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**Title:**

Decreased BOLD fluctuations in lateral temporal cortices of premature born adults

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**Abstract:**

Lasting volume reductions in subcortical and temporal-insular cortices after premature birth suggest altered ongoing activity in these areas. We hypothesized altered fluctuations in ongoing neural excitability and activity, as measured by slowly fluctuating blood oxygenation of resting-state functional MRI (rs-fMRI), in premature born adults, with altered fluctuations being linked with underlying brain volume reductions.

To investigate this hypothesis, 94 very preterm/very low birth weight (VP/VLBW) and 92 full-term (FT) born young adults underwent structural and rs-fMRI data acquisition with voxel-based morphometry and amplitude of low-fequency fluctuations(ALFF) as main outcome measure.

In VP/VLBW adults, ALFF was reduced in lateral temporal cortices, and this reduction was positively associated with lower birth weight. Regions of reduced ALFF overlapped with reduced brain volume. On the one hand, ALFF reduction remained after controlling for volume loss, supporting the functional nature of ALFF reductions. On the other hand, ALFF decreases were positively associated with underlying brain volume loss, indicating a relation between structural and functional changes. Furthermore, within the VP/VLBW group, reduced ALFF was associated with reduced IQ, indicating the behavioral relevance of ALFF decreases in temporal cortices.

These results demonstrate long-term impact of premature birth on ongoing BOLD fluctuations in lateral temporal cortices, which are linked with brain volume reductions. Data suggest permanently reduced fluctuations in ongoing neural excitability and activity in structurally altered lateral temporal cortices after premature birth.

**Key words:** premature birth, BOLD fluctuations, resting-state fMRI, lateral temporal cortices.

## Introduction

Premature birth, i.e., preterm birth before 37 weeks of gestation and/or birth at low birth weight below 2500g - has a worldwide prevalence of more than 10% (Blencowe, et al., 2012; Volpe, 2009). It is associated with an increased risk for birth complications and adverse long-term outcomes including brain functionality (Volpe, 2009). Particularly, premature born individuals have a higher risk for long-term neurocognitive impairments, psychiatric disorders, and lower socio-economic status (D'Onofrio, et al., 2013; Nosarti, et al., 2012). Risk for adverse outcomes increases substantially for very premature born individuals, i.e., born very preterm (VP; gestational age < 32 weeks) and/or with very low birth weight (VLBW; < 1500 g) (Nosarti, et al., 2012; Saigal and Doyle, 2008). The increased risk for adverse neurocognitive outcomes results from brain maturation abnormalities induced by adverse perinatal events such as brain injury due to hypoxia-ischemia, brain hemorrhage, infections, and other inflammatory processes as well as neonatal pain and stress (Volpe, 2009).

At the microscopic level, these processes primarily impair the development of pre-myelinating oligodendrocytes, GABA-ergic interneurons, and subplate neurons, which play a fundamental role in the development of cortical microstructure, morphology, and connectivity (Back, et al., 2002; Buser, et al., 2012; Dean, et al., 2013; Deng, 2010; Kinney, et al., 2012; Salmaso, et al., 2014). For example, during gestational weeks 15-35, different populations of subplate neurons control ingrowing of thalamocortical, basal forebrain cholinergic, and cortico-cortical afferents into cortical microcircuits (for review

Hoerder-Suabedissen and Molnar, 2015): these processes are often impaired in prematurity due to the vulnerability of subplate neurons to perinatal hypoxia (Volpe, 2009), resulting in reduced subplate neuron arborization and local microcircuit development (McClendon, et al., 2017). At the macroscopic level, while impairments in white matter integrity are widespread (Ball, et al., 2014; Ball, et al., 2012; Eikenes, et al., 2011; Meng, et al., 2015; Skranes, et al., 2007), gray matter volume reductions focus consistently on selected subcortical and cortical regions such as the thalamus, striatum, and medial and lateral temporal cortices (Ball, et al., 2013; Grothe, et al., 2017; Karolis, et al., 2017; Meng, et al., 2015; Nosarti, et al., 2008; Pierson, et al., 2007). Consistent grey matter changes, together with micro-structural changes, suggest that premature birth might impact very basic local physiological brain processes such as ongoing brain activity. Indeed, previous functional imaging studies - mainly task- and resting-state functional MRI (rs-fMRI) (Bauml, et al., 2014; Daamen, et al., 2015; Daamen, et al., 2014; Damaraju, et al., 2010; Doria, et al., 2010; Froudist-Walsh, et al., 2015; Lubsen, et al., 2011; Smyser, et al., 2010; White, et al., 2014), but also some PET studies such as striatal F-Dopa PET (Froudist-Walsh, et al., 2017) - demonstrated overlapping structural and functional brain changes in premature born individuals. For example, premature born adults with perinatal brain injury have reduced dopamine synthesis capacity in the striatum, measured by F-Dopa-PET, in which the volume is also typically reduced after premature birth (Froudist-Walsh, et al., 2017). The coherence of slowly fluctuating ongoing activity, measured by correlated blood oxygenation fluctuations of rs-fMRI, is altered in the striatum, thalamus, and lateral temporal cortices, with these

