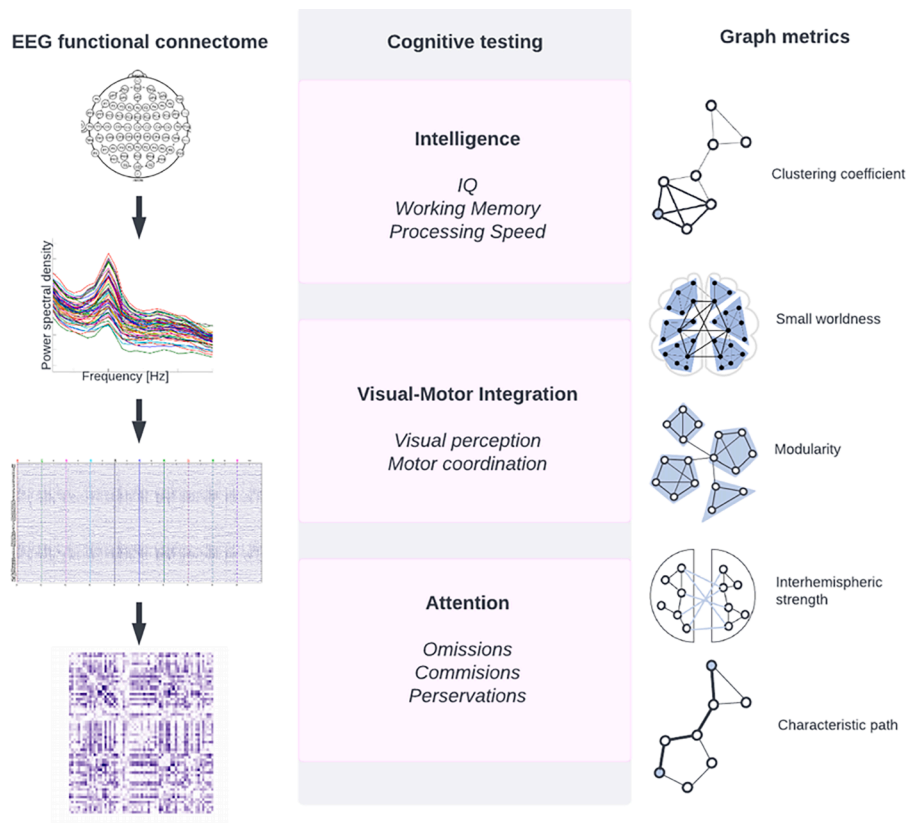


Fig. 3. Methodology protocol. The first column shows the EEG functional connectome calculation. The second column contains cognitive parameters, evaluated in this study and the third column enlists the analyzed graph metrics.

accordance with recent literature and standards (van Diessen et al., 2015; Haartsen et al., 2020). First, the data were down-sampled to 250 Hz. Then, a band-pass filter 0.5 Hz to 40 Hz was applied to reduce the influence of high frequency noise and slow wave drifts. Next, we manually inspected the data and power spectra to find and remove bad channels (channels with flat lines, signal jumps, muscle artefacts, etc.). The removed channels were replaced by performing a spherical interpolation of nearby channels. The channels in the outermost circumferences (FT9, FT10, TP9, TP10, Fp1, Fp2) were removed and not replaced by interpolation. We used the surface Laplacian reference-free transformation used to improve spatial filtering and reduce volume conduction (Carvalhoes and De Barros, 2015; van Diessen et al., 2015). After segmenting the data into 1-second epochs, we manually selected 120 epochs with the best quality. These epochs were then used as the basis for constructing the functional connectomes. Our final connectome consisted of 58 nodes. To calculate the functional connectome from both datasets, we used the FieldTrip software (Oostenveld et al., 2011). Vinck's dbWPLI (Vinck et al., 2011) was chosen for the connectivity measure, as it is expected to have the highest stability and test-retest reliability for many graph metrics (whole brain connectivity, normalized weighted clustering coefficient, normalized weighted path length, small world index), when the data are segmented into 120 1-second epochs (Haartsen et al., 2020). The Miljevic et al.'s checklist for optimal EEG connectivity study design was retrospectively reviewed and the present study achieved a total score of 5, which qualifies as a high-quality study (Miljevic et al., 2022). We studied the connectomes in the alpha-frequency band (8–13 Hz) since alpha-band is most commonly used in other developmental studies and it is less affected by muscle artefacts than other frequency bands (Haartsen et al., 2020). Also, our previous research showed that alpha frequency band is the most robust to study developmental changes in network metrics (Kavčić et al., 2023).

