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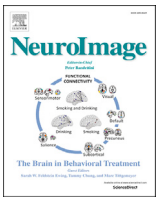

Multimodal assessment shows misalignment of structural and functional thalamocortical connectivity in children and adolescents born very preterm

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ABSTRACT

Thalamocortical connections are altered following very preterm birth but it is unknown whether structural and functional alterations are linked and how they contribute to neurodevelopmental deficits. We used a multimodal approach in 27 very preterm and 35 term-born children and adolescents aged 10–16 years: Structural thalamocortical connectivity was quantified with two measures derived from probabilistic tractography of diffusion tensor data, namely the volume of thalamic segments with cortical connections and mean fractional anisotropy (FA) within the respective segments. High-density sleep EEG was recorded and sleep spindles were identified at each electrode. Sleep spindle density and integrated spindle activity (ISA) were calculated to quantify functional thalamocortical connectivity. In term-born participants, the volume of the global thalamic segment with cortical connections was strongly related to sleep spindles across the entire head (mean $r = .53 \pm .10$; range = 0.35 to 0.78). Regionally, the volume of the thalamic segment connecting to frontal brain regions correlated with sleep spindle density in two clusters of electrodes over fronto-temporal brain regions ($.42 \pm .06$; 0.35 to 0.51 and $0.43 \pm .08$; 0.35 to 0.62) and the volume of the thalamic segment connecting to parietal brain regions correlated with sleep spindle density over parietal brain regions (mean $r = .43 \pm .07$; 0.35 to 0.61). In very preterm participants, the volume of the thalamic segments was not associated with sleep spindles. In the very preterm group, mean FA within the global thalamic segment was negatively correlated with ISA over a cluster of frontal and temporo-occipital brain regions (mean $r = -.53 \pm .07$; $-.41$ to $-.72$). No association between mean FA and ISA was found in the term-born group. With this multimodal study protocol, we identified a potential misalignment between structural and functional thalamocortical connectivity in children and adolescents born very preterm. Eventually, this may shed further light on the neuronal mechanisms underlying neurodevelopmental sequelae of preterm birth.

1. Introduction

Over the past decades, increasing numbers of preterm births have been reported, with infants born very preterm, i.e. those born before 32 weeks of gestation, accounting for 1% of all life-births in developed countries (Blencowe et al., 2012; Frey and Klebanoff, 2016; Rüegger et al., 2012). The majority of children and adolescents in contemporary cohorts of very preterm individuals grow up without any major disabilities, however, they remain at risk for deficits in a variety of neurodevelopmental domains – including lower general intellectual abilities and problems in higher-order cognitive functions (Adams et al., 2019; Brydges et al., 2018; Pascal et al., 2018). In parallel, impairments of brain development are frequently demonstrated, with both structure and function being affected. Structural injuries include perinatal brain injuries (Kidokoro et al., 2014; Miller et al., 2005), but also persistent global and regional grey and white matter alterations (Nosarti et al., 2008; Rogers et al., 2012; Taylor et al., 2011). Furthermore, disruptions of connectivity within and between structural (Fischi-Gómez et al., 2015;

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Pandit et al., 2013; Thompson et al., 2016) and functional (Gozzo et al., 2009; Schafer et al., 2009; Smyser et al., 2010; Wehrle et al., 2018) brain networks have been reported. Importantly, changes in different regions of the brain and in different imaging markers have been shown to be coupled (e.g., Ball et al., 2017).

The widespread alterations of the structural and functional neuroanatomy of the very preterm brain are assumed to largely depend on the impaired development of the thalamocortical system for the following reason: The establishment of thalamocortical connections, particularly to heteromodal cortical regions, are among the key neurogenetic events occurring during the last trimester of pregnancy, i.e., coinciding with the time of very preterm birth (Kostović and Judaš, 2010; Toulmin et al., 2015; Volpe, 2009). Thalamocortical connections play a critical role for the cortical organization, and the disruption of their formation may, thus, profoundly impact subsequent brain development (Kostović and Jovanov-Milošević, 2006).

The detrimental effects of very preterm birth on the 'developing thalamocortical connectome' (Ball et al., 2013) have been described repeatedly in infants using advanced structural and functional MRI techniques (Ball et al., 2013; Boardman et al., 2006; Counsell et al., 2007; Smyser et al., 2010; Toulmin et al., 2015). Preliminary evidence indicates that these impairments are associated with deficits in short-term cognitive outcome following very preterm birth (Ball et al., 2015). To date, it is unknown how the structural and functional integrity of the thalamocortical system is affected as very preterm infants reach adolescence, and how alterations are related to the increased risk of neurodevelopmental deficits observed in this population.

In this study, we thus aimed to examine whether structural and functional thalamocortical connectivity is altered in school-aged children and adolescents born very preterm compared to term-born peers. Particularly, we investigated whether structural and functional alterations co-occur and whether they are linked. For this, we applied a multimodal approach to gain a comprehensive understanding of the complex impact of preterm birth on the brain: Structural thalamocortical connectivity (i.e., neuroanatomical properties) was assessed by connectivity-based segmentation of the thalamus from probabilistic diffusion tensor tractography. This approach has been used previously in children and adolescents to investigate connectivity between the thalamus and the cortex (Alkonyi et al., 2011; Counsell et al., 2007; Nair et al., 2013). To assess functional thalamocortical connectivity, we examined spindles apparent in sleep EEG recordings. Sleep spindles are recurrent bursts of oscillation between 11 and 16 Hz during non-rapid eye movement (NREM) sleep, resulting from a complex interplay between thalamic nuclei and thalamocortical feedback-loops (Lüthi, 2013; Steriade, 2006). As EEG measures electrical activity of the brain directly, it provides proximal markers of brain functioning. In fact, sleep spindles are assumed to reflect global signal propagation between the thalamus and the cortex and, thus, have been described as electrophysiological markers of the integrity of the thalamocortical system in various physiological and pathological conditions (Andrillon et al., 2011; Ferrarelli et al., 2007; Latreille et al., 2015; Nir et al., 2011; Piantoni et al., 2013). Importantly, high-density EEG during sleep allows the monitoring of brain network activity over an extended period of time, independent of motivational and other factors related to wakefulness (Tononi and Cirelli, 2006). This characteristic may be particularly beneficial when studying children as other methods (e.g., fMRI) may be influenced by such factors (Lustenberger and Huber, 2012; Uddin et al., 2010). To the best of our knowledge, sleep spindles have not previously been investigated in children and adolescents born very preterm. This may, however, provide valuable information on the impact of preterm birth on functional thalamocortical connectivity. Moreover, sleep spindles have previously been linked to cognitive abilities in typically-developing children and adolescents (Bódizs et al., 2014; Chatburn et al., 2013; Geiger et al., 2011; Hahn et al., 2018). Thus, the investigation of sleep spindles may advance to the understanding of what underlies neurodevelopmental deficits following very preterm birth.

We hypothesize that in school-aged children and adolescents born very preterm, both structural and functional thalamocortical connectivity is impaired, with alterations in markers of structural and functional connectivity co-occurring and being linked. Further, we explore whether alterations in thalamocortical connectivity predict deficits in cognitive abilities.