alterations being linked with correspondent volume loss (Bauml, et al., 2014). Particularly, the last finding is of interest when looking for changed brain structure after premature birth accompanied with basic functional changes. Recent studies suggest that slowly fluctuating blood oxygenation of rs-fMRI reflect slowly fluctuating ongoing neural excitability and activity (Biswal, et al., 2010; Ma, et al., 2016; Mateo, et al., 2017; Matsui, et al., 2016; Raichle, 2011; Sanchez-Vives, et al., 2017; Schwalm, et al., 2017; Zang, et al., 2007), which – at least for the cortex – represents a kind of fundamental cortical 'default activity' generated by basic cortical microcircuits (Sanchez-Vives, et al., 2017). Therefore, the link between correlated blood oxygenation and underlying volume loss after premature birth suggests potential changes in basic, slowly fluctuating, ongoing neural excitability and activity particularly in regions of consistent brain volume loss, likely due to prematurity-induced brain microstructure changes. To address this issue, the current study tested the following hypothesis: fluctuations in ongoing neural excitability and activity, as measured by rs-fMRI, are lastingly altered in premature born individuals, with alterations occurring mainly in brain areas of significant brain volume loss, a loss in volume that could potentially be linked with these alterations.

To test this hypothesis, we assessed 94 VP/VLBW and 92 full-term (FT) born young adults at a median age of 26 years with rs-fMRI and structural MRI (sMRI). The amplitude of low frequency fluctuations (ALFF) of ongoing rs-fMRI signals is a widely used proxy of ongoing BOLD fluctuations (Zang, et al., 2007). Voxel-based morphometry (VBM) of sMRI data were used to estimate brain volume changes. To ensure the functional nature of prematurity effects

on ALFF, we controlled for effects of prematurity-related structural changes on ALFF by including VBM values as covariates in a voxel-wise fashion. To test whether group effects on ALFF were indeed linked with brain volume, prematurity and adult neurocognitive performance, we performed additional correlation analyses with variables of VBM values, prematurity and IQ scores in the VP/VLBW group.

## Materials and Methods

### Participants

Participants were recruited as part of the prospective Bavarian Longitudinal Study (BLS) (Riegel, et al., 1995; Wolke and Meyer, 1999), a geographically defined whole-population study of neonatal at-risk infants born in South Bavaria. Of the initial 682 infants born VP/VLBW, 411 were eligible for the 26-year follow-up assessment, and 260 (63.3%) participated in psychological assessments (Breeman, et al., 2015). Of the initial 916 term born control infants from the same obstetric hospitals and alive at 6 years, 350 were randomly selected as term controls within the stratification variables of sex and family socioeconomic status in order to be comparable with the VP/VLBW sample. Of these, 308 were eligible for the 26-year follow-up assessment, and 229 (74.4%) participated in psychological assessments. Of the sample assessed in adulthood, 101 VP/VLBW as well as 102 FT individuals underwent MRI at 26 years of age. MRI assessments were carried out at two different sites: the Department of Neuroradiology, Klinikum Rechts der Isar, Technische Universität München, Germany (N = 138), and the Department of Radiology, University Hospital Bonn, Germany (N = 67). The study was approved by the local ethics committees of the Klinikum Rechts der Isar and University Hospital Bonn. All study participants gave written informed consent and received travel expenses and a payment for attendance. A detailed description of participants, particularly including MRI-based brain abnormalities, can be found in the supplementary material.