The code for data preprocessing and connectome computation is available at <https://github.com/demsarjure/PedEEG>.

2.3. Graph metrics

We analyzed various graph metrics that were found to be correlated to cognitive functioning in the literature. We chose metrics reflecting network segregation, integration, and organization/topology. A detailed graph metrics description and formulas for their calculation can be found in the *Supplementary Material*.

Modularity is a characteristic of complex networks, reflecting sub-specialization of the network into smaller modules. Each module contains several densely interconnected nodes, while the connections between nodes in different modules are relatively scarce (Bullmore and Sporns, 2009).

Characteristic path length is traditionally defined as the minimum number of edges that must be transversed from one node to another (Bullmore and Sporns, 2009). However, this definition better applies to unweighted networks/graphs, while in weighted functional networks characteristic path length is merely a reflection of signal synchronization between nodes (in our case EEG channels) and higher characteristic path therefore indicates stronger functional connectivity between brain regions.

Total interhemispheric strength reflects the signal correlation between the two hemispheres and can be used as an index of interhemispheric functional connectivity (Yao et al., 2021).

Clustering coefficient quantifies the number of connections between node's nearest neighbors as the proportion of the maximum number of all node's connections in a graph. It is the most important metric of network segregation (Bullmore and Sporns, 2009).

Small world index is a metric of network topology. Small world topology places the network between random and regular organization, with higher clustering coefficient and lower characteristic path length compared to random networks (Bullmore and Sporns, 2009), therefore a small world network has an optimal balance between integration and

segregation (Farahani et al., 2019).

2.4. Cognitive assessment

To evaluate cognitive functioning of children included in our study, we applied a series of standardized cognitive tests that measure children's general intellectual abilities, attention, and visual-motor integration abilities. Every child from each group was invited to a single psychological assessment which took place at the Children's Hospital of University Medical Center Ljubljana and lasted approximately two hours, with breaks in-between tests. Tests were performed by a clinical psychologist, employed at the hospital. Reported results of cognitive tests are standardized across age groups. A table with results for every cognitive test for all participants can be found in the *Supplementary Material*.

2.4.1. General intellectual ability

Full Scale IQ was used to measure the general intellectual ability. Wechsler preschool and primary scale of intelligence—WPPSI-III (Wechsler, 2003) is a developmental intellectual test, which is carried out individually, and is used to assess general intellectual ability of children aged 2.6 to 7.3 years. It measures Full Scale IQ, Verbal and Nonverbal Intellectual Ability Index, Processing Speed Index, and General Language Composite. Wechsler Intelligence Scale for Children—WISC-V (Wechsler, 1991) is intended for individual assessment of a child's intelligence based on four factor-based indexes. It measures a child's general intellectual ability (Full Scale IQ) and 5 cognitive index scores: Verbal Comprehension Index, Visual Spatial Index, Working Memory Index, Fluid Reasoning Index, and Processing Speed Index. It is suitable for assessing children aged 6.6 to 16.6 years. Wechsler Adult Intelligence Scale—WAIS-IV (Wechsler, 2014) is an adult measure of cognitive ability. The test is carried out individually. It measures four index scores: Verbal Comprehension, Perceptual Organization, Working Memory, Processing Speed, and Full-Scale IQ. It is used for assessing adolescents from the age of 16 and adults up to the age of 85.

2.4.2. Processing speed and working memory index

For measuring Processing Speed Index and Working Memory we used Processing Speed Index and Working Memory Index of WISC-V (Wechsler, 1991) and WAIS-IV (Wechsler, 2014).

2.4.3. Attention and impulsive behavior

For measuring attention, we used Conners' Continuous Performance Test 3rd Edition—CPT-3 (Conners, 2014). CPT-3 is a task-oriented computerized assessment of attention-related problems in individuals aged 8 years and older. It measures inattentiveness, impulsivity, sustained attention, and vigilance. In our study, we focused on three types of errors made during the task:

- Omissions: missed targets and are generally an indicator of inattentiveness.
- Commissions: incorrect responses to non-targets. High commission error rates may indicate either inattentiveness or impulsivity.
- Perseverations: random, repetitive, or anticipatory responses made in less than 100 ms following the presentation of a stimulus, which indicates impulsivity.

