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The degree of prematurity affects functional brain activity in preterm born children at school-age: An EEG study

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ABSTRACT

Prematurely born children are at higher risk for long-term adverse motor and cognitive outcomes. The aim of this paper was to compare quantitative measures derived from electroencephalography (EEG) between extremely (EP) and very prematurely (VP) born children at 9–10 years of age.

Fifty-five children born < 32 weeks' of gestation underwent EEG at 9–10 years of age and were assessed for motor development and cognitive outcome. Relative frequency power and functional connectivity, as measured by the Phase Lag Index (PLI), were calculated for all frequency bands. Per subject, power spectrum and functional connectivity results were averaged over all channels and pairwise PLI values to explore differences in global frequency power and functional connectivity between EP and VP children. Brain networks were constructed for the upper alpha frequency band using the Minimum Spanning Tree method and were compared between EP and VP children. In addition, the relationships between upper alpha quantitative EEG results and cognitive and motor outcomes were investigated.

Relative power and functional connectivity were significantly higher in VP than EP children in the upper alpha frequency band, and VP children had more integrated networks. A strong positive correlation was found between relative upper alpha power and motor outcome whilst controlling for gestational age, age during EEG recording, and gender ($\rho = 0.493$, $p = 0.004$).

These results suggest that 9–10 years after birth, the effects of the degree of prematurity can be observed in terms of alterations in functional brain activity and that motor deficits are associated with decreases in relative upper alpha power.

1. Introduction

Preterm birth is a major public health concern worldwide. In the past decades, survival rates of prematurely born children have increased significantly due to improved neonatal care [1]. Long-term adverse consequences of preterm birth, such as cognitive and motor problems, increase with decreasing gestational age (GA). The World Health Organization subdivides preterm birth based on GA in very preterm (GA from 28 to 32 weeks) and extremely preterm (GA below 28 weeks). The cut-off at 28 weeks is not arbitrary; survival rates increase from about 20% at 22 weeks to 90% at 28 weeks of gestation, and most motor and cognitive problems among preterm children are more evident in extremely prematurely born (EP) children [2]. Most problems associated with preterm birth, such as lower academic performance and IQ scores, are first identified at school-age [3,4].

The adverse developmental outcomes in very prematurely born (VP)

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Abbreviations

EP	extremely prematurely born
VP	very prematurely born
GA	gestational age
qEEG	quantitative electroencephalography
PLI	Phase Lag Index
MST	Minimum Spanning Tree
maxDEG	maximum degree
LF	leaf fraction
maxBC	maximum betweenness centrality
TH	tree hierarchy
MABC	Movement Assessment Battery for Children
WISC	Wechsler Intelligence Scale for Children

children are associated with structural alterations in brain development, as can be seen in white matter abnormalities and the reduction in (sub)cortical grey matter volume [5,6]. However, in contrast to structural changes, little is known about how differences in functional brain activity relate to neonatal variables and cognitive and motor outcome at school-age.

Functional brain activity can be investigated using quantitative electroencephalography (qEEG). The oscillatory activity of the brain can be analysed with the power spectrum of the recorded EEG signal. The oscillatory synchrony of two spatially remote locations, a phenomenon which is called 'functional connectivity', can be quantified with the Phase Lag Index (PLI) [7]. The PLI is an index of the consistency with which one signal is phase lagging another signal and discards phase differences that centre around zero. Since a non-zero phase lag cannot be explained by common sources, the influence of volume conduction on the functional connectivity analysis is diminished [7]. The PLI can be successfully used as a measure for detecting differences between functional network organizations in a wide age- and pathology-range [8–10]. The Minimum Spanning Tree (MST) method can be used to construct a network that connects all nodes with the strongest functional connectivities without forming cycles [11]. An advantage of using this method is that MST networks can be compared in different conditions across groups, since it has a fixed number of connections. Network topologies vary from a less integrated line-like to a more integrated star-like structure and it is thought that efficient networks represent an optimal, intermediate state.

As outlined above, the existing knowledge on qEEG measures including power spectrum, functional connectivity and network analysis in EP and VP children at school-age and importantly, how these measures relate to neurodevelopmental outcome, is very scarce. On the contrary, much neonatal EEG research has been done into (preterm) functional brain development [12–14]. Toth et al. showed that network measures in the alpha frequency band change with GA in full-term neonates, which might indicate that the alpha network starts to develop in the neonatal period [15]. Therefore, we hypothesized that functional brain activity would differ between EP and VP children in the alpha frequency band and that it would be related to motor and cognitive outcome. Therefore, the aim of this study is to investigate differences in functional brain activity in a group of EP and VP children at-school age with variable motor and cognitive outcomes in order to proof that preterm birth has long-term consequences on functional brain activity, and that changes in functional brain activity might be related to adverse neurodevelopmental outcome in this population.

2. Methods

2.1. Study protocol

Participants were involved in a prospective longitudinal cohort of 113 preterm infants (GA < 32 weeks) born between May 2006 and October 2007 and were previously recruited for a study at the Leiden University Medical Center. For a detailed description of the project outline, baseline characteristics and neonatal MRI findings of the total cohort we refer to previously published studies [16,17].