### Birth-related variables

Gestational age (GA) was estimated from maternal reports on the first day of

the last menstrual period and serial ultrasounds during pregnancy. In cases where the 2 measures differed by more than 2 weeks, clinical assessment at birth with the Dubowitz method was applied (Dubowitz, et al., 1970). Maternal age, birth weight (BW), and Intensity of Neonatal Treatment Index (INTI), which reflects the duration and intensity of medical treatment after birth, and family socioeconomic status (SES) at birth, were obtained from obstetric records (Gutbrod, et al., 2000; Riegel, et al., 1995).

**Cognitive assessments**

General cognitive performance was assessed by independent trained psychologists using the German version of the Wechsler Adult Intelligence Scale (WAIS III) (von Aster, et al., 2006) and converted to age-normalised and Full-Scale IQ (FSIQ) scores at the median age of 26 years.

**Image Acquisition**

At both sites, MRI data acquisition was initially performed on Philips Achieva 3T TX systems (Achieva, Philips, the Netherlands), using an 8-channel SENSE head coil. Due to a scanner upgrade, data acquisition in Bonn had to switch to Philips Ingenia 3T system with an 8-channel SENSE head coil after N = 17 participants. After N = 133 participants, data acquisition in Munich switched to the same Philips Ingenia 3T model as in Bonn. To account for possible confounds introduced by scanner differences, data analyses included scanner identities as covariates of no interest. Across all scanners, sequence parameters were kept identical. Scanners were checked regularly to provide optimal scanning conditions. MRI physicists at the University Hospital Bonn and Klinikum rechts der Isar regularly scanned imaging phantoms, to ensure

within-scanner signal stability over time. Signal-to-noise ratio (SNR) was not significantly different between scanners (one-way ANOVA with factor “scanner-ID” [Bonn 1, Bonn 2, Munich 1, Munich 2]; $F(3,182) = 1.84$ , $p = 0.11$). Resting-state fMRI data were collected for 10 min 52 s from a gradient-echo echo-planar sequence (TE = 35 ms, TR = 2608 ms, flip angle = 90°, FOV = 230 $mm^2$, matrix size = 64 × 63, 41 slices, thickness 3.58 and 0 mm interslice gap, reconstructed voxel size = 3.59 × 3.59 × 3.59 $mm^3$) resulting in 250 volumes of BOLD fMRI data per subject. Subsequently, a high-resolution T1-weighted 3D-MPRAGE sequence (TI = 1300 ms, TR = 7.7 ms, TE = 3.9 ms, flip angle = 15°; 180 sagittal slices, FOV = 256 × 256 × 180 mm, reconstruction matrix = 256 × 256; reconstructed voxel size = 1 × 1 × 1 $mm^3$) was acquired. Immediately before undergoing the resting-state sequence, subjects were instructed to keep their eyes closed and to restrain from falling asleep. We verified that subjects stayed awake by interrogating via intercom immediately after the rs-fMRI scan.

**Data preprocessing**

Preprocessing and measure definition were carried out using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and DPARSF (Chao-Gan and Yu-Feng, 2010). For each participant, functional volumes were realigned to correct for head motion and coregistered to each subject’s high-resolution structural T1 image. Subsequently, the T1-weighted image was segmented using Unified Segmentation (Ashburner and Friston, 2005). To transform individual images into common MNI (Montreal Neurological Institute) space, segmentation-based normalization parameters were applied to the coregistered structural and functional data. Data from 17 subjects (7 VP/VLBW

subjects and 10 FT subjects) were excluded from further analysis due to excessive head motion defined as a cumulative translation or rotation >3mm or 3° (cumulative translation VP/VLBW 1.14+/-0.9mm, FT 1.22+/-0.8mm; cumulative rotation VP/VLBW 0.6+/-0.5°, FT 0.64+/-0.52°). To estimate motion-induced artifacts, temporal SNR (tSNR), point-to-point head motion, and frame-wise displacement were assessed for each subject (Murphy, et al., 2007; Power, et al., 2012; Van Dijk, et al., 2012). Two-sample t-tests yielded no significant differences between groups regarding mean point-to-point translation or rotation of any direction ($p > 0.1$), tSNR ($p > 0.25$), and frame-wise displacement ($p > 0.3$). One should note that we did not apply additional 'scrubbing' procedures to remove outliers in fMRI volumes (Power, et al., 2012), as suggested by (Babu and Stoica, 2010; Yan, et al., 2013). Removal of non-contiguous time points alters the underlying temporal structure of the data, precluding conventional frequency-based analyses of rs-fMRI data i.e., the fast Fourier transformation-based ALFF, the main outcome of our study.