2.4.4. Visual-motor integration

Visual-motor integration abilities were measured with the Beery-Buktenica developmental test of visual-motor integration—BEERY VMI, sixth edition (Beery and Buktenica, 2010). It measures the degree to which an individual can integrate visual and motor stimuli. It is used to identify individuals who have problems in the field of visual motor coordination and helps in determining the most appropriate assistance procedures. It consists of three scales: Visual-Motor Integration Scale, Visual Perception Scale, and Motor Coordination Scale. It is suitable for

assessing individuals aged 2.0 to 99.11.

2.5. Statistical analysis

We used Bayesian statistics to analyze the results. All analyses were conducted using Stan—a state-of-the-art platform for executing modern Bayesian statistical analyses (Stan Development Team, n.d.). Since observed metrics are known to change with age (Boersma et al., 2011; Kavčič et al., 2023; Miskovic et al., 2015), we used pair-wise statistical tests, in which we first calculated the difference in a given metric between a test participants and their matched control participants and then tested whether these differences differ from the value 0 or if there is a correlation between the differences of two metrics. We matched each test participant with control participants that were at most 1 year older or younger, we based this on our previous work which showed that connectome metrics in children change with age (Kavčič et al., 2023). Besides pairing comparable participants, this procedure also increased our sample size and statistical power and allowed the work to be reliably replicated in the future. A table that lists all matched test-control pairs can be found in the *Supplementary Material* for this manuscript.

Since our pairing approach might introduce bias and since some participants from the perinatal stroke group were matched with more control participants than others, we had verified that this approach does not introduce any biases and does not skew our results one way or the other. To do this, we used bootstrapping, where we created a replicate dataset by drawing samples with replacement from our original data set until we had a new data set of the same size as the original one. Next, we executed statistical analyses on these replicate data sets. We repeated this many times and found out that our results are extremely robust, and the same conclusions as presented in this manuscript and reached on the original data sets can be reached on replicate data sets as well.

To analyze how metrics differ between the perinatal stroke and the control group, we used the pair-wise Bayesian robust t -test:

$$y | \mu, \sigma \sim \text{Cauchy}(\mu, \sigma).$$

Here, Stan's default non-informative priors were used for all parameters. In all cases, the value of the metric of the test subject was subtracted from its control counterpart. This means that negative values of the difference indicate that the metric was higher in the perinatal stroke group.

To analyze the correlation between graph metrics and cognitive function we used the Bayesian robust regression:

$$y | \alpha, \beta, \sigma \sim \text{Cauchy}(\alpha + x\beta, \sigma),$$

$$\beta \sim \text{Cauchy}(0, 2.5).$$

We set the standard weakly informative prior on the beta coefficient of the regression (β) [Gelman2008] and set no prior on the intercept (α), which means that the default, non-informative (uniform) prior was used in this case.

The Cauchy distribution was used in both cases since our data had some outliers and the Cauchy model is more robust to them than the traditional Normal model. We believe that without a strong reason, one should not remove outliers as they carry information as well. Furthermore, outlier removal techniques have their own problems, such as setting arbitrary thresholds that separate outliers from non-outliers. Which is why we opted to alleviate the issues caused by outliers by using robust versions of statistical models.

To analyze if there are differences in the age or in parents' education between the stroke and the control group, we used a Bayesian Poisson model:

$$y | \lambda \sim \text{Poisson}(\lambda).$$

Poisson model is suitable when the data we are analyzing comes in the form of positive integers, in our case these are the age difference and the education levels. We used a commonly used scale in Slovenia to

assign numerical values to education levels: elementary, vocational, high, professional, BSc or MSc, PhD.

To assure that possible demographic differences between the stroke and the control group do not influence analyses that compare the two groups, we also executed an analysis with a more complex model. We used a Bayesian regression model where participant's age and parent education were used as confounding factors:

$$y | \alpha, \beta_{age}, \beta_{education}, \sigma \sim \text{Cauchy}(\alpha + x_{age} \beta_{age} + x_{education} \beta_{education}, \sigma).$$

Since y , x_{age} and $x_{education}$ denote the difference in the metric of interest, age or education between matched participants, we can use α to compare the two groups and remove any confounding effects of differences in age and education. Since the results of this analysis were practically the same (probabilities calculated with this analysis were at most 2 % different than those acquired with the simpler analysis), we decided to report only results obtained by the simpler analysis as.

