

Maternal Pre-pregnancy BMI Associates With Neonate Brain Local Synchrony in the Left Superior Frontal Gyrus: a Pilot Study

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Abstract

Introduction: Maternal obesity/overweight during pregnancy has reached epidemic proportions and has been linked with adverse outcomes for the offspring, including cognitive impairment and increased risk for neuropsychiatric disorders. Prior neuroimaging investigations have reported widespread aberrant functional connectivity and white matter tract abnormalities in neonates born to obese mothers. Here we explored whether maternal pre-pregnancy adiposity is associated with alterations in local neuronal synchrony in the neonate brain.

Methods: 21 healthy mother-neonate dyads from uncomplicated pregnancies were included in this study (age at scanning 26.14 ± 6.28 days, 12 male). The neonates were scanned with a 6-minute resting-state functional magnetic resonance imaging (rs-fMRI) during natural sleep. Regional homogeneity (ReHo) maps were computed from obtained rs-fMRI data. Multiple regression analysis was performed to assess the association of pre-pregnancy maternal body-mass-index (BMI) and ReHo.

Results: Maternal adiposity measured by pre-pregnancy BMI was positively associated with neonate ReHo values within the left superior frontal gyrus (FDR/FWE – corrected $p < 0.005$).

Conclusions: Our results imply that maternal pre-pregnancy BMI associates with local functional synchrony within the neonate left superior frontal gyrus. In line with previous studies, our findings indicate that maternal pre-pregnancy BMI has a programming influence on the developing neonate brain functional networks.

Introduction

Maternal obesity (BMI ≥ 30 kg/m²) and overweight (BMI ≥ 25 –30 kg/m²) during pregnancy have become prevalent worldwide within the last few decades ¹. While the risks of obesity and overweight pregnancies have been extensively studied from obstetric point of view, and is identified as a risk factor for delivery and congenital structural abnormalities ¹, less is known about its association to child neurodevelopment. Studies focusing on neurobehavioral and neurodevelopmental aspects have linked maternal obesity and overweight during pregnancy to impaired offspring cognitive development ^{2,3}, emotional/behavioural problems and consecutive increased risk in obtaining a diagnosis for neuropsychiatric disorders, including anxiety and depressive disorders, autism spectrum disorder, attention deficit hyperactivity disorder and even psychotic disorders ^{2,3}.

Obesity and overweight are related to complex alterations in metabolism, e.g. insulin resistance, increased circulating levels of lipids, dysfunction of adipose tissue and skeletal muscle, hepatic and pancreatic tissue as well as low grade oxidative stress and inflammation ^{4–6}. During pregnancy, these adverse processes may cause placental dysfunction ⁷, likely increasing fetal vulnerability to endo- and exogenous exposures through altered placental vascular permeability. Obesity and overweight are also accompanied by humoral dysregulation with increased levels of estrogen and adipokines, e.g. leptin ⁸,

which may further contribute to placental dysfunction⁶. These metabolic, humoral and inflammatory alterations coupled with possible placental dysfunction are highly plausible factors to exert a programming effect on the developing fetal brain. Animal model investigations into maternal obesity and offspring brain development have provided some insight on the mechanisms, including dysregulation within serotonergic and dopaminergic systems^{9,10}, altered hypothalamic-pituitary-adrenal axis (HPA-axis) responses¹¹, fetal neuronal damage¹² and changes in offspring brain gene expression patterns¹².

Recent advances in brain imaging techniques, such as diffusion tensor imaging (DTI) and resting-state functional magnetic resonance imaging (rs-fMRI), have provided the opportunity to probe gestational effects of various states and factors on human fetal and neonate brain development¹³, including maternal obesity and overweight. In adults, functional resting-state networks (RSNs) have been shown to remain stable over time with little variability over imaging sessions, revealing the distributed intrinsic functional organization of the brain where long-range connections dominate¹⁴. During the first year of life, there is a formidable gradual shift from local, intra-hemispheric network connectivity seen already *in utero* and in the neonatal stage to more distributed network connectivity in older children and adults¹⁵⁻¹⁷. These macro-scale network changes are described with prominent alterations to functional hub localization, proliferation of connector hubs and progression of functional segregation of networks, likely indicating more efficient information processing within and between networks over the first postnatal years in normal development^{16,18,19}. Further, alterations in network topology temporally coincide with increased white matter myelination²⁰ and synaptic pruning²¹. The delicate developmental and reconfiguration processes in brain functional networks during gestation and the first years, respectively, present a time window in brain development, that has been shown to be particularly vulnerable for disruption by endogenous and exogenous factors¹³. Prior human MRI neonate studies focusing on obese and overweight pregnancies have revealed that maternal adiposity is associated with widespread alterations in the anterior brain white matter tract integrity²² and in functional networks^{23,24} with emphasis on sensory cue and reward processing, cognitive and motor control in the neonate brain²⁵.