2. Materials and methods

2.1. Participants and experimental design

Details on the experimental design of this study have been described previously (Wehrle et al., 2016, 2017, 2018). In summary, children and adolescents born very preterm were eligible to participate if they met the following criteria: They were born before 32 weeks of gestation at the University Hospital Zurich, Switzerland, they had not been diagnosed with severe brain injuries on neonatal ultrasound, they had shown normal motor and intellectual development at the age of 5 years at the routine follow-up consultation at the University Children's Hospital Zurich and they were between 10 and 16 years old at the time of the study. In total, 41 children and adolescents born very preterm participated. In addition, 43 typically-developing term-born children and adolescents were recruited. They were siblings and friends of very preterm participants or individuals recruited from local schools and through flyers. Inclusion criteria were birth at term ($\geq$37 weeks of gestation), no perinatal complications, no neurodevelopmental disorders such as attention-deficit-hyperactivity-disorder and aged between 10 and 16 years at the time of the assessment.

The study protocol included a neurodevelopmental assessment, an overnight sleep EEG recording and cerebral MR imaging. More precisely, an examiner who was aware of the birth status but unaware of the medical history of the participants conducted a neurodevelopmental assessment over the course of a full afternoon. Following dinner, the sleep EEG recording was prepared. Bed times were adjusted to the participants' habitual bedtimes and to their individual routines (e.g., school attendance). Either in the evening before dinner or in the morning following breakfast, participants underwent MR imaging. All data was collected between January and December 2013 at the Child Development Center, the Sleep Laboratory and the Center for MR Research, at the University Children's Hospital Zurich. The study was approved by the ethical committee of the Canton of Zurich, Switzerland. Parents and participants older than 15 years provided written informed consent, younger participants provided oral consent. Participants were compensated with a gift certificate and travel expenses were reimbursed.

2.2. Neurodevelopmental assessment

To investigate whether the markers of thalamocortical connectivity are related to general cognitive abilities, intelligence quotient (IQ) was estimated with four subtests of the Wechsler Intelligence Scale for Children, Forth edition (WISC-IV, German version; Petermann and Petermann, 2006). This subtest combination has been shown to correlate highly with the full version of the WISC-IV ($r = 0.95$) while retaining its conceptual format (Waldmann, 2008). Socio-economic status (SES) was estimated from maternal education and paternal occupation (Largo et al., 1989). Medical records were reviewed for perinatal and routine follow-up data of the very preterm participants.

2.3. MR imaging and preprocessing

MRI data was collected on a 3T GE MR750 whole-body scanner with an eight-channel receive-only head coil. Foam pads were placed inside the head coil around participants' heads and verbal instructions to stay still throughout the scanning session were given to minimize possible head movement. Earplugs and MR-compatible headphones were used to protect hearing. A high-resolution three-dimensional T1-weighted

spoiled gradient-recalled echo sequence (repetition time = 11 ms, echo time = 5 ms, inversion time = 600 ms, flip angle 8°) was used to acquire anatomical images of the entire brain. Diffusion tensor imaging data was collected with a pulsed gradient spin echo (PGSE) EPI sequence with 35 encoding directions, a b-value of 1000 s/mm^2, a repetition time (TR) of 6 s, an echo time of 80 ms, a field of view of 240 mm, an acquisition matrix of 96x96, and a slice thickness of 3 mm. The images were anatomically evaluated by an experienced neuroradiologist.

The three-dimensional T1-weighted images were segmented in native space with the Freesurfer image analysis suite, which is documented and freely available for download online (Fischl, 2012; http://surfer.nmr.mgh.harvard.edu; version 5.3.0). Masks used for subsequent probabilistic tractography were extracted for the thalamus, the white matter and the specified cortical regions of interest (ROIs), i.e., frontal lobe (including anterior cingulate), parietal lobe (including posterior cingulate), precentral gyrus, postcentral gyrus, temporal and occipital lobe (see Fig. 1A). The segmentation procedure has been shown to have good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006; Reuter et al., 2012) and was found to accurately align cortical landmarks in children's brains (Ghosh et al., 2010).

Pre-processing of DTI data involved eddy current correction (using FSL 'eddy correct'), fitting the diffusion tensor at each voxel (using FSL 'dtifit') and preparing the data for further probabilistic tractography (using FSL 'bedpostx'). The T1-weighted anatomical images were then registered from Freesurfer's conformed space (in which the images were segmented) to the native diffusion images for each participant using FSL-FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001). The same transformations were then applied to the extracted ROI images from Freesurfer (for the thalamus and the cortical lobes) in order to overlay the masks with the diffusion images. Finally, registrations were checked manually to ensure correct overlay of the co-registered images.

2.4. Probabilistic tractography and connectivity-based segmentation of thalamus

For the connectivity-based segmentation of the thalamus, generally, the method first described by Behrens et al. (2003) was used. This method allows tracing of connections between grey matter structures, i.e., the thalamus and cortical grey matter, using DTI data. In short, for each thalamic voxel, the probabilities for connectivity with a set of pre-defined cortical ROIs is calculated (Behrens et al., 2003, 2007). For the current analyses, Freesurfer-derived rather than manually delineated thalamic masks and cortical ROIs were employed (as described above). Probabilistic tractography was performed using FSL 'probtrackx2' for tracking thalamo-cortical connections, using the whole thalamus as a seed mask, the white matter as a waypoint mask, and each of the cortical ROIs as target masks. The tractography was performed using the following options in probtrackx2: curvature threshold = 0.2, number of steps per sample: 2000, steplength (mm) = 0.5, number of samples = 5000, volume fraction before subsidary fibre orientations are considered = 0.01. Tractography was run separately for the left and right hemispheres. Each thalamic voxel was classified according to the cortical ROI with which it had the highest probability of connectivity using the FSL "find_the_biggest" hard clustering approach. Thalamic voxels connecting to the same cortical ROI (as shown in Fig. 1A) were combined into segments. Of these segments, the volume was calculated by summing up the volume of the respective voxels within the segment. Further, mean fractional anisotropy (FA) was extracted for each segment by masking the FA maps for each participant with the corresponding regions for each thalamic segment, and calculating the mean FA within the masked region using fslmaths. This tractography method has proven to be reproducible between subjects (Behrens et al., 2003) and has been employed before in children and adolescents (e.g., Counsell et al., 2007; Nair et al., 2013). Fig. 1B illustrates the connectivity-based segmentation of the thalamus resulting from probabilistic tractography.

For further analyses of the volume of thalamic segments with cortical connections, the segment connecting to the frontal lobe was combined with the segment connecting to the precentral gyrus to account for potential labelling differences between participants resulting from small registration errors and to decrease the dependence on the segmentation of substructures within specific cortical lobes. Following the same line of reasoning, the segment connecting to the parietal lobe was combined with the segment connecting to the postcentral gyrus. The segment connecting to the occipital lobe was not considered for further analyses, since in four participants the thalamic segments with connectivity to the occipital lobe were very small, consisting of less than 10 voxels, and, thus, considered unreliable. Volumes of homologous thalamic segments connecting to the frontal/precentral, the parietal/postcentral and the temporal cortical ROIs were combined across hemispheres. Further, a global marker of structural thalamocortical connectivity was estimated by combining the volume of all thalamic voxels with connections to the cortex into one segment. For further analyses of mean FA within specific thalamic segments, the segments were derived using the identical regions of interest to those used for volumetric analyses. In order to derive the FA