To distinguish reported Bayesian probabilities from frequentist p -values we denote them with a capital P. Unlike p -values, the reported probabilities directly describe the percentage by which we can claim that our hypotheses are true or not. Since we report probabilities as percentages, the probability that the opposite of our claim is true can be calculated as 100 % - P.

We used the Monte Carlo standard error (MCSE) measure to quantify uncertainty in all our analyses. However, since the uncertainty measure was always smaller than 1 %, we decided to omit it from the results section for the sake of brevity.

All data, along with the source code for data preprocessing, connectome computation and statistical methods are available in a public online repository: <https://github.com/demsarjure/PedEEG>.

3. Results

First, we analyzed the differences in cognitive test scores (IQ, Working Memory, Processing Speed, Visual-Motor Integration, Omissions, Commissions, and Perservations Rate) between the perinatal stroke and the control group. Next, we analyzed the differences in graph metrics (characteristic path length, interhemispheric strength, modularity, clustering coefficient and small world index) between the two groups. Finally, we visualized the correlations between all the chosen graph metrics and different cognitive measures on the whole study sample.

Detailed results of individual's cognitive performance, group differences in graph metric and cognitive tests results, correlation probabilities between graph metrics and cognitive functions are reported in the *Supplementary Material*. Below, we focus only on the core results that are supported with high probabilities.

3.1. Cognitive performance differences between the two groups

The control group of typically developing individuals had higher IQ, higher Processing Speed and better Working Memory ($P \approx 100$ % in all three domains) compared to individuals after perinatal stroke. Typically developing children had higher scores on measures of visual motor integration, visual perception, and motor coordination than the individuals with perinatal stroke ($P \approx 100$ % for all three domains). Children with perinatal stroke reached higher number Omissions, Commissions and Perservations on CPT compared to the control group ($P = 99.98$ %, $P \approx 100$ % and $P = 99.05$ %, respectively). The results are visualized in Fig. 4.

3.2. rs-EEG functional network differences between the two groups

The connectomes of the control group had higher modularity than the connectomes of the perinatal stroke group ($P = 100$ %). All the other graph metrics were higher in the connectomes of the perinatal stroke