**Data analysis: outcome variables and statistical analysis**

***ALFF*.** As a first step of analysis, nuisance covariates, including six head motion parameters, white matter, global brain signal, and cerebrospinal fluid signal intensities were regressed out from preprocessed resting-state fMRI data. Subsequently,the data was smoothed using a Gaussian kernel with a full-width at half-maximum of 6 mm. Then, after linear-trend removal, the time series were transformed to the frequency domain using Fast Fourier Transformation to obtain the power spectrum. To calculate the ALFF, the power spectrum was square-rooted and averaged across 0.01–0.1 Hz at each voxel. Finally, the ALFF of each voxel was then divided by the global mean of

ALFF values for standardization (Zang, et al., 2007). To test for group differences, voxel-wise ALFF maps per subject were entered into a general linear model as implemented in SPM12, with the factor ‘group’, and the covariates ‘sex’, ‘scanner identity’, and ‘frame-wise displacement’. Significance was tested using two-sample t-tests ($p<0.05$, corrected for family-wise error (FWE) at cluster-level).

***Voxel-based morphometry (VBM) and ALFF.*** We analyzed gray matter volumes in order to investigate the relationship between ALFF and underlying gray matter volume changes. Voxel-wise gray matter volumes were analyzed using voxel-based morphometry as implemented in VBM8 (http://dbm.neuro.uni-jena.de/vbm.html). T1-weighted images were corrected for bias-field inhomogeneity, registered using linear (12-parameter affine) and nonlinear transformations, and segmented into gray matter (GM), white matter, and cerebro-spinal fluid within the same generative model. The resulting GM images were modulated to account for structural changes resulting from the normalization process. Here, we only considered nonlinear changes so that further analyses did not have to account for differences in head size. Finally, images were smoothed with a Gaussian kernel of 6 mm (FWHM). For group comparisons, voxel-wise two-sample t-tests were performed ($p<0.05$ FWE-corrected), controlling for sex and scanner identity.

Recent findings suggest that between-group differences in measures derived from fMRI signals may potentially be influenced by underlying structural differences in gray matter volumes (He, et al., 2007; Oakes, et al., 2007). To ensure the functional nature of potential ALFF changes in premature born adults, we performed voxel-wise linear regression analysis, namely

residualizing ALFF values for gray matter volume, as an approximation to correct for likely non-linear impact of brain structure changes on ALFF. Resulting residuals entered voxel-wise general linear models (see above) and were tested for significance using two-sample t-tests ($p<0.05$, FWE cluster-level corrected), controlling for sex, scanner identity and FD.

***Correlation between ALFF, underlying gray matter, prematurity, and cognitive performance variables.*** To analyze the association between aberrant ALFF and underlying gray matter, prematurity and cognitive performance averaged ALFF values among voxels of brain areas with ALFF abnormalities were extracted for all 94 VP/VLBW subjects and associated with averaged VBM values (the same voxels as for averaged ALFF), birth-related variables (namely GA, BW, and INTI), and the cognitive performance variable (namely full-scale IQ), respectively. These associations were investigated via three partial correlation analyses, as implemented in SPSS (Statistical Package for the Social Sciences). Each correlation approach was controlled for sex, scanner identity, and frame-wise displacement, and the significance threshold was set at 0.05.

## Results

### Sample Characteristics

Group demographic characteristics and clinical background variables are shown in Table 1. VP/VLBW and FT group did not differ with respect to age ($p=0.277$), gender ($p=0.786$), SES at birth ($p=0.253$) or maternal age ($p=0.956$). By design, VP/VLBW adults had significantly lower GA ($p<0.001$), and BW ($p<0.001$), and were hospitalized for longer time ($p<0.001$). VP/VLBW individuals had significantly lower WAIS-III Full-Scale IQ scores ($p=0.001$).