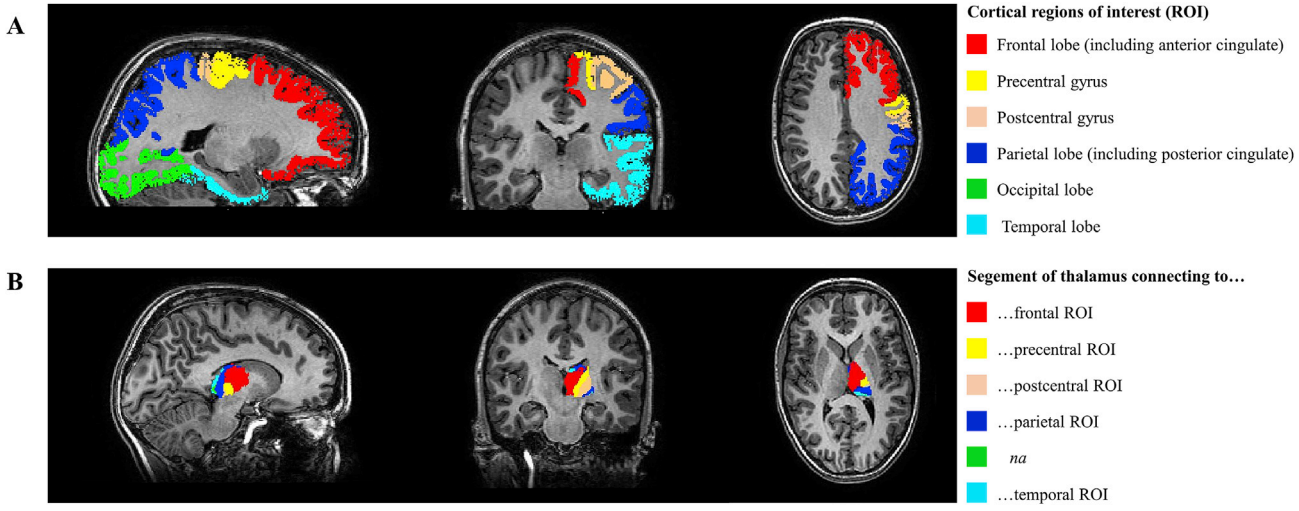

Fig. 1. Probabilistic tractography and connectivity-based segmentation of the thalamus. Illustration of cortical regions of interest (A) and connectivity-based segmentation of the thalamus (B) of one exemplary participant (very preterm girl, aged 14.1 years at assessment). Sagittal, coronal and axial view. *na*: Thalamic voxels with connections to the occipital lobe were not considered for further analyses of regional associations between structural and functional markers of thalamocortical connectivity (please refer to the text for details).

across regions consisting of multiple segments, a weighted average of the FA was calculated, by multiplying the FA of each specific segment by the respective volume, summing and normalizing by the volume of all considered segments.

All these global and regional markers of structural thalamocortical connectivity (i.e., volume and mean FA of the described thalamic segments) were used for further statistical analyses.

Of the 41 very preterm and 43 term-born participants, one very preterm participant refused MR scanning at the day of testing and one was excluded from further analyses due to an arachnoid cyst and subsequent left cerebellar hypoplasia. Two very preterm participants showed mild dilatation of the lateral ventricles, this was, however, not of clinical significance and participants were retained for further analyses. No other brain abnormalities were seen on conventional images. Further, DTI quality was insufficient for probabilistic tractography, due to dental braces ($n = 15$), excessive head movement ($n = 2$) or missing DTI data ($n = 2$). Thus, for 28 very preterm and 35 term-born participants, probabilistic tractography data and subsequent connectivity-based segmentation data for the thalamus were available.

2.5. All-night sleep EEG recording and preprocessing

Sleep was recorded with a high-density EEG amplifier with 128 channels (Electrical Geodesic Inc.). Detailed information regarding data acquisition and pre-processing has been described previously (Wehrle et al., 2017). In short, nets were adjusted to the vertex, electrodes were filled with gel electrolyte to allow long-term monitoring and impedances were kept below 50 kΩ. The sampling rate was set to 500 Hz (filtered between 0.01 and 200 Hz) and the EEG data was referenced to the vertex (Cz). Further processing steps included band-pass filtering between 0.5 and 40 Hz, downsampling to 128 Hz, sleep staging according to standard criteria (Iber et al., 2007), semi-automated artefact-correction (Lustenberger et al., 2014) and re-referencing to the average of all 109 good quality channels above the ears.

Of the 41 very preterm participants, two refused the overnight stay in the sleep laboratory on the day of testing, thus no EEG was recorded. For one very preterm participant, EEG data was lost due to technical difficulties. Thus, sleep EEG data was available for 38 very preterm and 43 term-born participants.

2.6. Automated sleep spindle detection

An algorithm to automatically detect sleep spindles as developed by Ferrarelli et al. (2007) was employed to identify spindle events during the first hour of artefact-free NREM sleep. This time interval constitutes the most consolidated part of sleep and consists of the same number of sleep epochs in all participants, thus, accounting for individual differences in the duration of sleep episodes. In short, the EEG signal was band-pass filtered between 10 and 16 Hz. Spindle events in the filtered signal were identified for each channel separately if the signal fell between a lower threshold of 2 times the mean of the filtered signal and an upper threshold of 6 times the mean of the filtered signal. The upper threshold was modified from the original algorithm (Ferrarelli et al., 2007) as detection performance has been shown to be optimal with 6 times the mean of the signal (Warby et al., 2014). This algorithm has previously been successfully applied in children to detect sleep spindles (McClain et al., 2016; Page et al., 2018). Sleep spindle density (i.e., the number of sleep spindles per minute NREM sleep) and integrated spindle activity (ISA, i.e., integrated amplitude over time of each spindle) was calculated electrode-wise for all 109 good-quality channels above the ears. Density has previously been reported to reflect trait-like aspects of sleep spindles, i.e., sleep spindle density is thought to be relatively stable over time and not restricted to specific situations (Lustenberger et al., 2014). ISA combines information on amplitude and duration of individual spindles and has previously been reported as a reliable marker of impaired thalamocortical connectivity (Ferrarelli et al., 2007). Thus, sleep spindle density and ISA were chosen as markers of functional thalamocortical connectivity in this study.

2.7. Statistical analyses

For further statistical analyses, only participants with complete datasets were retained, i.e., when data was available for markers of structural and functional thalamocortical connectivity and estimated IQ. This resulted in a final sample of 27 very preterm and 35 term-born participants. Participants excluded from further analyses did not differ from those who were retained with regard to birth status ($p = .11$), sex ($p = .15$), SES ($p = .15$) and IQ ($p = .11$). Those excluded were significantly older than those who were retained for further analyses ($p = .04$). Results are reported as means, standard deviations and range (M [SD], range) if not otherwise specified. Groups were compared with Chi-square test for categorical variables and independent Student's *t*-test for continuous variables. Non-parametric alternatives were applied in case of violation of assumptions of normal distribution.

Electrode-wise Spearman correlations were performed between sleep spindle density/ISA and the volume/mean FA of the global thalamic segment connecting to any cortical region and the volume/mean FA of the thalamic sub-segments connecting to either the frontal/precentral, the parietal/postcentral or the temporal cortical ROI, respectively. Correlation coefficients were calculated separately for the very preterm and the term-born group and compared between groups using Fisher's *r*-to-*z* transformation. Only clusters consisting of at least seven significant neighboring electrodes were considered, as 6 out of 109 electrodes are expected to be false positives at an alpha level of 0.05. Mean correlations within clusters were calculated after *r*-values were z-transformed (Corey et al., 1998).