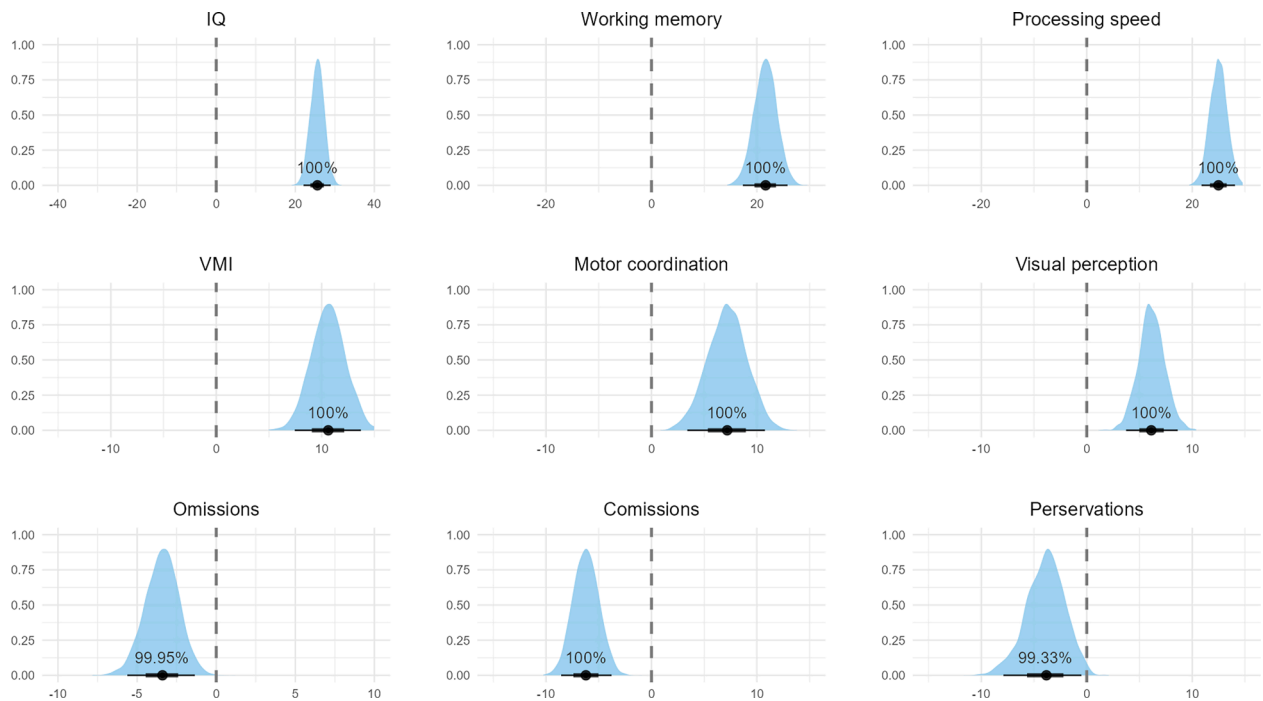


Fig. 4. Comparison of cognition parameters between the perinatal stroke group and the control group. Shaded area visualizes the distribution of differences between the perinatal stroke group and the control group when comparing scores achieved on cognitive tests. If the difference is higher than 0, the parameter was higher in the control group and vice versa. Percentages represent the probabilities that difference between groups exists. The black dot represents the mean, the thick black horizontal line the 66 % confidence interval and the thin black horizontal line the 95 % confidence interval.

group ($P = 98.45\%$ for characteristic path length, $P = 95.67\%$ for interhemispheric strength, $P = 99.22\%$ for clustering coefficient and $P = 98.70\%$ for small world index), meaning the connectomes after perinatal stroke were more segregated, but demonstrated stronger whole-brain and interhemispheric connectivity. The results are visualized in Fig. 5.

3.3. Correlation between cognitive functions and functional network properties

We found that IQ and Processing Speed positively correlated with modularity ($P = 95.23\%$ and $P = 99.68\%$, respectively), meaning that children with more modular organization of functional brain networks had higher IQ score and higher processing speed. Clustering coefficient correlated negatively with IQ ($P = 91.95\%$), meaning that children with more segregated functional brain networks had lower intelligence. Impulsivity measure (Perservations Rate) correlated positively with measures of functional connectivity strength—characteristic path length ($P = 94.32\%$) and interhemispheric strength ($P = 97.03\%$) and with measures of network segregation—clustering coefficient ($P = 93.35\%$) and small world index ($P = 94.55\%$). These results show that children with segregated functional brain networks and stronger whole-brain and interhemispheric connectivity demonstrated a tendency to impulsive

decision making. None of the graph metrics correlated with Visual-Motor Integration abilities. The results are visualized in Fig. 6.

4. Discussion

To the best of our knowledge, this was the first study of functional brain network analysis based on EEG connectivity. Our research showed that functional networks in children and adolescents after perinatal stroke differ from typically developing individuals and that some brain network characteristics correlate with specific cognitive functions. Below we further discuss our findings.

4.1. Cognitive performance differences between the two groups

Children after perinatal stroke reached lower scores on measures of IQ, Processing Speed, Working Memory, Visual Perception, Motor Coordination and Visual-Motor Integration. They also reached higher rates of Omission, Commission, and Perservation errors on CPT, indicating inattentiveness and impulsive decision making. Other studies showed that children after perinatal stroke have lower intelligence, poorer inhibitory control and slower processing speed, problems with flexibility and planning when compared to their typically developing peers (Bosenbark et al., 2017; Fuentes et al., 2016; Kolk et al., 2011;

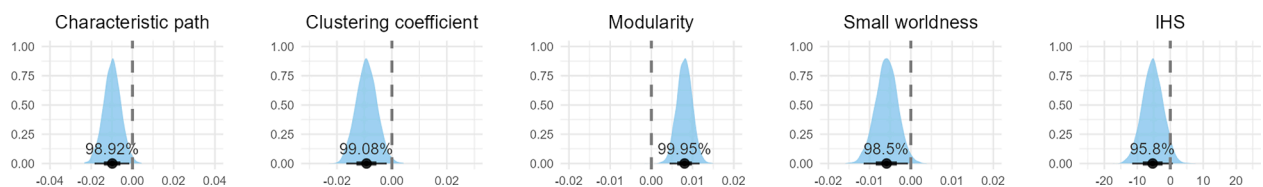


Fig. 5. Comparison of graph metrics between the perinatal stroke group and the control group. Shaded area visualizes the distribution of differences between the perinatal stroke and control group, when comparing graph metric values. If the difference is higher than 0, the measure was higher in the control group and vice versa. Percentages represent the probabilities that difference between groups exists. The black dot represents the mean, the thick black horizontal line the 66 % confidence interval and the thin black horizontal line the 95 % confidence interval.