As part of the Dutch national neonatal follow-up program, all neonates with a GA < 32 weeks are invited at the outpatient department at the age of 6 months, 1, 2, 5, 9 years old. In this study, each child underwent standardized paediatric and neurologic examination, neuromotor evaluation and neuropsychological testing at the age of 9 years by an experienced child neurologist, neonatologist, paediatric physiotherapist, and child psychologist as part of this clinical protocol. All children were additionally asked to participate in a study, in which among others an EEG was performed at the age of 9–10 years.

The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). Approval for the study was given by the Ethical Committee of the LUMC, and informed parental consent was obtained for each child.

2.2. EEG recording and post-processing

EEG recordings (Nihon Kohden EEG-1200 system, software version 02.20, Germany) were made between September 2017 and April 2018 at the Department of Clinical Neurophysiology, using Polaris.one software (Nihon Kohden, software version 3.1.1.0, Germany). During recording, subjects were in the supine position with the eyes open for 5 min and closed for 15 min during a state of relaxed wakefulness. Twenty-one Ag/AgCl electrodes were attached to the scalp at the positions of the International 10–20 system. Impedance was kept below 5 kΩ. The sampling rate was 500 Hz and the EEG was digitized with 16 bit resolution. The bandpass lower cut-off frequency was 0.16 Hz and the bandpass upper cut-off frequency was 70 Hz.

The EEG recordings were re-referenced to a source derivation and were converted into ASCII-format, with the channels arranged according to the BrainWave software (version 0.9.152.10.45, available from http://home.kpn.nl/stam7883/brainwave.html). The sampling frequency was 500 Hz and the epoch length was 4096 samples (8.192 s). EEG quality was assessed by one of the authors (CvtW). For each subject, five epochs, i.e. 40.96 s in total, with optimal quality were selected during the eyes closed period. The recordings that were visually assessed on substantial amounts of unwanted non-brain signals such as electric fields generated by muscle contractions and (eye-) movements were excluded from the analyses. The main analyses only included the EEG recordings that were artefact-free or had tolerable artefacts. All channels were included in the analyses.

EEG recordings were bandpass filtered offline into seven frequency bands: broad band: 0.5–45 Hz; delta: 0.5–4 Hz; theta: 4–8 Hz; lower alpha (A1): 8–10 Hz; upper alpha (A2): 10–13 Hz; beta: 13–30 Hz; gamma: 30–45 Hz. The used methods were based on the work of van Diessen et al. [18].

2.3. Frequency analysis

Frequency analysis was conducted using the Fast Fourier Transform option in BrainWave. The relative power contribution per frequency band, normalized by the sum of the frequencies power from 0.5 to 45 Hz, was calculated across all time points and averaged over the five epochs. Spatial as well as global analyses, including the average of 21 electrodes, were performed.

2.4. Functional connectivity

As a measure of functional connectivity between different scalp locations, the PLI was calculated between all EEG channel pairs. The PLI is calculated using the following equation:

$$PLI = |\langle sign[\sin(\Delta\varphi(t_k))]\rangle| \quad (1)$$

where $\Delta\varphi(t_k)$ is the phase difference, calculated for time point t_k with k = 1…N, dependent on the sampling frequency. Sign refers to the signum function, which translates a positive value for the phase difference into 1, a negative value for the phase difference into −1 and no phase difference into 0. ◇ refers to the mean value and || denotes absolute values. Functional connectivity analysis was performed with BrainWave software.

PLI values were calculated per frequency band and averaged across all electrode pairs for each matrix, followed by calculation of the mean over the five epochs per subject.

2.5. Brain networks

The MST method was used to construct brain networks [11,19]. The MST method is applied per PLI matrix and results in trees that can be seen as the backbone of a network, showing the strongest connections that exist between all nodes without forming cycles. Trees of 21 nodes were generated separately for each child, epoch and frequency band by using the BrainWave software.

The most commonly used network measures are described by Stam et al. in 2014 [11]. "Degree" (DEG), "Betweenness Centrality" (BC), "Leaf Fraction" (LF) and "Tree Hierarchy" (TH) were used to analyse the constructed networks. DEG was calculated as the fraction of links a node has, and the node with the highest value, the maxDEG, was selected per MST. LF was calculated as the fraction of nodes with a degree of one. The BC is an index that indicates the fraction of shortest paths within the MST network that pass through a given node. The node with the highest BC has the highest load, i.e. the highest number of paths that run through this node, and is represented in the value of maxBC.

The TH is a measure that integrates criteria for an optimal performance of the network [20]. In a good performing network, efficient communication between nodes (i.e. integration) is necessary. However, segregation within the network is necessary as well, since higher-order networks require information processing in separate groups of nodes and strong hubs might easily be overloaded due to high BC. By setting a maximal BC, an overloaded hub can be avoided. The TH shows the balance between obtaining a high leaf number and preventing hub overload. The more the network approaches a line-like topology, i.e. having less leafs, the lower the TH outcome will be. On the contrary, when there is a star-like topology, the TH outcome will be 0.5. Every other topology in between, with a lower value for maxBC and a higher amount of leafs, will provide a value that is higher than 0.5.

All network measures were averaged across the five epochs per child.