Separate linear regression models for the very preterm and the term-born group were used to investigate the associations between thalamocortical connectivity and estimated IQ: In both groups, the predictive value of socio-demographic variables (i.e., sex, age at assessment and family SES) and markers of structural thalamocortical connectivity (i.e., volume/mean FA of thalamic segment with cortical connections), functional thalamocortical connectivity (i.e., sleep spindle density/ISA) and the interaction between these markers for estimated IQ was assessed. Continuous predictors were mean-centered before being entered into the model.

All analyses were performed using MATLAB (MathWorks) and *R* (Bengtsson, 2015; Fletcher, 2012; R Core Team, 2015, 2016; Revelle, 2017; Wickham, 2016). The significance level was set at $p < .05$ (two-tailed).

2.8. Data availability

The approval granted by the ethical committee does not allow the publication of the raw data online. If readers would like to re-analyze the data set (for different purposes), additional ethical approval (on an individual user and purpose basis) will be required. The authors are happy to support additional ethical approval applications from researchers for access to this data set.

3. Results

3.1. Participant characteristics

Mean gestational age in the very preterm group was 29.6 weeks (1.9; 25.4–32.0), mean birth weight was 1290 g (343; 840–1990). All term-born participants were born after 37 weeks of gestation and with a birthweight of more than 2500 g (see Table 1 for detailed perinatal data). Participant characteristics are summarized in Table 1. Age at assessment, sex distribution and SES were not significantly different between the two groups ($U = 476$, $p = .97$, χ^2 (1) $= 0.02$, $p = .89$ and $U = 599$, $p = .07$, respectively). Also, the group difference in estimated IQ was not

Table 1
Participant characteristics.

	Very preterm participants ($n = 27$)	Term-born participants ($n = 35$)	p
Demographic and socio-economic data			
Age at assessment in years (M [SD], range)	12.7 [1.5], 10.6–15.8	12.8 [2.0], 10.0–16.9	.97
Sex (male/female)	16/11	19/16	.89
SES[a] (M [SD], range)	9.3 [1.8], 6 - 12	10.1 [1.6], 7 - 12	.07
Perinatal characteristics			
Gestational age in weeks (M [SD], range)	29.6 [1.9], 25.4–32.0	≥ 37.0	
Birthweight in grams (M [SD], range)	1290 [343], 840 - 1990	≥ 2500	
SGA, n (%)	2 (7.4)	na[d]	
BPD, n (%)	4 (14.8)		
NEC, n (%)	1 (3.7)		
ROP ≥ grade 3, n (%)	0 (0.0)		
PDA, n (%)	10 (37.0)		
Sepsis, n (%)	5 (18.5)		
Twin, n (%)	7 (25.9)[b]		
Chorioamnionitis, n (%)	5 (18.5)		
Brain injury[c]			
No brain injuries, n (%)	18 (66.7)		
IVH Grade I or II, n (%)	9 (33.3)		
Neurodevelopmental assessment			
Estimated IQ (M [SD], range)	105.6 [6.2], 94 - 118	109.4 [7.1], 99 - 129	.09

[a] Mean value of maternal education and paternal occupation; 2 = lowest SES, 12 = highest SES.
[b] Three pairs of twins, one individual twin.
[c] brain injuries seen on neonatal ultrasound.
[d] Parents reported no perinatal complications. (ROI). BPD: Bronchopulmonary dysplasia; IVH: Intraventricular hemorrhage; NEC: Necrotizing enterocolitis; PDA: Patent ductus arteriosus; ROP: Retinopathy of prematurity; SES: socio-economic status; SGA: small for gestational age.

significant ($U = 353$, $p = .09$).

3.2. Group differences in structural and functional thalamocortical connectivity

Total brain volume (based on Freesurfer segmentation) was not different between the very preterm and the term-born group ($M = 1130$ cm^3, $SD = 93$ cm^3 and $M = 1159$ cm^3, $SD = 98$ cm^3, respectively, $p = .24$) and not associated with age at assessment ($r = 0.07$, $p = .58$). Thus, total brain volume was not considered for further analyses.

While the expected patterns of thalamocortical connectivity were found for both groups (Behrens et al., 2003), no difference between the very preterm and the term-born group was found for any of the markers of structural thalamocortical connectivity, i.e., neither the volume/mean FA of the global thalamic segment connecting to any cortical ROI nor the volumes/mean FA of the thalamic segments with region-specific cortical connections was significantly different between the groups (see Table 2).

Sleep efficiency (i.e., total time asleep as percentage of total time in bed) was high and similar between the very preterm and the term-born group (86.2 [9.4]; 57.7–96.4% and 86.3 [8.9]; 60.3–96.3%, respectively in the very preterm and term-born group, $p = .96$). None of the assessed sleep architecture parameters were different between the groups (e.g., amount of NREM sleep; data not shown). Neither the topographical distribution across the head (Fig. 2A, no cluster ≥ 7 electrodes) nor mean sleep spindle density averaged across all electrodes ($p = .30$, Table 2) were significantly different between the groups. ISA was significantly higher in the very preterm group over frontal and occipito-temporal brain regions compared to the term-born group (Fig. 2B). ISA averaged across all electrodes was significantly higher in the very preterm compared to the term-born group ($p = .03$, Table 2).

Table 2
Parameters of structural and functional markers of thalamocortical connectivity.

	Very preterm participants ($n = 27$)	Term-born participants ($n = 35$)	p
Structural thalamocortical connectivity			
Volume of thalamic segments[a]			
Volume of global segment	16.4 [2.0]; 12.3–20.0	17.0 [2.1]; 11.9–20.9	.25
Volume of frontal/precentral segment	9.2 [2.0]; 3.7–12.1	9.7 [1.8]; 4.7–14.1	.50
Volume of parietal/postcentral segment	4.6 [1.1]; 1.7–6.9	4.3 [1.1]; 2.4–7.0	.40
Volume of temporal segment	2.3 [0.8]; 0.6–4.2	2.7 [0.9]; 1.0–4.2	.15
FA within thalamic segments[b]			
FA within global segment	0.29 [0.2]; 0.26–0.39	0.29 [0.2]; 0.24–0.35	.52
FA within frontal/precentral segment	.29 [.04]; .25-.40	.30 [.03]; .24-.38	.44
FA within parietal/postcentral segment	.30 [.03]; .26-.42	.30 [.02]; .25-.38	.44
FA within temporal segment	.26 [.02]; .23-.32	.27 [.02]; .21-.32	.59
Functional thalamocortical connectivity			.55
Mean sleep spindle density across all electrodes[c]	4.6 [1.4]; 2.6–9.2	4.3 [1.3]; 2.3–9.1	.30
Mean ISA across all electrodes (μVs)[d]	861.7 [267.0]; 440.4–1655.7	706.3 [284.3]; 279.3–1472.6	.03

[a] Volume of thalamic segments connecting to different cortical regions of interest (in cm^3).
[b] Fractional anisotropy (FA) within segments connecting to different cortical regions of interest.
[c] Sleep spindle density in #/minute.
[d] ISA: Integrated spindle activity.

Thus, structural thalamocortical connectivity was not different between the very preterm and term-born group while ISA but not spindle density was increased in the very preterm compared to the term-born group. Next, we investigated the association between these markers.

3.3. Association between markers of structural and functional thalamocortical connectivity

Fig. 3 depicts the Spearman correlation coefficients calculated within each group between sleep spindle density at each electrode and the volume of the global thalamic segment and the individual thalamic segments connecting to different cortical ROIs, separately. In the term-born group, for the volume of the global thalamic segment connecting to any cortical region (Fig. 3A), significant positive associations were found with sleep spindle density in 103 electrodes (mean r across all significant electrodes = 0.53 [0.10]; 0.35 to 0.78). No significant correlations were apparent in the very preterm group. A direct group comparison revealed that the correlation coefficients were significantly different between the two groups in 75 electrodes distributed across the head (mean r in this cluster 0.54 [0.12]; 0.27 to 0.78 in the term-born group and -.15 [0.10]; -.37 to 0.10 in the very preterm group, respectively; Supplementary Figure 1A).