Regional homogeneity (ReHo) is an efficient, reliable and widely used index of local fMRI connectivity^{26,27}. Based on the assumption that hemodynamic characteristics of every voxel in a functional cluster should be similar to the neighbour voxels, ReHo is commonly interpreted as an index of ongoing brain activity²⁶. ReHo measured at rest is altered in adolescents with autism²⁸ and in adults, shows promising sensitivity to functional changes in schizophrenia²⁹, cognitive impairment³⁰ and even presymptomatic stages of genetic dementia³¹. To the best of our knowledge, there have been no investigations into maternal adiposity induced alterations in local connectivity of the neonate brain. In the present study, we hypothesized that correlations between maternal pre-pregnancy BMI and ReHo may reveal functional abnormalities associated with altered neurodevelopment. For future reference we also provide the average ReHo maps of the neonate brain at 26.14 ± 6.28 days after birth in the supplementary materials.

Materials And Methods

This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethics Committee of the Hospital District of Southwest Finland (15.03.2011) § 95, ETMK: 31/180/2011. Informed written consents were obtained from parents before MRI scans were conducted.

Participants

This study was performed as a part of FinnBrain Birth Cohort Study (www.finnbrain.fi)³². 28 dyads of full-term born healthy infants and mothers (Table 1) were randomly recruited from the cohort and participated to fMRI scans (performed during year 2015). Exclusion criteria for infants included complications of neurological involvement, less than 5 points in the 5 min Apgar, previously diagnosed central nervous system anomaly, gestational age at delivery less than 32 weeks and birth weight less than 1500 g. Seven dyads were excluded from the study due to excessive neonate motion during the MRI scanning session. All mothers reported having stopped ingesting alcohol and possible use of illicit substances after being informed of being pregnant, although three participants with minor exposure to alcohol or illicit substances (cannabis) during early gestation were included. The sample likely reflects the general Finnish population. None of the included mothers suffered from hypertension, hypercholesterolemia or any form of diabetes mellitus. All scans were carried out during natural sleep at the gestation corrected age of 26.14 ± 6.28 days. To facilitate natural sleep, infants were fed with (breast) milk prior to the scanning session.

Table 1

Sample demographics of included dyads (N = 21) comprising of neonates and mothers that participated in this study. Variable selection was based on previous recommendations³³. Abbreviations: M = Mean; SD = Standard deviation; MAD = Mean absolute deviation; EPDS = Edinburgh postnatal depression scale 10-point questionnaire sum score filled out at 24th gestational wee

Variable	Whole sample (N = 21)	Boys (N = 12)	Girls (N = 9)
<i>M ± SD (range)</i>			
Age from birth (days)	26.95 ± 9.01 (11–53)	24.50 ± 7.67 (11–36)	30.22 ± 10.07 (23–53)
Age from term (days)	26.14 ± 6.28 (17–45)	23.17 ± 4.26 (17–30)	30.11 ± 6.23 (23–45)
Gestational age when born (weeks)	43.78 ± 0.91 (42.43–46.43)	43.39 ± 0.71 (42.43–44.43)	44.30 ± 0.93 (43.43–46.43)
Offspring birth weight (grams)	3524.76 ± 338.05 (3085–4395)	3562.50 ± 295.82 (3105–3980)	3474.33 ± 400.45 (3085–4395)
Offspring head circumference when born (cm)	35.29 ± 1.22 (33.0–37.5)	35.67 ± 1.21 (34.0–37.5)	34.78 ± 1.09 (33.0–37.0)
Maternal age (years)	28.95 ± 4.20 (19–37)	29.08 ± 4.78 (19.00–37.00)	28.78 ± 3.56 (24.00–36.00)
Maternal pre-pregnancy BMI (kg/m ²)	25.57 ± 4.05 (20.03–34.42)	25.92 ± 4.49 (20.03–34.42)	25.10 ± 3.59 (21.05–33.06)
Apgar points at 1 min (MAD)	8.38 (1.15)	8.08 (1.22)	8.78 (0.25)
Apgar points at 5 min (MAD)	9.05 (0.46)	9.00 (0.49)	9.11 (0.40)
Maternal EPDS-score	4.7 ± 4.2 (0–17)	3.8 ± 2.4 (0–8)	5.9 ± 5.7 (1–17)
<i>Frequencies</i>			
Maternal pre-pregnancy BMI (kg/m ²) (1 = < 25.00 / 2 = 25.00–29.99 / 3 = ≥ 30)	10/7/4	6/3/3	4/4/1
Maternal monthly income (€) (1 = < 500 / 2 = 501–1000 / 3 = 1001–1500 / 4 = 1501–2000 / 5 = 2001–2500 / 6 = 2501–3000 / 7 = 3001–3500 / 8 = 3501–4000 / 9 = > 4000)	2/1/2/11/4/1/0/0/0	1/0/2/5/4/0/0/0/0	1/1/0/6/0/1/0/0/0