2.6. Developmental testing

Cognitive development was assessed using the Dutch translation of the Wechsler Intelligence Scale for Children 3th Ed. (WISC-III-NL) [21]. The WISC-III-NL is a cognitive ability test assessing three domains: verbal IQ, performance IQ and processing speed. Full-scale IQ can be determined from the 10 subsets of the verbal and performance IQ. The normal distribution of IQ is a mean score of 100 with a standard deviation of 15.

Motor function was assessed by a paediatric physiotherapist with the test component of the Dutch translation of the Movement Assessment Battery for Children, second edition (MABC-2-NL) [22], developed for age band two that is normed for ages 7–10 years. The MABC-2 comprises eight tasks that include sub-tests for manual dexterity, ball skills, and static and dynamic balance and results in a total raw score (normal; > 67, mildly impaired; 57–67, severely impaired; < 57).

2.7. Statistical analysis

Data management and analyses were performed using Statistical Package for the Social Sciences (SPSS)® version 23.0 for Windows (SPSS Inc., Chicago, IL USA).

Student's *t*-tests, Phi-Coefficient Tests and Mann-Whitney *U* tests were used to test for group differences. The Benjamini-Hochberg procedure was applied to correct for multiple comparisons ($p < 0.05$, corrected, q = 0.1). Given their non-parametric nature, differences in network measures (maxDEG, maxBC, LF, TH) were explored by performing Mann-Whitney *U* tests. To test for associations between developmental testing outcomes and qEEG measures, Spearman's rank correlation coefficients were calculated within the VP group, so that the influence of GA was diminished. The most significant result was further explored within the total group by using a partial Spearman's rank correlation coefficient that corrected for gender, continuous GA and age during recording. Significance levels were set at a *p*-value of < 0.05.

Table 1
Demographic and clinical variables of the total group of 55 children with an EEG recording classified as 'artefact-free or tolerable artefacts', and comparisons between the EP and VP group.

	Total group (n = 55)	EP children (n = 19)	VP children (n = 36)	*p* value
Gender (male/female)	28/27	15/4	13/23	0.003‡,**
GA (weeks, days), median (range)	29w1d (25w4d–31w6d)	26w4d (25w4d–28w0d)	30w0d (28w3d–31w6d)	< 0.001§,***
BW (g), median (range)	1271 (650–1960)	1024 (650–1150)	1423 (720–1960)	< 0.001§,***
Age during EEG recording (years, months), mean (SD)	9y9m (0y8m)†	9y6m (0y6m)	9y10m (0y8m)	0.072¶
DMV (days), median (range)	3 (0 − 30)	13 (0–30)	0 (0–7)	< 0.001§,***
MRI scored at TEA (normal-mild/moderate/severe)	21/29/5	8/7/4	13/22/1	0.048‡,*
Postnatal steroid use, n (%)	7 (12.7)	7 (36.8)	0 (0)	< 0.001‡,***

EP = extreme prematurely born, VP = very prematurely born, GA = gestational age, BW = birth weight, DMV = Days on invasive Mechanical Ventilation, TEA = term equivalent age.

† Missing value.
‡ Phi coefficient.
§ Mann-Whitney *U*.
¶ Student's t.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

3. Results

3.1. Description of the cohort

From the original cohort of 113 subjects, 67 children underwent an EEG recording at the age of 9–10 years in addition to developmental testing. The flowchart of the inclusion process is shown in Fig. A.1. The EEG recording of one child was postponed due to problems with the planning and was not included in this study. Within the group of 66 children, 55 children had an EEG of sufficient quality for epoch selection. The 55 children with an EEG of sufficient quality did not differ from the rest of the initial cohort ($n = 58$) regarding GA and birth weight (BW), however, significantly less men were present in the studied group ($\varphi = 0.189$, $p = 0.05$).

3.2. Demographics

Table 1 shows the baseline demographic and clinical variables of the group of children with epochs of sufficient quality. Gender, GA, BW, duration of mechanical ventilation, postnatal steroid use, and neonatal MRI scores were significantly different between EP and VP children.

3.3. Frequency and functional connectivity analysis

Relative frequency power and functional connectivity in the A2 frequency band were significantly higher in VP children than in the EP children after multiple comparison correction ($U = 478.5$, $p = 0.016$ and $U = 492.5$, $p = 0.008$, respectively). Table 2 presents the results for all the comparisons between EP and VP children for relative power spectrum and functional connectivity analysis.

3.4. Relationship relative power and functional connectivity in the A2 frequency band

There was a strong correlation between relative power and functional connectivity in the A2 frequency band, as shown in Fig. 1 ($R = 0.695$, $p < 0.001$). Fig. 1 illustrates that all EP children have low relative power and functional connectivity outcomes in the A2 frequency band, whereas VP children can have low as well as high relative power and functional connectivity outcomes.

3.5. Brain network analysis

Based on the significant results in the A2 frequency band, differences in MST networks in the A2 frequency band between the EP and VP group were explored. maxDEG and LF were significantly higher in VP children compared to EP children ($U = 491.5$, $p = 0.008$ and $U = 473.0$, $p = 0.020$, resp. See Fig. A.2). No differences were found for maxBC and TH. Fig. 2 shows the result of group-averaged MSTs projected on the scalp.