### ALFF decrease in temporal cortices and its relation to underlying brain structure in VP/VLBW born adults

Voxel-wise two-sample t-tests of ALFF maps demonstrated significant ALFF reductions in an extended cluster of the left lateral temporal and insular cortex as well as ALFF increases in the thalamus of VP/VLBW born adults compared with mature born adults ($p<0.05$, FWE cluster-level corrected) (Fig. 1, Table 2). To ensure that observed ALFF reductions were independent from our methodological approach including global brain signal removal, we controlled for global brain signal removal by performing the same analysis pipeline but without global signal removal. We found again ALFF reductions in lateral temporal cortices (see Figure S1), demonstrating that temporal cortices ALFF reductions in premature born adults are not confounded by global brain signal removal.

To assure the functional nature of ALFF reductions, we controlled for confounding influences of volumetric changes in VP/VLBW born adults, using VBM analyses of sMRI data (Fig. 2). First, we found volume reductions in the

VP/VLBW group for temporal cortices and subcortical structures such as the thalamus and basal ganglia (Fig. 2A, Table S1). Volume reductions overlap with ALFF reductions in the left lateral temporal cortex and with ALFF increases in the thalamus (Fig. 2B). Second, after controlling for voxel-wise VBM scores, a two-sample t-test still revealed residualized ALFF reductions in the left temporal cortex in VP/VLBW, while ALFF increases in the thalamus did not remain (Fig. 2C). This result supports the idea that ALFF reductions in the left temporal cortex are of physiological nature and not totally explained by underlying volume loss.

To further test whether 'true' temporal ALFF reductions were indeed related to prematurity, we performed partial correlation analyses between ALFF (i.e., averaged ALFF scores of group difference clusters) and birth-related variables (i.e., GA, BW, INTI) in the VP/VLBW group only (Fig. 3). We found a positive correlation between left temporal ALFF and BW ($r=0.251$, $p=0.019$), demonstrating that temporal ALFF reductions were linked with prematurity.

To further analyze the relationship between temporal ALFF reductions and underlying brain structure, we correlated – in the VP/VLBW group only – averaged ALFF values with VBM values (Fig. 2D). We found a positive correlation between ALFF and VBM values in the left lateral temporal cortex ($r=0.231$, $p=0.029$), demonstrating that temporal ALFF reductions are associated with underlying brain volume loss. To test whether this relation between temporal cortex activity fluctuations and brain structure is specific for premature born adults, we performed additional correlation analysis for the link between ALFF and VBM across full-term born persons. We did not find a significant correlation, indicating the specificity of the link between temporal

cortex activity fluctuations and underlying structure for prematurity.

**ALFF reductions and cognitive performance**

To test whether temporal ALFF reductions are associated with changes in cognitive performance, we performed correlation analyses between averaged ALFF values and general cognitive performance in the VP/VLBW group only (Fig. 4). We found a positive correlation between ALFF in full-scale IQ ($r=0.267$, $p=0.013$), indicating the cognitive relevance of temporal ALFF reductions after premature birth.

**Discussion:**

To investigate whether BOLD fluctuations are altered after premature birth, we explored the amplitude of low BOLD frequency fluctuations, ALFF, based on resting-state fMRI data from 94 VP/VLBW and 92 full-term born adults. ALFF was reduced in left lateral temporal cortices of VP/VLBW adults. To the best of our knowledge, this is the first report of aberrant BOLD fluctuations in premature born individuals. Furthermore, we found that temporal ALFF reductions remained after controlling for overlapping gray matter volume reductions, pointing towards the functional nature of temporal ALFF decreases. On the other hand, temporal ALFF reductions were linked with volume reductions, suggesting the dependence of ALFF decreases on underlying structural changes. Finally, temporal ALFF reductions were linked with IQ reductions, demonstrating their behavioral significance. In the following section, we discuss these single findings in more detail, focusing particularly on the relation between temporal ALFF reductions and underlying structural changes.

In very premature born adults, ALFF was reduced in both the insula and the lateral and anterior temporal cortices, and increased in the thalamus (Fig. 1, Table 2). ALFF changes overlapped with gray matter volume reductions in VP/VLBW adults, particularly in the temporal cortices and thalamus (Fig. 2A&B). The pattern of volume reductions in subcortical areas, such as the thalamus and striatum as well as in temporal-insular cortices, is in line with previous studies (Ball, et al., 2013; Karolis, et al., 2017; Nosarti, et al., 2008; Pierson, et al., 2007). In the left temporal cortex, reduced ALFF remained after controlling for gray matter volume (Fig. 2C), supporting the functional nature of

temporal ALFF reductions in VP/VLBW born adults. Furthermore, temporal ALFF reductions correlated with birth weight (Fig. 3), independently from gestational age or medical complications at birth, suggesting that ALLF reductions are indeed linked with premature birth. Finally, temporal cortex ALFF reductions correlated with IQ reductions in premature born persons (Fig. 4), indicating the functional relevance of temporal ALFF changes. Based on these findings, we conclude that premature birth has lasting, relevant long-term effects on slowly fluctuating ongoing BOLD activity in the lateral temporal cortex.