Variable	Whole sample (N = 21)	Boys (N = 12)	Girls (N = 9)
Maternal education level (1 = High school graduate or lower; 2 = College degree; 3 = University degree)	5/7/9	2/3/7	3/4/2
Race/Ethnicity (Caucasian/Other)	21/0	12/0	9/0
Maternal use of alcohol during pregnancy (yes/no)	3/18	2/10	1/8
Frequency of maternal use of alcohol during pregnancy (More than 1–2 times a month / 1–2 times a month / less frequently)	0/1/2	0/1/1	0/0/1
Maternal use of illicit substances during pregnancy (yes/no)	1/20	0/12	1/8
Frequency of maternal use of illicit substances during pregnancy (More than 1–2 times a month / 1–2 times a month / less frequently)	0/0/1	0/0/0	0/0/1

Measures and procedures

Obstetric data were obtained from the Finnish Medical Birth Register of the National Institute for Health and Welfare and included age from birth and term, gestational age when born, Apgar points at 1 and 5 minutes, gestational weight, head circumference, maternal age in years, race/ethnicity, maternal pre-pregnancy BMI and exposure to alcohol and/or illicit substances. Education levels were trichotomized (low: high school or lower; middle: college degree; high: university degree). Maternal symptoms of depression were measured by Edinburgh postnatal depression symptom (EPDS) 10-point questionnaire, filled out by mothers during 24th gestational week. Variable selection was based on previous recommendations³³. EPDS was chosen as a proxy for maternal psychological distress as prior reports have indicated that maternal depressive symptoms may reflect such distress that can affect offspring development³⁴.

Image acquisition

28 infants underwent an MRI brain scanning session, including a 6 minute resting-state fMRI sequence. MRI scans were conducted on a Siemens Magnetom Verio 3T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a 12-element Head Matrix coil. Field-of-view (FOV) parameters were optimized for future replication by linear alignment to the anterior and posterior commissure line. The whole duration of the scanning protocol was 60 minutes, comprising of five major sequences in the following order: 1) Axial PD-T2-weighted TSE (Turbo Spin Echo), 2) Sagittal T1-MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo), 3) GRE field mapping, 4) DTI and 5) a 6-minute rs-fMRI EPI (Echo-planar imaging) sequence. Fat saturation was applied and following acquisition parameters were used in rs-fMRI sequence: TR of 2500 ms, TE of 30 ms, FOV of 216 x 216 mm², flip-angle (FA) of 80 degrees, GRAPPA acceleration of 2 and bandwidth of 1310 Hz/Px. Acquired rs-fMRI data consisted of 140 volumes with 42 slices and a voxel size of 3.0 x 3.0 x 3.0 mm³.

Image preprocessing

Data were slice timing corrected and motion corrected in FMRIB Software Library (FSL) ³⁵ v6.0 relative to a manually chosen reference volume, free of major artefacts. Motion outliers were estimated by ART (http://www.nitrc.org/projects/artifact_detect; Composite motion threshold (CMT) < 2 mm, DVARS < 9). As neonates commonly exhibit more jerk-like and rigid body movements in the scanner than older infants and adults, more stringent CMT values would have resulted in considerable increase in rejection rate of available data. At this initial step, rs-fMRI data of seven subjects were rejected from further analyses based on major artefacts (with most having ca. 4 / 6 min of data outliers), yielding an included sample size to 21. Anatomical masks for white matter and CSF were defined by the UNC neonate segmentation model ³⁶ and registered to functional data with affine transformation. Average signal in white matter average and CSF as well as 24 motion covariates ³⁷ were included as nuisance covariates. Thus, denoising consisted of nuisance regression followed by outlier rejection, detrending, and high-pass filtering (0.008 Hz).