3.6. Neurodevelopmental testing

IQ testing was performed in 53 children and motor assessment was performed in 52 out of 55 children. Table 3 shows the developmental outcome of the total group, the EP group and VP group.

To further explore the broad distribution of qEEG outcomes in the A2 frequency band, potential relationships between qEEG outcomes and data from developmental testing were investigated. The EP group was excluded to diminish the effect of GA. The results after multiple comparison correction are shown in Table A.1. There was a strong correlation between the MABC score and relative A2 power, which remained significant after multiple comparison correction ($\rho = 0.489$, $p = 0.003$). Fig. 3 shows the spatial distribution of the correlation coefficients, projected on the scalp, between relative A2 power and MABC score. The correlation coefficients of $n = 8$ channels remained significant after multiple comparison correction, but especially electrodes T3, F4 and Cz showed a strong correlation with MABC score ($\rho = 0.530$, $p = 0.001$, $\rho = 0.495$, $p = 0.002$ and $\rho = 0.386$, $p = 0.006$).

A partial Spearman's ranked correlation coefficient was performed in the total group of EP and VP children ($n = 52$) to further explore the strong association between relative A2 power and MABC. The correlation was still present, whilst controlling for GA and age during EEG recording as continuous variables and gender as a categorical variable ($\rho = 0.493$, $p = 0.004$). Fig. 4 shows the scatterplot of the relative A2 power and the raw scores of the MABC for the total group.

4. Discussion

We report the first qEEG study that analysed brain activity of EP and VP children at 9–10 years of age at oscillatory, functional connectivity and brain network level. We showed that EP children have reduced relative power and functional connectivity in the upper alpha frequency band as compared to VP children. However, Twilhaar et al. reported that the differences between prematurely born children and controls were largest for relative beta power, whereas our study did not show any significant results in the beta frequency band. Possible explanations for this might be that different groups were compared and/or that epochs were selected in other resting state conditions [23]. Whilst the research on functional brain activity in EP and VP children remains scarce, some studies have an area of overlap with our study. Slowing of the peak frequency in the alpha frequency band, as well as different patterns of task-dependent alpha synchronization between VP and full-term born children have been reported at 7 years of age [24–26]. In addition, increases in the gamma/alpha ratio in EP compared to VP children have been shown, whereas there were no significant differences present between VP and term-born children at 9 years of age [25].

The question is raised how alterations in the alpha frequency band originate in the prematurely born population. Doesburg et al. propose that disruptions in the thalamocortical system might underlie functional brain alterations in VP children [25]. Evidence shows that the thalamocortical system is involved in the generation of alpha oscillations and that there is altered structural and functional thalamocortical connectivity present in VP infants at TEA [27–29]. In addition, human

Table 2
Results of relative power and functional connectivity comparisons between EP and VP children tested across six frequency bands (EEG recordings classified as 'artefact-free or tolerable artefacts').

	Total group ($n = 55$)	EP children ($n = 19$)	VP children (n = 36)	p value[†]
Relative power				
Delta (mean)	0.210	0.192	0.220	0.986
Theta (mean)	0.245	0.122	0.106	0.124
Alpha 1 (mean)	0.066	0.072	0.063	0.565
Alpha 2 (mean)	0.074	0.063	0.079	0.016[‡,*]
Beta (mean)	0.269	0.273	0.267	0.958
Gamma (mean)	0.356	0.278	0.356	0.671
Functional connectivity (PLI)				
Delta (mean)	0.146	0.144	0.147	0.553
Theta (mean)	0.124	0.124	0.124	0.601
Alpha 1 (mean)	0.180	0.180	0.181	0.922
Alpha 2 (mean)	0.152	0.138	0.160	0.008[‡,**]
Beta (mean)	0.067	0.064	0.068	0.212
Gamma (mean)	0.067	0.063	0.069	0.710

EP = extreme prematurely born, VP = very prematurely born, PLI = Phase Lag Index.
[†] Mann-Whitney U.
[‡] Significant after multiple comparison correction (Benjamini-Hochberg).
[*] $p < 0.05$.
[**] $p < 0.01$.

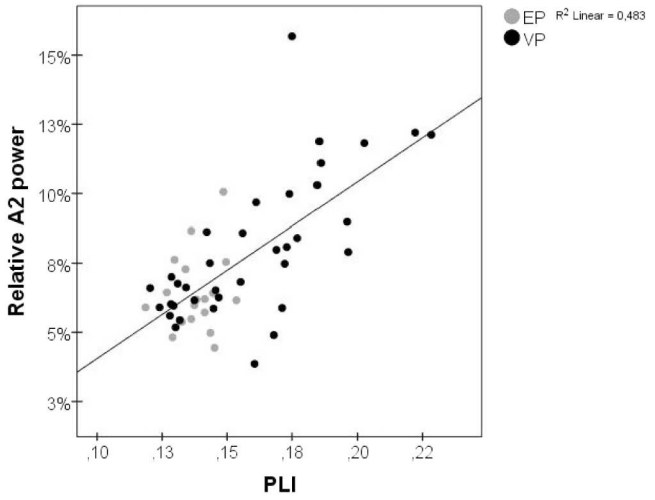

Fig. 1. Relationship between relative power and PLI in the A2 frequency band (R^2 = 0.483). EP children are indicated as grey dots (n = 19) and VP children are indicated as black dots (n = 36). EP = extreme prematurely born, VP = very prematurely born, PLI = Phase Lag Index.

thalamocortical axons show growth between 7.5 and 34 weeks of PMA, indicating that the thalamocortical system is developing during preterm birth, which makes the thalamocortical system vulnerable for disruptions [30]. A possible explanation might be that a disrupted thalamocortical system results in slowing of the alpha frequency; Table 2 shows that EP children have higher power in the theta and lower alpha frequency bands than VP children. However, these results were not significant, and this explanation must therefore be interpreted with caution.