Previous studies demonstrated that ALFF, particularly in the lateral temporal cortices, is not only sensitive to the effects of typical brain development and aging, but also to changes in neuro-developmental disorders (Biswal, et al., 2010; Itahashi, et al., 2015; Yu, et al., 2014). For example, Biswal and colleagues showed aging effects on ALFF mainly in cortical midline structures such as anterior and posterior cingulate but also in lateral temporal cortices (Biswal, et al., 2010); decreased ALFF has been observed in temporal cortices and insula of patients with schizophrenia (Yu, et al., 2014) and in lateral and inferior temporal cortices of patients with autism (Itahashi, et al., 2015). This overlap of findings suggests that ALFF variation, particularly in the temporal cortices, may strongly covary with developmental brain changes and thus may represent a potential surrogate marker for neurodevelopmental brain disorders. This overlap, however, does not point to identical mechanisms underlying ALFF changes in temporal cortices across distinct developmental conditions, i.e. ALFF reductions in prematurity and schizophrenia may have distinct

underlying causes, but they may converge on macroscopically similar ALFF alteration patterns.

Fluctuations in blood oxygenation, as reflected by ALFF, are assumed to indicate slow fluctuations of macroscopic brain activity, which in turn reflect fluctuations in ongoing neuronal activity and excitability (Biswal, et al., 2010; Ma, et al., 2016; Mateo, et al., 2017; Matsui, et al., 2016; Raichle, 2011; Sanchez-Vives, et al., 2017; Schwalm, et al., 2017; Zang, et al., 2007). In more detail, restricted to the cortex, local cortical microcircuits generate spontaneously slow activity fluctuations of alternating active (i.e., up-state) and inactive (i.e., down-state) phases at frequencies of below 1Hz (Sanchez-Vives, et al., 2017). Recent studies using simultaneous neuronal imaging and optical imaging/fMRI in animals, providing both simultaneous neuronal and hemodynamic blood oxygenation-related information, have demonstrated that blood oxygenation fluctuations reflect slow fluctuations in excitatory activity (Ma, et al., 2016; Schwalm, et al., 2017) and their coherence (Mateo, et al., 2017; Matsui, et al., 2016). Applying these findings to reduced ALFF in temporal cortices of premature born adults, they suggest that correspondent changes in slow neuronal activity fluctuations may exist in prematurely born subjects (Arichi, et al., 2012). To get definitive evidence for this suggestion, simultaneous EEG-fMRI experiments in premature born individuals are necessary (Arichi, et al., 2017).

Furthermore, slow fluctuations in ongoing neural activity and excitability are thought to represent basic cortical ‘default’ activity, which is generated locally

by basic microcircuits (Sanchez-Vives, et al., 2017). For example, cortical in-vitro slices produce slow fluctuating ongoing activity spontaneously (Sanchez-Vives and McCormick, 2000), and simple artificial cell assembly architectures simulate slow ongoing activity fluctuations (Markram, et al., 2015). These findings indicate that slow ongoing fluctuations depend on basic underlying structural micro-circuitry, which, in turn, are aberrant after premature birth (Ball, et al., 2013; Dean, et al., 2013; McClendon, et al., 2017). For example, while Ball and colleagues showed impaired cortical microstructure in preterm born infants via diffusion imaging (Ball, et al., 2013), Dean and colleagues demonstrated that aberrant cortical diffusion imaging signals were associated with reduced dendritic arborization in premature born sheep (Dean, et al., 2013). McClendon and colleagues, in turn, showed that transient hypoxic episodes in premature born sheep reduce their subplate neuron dendritic arborization and subsequent microcircuit development (McClendon, et al., 2017). These points together suggest that aberrant cortical slow fluctuations in premature born individuals might be linked to aberrant underlying gray matter structure. Indeed, we found that reduced temporal ALFF was associated with reduced underlying brain volume (Fig. 2D). This finding suggests that impaired cortical development after premature birth may impact on basic ongoing cortical activity, particularly in the lateral temporal cortices via aberrant structural microcircuits. One possibility to test this further might be to link cortical micro-structural indices (such as those derived from diffusion imaging, for example in Ball, et al., 2013) with ALFF-based measures. Conclusively, premature birth might alter ‘default’ slow fluctuations in ongoing neural activity and excitability in the temporal cortices, potentially via changes

in underlying microstructure.