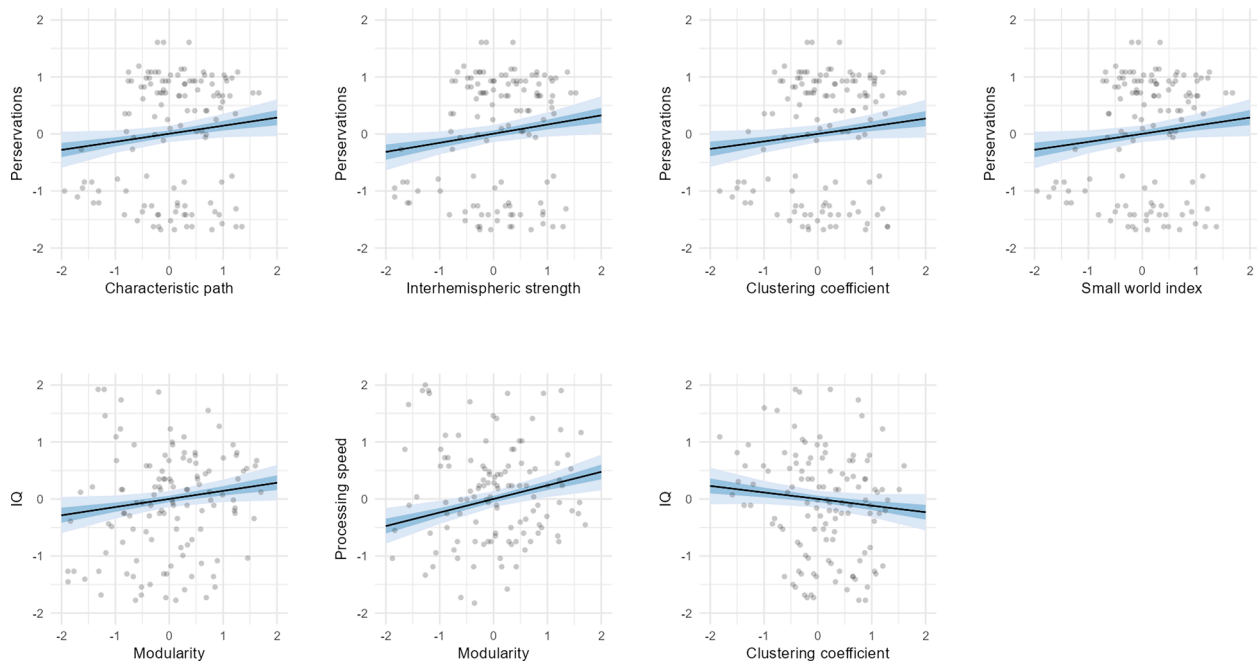


Fig. 6. Correlation between cognitive functions and functional network properties. The graphs show correlations between different cognitive functions (IQ, Processing Speed and Perservations) and graph metrics (Characteristic Path Length, Interhemispheric Strength, Clustering Coefficient, Small World Index and Modularity). In all graphs uncertainty visualizations denote 66 % and 90 % confidence intervals.

Westmacott et al., 2009). Cognitive deficits after perinatal stroke are especially common in patients with arterial ischemic stroke (prevalence up to 69 %) (Dunbar and Kirton, 2018; Lehman and Rivkin, 2014). Our study was able to detect several cognitive deficits in various specific cognitive domains, mainly due to the age of the follow-up (lower limit of 5 years), when these deficits already became apparent and could be evaluated with psychometric tests.

4.2. rs-EEG functional network differences between the two groups

Functional connectomes of children after perinatal stroke had stronger whole-brain and interhemispheric connectivity, reflected in higher characteristic path length and higher interhemispheric strength. Their functional networks were also more segregated with higher clustering coefficient and higher small world index. Functional connectomes of typically developing controls had higher modularity compared to those of children after perinatal stroke. It is known that localized brain lesions cause global network changes, but the lesion location is important in predicting the scale of this effect. Brain hubs are central, highest degree nodes in a network are thought to be a backbone of every brain network. According to previous studies, regions rich with hubs are most vulnerable to injury and hub failure is supposed to be a universal feature of brain disease, seen in Alzheimer disease, multiple sclerosis, traumatic brain injury, etc. One of the theories is that due to diminished capacity of injured nodes there is an increased traffic load higher in the network hierarchy, particularly in the hubs with highest centrality. This results in hub overload and hub failure, which is a characteristic feature of several brain diseases (Stam, 2014). Damage to connector hubs, located in the cortical midline (medial frontal and medial parietal regions) and temporo-parietal junction—the default mode network (DMN), results in higher small-world index, clustering coefficient and characteristic path length and lower modularity (Aerts et al., 2016; Gratton et al., 2012; Sporns et al., 2007). Unfortunately, due to poor spatial resolution of EEG and its limits to assess the subcortical connectivity, the identification of brain hubs in our study was not possible but taking previous knowledge and our clinical data into account, our perinatal stroke group could suffer an injury to these important brain network structures.