The MST method was used to construct functional brain networks. We found a significant increase in LF and maxDEG in the upper alpha frequency band for VP children compared to EP children. No significant differences were found for maxBC and TH. The increases in LF and maxDEG point toward a shift from a more line-like (less integrated) topology in EP children to a more star-like (more integrated) topology in VP children. However, since maxBC and TH were not significantly different, caution must be applied, as the evidence for more integrated networks in VP children is not consistent. In addition, this finding was somewhat unexpected, since Boersma et al. reported decreases in number of leafs and maxDEG in the alpha frequency band in healthy children during development between 5 and 7 years of age, also by using the MST method [20]. Toth et al. studied MST networks in full-term neonates and found significant decreases in maxDEG, maxBC, LF and TH in the upper alpha frequency band with increasing GA [15]. It is possible, therefore, that the upper alpha network starts to develop during gestation and that it is closely linked to cerebral maturation. Due to preterm birth, this upper alpha network development might be severely disrupted, dependent on whether the disruption takes place during a critical period of cerebral maturation.

We found a strong correlation between relative power and functional connectivity in the upper alpha frequency band. A possible explanation for this is that relative power and functional connectivity are not independent aspects of the EEG. Tewarie et al. investigated relationships between oscillatory amplitudes and functional connectivity and state that it remains unanswered whether amplitude and connectivity are genuinely coupled or whether the increased connectivity is due to increased signal-to-noise ratios [31]. Therefore, these data must be interpreted with caution. However, it also suggests that time-frequency spectrograms are not merely a description of local synchrony but also reflect connectivity. Moreover, there was a stronger correlation between the PLI and GA than between the relative upper alpha power and GA in our study. The observed changes in functional connectivity are not fully explained by the dependence on power, which seems to indicate that at least partly true functional connectivity differences in the upper alpha frequency band are detected.

The second aim of this study was to investigate whether qEEG outcomes were related to motor and cognitive outcomes. The most interesting finding was that relative upper alpha power was significantly correlated with MABC score, whilst controlling for GA, gender and age at the time of EEG recording and correcting for multiple comparisons. This finding is consistent with that of Twilhaar et al. who reported higher MABC scores within a group of full-term and preterm born children with higher relative alpha power [32]. It seems that the alpha

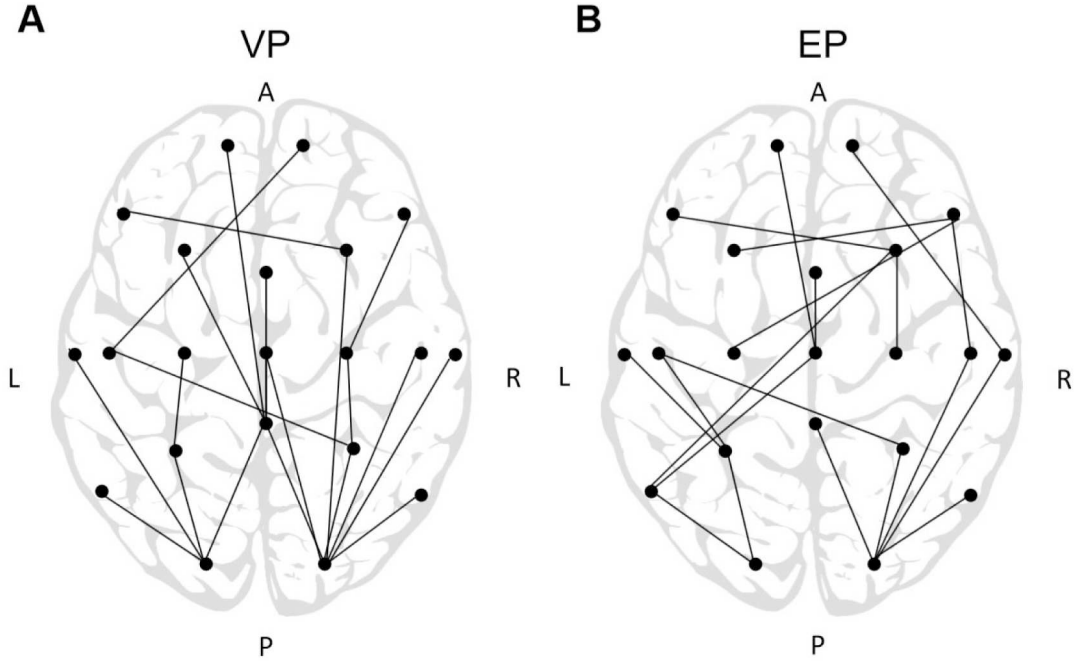

Fig. 2. Group-averaged MST networks are projected on the scalp for the VP group (n = 36) (A) and the EP group (n = 19) (B). MST = Minimum Spanning Tree, EP = extreme prematurely born, VP = very prematurely born.