The main outcome metric for functional organization of the neonate brain was ReHo, which is estimated in a data-driven manner and provides a voxel-wise, local connectivity measure ^{26,38}. ReHo is based on calculating the Kendall's coefficient of concordance over a target voxel and neighboring voxels. ReHo was computed as implemented in DPABI (number of voxels in a cluster; N = 27) (<http://rfmri.org/DPABI>). For group analysis, ReHo maps were normalized to the UNC neonate template with 1.0 x 1.0 x 1.0 mm³ voxel dimensions. Finally, the data were smoothed with a Gaussian filter of 6 mm full width at half maximum (FWHM).

Statistical analysis

All statistical analyses were performed with SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) software with multiple regression design for ReHo maps. Maternal pre-pregnancy BMI was set as the main explanatory variable (EV), and gestation corrected age and neonate sex were set as primary independent variables (IV). Statistical threshold was set to p < 0.005 and corrected with FWE/FDR at the cluster level. Images were inclusively masked after

cluster correction with averaged UNC template GM mask to limit the statistics to the grey matter. We ran separate sensitivity analyses with identical design except for the added fourth regressor of no interest for the following: Apgar points at 1 and 5 minutes, neonate birth weight, maternal age in years and EPDS questionnaire score filled out by mothers at the 24th gestational week. Models with Apgar points at 1 and 5 minutes were performed with Statistical nonparametric mapping due to non-normal distribution of the Apgar data (SnPM13; www.warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/software/snpm). Voxel-wise results were visualized with Mango software version 4.0.1 (www.ric.uthscsa.edu/mango).

Results

Multiple regression analysis for neonate brain ReHo maps and maternal pre-pregnancy BMI revealed a positive association [$p < 0.005$ ($p < 0.003$ FDR-correction; $p < 0.002$ FWE-correction, cluster size (kE) 869 voxels)] for left superior frontal gyrus (SFG); as identified from the UNC-neonate-atlas³⁶. ReHo values were principally increased in the dorsal and medial aspects of the left SFG (Fig. 1). Cluster coordinates are displayed in Supplementary materials, Table 1. No negative associations were detected between maternal pre-pregnancy BMI and neonate ReHo maps.

In the performed sensitivity analyses (Supplementary materials, Tables 1–2), Apgar points at 1 and 5 minutes after birth did not have any statistically significant effect on the ReHo-BMI correlation maps. Including maternal age as an additional IV to the original model reduced the original effect to statistical insignificance at $p < 0.05$ level (explained by the high correlation of $r_s = 0.570$ between maternal age and pre-pregnancy BMI). Maternal age had no independent statistically significant effects on neonate ReHo maps at $p < 0.005$ or lenient thresholds as investigated by a separate model with neonate age, sex and maternal age as covariates.

IVs that had effects on the original model included offspring birth weight and EPDS sum score filled out at the middle of the 24th gestational week (Supplementary materials, Sect. 2, Figs. 2–5). Neither had independent statistically significant effects on neonate ReHo maps at $p < 0.005$ or lenient thresholds. Including offspring birth weight as a fourth IV increased the statistical significance of maternal pre-pregnancy BMI effect on neonate ReHo-BMI maps (at $p < 0.001$ level; cluster size of 609 voxels and at $p < 0.005$ level with cluster size of 1437 voxels) with similar spatial distribution. Computing EPDS sum score as the fourth IV increased statistical significance of maternal pre-pregnancy BMI effect on neonate ReHo maps up to FDR/FWE corrected $p < 0.001$. Further, the spatial distribution of statistically significant results revealed altered right SFG ReHo values in addition to the original left SFG effect as two separate clusters. The cluster size for left SFG and right SFG were 487 and 645 voxels, respectively, at $p < 0.001$ level. The observed additive effects of included two IVs (EPDS sum score, gestational weight) likely stem from collinearity or from inclusion of too many IVs for a model with relatively small sample size.