While these points provide a general argument for the link between ALFF and, on the one hand, slow fluctuations in local cortical activity and, on the other hand, underlying brain structure and cortical microcircuits, it is not clear why ALFF changes arise specifically in the temporal cortices. Specific lateral temporal cortex changes after premature birth have been reported also in other modalities, such as task-fMRI studies (Gozzo, et al., 2009; Schafer, et al., 2009; Wilke, et al., 2014), resting-state fMRI (Bauml, et al., 2014; White, et al., 2014), or diffusion tensor imaging (DTI) (Aeby, et al., 2013; Northam, et al., 2012). In particular, we recently found in, largely the same individuals, that coherence of ongoing BOLD fluctuations, i.e. intrinsic functional connectivity (iFC), is aberrant in temporal cortices, and that these functional connectivity changes were linked with underlying temporal gray matter loss (Bauml, et al., 2014). One should note the difference between basic ongoing BOLD fluctuations, i.e. ALFF, and correlated ongoing BOLD fluctuations, i.e. iFC. Such remarkable convergence of changes across distinct modalities and ages after premature delivery supports the idea that a basic process of temporal cortex-dependent brain development might be affected by prematurity. In the following section we will speculate as to whether some specific microscopic developments might underpin such focus on the temporal cortex. We are aware that this speculation is clearly beyond our experimental approach, but it might be a useful way to better understand the regional specificity of our findings in terms of testable hypotheses.

Cortical development depends critically on subplate neurons and their

development (Hoerder-Suabedissen and Molnar, 2015; McClendon, et al., 2017; Salmaso, et al., 2014; Volpe, 2009). The subplate zone below cortical layer 6, which includes different populations of subplate neurons, represents a dynamic ‘waiting compartment’ for ingrowing thalamocortical afferents (Rakic, 1976), basal forebrain cholinergic afferents (Kostovic, 1986) and corticocortical afferents (deAzevedo, et al., 1997), showing the largest activity in gestational week 15-35 and being critical for local microcircuit development. In particular, in lateral temporo-parietal regions, subplate neuron growth has its highest rates (Corbett-Detig, et al., 2011). As premature birth is known to affect subplate neuron development (Deng, 2010; Kinney, et al., 2012; Salmaso, et al., 2014; Volpe, 2009), we speculate – due the overlap of our findings of lateral temporal cortex-focused ALFF reductions with high rate subplate growth in the temporal cortices – that ALFF in the temporal cortices might reflect late consequences of subplate neuron development aberrances in prematurity. It is clear that, to test this idea, future neuropathological and/or translational studies with animal models are necessary.

*Strength and limitations*

Some points should be carefully considered when interpreting our results. First, the current sample is biased to VP/VLBW adults with less severe neonatal complications, less functional impairments, and higher IQ. Individuals with stronger birth complications and/or severe lasting impairments in the initial BLS sample were more likely to be excluded in initial screening for MRI or to reject MRI scanning or even continuation in the study. Thus, differences in ALFF between VP/VLBW and term control adults reported here are

conservative estimates of true differences. Second, the study sample was limited by MRI- and study-related contraindications including a history of severe neurological disorders (e.g. epilepsy, multiple sclerosis, cerebral hemorrhage, traumatic brain injury, tinnitus), severe back problems, (potential) pregnancy, severely impaired vision, as well as non-removable ferromagnetic implants (e.g. pacemakers). Third, the current sample size is large (94 VP/VLBW and 92 FT adults), enhancing the generalizability of our findings. Fourth, head motion in VP/VLBW adults during scanning and scanning at multiple scanners used in this study may confound imaging-derived brain connectivity measures. The current study controlled for these effects as strictly as possible; however, subtle influences of these confounds cannot be ruled out completely.

*Conclusion*

Slowly fluctuating BOLD activity is reduced in lateral temporal cortices after very premature birth, with these functional changes being linked with underlying structural changes.