Table 3
Developmental outcomes in the total group and comparisons between the EP and VP groups (EEG recordings classified as 'artefact-free or tolerable artefacts').

	Total group (n = 55)	EP children (n = 19)	VP children (n = 36)	p value
Full-scale IQ mean (SD)	97.36 (15.75) n = 53	93.82 (15.04) n = 17	99.03 (16.01) n = 36	0.266[†]
MABC raw score median (range)	82 (39–96) n = 52	78 (47–96) n = 17	84 (39–91) n = 35	0.028[‡]

EP = extreme prematurely born, VP = very prematurely born, MABC = Movement Assessment Battery for Children.
[†] Student's t.
[‡] Mann-Whitney U.

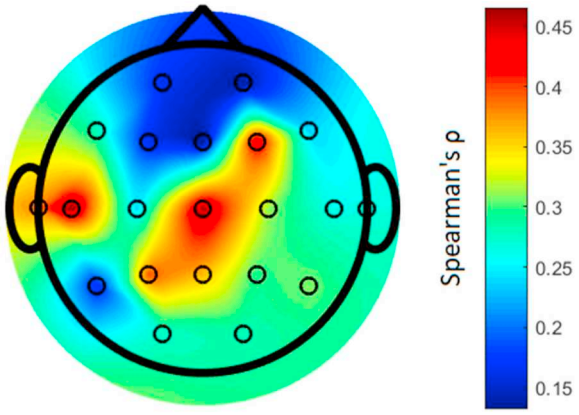

Fig. 3. Correlation coefficients of relative A2 power with raw MABC scores per channel. Results are projected on the scalp* and the analyses included n = 55 subjects. MABC = Movement Assessment Battery for Children. *Copyright (c) 2019, Víctor Martínez-Cagigal[1].

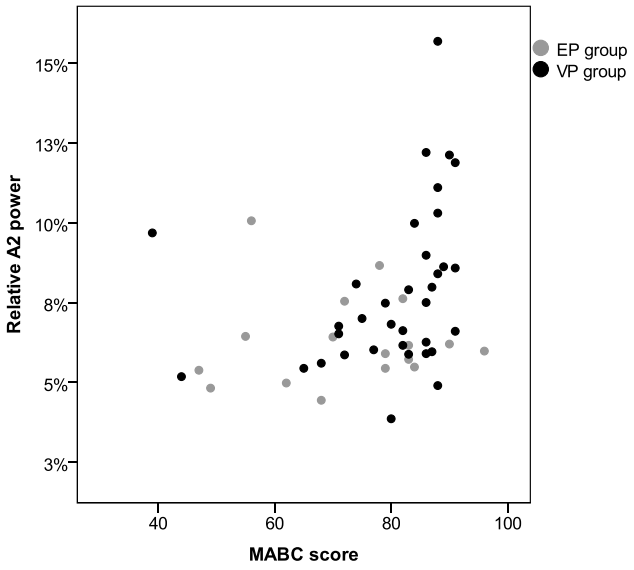

Fig. 4. Scatterplot of relative A2 power and raw scores of the MABC. EEGs classified as 'artefact-free or tolerable artefacts' are indicated as black dots (n = 55) and EEGs classified as 'substantial artefacts' are indicated as grey dots (n = 11). Dots correspond to individual subjects. MABC = Movement Assessment Battery for Children.

frequency band is (one of) the most interesting frequency bands to study motor outcome in prematurely born children. De Kieviet et al. found positive associations between fractional anisotropy values and MABC outcome in various white matter tracts in prematurely born children at 8 years of age [33]. Furthermore, they reported a positive correlation between thalamic volume and MABC outcome. It is possible, therefore, that there is a relationship between white matter and thalamic development and the observed alterations in functional brain activity, which subsequently (partly) explain the variable motor outcomes in this population. Furthermore, the current study found that electrode position T3 had the strongest positive correlation with MABC score (ρ = 0.530, p = 0.001). Though, 8 out of 21 channels remained significant after multiple comparison correction. According to these data, it might be concluded that the correlation between global upper alpha power and MABC score does not simply reflect substantial localised alpha frequency changes.

Alpha rhythms are known to be modulated by cognitive tasks [34]. In addition, synchronization of alpha oscillations seems to underlie age-related changes in cognition [35,36]. Therefore, it was surprising that the results of this study did not show any significant relationship between qEEG measures and IQ. Interestingly, Doesburg et al. showed that changes between VP and full-term born children in the speed and synchronization of alpha oscillations were not related to IQ either [25,26]. Moreover, Boersma et al. tested for associations between IQ and network measures in children from 5 to 7 years old and reported that there were no significant correlations [20]. A possible explanation would be there that altered patterns of functional connectivity in the alpha frequency band may underlie selective cognitive difficulties, rather than general intelligence that is measured by IQ scores [26]. It may be worthwhile to further analyse the association between qEEG measures and different cognitive measures, such as attention and executive function, since deficits in these cognitive domains have been related to preterm birth [37].