Discussion

In this study we explored whether maternal pre-pregnancy BMI affects neonate brain local functional connectivity. Multiple regression analysis revealed that maternal pre-pregnancy BMI and neonate ReHo values were positively associated (FDR/FWE – corrected $p < 0.005$, cluster size of 869 voxels) within the left SFG, suggesting that higher maternal BMI during pre-pregnancy or early pregnancy influences neonatal local brain connectivity.

In neonates soon after birth, high ReHo values are encountered symmetrically in primary somatosensory and visual networks (mean ReHo map shown in Supplementary materials, Figs. 1 and ³⁹). Notably, previous developmental fMRI connectivity studies have estimated that these networks achieve adult-like network topology and function earlier than e.g. frontoparietal, executive control and default-mode networks ^{16,18,19}. In line with this idea, prior modelling studies have suggested an inverse relationship between distal connectivity and ReHo regarding a given voxel ³⁸, suggesting that as functional segregation of networks ensues, ReHo values decrease. In this framework, our observation that ReHo in the left SFG was higher in neonates born to mothers with higher BMIs likely relates to amplified local, and conversely, decreased distal connectivity in this region.

The left SFG has been identified as a key hub in the left frontoparietal network (FPN), which holds a central role in executive control, working memory and fluid intelligence in adults ⁴⁰. Furthermore, SFGs have been recognized as crucial areas for global networks in terms of network centrality in adults ⁴¹ and identified as a possible connector hub between executive control network and default-mode-network ⁴². However, in their immature state, brain networks in neonates likely have divergent functions as compared to corresponding networks in older infants and adults, complicating network-related change interpretation and comparison between populations of different age. For the left FPN, increase in within-network and in inter-network connectivity between lateral visual, auditory/language and right FP networks with simultaneous decreases in inter-network connectivity between medial visual and salience networks take place during the first year of life ¹⁸. In light of previous studies into functional resting-state-network development and ReHo interpretation, the observed positive association between maternal pre-pregnancy BMI and neonate left SFG ReHo values in this study may suggest accelerated within-network development. Whether this is reflected as altered inter-network connectivity regarding lateral visual, auditory/language and right FP or other networks, remains unclear. If inter-network and distal connectivity are altered, it might explain some of the observed cognitive performance differences seen in older children born from obese and overweight pregnancies ^{2,3}.

Prior investigations into maternal obesity and overweight during pregnancy related infant neurodevelopment have revealed widespread functional connectivity and white matter tract alterations in the neonate brain ²²⁻²⁵. Similarly, a recent study found that higher pre-pregnancy maternal BMI during gestation associated with variations in functional connectivity in fetal prefrontal, frontal and insular brain regions ⁴³. These results suggest that at least some group differences observed in obese/overweight and normal-weight populations could begin during the gestational period and may be attributed to metabolic, humoral and inflammatory processes in obese mothers. Indeed, obesity/overweight related changes in

brain network organization have been well documented in adult populations with alterations emphasizing to four distinct domains concerned with feeding behavior: Sensory cue processing⁴⁴, reward processing⁴⁵, cognitive⁴⁴ and motor control⁴⁶. A recent seed-based connectivity study hypothesized that these network abnormalities could be inherited through genetic or environmental effects and observed similar functional connectivity differences in neonates exposed to maternal obesity during gestation²⁵. To the best of our knowledge, no structural MRI studies have been performed on neonates born from pregnancies with maternal obesity, but studies focusing on older obese/overweight children have found grey matter abnormalities within the frontal, prefrontal and limbic areas⁴⁷. Moreover, the observed GM reduction were partly associated with impaired executive function⁴⁷. These abnormalities mainly spatially overlap with functional changes seen in neonates born from pregnancies with maternal obesity/overweight and likely precede structural abnormalities seen in older children and may begin as early as gestation.

Despite the observable widespread connectivity differences between neonates born from normal-weight and pregnancies with maternal obesity, it is unclear whether these changes are driven by systemic effects of insults or caused by localized impairment of key regions, e.g. connector hubs, followed by plasticity induced changes within plural functional networks, causing global differences in connectivity. It is likely that divergent detrimental factors have a heavier impact on specific regions and those most vulnerable are presumably areas crucial for networks that take years to reach maturity and obtain coherent function¹³.