Correlating sleep spindle density at every electrode separately with the volumes of the thalamic segments connecting to the frontal/precentral, to the parietal/postcentral and to the temporal cortical ROI respectively, revealed regionally specific associations in the term-born group (Fig. 3B): The volume of the thalamic segment connecting to the frontal/precentral ROI was positively related to sleep spindle density in two large clusters of 12 and 19 electrodes over fronto-temporal brain regions (mean r across significant electrodes within clusters = 0.42 [0.06]; 0.35 to 0.51 and 0.42 [0.08]; 0.35 to 0.62, respectively). The volume of the thalamic segment connecting to the parietal/postcentral ROI was positively related to sleep spindle density in a cluster of 25

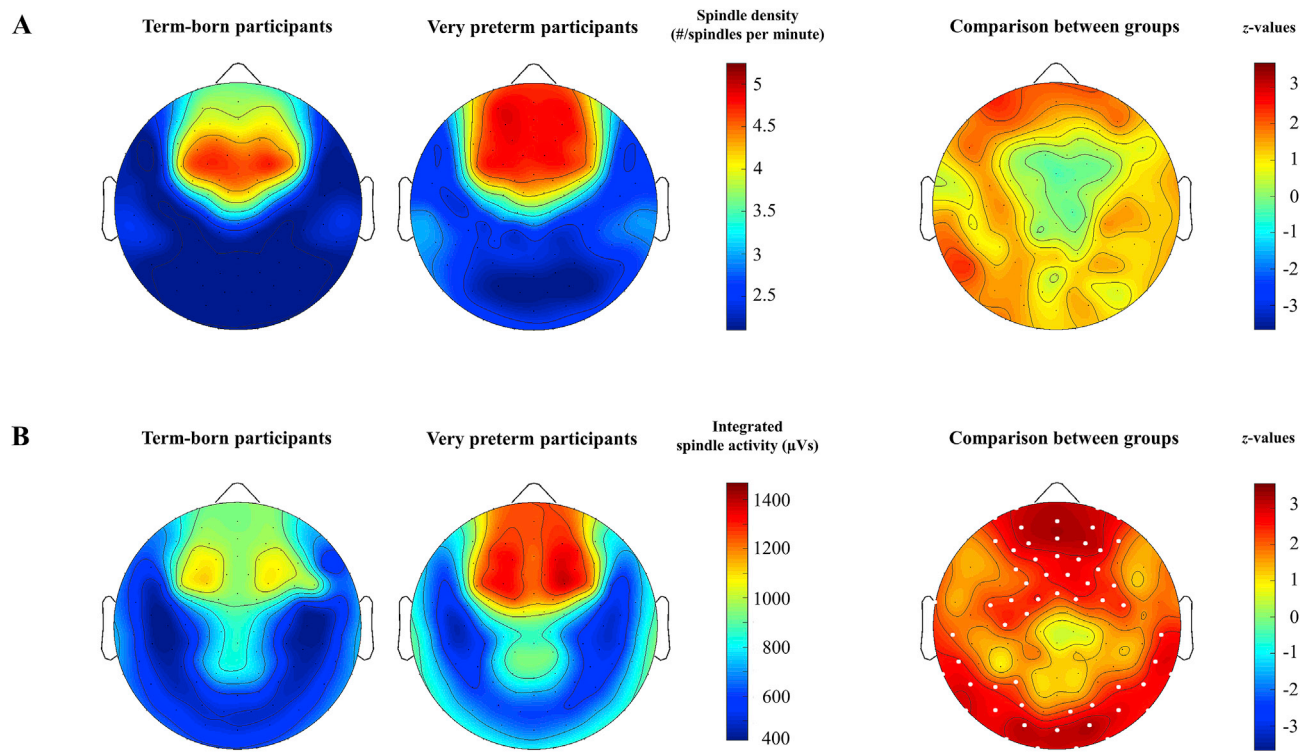

Fig. 2. Difference in sleep spindle density and integrated spindle activity between very preterm and term-born children and adolescents. Results of the electrode-wise comparison of sleep spindles density (A) and integrated spindle activity (B) between the very preterm and the term-born group is plotted on the planar projection of the hemispheric scalp model. White dots indicate significant differences ($p < .05$; only clusters with ≥7 electrodes are considered significant; please refer to text for details).

electrodes over central and parietal brain regions (mean r across significant electrodes within cluster = 0.43 [0.07]; 0.35 to 0.61). The thalamic volume connecting to the temporal ROI was not significantly related to sleep spindle density. No significant correlations between the volume of any of the thalamic sub-segments and sleep spindle density were found in the very preterm group.

Fig. 4 shows the Spearman correlation coefficients calculated within each group between ISA at each electrode and mean FA of the global thalamic segment and the individual thalamic segments connecting to different cortical ROIs, separately. In the very preterm group, significant negative associations were found in a cluster of 51 electrodes over frontal and temporo-occipital brain regions (mean r across all significant electrodes = -.53 [0.07]; -.41 to -.72). No significant correlations were apparent in the term-born group. A direct group comparison revealed that the correlation coefficients were significantly different between the two groups in 13 distributed electrodes without forming a cluster of ≥7 electrodes.

Correlating ISA at every electrode separately with mean FA of the thalamic segments connecting to the frontal/precentral, to the parietal/postcentral and to the temporal cortical ROI respectively, revealed no clear pattern of regional associations (Fig. 4B).

Neither in the very preterm nor in the term-born group, any significant correlations between sleep spindle density at each electrode and mean FA within the global thalamic segment or between ISA at each electrode and the volume of the global thalamic segment were observed (all $p > .05$, no cluster ≥ 7 electrodes). The reported patterns were similar when comparing subgroups of very preterm children with and without signs of intraventricular hemorrhage grade I/II (data not shown).

3.4. Association between thalamocortical connectivity and estimated IQ

Finally, we explored whether sociodemographic variables and the markers of structural and functional thalamocortical connectivity were predictive of estimated IQ. For this, mean sleep spindle density and mean ISA across all electrodes was calculated to reflect markers of global functional thalamocortical connectivity. The volume and mean FA of the global thalamic segment connecting to the cortex were used as markers of global structural thalamocortical connectivity.

In the very preterm group, estimated IQ was significantly predicted by the model including socio-demographic variables (namely, age at assessment, sex and family SES), the volume of the global thalamic segment with cortical connections, mean sleep spindle density across all electrodes and the interaction of these markers ($F(6, 20) = 3.678$, $p = .05$, adjusted $R^2 = 0.38$). Family SES ($\beta = 0.50$, $p = .01$) but not age at assessment or sex ($p > .05$) predicted estimated IQ. Further, while the individual markers of thalamocortical connectivity did not significantly predict estimated IQ ($p > .05$), their interaction did ($\beta = 0.47$, $p = .04$). In the term-born group, these predictors did not significantly contribute to explaining estimated IQ ($F(6, 28) = 1.457$, $p = .31$, adjusted $R^2 = 0.08$). The model including socio-demographic variables, mean FA within the global thalamic segment with cortical connections and mean ISA across all electrodes did not significantly predict estimated IQ, neither in the very preterm nor in the term-born group ($F(6, 20) = 2.203$, $p = .17$, adjusted $R^2 = 0.22$ and $F(6, 28) = 1.085$, $p = .40$, adjusted $R^2 = 0.01$, respectively; p-values of overall models are adjusted according to the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) to account for multiple testing).