The main weakness of this study is that no healthy controls were included. Notwithstanding this limitation, this study offers some insight into how the degree of prematurity might affect functional brain activity. Smit et al. investigated the development of PLI throughout the lifespan in healthy subjects and showed that the PLI is significantly higher in adolescents at 16 years of age compared to children at seven years of age and that several network measures pointed toward development of a line to a more star-like network topology [38]. Based on functional MRI data, Fair et al. showed, among others, that long-range connections in resting-state networks strengthen with development in healthy subjects (7–30 years old) [39,40]. Our findings, i.e. the observed decrease in functional connectivity and the less integrated networks in the EP group, possibly reflect a delay in the development of resting-state brain networks in EP children.

This study has shown that the impact of extremely low GA can still be observed in terms of functional brain activity 9–10 years after birth and indicates that studying functional brain activity of children born before 32 weeks of GA might play an important role in understanding the biological basis of long-term motor outcomes in this vulnerable population.

CRediT authorship contribution statement

Charlotte van 't Westende: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft.**Cacha M.P.C.D. Peeters-Scholte:** Conceptualization,

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Investigation, Methodology, Supervision, Writing - review & editing.**Lisette Jansen**: Investigation, Methodology, Writing - review & editing.**Janneke C. van Egmond-van Dam**: Investigation, Methodology, Writing - review & editing.**Martijn R. Tannemaat**: Conceptualization, Investigation, Methodology, Writing - review & editing.**Francisca T. de Bruïne**: Methodology, Writing - review & editing.**Annette A. van den Berg-Huysmans**: Methodology, Writing - review & editing.**Victor J. Geraedts**: Investigation, Methodology, Supervision, Writing - review & editing.**Alida A. Gouw**: Investigation, Methodology, Supervision, Writing - review & editing.**Sylke J. Steggerda**: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing - review & editing.**Cornelis J. Stam**: Conceptualization, Investigation, Methodology, Software, Supervision, Writing - review & editing.**Laura A. van de Pol**: Conceptualization, Investigation, Methodology, Supervision, Writing - original draft.

Declaration of competing interest

CPS is founder and consultant at Neurophyxia BV. She holds several patents and stocks of Neurophyxia BV. None of this work has a relationship with the current manuscript.

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Statements

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Appendix A

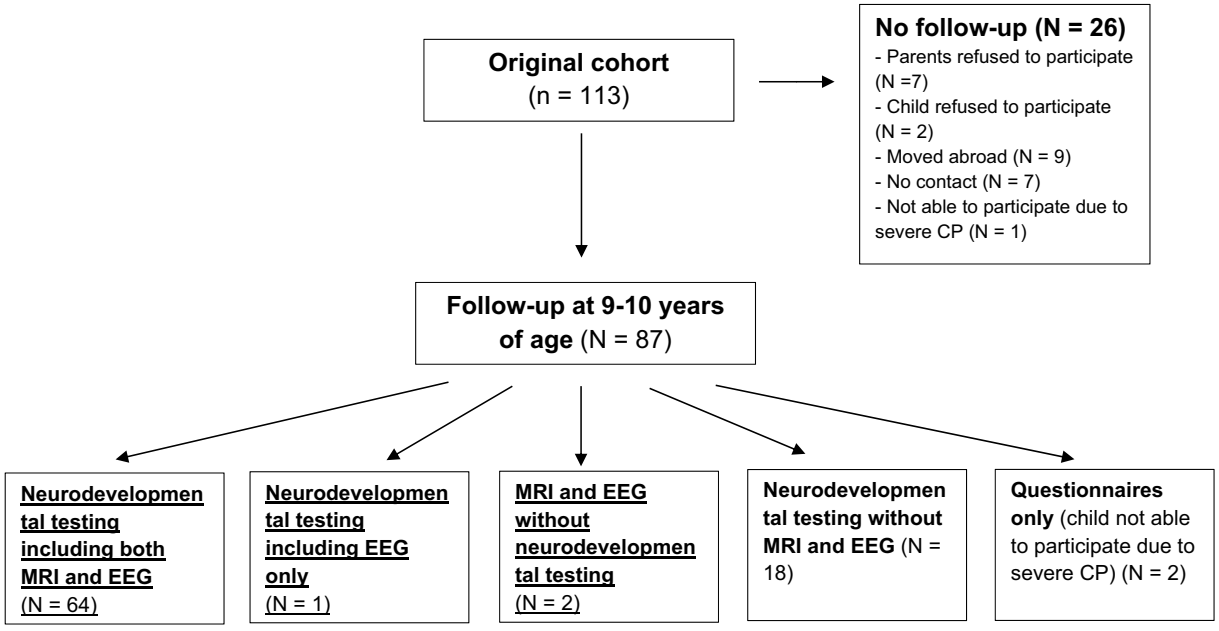

Fig. A.1. Flowchart of inclusion process of the group of prematurely born children at 9–10 years of age. The children who underwent an EEG (n = 67) are underlined.