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**Tables:**

**Table 1. Sample characteristics**

| | Full-term born group (n=92) | | | VP/VLBW born group (n=94) | | | Statistical comparison |
|---|---|---|---|---|---|---|---|
| | M | SD | Range | M | SD | Range | |
| Sex (male/female) | 53/39 | | | 56/38 | | | p=0.786 |
| Age (years) | 26.8 | ±0.7 | 26-29 | 26.7 | ±0.6 | 26-28 | p=0.277 |
| GA (weeks) | 39.7 | ±1.1 | 37-42 | 30.5 | ±2.0 | 25-36 | p<0.001 |
| BW (g) | 3413 | ±433 | 2450-4670 | 1319 | ±309 | 630-2070 | p<0.001 |
| Hospital (days) | 6.8 | ±2.4 | 2-15 | 72.8 | ±26.0 | 24-170 | p<0.001 |
| INTI | - | - | - | 11.70 | 3.84 | 3-19.8 | - |
| SES[a] | 29/41/22 | | 1-3 | 27/42/25 | | 1-3 | p=0.253 |
| Maternal age | 29.4 | ±5.2 | 18-42 | 29.4 | ±4.7 | 17-41 | p=0.956 |
| Full-scale IQ[b] | 102.9 | ±11.9 | 77-130 | 94.5 | ±12.9 | 64-131 | p<0.001 |

Abbreviations: GA, gestational age; BW, birth weight; Hospital, duration of hospitalization; INTI, Intensity of Neonatal Treatment (Morbidity) Index; SES, socioeconomic status at birth; maternal age, maternal age at birth; IQ intelligence quotient.
Statistical comparisons: sex, SES with $\chi^2$ statistics; age, GA, BW, Hospital, maternal age, IQ with two sample t-tests.
[a]1=upper class, 2=middle class, 3=lower class
[b]Data are based on 90 VLBW preterm and 89 full-term subjects, respectively.

**Table 2. Group-different brain clusters for ALLF**

| Brain region | Cluster size | T-values | MNI | | | p-value |
|---|---|---|---|---|---|---|
| | | | x | y | z | |
| Thalamus | 66 | 4.29 | -3 | -12 | -12 | 0.006 |
| Temporal-insular cortex | 224 | -6.65 | -36 | 9 | -24 | <0.001 |
| | | -5.36 | -54 | -3 | -15 | |
| | | -4.45 | -54 | 6 | 0 | |

Statistical analysis: two sample t-test ($p<0.05$, FWE cluser-level correction), correct for gender, scanners, and frame-wise displacement as covariates of no interest.

**Figure legends:**

***Figure 1. Aberrant ALFF in premature born adults.*** Statistical parametric map of group comparison for ALFF between VP/VLBW and FT born adults, two-sample t-test, $p<0.05$ FWE-corrected (Table 2). Color bars indicate t-values for increased/decreased ALFF in the VP/VLBW group. Abbreviations: ALFF, amplitude of low frequency fluctuations; FT, full-term; VP/VLBW, very preterm/very low birth weight.

***Figure 2. ALFF and volumetric changes in premature born adults.*** A) Statistical parametric map of group comparison for VBM between VP/VLBW and FT born adults, two-sample t-test, $p<0.05$ FWE-corrected (Table S1). Decreased VBM on VP/VLBW group in yellow, increased VBM in turquoise. B) Overlap (red) of changes in ALFF (green and blue; see Fig. 1) and VBM (yellow, only VBM reductions) in premature born adults. C) VBM-residualized ALFF reductions in premature born adults, two-sample t-test, $p<0.05$ FWE-corrected. D) Temporal cortices ALFF reductions are correlated with temporal cortices VBM reductions, partial correlation, $p<0.05$. Abbreviations: ALFF, amplitude of low frequency fluctuations; FT, full-term; VBM, voxel-based morphometry; VP/VLBW, very preterm/very low birth weight.

***Figure 3. Temporal cortices ALFF and birth weight in premature born adults.*** Reduced temporal cortices ALFF (see Fig.1) is correlated with reduced BW, partial correlation, $p<0.05$. Abbreviation: BW, birth weight.

***Figure 4. Temporal cortices ALFF and IQ in premature born adults.*** Reduced temporal cortices ALFF (see Fig.1) is correlated with reduced full-scale IQ, partial correlation, $p<0.05$. Abbreviation: IQ, intelligence quotient.