4. Discussion

In this study, we used a multimodal approach including diffusion tensor MRI and high-density EEG during sleep to investigate structural and functional markers of thalamocortical connectivity in school-aged children and adolescents born very preterm and at term. Thereby, we identified a striking misalignment of structure and function in very preterm individuals in the absence of any large-scale differences in the

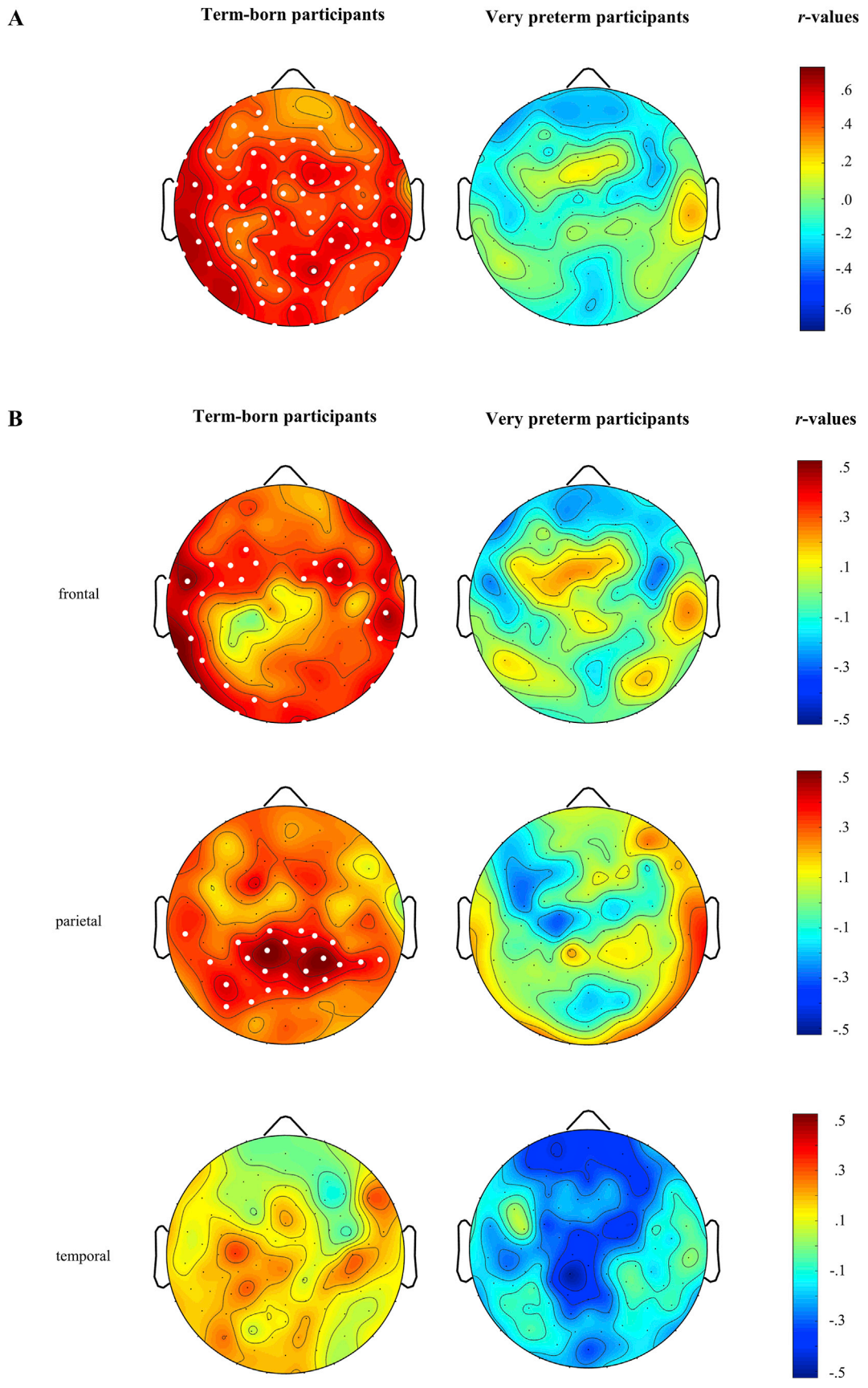

Fig. 3. Associations between the volume of thalamic segments with cortical connections and sleep spindle density. Global (A) and regional (B) associations between the volume of thalamic segments with cortical connections and sleep spindle density at every electrode within the very preterm and the term-born group are shown. White dots mark electrodes with significant *r*-values (Spearman correlation $p < .05$; only clusters with ≥7 electrodes are considered significant; please refer to text for details).