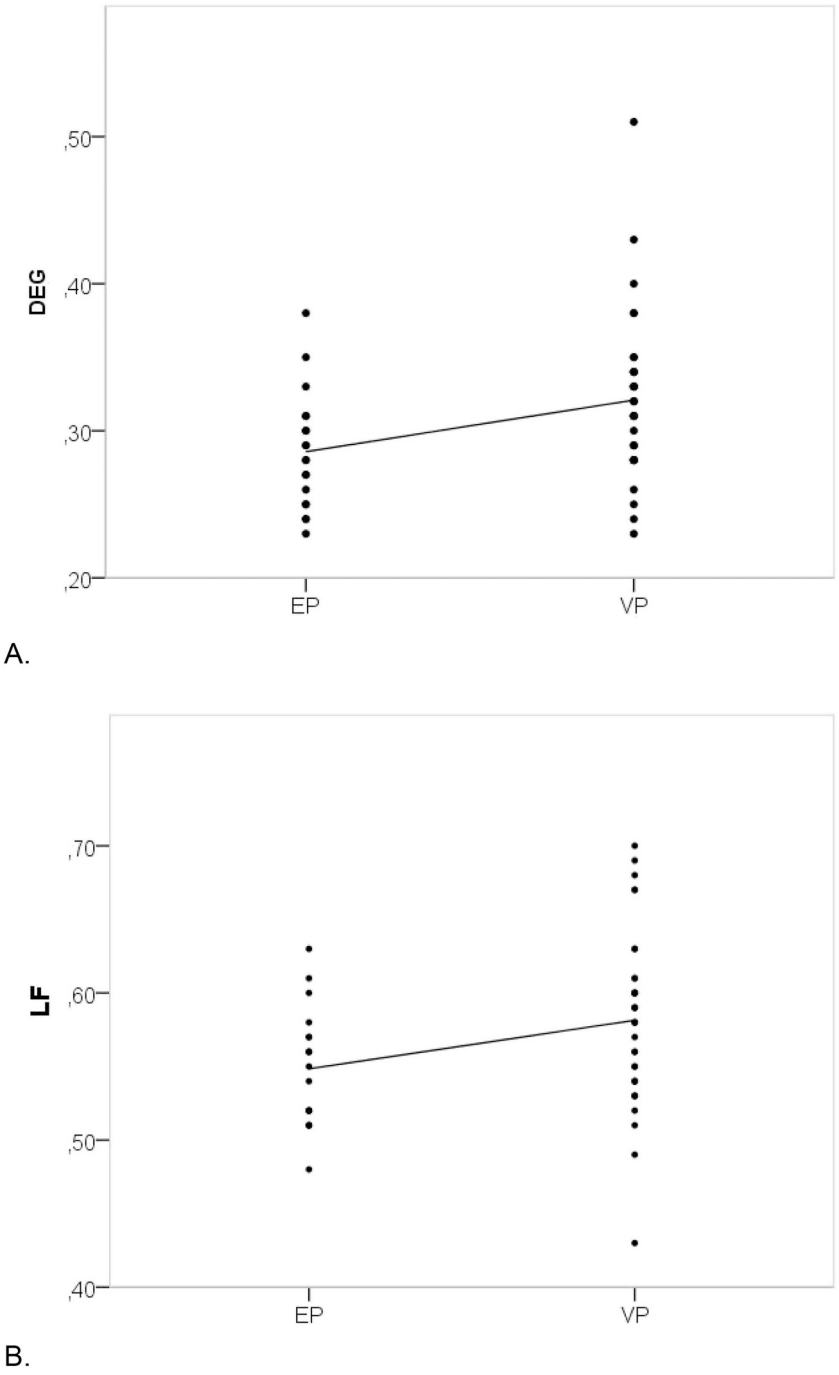

Fig. A.2. maxDEG (A) and LF (B) distribution in the A2 frequency band including mean normalized values averaged separately for EP and VP group. The mean normalized maxDEG and LF were significantly higher in VP children (U = 491.5, p = 0.008, and U = 473.0, p = 0.020, respectively). Dots correspond to individual subjects (n = 55).

Table A.1
Results of qEEG measures in the A2 frequency band and developmental outcomes in the VP group.

A2 frequency band in the VP group (n = 36)	Correlation coefficient	p value[†]
MABC (n = 35)		
Relative power	0.489	0.003[‡,*]
PLI	0.377	0.025[*]
maxDEG	0.154	0.378
maxBC	0.018	0.918
Leaf fraction	0.246	0.155
Tree hierarchy	0.297	0.083

(*continued on next page*)

Table A.1 (*continued*)

A2 frequency band in the VP group (n = 36)	Correlation coefficient	p value[†]
Full-IQ score (n = 36)		
Relative power	0.119	0.488
PLI	0.015	0.933
maxDEG	0.161	0.348
maxBC	−0.020	0.909
Leaf fraction	−0.065	0.704
Tree hierarchy	−0.012	0.944

PLI = Phase Lag Index, DEG = degree, BC = betweenness centrality, Movement Assessment Battery for Children.
[†] Spearman's rho.
[‡] Significant after multiple comparison correction (Benjamini-Hochberg).
[*] $p < 0.001$.

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