4.3. Correlation between cognitive functions and functional network properties

We found that higher network modularity correlated positively with IQ and Processing Speed. Children after perinatal stroke had lower network modularity compared to healthy controls and achieved lower scores of IQ, Working Memory and Processing Speed. Modularity of functional networks is often associated with cognitive functioning. Different studies have found correlations between working memory and modular brain structure (Stanley et al., 2014; Stevens et al., 2012). Liang et al., 2016 showed that integration of modules through dynamic interactions is necessary in order to perform complex cognitive tasks. Network modularity also seems to be a promising marker of network resilience and rehabilitation. According to the study by Arneemann et al., 2015, baseline modular brain network organization predicted improvement in attention and executive function after cognitive training, where individuals with higher baseline modularity exhibited greater improvements with cognitive training.

Children with perinatal stroke also had higher network clustering coefficient and this correlated negatively with the IQ. Brain lesions of different etiologies seem to be associated with higher network segregation, especially when the damage involved connector hub regions (Aerts et al., 2016). Hub regions are considered crucial for cognitive processing, which could explain our results where higher network segregation after perinatal stroke correlated with lower intelligence score in our sample. It is interesting that clustering coefficient and modularity, have an opposite correlation with IQ. One explanation could be, that lower modularity reflects hub damage, since its definition is to estimate the segregation into modules, defined as groups of nodes with maximal number of within group links and minimal number of between group links. As such, modularity is a marker of network organization into modules or subspecialized subnetworks. On the other hand, clustering coefficient is a marker of network segregation (Rubinov and Sporns, 2010). Another measure of network segregation and topology, which was higher in the connectomes of children with perinatal stroke was small world index. Wang et al. (2010) observed the same effect of stroke on a functional network and debated whether this was an

adaptive recovery process acutely after stroke, while our findings suggest that these changes persist years after the initial insult. Small worldness is also an inherent property of brain networks, meaning that brain networks have high clustering coefficients and low characteristic path lengths, which optimizes information flow at the lowest possible cost. If we would interpret our results on a purely mathematical level, we could say that clustering coefficient after perinatal stroke increases more than characteristic path length, which results in a shift to higher values of small world index, since the mathematic formula for small world index is a ratio between the clustering coefficient value and the characteristic path length value. Our results show that inattention and impulsivity correlated with graph metrics, which reflect network segregation (clustering coefficient and small world index). Observations regarding network segregation and ADHD have been published before. A study by Lin et al. (2021) showed that rs-fMRI functional connectomes of individuals with ADHD exhibited higher functional segregation in the salience network, which is crucial for maintaining attention. Interestingly, out of different measures of inattention/impulsivity, only Perseverations rate correlated with the above-mentioned metrics, while no such correlation was found for Commissions and Omissions.

Functional connectomes of children after perinatal stroke had higher characteristic path length and higher interhemispheric strength, compared to connectomes of typically developing children. Both metrics reflect stronger functional connectivity and also positively correlated with the Perseverations rate. Other studies have reported similar findings regarding inattention/impulsivity. Shappell et al. (2021) studied dynamic functional connectivity with rs-fMRI in children with ADHD and found that their functional networks spent more time in the hyper-connected state than those of healthy controls. A study of EEG connectivity by Kiiski et al. (2020) showed that inattentive symptoms of ADHD correlated with higher connectivity of interhemispheric long connections. However, the background of functional connectivity in ADHD is much more complicated, since several studies report different results regarding connectivity changes in specific regions of brain network, especially within the default mode network (DMN) (Konrad and Eickhoff, 2010; Tian et al., 2006). Ilves et al. also showed that patients with perinatal arterial ischemic stroke had significantly higher functional connectivity in the posterior precuneus part of the default mode network, which in their case correlated with serious cognitive deficits (Ilves et al., 2016). On the other hand, Meghji et al. found that functional connectivity after perinatal stroke is significantly lower in several network regions, including the default mode network and these characteristics correlated with executive function and ADHD symptomology (Meghji et al., 2023).