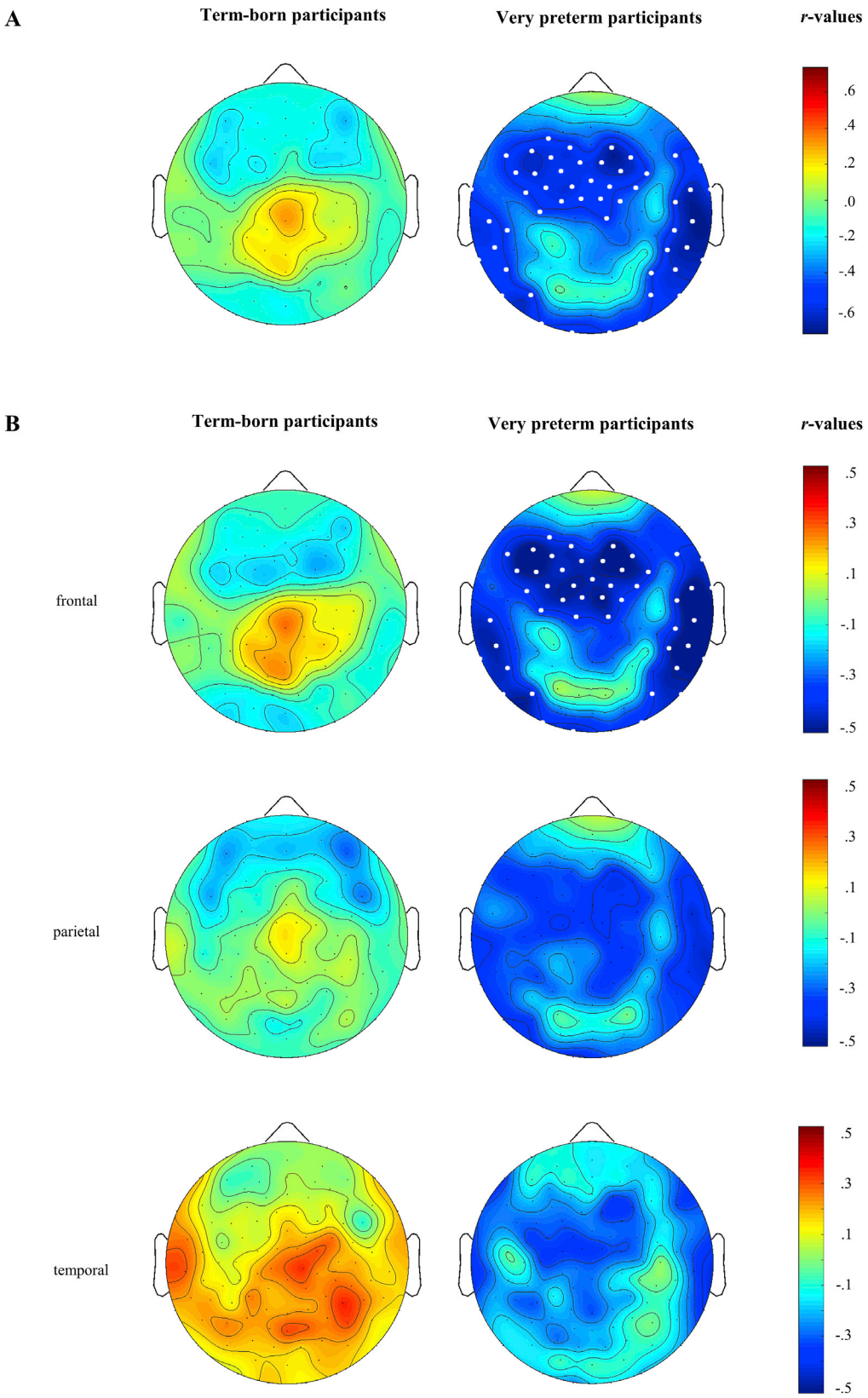

Fig. 4. Associations between mean FA within thalamic segments with cortical connections and integrated spindle activity (ISA). Global (A) and regional (B) associations between mean FA within thalamic segments with cortical connections and ISA at every electrode within the very preterm and the term-born group are shown. White dots mark electrodes with significant *r*-values (Spearman correlation $p < .05$; only clusters with ≥7 electrodes are considered significant; please refer to text for details).

individual markers of connectivity compared to term-born peers. However, the markers of structural and functional thalamocortical connectivity contributed only moderately to predicting neurodevelopmental outcome in this high-functioning group of very preterm children and adolescents.

It has been suggested previously that combining complementary neuroimaging methods may hold great potential to advance our understanding of the complex patterns of altered brain development following preterm birth (see Tusor et al., 2014 for a review). The findings of the current study provide compelling evidence in this regard: When comparing markers of structural and functional thalamocortical connectivity separately between very preterm and typically-developing children and adolescents, alterations were observed only in one of the assessed markers. Neither the volume of thalamic segments with cortical projections nor the microstructural properties within these segments (indexed as mean FA) differed between the groups. Moreover, the density of sleep spindles was similar in both groups. Only integrated spindle activity was found to be higher over frontal and occipito-temporal brain regions in the very preterm compared to the term-born group. However, jointly investigating these markers of thalamocortical connectivity revealed marked differences between the two groups: In typically-developing children and adolescents, globally, the volume of thalamic segments with cortical projections was strongly correlated with sleep spindle density over the entire cortex. Further, region-specific associations between structural and functional markers of connectivity were apparent in frontal and central cortical regions. This is in line with the assumption that functional connectivity, generally, reflects structural connectivity, even if the exact alignment may not be straightforward and is still a matter of debate (see Damoiseaux and Greicius, 2009 for a review). In contrast to the typically-developing group, in the very preterm group the alignment between these structural and functional markers of thalamocortical connectivity was completely absent. Even more, investigating mean FA and ISA – two other markers of structural and functional thalamocortical connectivity – also revealed a differential pattern of association between the two groups: In the term-born group, no association between these two markers was found. In contrast, in the very preterm group, mean FA was negatively associated with ISA in a widespread area of frontal, central, temporal and occipital brain regions, without any region-specific patterns being apparent. This negative association between structural and functional markers of thalamocortical connectivity is contrary to what may be expected from previous findings: In typically-developed adults, positive associations between spindle power and the microstructural integrity of white matter tracts of frontal and temporal cortical regions and within and surrounding the thalamus have been found (Piantoni et al., 2013). Methodological differences (*e.g.*, focus on thalamocortical connectivity vs. whole-brain white matter tracts) limit the direct comparison of the results and additional studies need to confirm these findings. Nonetheless, the inverse association in the very preterm group does provide further hints of a misalignment of structural and functional thalamocortical connectivity following preterm birth. Importantly, only the employment of a multimodal approach was able to reveal the interrelated alterations of structural and functional neuroanatomy in the preterm brain. Along the same lines, in very preterm infants, a variety of independent patterns of neuroanatomical variations have previously been identified through a data-driven analysis combining multiple imaging modalities (Ball et al., 2017).

While the benefit of the concurrent assessment of structure and function may hold generally true for investigating the preterm brain, in the current study, we specifically focused on thalamocortical connections. Their establishment coincides with the time of very preterm birth, thus, placing the 'developing thalamocortical connectome' (Ball et al., 2013) at particular risk for impairments (Kostović and Jovanov-Milošević, 2006; Volpe, 2009). Indeed, a number of previous studies in very preterm infants have reported impaired thalamocortical connectivity: For example, Ball et al. (2013) mapped structural thalamocortical connections across the whole cortex and reported widespread connectivity reductions. Also, less mature functional networks were reported in an fMRI study, specifically with regard to thalamocortical connections (Smyser et al., 2010). Toulmin et al. (2015) further found reduced functional connectivity between the thalamus and heteromodal cortices while connectivity was increased between the thalamus and primary sensory cortices in very preterm compared to term-born infants. Also, at seven years of age, structural connectivity between the thalamus and the motor cortex was reduced in very preterm children compared to typically-developing peers (Thompson et al., 2019) and in very preterm adults, substantial alterations of the subcortical (thalamic)-cortical system have also been reported (Bäuml et al., 2014; Meng et al., 2016).

In contrast to these previous findings, in the current study, differences in the individual markers of thalamocortical connectivity were limited to ISA while none of the other markers were significantly different between the two groups. This, likely, resulted from methodological aspects of the current study, namely, the inclusion of only healthy, typically-developing very preterm individuals (as detailed in the methods section and further discussed in the limitations section). Rather, we observed a complex pattern of structure-function-misalignment in very preterm individuals. Interpreting these findings against those of previous studies is difficult as this is the first study to investigate structural and functional thalamocortical connectivity concurrently in very preterm individuals. Previously, a MR study investigating connectome formation in very preterm infants before term-equivalent age found a clear overlap between the structural and functional connectivity layout and an increase in structural-functional-coupling between 30 and 40 weeks of gestational age (van den Heuvel et al., 2014). However, this study focused on cortical nodes and did not take the thalamus into account. It, thus, remains unclear whether the finding of altered structure-function-alignment may be conferred to thalamocortical connections, i.e., connections particularly vulnerable to impairments due to risk factors associated with preterm birth (e.g., Ball et al., 2013; Boardman et al., 2006). Along those lines, a study in very preterm adults reported concurrent alterations of grey matter volume and intrinsic network connectivity in overlapping regions of the ventral brain, particularly the thalamus (Bäuml et al., 2014).

Previously, impairments in thalamocortical connectivity have been implicated in a number of clinical conditions, particularly, in schizophrenia (Ferrarelli et al., 2007, 2010; Woodward and Heckers, 2016) and in autism spectrum disorder (ASD) (Nair et al., 2013, 2015). Interestingly, these are two neuropsychiatric disorders very preterm individuals are at an increased risk for developing (Johnson and Marlow, 2011; Nosarti et al., 2012). Strikingly, a study in children and adolescents with ASD reported a less reliable overlap between structural and functional connectivity-based thalamic parcellation in the patient compared to the typically-developing group (Nair et al., 2013). Together with the findings of the current study, this may suggest a specific misalignment between structure and function in conditions of impaired thalamocortical connectivity such as preterm birth, ASD or schizophrenia.