Limitations

We acknowledge that a larger sample size would have increased statistical power and possibly revealed more subtle local connectivity variations as well as allowed studying e.g. sex-differences. Similarly, due to sample size, we were unable to perform statistically reliable group difference tests for normal versus elevated BMI exposed subjects. Further, while BMI is a sound indicator for obesity and overweight, it does not take into account the variability in body composition, e.g. fat and muscle ratios. This study unfortunately lacks background information on the types of maternal food intake, which is likely a contributing factor in obesity induced effects. Finally, no data was available for maternal BMI variability during the course of pregnancies and such data would be valuable in future studies (ideally coupled to other metabolic biomarkers).

Conclusions

In this study, we showed that maternal pre-pregnancy BMI is positively associated with ReHo values within the neonate left SFG, suggesting an increase in local functional connectivity and amplified within-network connectivity. Our findings provide further evidence for maternal BMI influenced changes in functional brain development seen in neonates born from obese/overweight pregnancies. The observed alterations in local connectivity within the left SFG are unlikely to be independently detrimental but may

contribute to unfavorable neurodevelopmental outcomes if negative exposures on the developing brain are encountered.

Declarations

Conflict of interest

None.

Author contributions

JJT, MB, NMS, HK, MB planned and/or funded the MR measurements. JS planned and implemented the image acquisition parameters. JJT and SL collected the imaging data. OR and JJT planned the analytical approach and performed the data analyses. SH aided in the data preprocessing and interpretation. RP provided neuroradiological expertise for screening the acquired MRI images for incidental findings. HK and LK established the cohort and built infrastructure for carrying out the study. All authors participated in writing the manuscript and accepted the final version.

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Data availability statement

The Finnish law and ethical permissions do not allow the sharing of the data used in this study.

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Figures

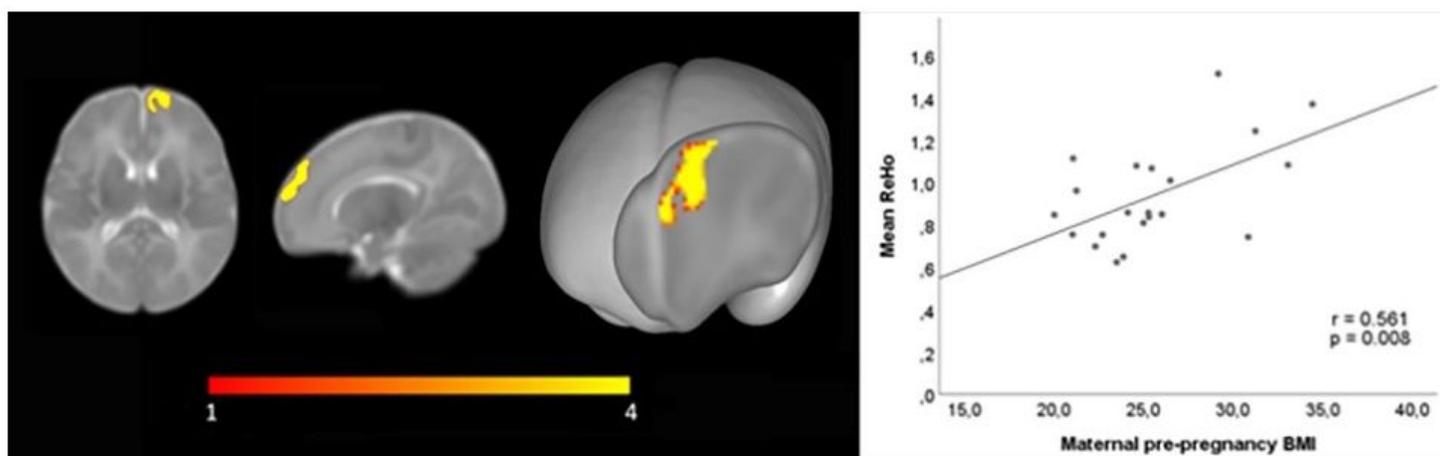


Figure 1

Regions where ReHo significantly correlated with maternal pre-pregnancy BMI ($p < 0.005$ threshold; $p < 0.003$ FDR-correction; $p < 0.004$ FWE-correction) highlighted left SFG within the naturally sleeping neonate ($N = 21$). Color bar represents T-scores. Images are displayed in radiological convention on the UNC template in axial, sagittal and oblique slices. Oblique section was created with Mango surface builder. Abbreviations: ReHo = regional homogeneity; SFG = superior frontal gyrus.

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