We observed an increase in interhemispheric connectivity after perinatal stroke, which could be interpreted as a compensating mechanism for the loss of function within injured hemisphere. Interestingly, stronger interhemispheric connectivity correlated with a tendency to impulsive decision making. Some studies on adult stroke showed a positive correlation between interhemispheric connectivity and recovery from specific deficits (aphasia, visuospatial neglect), while others reported that stronger engagement of the contralesional hemisphere was not an indicator of efficient cortical reorganization and improved functioning (De Vico Fallani et al., 2009; Wang et al., 2010).

Our study could not confirm the correlation between brain network properties and visual-motor integration abilities. We found no similar EEG studies which would explore this connection. However, impairment of sensory-motor integration is expected after perinatal stroke (Yeates et al., n.d.) and a f-MRI study from Thickbroom et al., 2001 proposed this is due to interhemispheric dissociation between afferent kinesthetic inputs and efferent corticomotor outputs. It seems that our methodology, designed to investigate global brain network properties, was unable to detect subtler changes in brain motor and sensory subnetworks.

4.4. Limitations

The main limitations of this study are a relatively small sample size and a heterogeneous group of participants with a wide age-range and different social backgrounds. We aimed to alleviate this by designing a matched case-control study. Nevertheless, the results should be interpreted with caution and larger samples would probably be needed for firmer conclusions. We would also like to expose that the processing pipeline did not include the heart rate and respiratory rate interference detection and removal, since this was not included in the existing EEG functional connectivity studies guidelines (Miljevic et al., 2022). We addressed noise artefacts by several other measures, proposed in the literature and described in our methodology.

Some patients with perinatal stroke later developed epilepsy, which undoubtedly influences functional connectivity and cognitive outcome. However, due to a small sample, we decided against performing additional statistical analyses on this subgroup. Similarly, the group of perinatal stroke patients is heterogeneous due to different lesion types (ischemia or hemorrhage) and different lesion locations and as mentioned above, the location is a very important predictive marker for the functional network disruption scale (Grefkes and Fink, 2011).

Another pitfall is the inherent EEG restraint to assess the connectivity of subcortical regions, relevant for cognitive functioning. However, subcortical lesions influence cortical network dynamics via changes in neurotransmitter layout and metabolism, as positron emission tomography (PET) studies have shown (Kwan et al., 1999). Therefore, EEG has the ability of indirectly assessing the damage of subcortical structures as well. Also, an EEG estimated connectivity can be influenced by volume conduction, which we tried to minimize with described methodologic steps (the use of dbWPLI for a connectivity measure, and the use of surface Laplacian). We were aware of these restrictions in advance, but our aim was to evaluate the value of EEG as a tool for estimating functional connectivity as a marker of cognitive processes, despite its known limitations.

5. Conclusions

This study aimed to identify cognitive deficits in children after perinatal stroke and their correlation to functional brain network properties. We found that functional networks after perinatal stroke are highly segregated but have a less modular organization. Functional brain networks after perinatal stroke also exhibited stronger interhemispheric and whole-brain connectivity. Functional network modularity correlated positively with IQ and processing speed. Higher network segregation (clustering coefficient and small world index) and stronger whole-brain and interhemispheric connectivity (characteristic path length and interhemispheric strength) correlated positively with a tendency to impulsive decision making. In conclusion, our study showed that specific cognitive functions correlated with different brain network properties and that functional network characteristics after perinatal stroke reflected poorer cognitive functioning.

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Ethics statement

The study protocol was reviewed and approved by the Slovenian

National Medical Ethics Committee, approval number 0120-328/2021/3. A written informed consent was obtained from participants (and parents/legal guardians) to participate in the study.

CRedit authorship contribution statement

Alja Kavčić: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Daša Kocjancić Borko:** Writing – original draft, Methodology, Investigation. **Jana Kodrić:** Writing – original draft, Methodology, Investigation, Conceptualization. **Dejan Georgiev:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Jure Demšar:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Aneta Soltirovska-Šalamon:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Data availability

All data, along with the source code for data preprocessing, connectome computation and statistical methods are available in a public online repository: <https://github.com/demсарjure/PedEEG>.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2024.120743](https://doi.org/10.1016/j.neuroimage.2024.120743).

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