Neurodevelopmental deficits including lower general cognitive abilities, executive dysfunctioning and poor academic abilities are frequent in very preterm children and adolescents even in the absence of major neurodevelopmental impairments (Aarnoudse et al., 2009; Brydges et al., 2018; Latal, 2009; Twilhaar et al., 2018). Importantly, intact thalamocortical connectivity has previously been shown to be essential for efficient cognitive functioning: For example, functional connectivity, particularly within the thalamus-salience network, predicted cognitive abilities at one year of age in healthy infants who underwent fMRI as neonates (Alcauter et al., 2014). Also, different features of sleep spindles – characterizing the integrity of the thalamocortical system (e.g., number of spindles) – have been linked to cognitive abilities in children, adolescents and adults (e.g., Bódizs et al., 2014; Chatburn et al., 2013; Geiger et al., 2011; Hahn et al., 2018; Lustenberger et al., 2012; Schabus et al., 2006). Recently, a study in a large cohort of adolescents could, however, not confirm an association between spindle characteristics and cognitive abilities (Pesonen et al., 2019). In very preterm infants, global structural thalamocortical connectivity has previously been shown to predict

cognitive outcome at two years of age (Ball et al., 2015). Also, a study in very preterm children at six years of age reported reduced structural connectivity in a cortico-basal ganglia-thalamo-cortical loop to be associated with lower cognitive abilities and poorer socio-emotional skills (Fischi-Gómez et al., 2015). In contrast, Thompson et al. (2019) only found evidence for an association between thalamocortical connectivity and motor abilities but not IQ, executive functions or general behavioral problems. In adults born very preterm, an association between impairments in structural subcortical-cortical connectivity and lower IQ has been reported (Meng et al., 2016). The current study explored how global structural and functional thalamocortical connectivity, jointly, are related to general cognitive abilities, namely IQ. The results suggest that the markers of thalamocortical connectivity employed in this study contribute only moderately to predicting neurodevelopmental outcome in a cohort of high-functioning very preterm children and adolescents. Likely, the complex patterns of altered brain development identified here do not translate into neurodevelopmental deficits in a linear fashion or are masked by other factors. Recognizing these complex patterns is, however, essential in the search for the causes of neurodevelopmental deficits in very preterm individuals. Along these lines, Ball and colleagues identified a set of multimodal imaging markers comprising volumetric and microstructural information to jointly predict neurodevelopmental outcome in very preterm infants (Ball et al., 2017). Notably, in the current study, family SES was a strong predictor of estimated IQ. Similarly, Ball et al. (2015) also reported a strong effect of family SES when investigating the impact of impaired thalamocortical connectivity on neurodevelopmental outcome in two-year old very preterm children. Future studies should continue to investigate the impact of altered structural and functional thalamocortical development on long-term outcome in very preterm children and adolescents, taking into account individuals with varied degrees of impairment (see also limitations section for details). The findings of the studies so far do, however, highlight the importance of also taking into account factors other than those related to neuroanatomy when investigating what may underlie neurodevelopmental deficits following preterm birth.

4.1. Limitations

While this study adds to the current understanding of how preterm birth impacts brain development, several limitations need to be taken into account. First, the study groups were relatively small with 27 very preterm and 35 term-born individuals with complete datasets being included into the analyses. Consequently, the absence of significant group difference in individual structural and functional markers of thalamocortical connectivity, potentially, may be explained by the limited statistical power due to the small sample size. The comprehensive study protocol, including an overnight stay at the University Children's Hospital Zurich prohibited the inclusion of a larger sample to overcome this issue. Nonetheless, we identified striking differences in the structure-function-alignment between the very preterm and the term-born group. This feature of altered neuroanatomy following preterm birth may, thus, be particularly relevant as the effects are large enough to be detected even in relatively small samples.

Secondly, the very preterm group consisted of only high-functioning individuals with cognitive abilities in the normal range and no severe brain injuries on neonatal ultrasound. It has been noted previously that connectivity studies frequently include only the healthiest of the preterm population, likely introducing a bias towards underestimation of connectivity impairments following preterm birth (Kwon et al., 2016). Presumably, the selection of this particular group of children and adolescents has further contributed to the absence of any obvious group differences in structural and functional markers of thalamocortical connectivity. However, the identification of specific patterns of neuroanatomical alterations (as discussed above) in this group of individuals may be of particular relevance as children and adolescents without any severe neurodevelopmental impairments account for the majority of today's very preterm cohorts (Adams et al., 2019).

Thirdly, for the connectivity-based segmentation of the thalamus, we chose relatively large cortical ROIs (i.e., frontal/precentral, pariental/postcentral, temporal). While this approach generally follows that of previous studies (e.g., Fair et al., 2010; Nair et al., 2013), it limits the detailed investigation of connectivity with smaller functional regions. To investigate the link between alterations in thalamocortical connectivity and general cognitive abilities – which are thought to rely on a distributed neuronal system (e.g., Gläscher et al., 2010) – this may nonetheless be appropriate. Also, Toulmin et al. (2015) found rather widespread and overlapping thalamic representations, particularly of heteromodal cortical regions, when assessing functional thalamocortical connectivity in infants. The current study provides evidence for the appropriateness of employing two very distinct methods, i.e., DTI and high-density EEG, to investigate structure-function-associations and respective alterations thereof in individuals at risk for thalamocortical impairments. With the increased use of multimodal assessments of thalamocortical connectivity in the future, it will be important to investigate these connections and their association among each other and with particular neurodevelopmental abilities in more detail. Along the same line, additional parameters to quantify thalamocortical connectivity should be taken into account in future studies.

Further, children and adolescents who were included in the final sample were approximately one year younger than those who were excluded due to missing data in any of the relevant parameters. Likely, this age difference may be explained by the fact that artefacts due to dental braces were the primary reason for exclusion and it becomes more likely that children wear dental braces when they are older. Lastly, twin status was not considered in the analyses because no reliable information was available on whether twin pairs were mono- or dizygotic (i.e., informing about genetic similarity). The inclusion of siblings of very preterm participants and pairs of term-born siblings into the control group further complicated the adequate consideration of similarity between pairs of participants within and across the two groups. Future studies should assess relevant data systematically to address these issues.

5. Conclusion

This study strongly supports the use of multimodal techniques when investigating the impact of preterm birth on brain development: The parallel assessment of structural and functional features of neuroanatomy, for example of the thalamacortical system, in the same individuals is necessary for a comprehensive understanding of potential alterations. This conclusion may be particularly true for today's and future cohorts of very preterm individuals, in which overt brain lesions seem to be replaced by complex patterns of interrelated alterations of brain structure and function. Eventually, investigating such complex patterns may shed further light on the neuronal mechanisms underlying neurodevelopmental sequelae of preterm birth.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

CRediT authorship contribution statement

Flavia M. Wehrle: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Caroline Lustenberger:** Software, Formal analysis, Writing - review & editing. **Andreas Buchmann:** Software, Writing - review & editing. **Beatrice Latal:** Conceptualization, Writing - review & editing. **Cornelia F. Hagmann:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition. **Ruth L. O'Gorman:** Conceptualization, Methodology, Software, Writing - review & editing, Visualization. **Reto Huber:** Conceptualization, Methodology, Writing - original draft, Supervision.

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Appendix A. Supplementary data

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