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ORIGINAL CONTRIBUTION

Associations between children's family environment, spontaneous brain oscillations, and emotional and behavioral problems

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Abstract
The family environment in childhood has a strong effect on mental health outcomes throughout life. This effect is thought to depend at least in part on modifications of neurodevelopment trajectories. In this exploratory study, we sought to investigate whether a feasible resting-state fMRI metric of local spontaneous oscillatory neural activity, the fractional amplitude of low-frequency fluctuations (fALFF), is associated with the levels of children's family coherence and conflict. Moreover, we sought to further explore whether spontaneous activity in the brain areas influenced by family environment would also be associated with a mental health outcome, namely the incidence of behavioral and emotional problems. Resting-state fMRI data from 655 children and adolescents (6–15 years old) were examined. The quality of the family environment was found to be positively correlated with fALFF in the left temporal pole and negatively correlated with fALFF in the right orbitofrontal cortex. Remarkably, increased fALFF in the temporal pole was associated with a lower incidence of behavioral and emotional problems, whereas increased fALFF in the orbitofrontal cortex was correlated with a higher incidence.

Keywords Development · Family environment · Neuroimaging · Psychopathology · Resting state

Introduction

Environmental factors play a critical role in the etiology of mental disorders; yet, the mechanisms by which such factors affect brain development are largely unknown [54]. However, an increasing number of studies in the last few years have examined the biological correlates of environmental factors related to mental health outcomes [39, 57, 58, 77]. Among these recent studies, considerable efforts have been undertaken to determine the effects of exposure to poverty during childhood on brain structure [14, 27, 28, 42, 57, 58, 69, 73, 59]. Effects of poverty have been reported

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in structural features of specific areas such as the prefrontal cortex, temporal regions, insula, and the amygdala [42, 57–59, 69].

Conceptually, neuroplasticity might be considered as part of the mechanisms by which early experiences are biologically embedded into the brain [14, 70]. Cortical volume reliably changes with age in a regionally specific fashion [24], reflecting regional reductions in synaptic density and increases in myelination during childhood and adolescence [72, 76]. Critically, these developmental changes are prone to modulation by environmental factors [36, 44, 47, 72, 76]. Furthermore, structural maturity follows a stereotyped pattern with early stabilization of primary sensory regions and a protracted stabilization of heteromodal regions [23, 25, 29, 51, 60, 78]. Along with the recent findings on the strong effects of poverty on brain structural features, these findings and conceptual framework provide a foundation for the hypothesis that the relationship between mental health outcomes and early life environmental factors is mediated by impacts on the developmental trajectories of specific brain networks.

Despite the emerging evidence for specific effects of early experiences on brain development, less attention has been paid to factors related to the family environment [85]. As a matter of fact, childhood family environments strongly affect mental and physical health throughout life [61]. Children exposed early to conflictive or aggressive environments are more likely to develop mental disorders in adulthood [11, 20, 52]. Interparental conflict has been associated with externalizing problems in children [21, 50] and with the severity of both externalizing and internalizing symptoms in adolescents [15, 45]. In contrast, higher family cohesion has been associated with lower incidences of internalizing [50] and externalizing behaviors [62]. In a longitudinal cohort of adolescents from age 11 to 20, a positive parenting style was found to moderate the effects of socioeconomic disadvantage on structural features of the prefrontal cortex and the amygdala [85]. Moreover, the thickness of the prefrontal cortex was in turn associated with positive academic outcomes.

Besides brain structural features, the architecture of large-scale functional networks also presents reliable developmental changes [27, 29, 60, 78]. Consistent with structural long term-trajectories, sensorimotor networks exhibit less variation with age throughout childhood and adolescence than attentional and default mode (DMN) networks [29, 30]. Such functional trajectories arguably coincide with the emergence of behavioral and cognitive abilities [29, 60, 78]. As early as in infancy (6–12 months), the strength of resting-state functional connectivity between the core nodes of the DMN was shown to mediate the relationship between interparental conflict and infant emotionality [28].

Most developmental functional magnetic resonance imaging (fMRI) studies to date are based on the strength of the temporal correlations between spontaneous low-frequency oscillations (LFOs) of the BOLD signal or functional connectivity [22, 71, 79]. But other features of LFOs may also carry useful information regarding underlying brain processes [6, 12, 81, 93]. The fractional amplitude of low frequency fluctuations (fALFF; [93], for instance, has been reported to vary across brain areas and to be especially high in DMN nodes, where it is correlated with the expression of specific genes [81, 93, 94]. Unlike conventional functional connectivity measures, fALFF allows the evaluation of local activity properties on a voxel-by-voxel basis, does not depend on the a priori specification of seed regions, and is less susceptible to motion artifacts [64, 88, 89]. Moreover, the amplitude of LFOs in an area has been shown to be correlated with the strength of its functional connectivity with other areas [16]. These characteristics and advantages make fALFF particularly suitable as a neuroimaging exploratory tool [7]. Accordingly, alterations in fALFF have been reported in exploratory studies addressing psychotic conditions, bipolar disorder, depression, and mild cognitive impairment [32, 53, 82, 87, 92]. Previously, we constructed a maturational index based on fALFF, which was able to capture a correlation between delayed DMN maturation and the incidence of behavioral and emotional problems [68].

Considering the importance of the family environment during childhood for long term mental health, the putative mediation of brain functional trajectories on these outcomes, and the suitability of the fALFF measure as a proxy of neural spontaneous oscillations [2, 12, 81], we sought to explore the relationships between the quality of family environment, regional fALFF, and the expression of behavioral and emotional problems in a large cohort of children (6–15 years old). First, the brain regions where fALFF correlate with the quality of the family environment were mapped. Then, we tested if the average fALFF in these same regions also correlates with the level of behavioral and emotional problems. Finally, we directly tested whether fALFF values in the mapped regions mediate the relationship between family environment quality and the expression of behavioral and emotional problems. Given the previous findings of effects of environmental factors (e.g., poverty and the interaction between poverty and family environment; [57, 58] on structural features of frontal and temporal heteromodal areas and the convergent evidence for the structural and functional maturation of heteromodal areas during late childhood and adolescence, we expected to find correlations between family environment quality and fALFF in these areas. Moreover, correlations between fALFF and the two environmental/behavioral measures were expected to have opposite directions [21, 50, 61, 85]. For example, if better family quality (low conflict and high cohesion) correlates with higher fALFF, the level of behavioral problems should be correlated with lower fALFF in the same area.

Method

Desensitization activities

In the MR Center, a psychologist explained the importance of participating in the research and the function of the MRI exam to the children using age-appropriate language. Dancing techniques, theater, relaxation, music, and various recreational and interactive games were used to engage children and as desensitization methods. All intervention procedures were conducted by an experienced child psychologist. A simulation of the brain MRI procedure was played, using a cloth tunnel on a stretcher with simultaneous presentation of the background noise of each MRI sequence to be performed in the research protocol. Children were invited to represent characters related to the environment of an MRI center, such as the doctor, the nurse, the researcher, the technician, and the patient, alternating roles. After the procedure of play and techniques to reduce possible states of anxiety, the children were invited to see the MRI equipment and the brain images acquired. The total time of the desensitization procedure was 30 min. Finally, the children performed the MRI exam. Technicians monitored the children closely during scanning. If movement was detected at this stage, image acquisition was halted. Instructions about the importance of remaining still were repeated via the intercom and headphones, and the sequence was repeated. After the exam, children received an immediate reward: a certificate and a gift package with age-appropriate toys (dolls, car toys, educational games, among others) and candies (chocolates and lollypops), whether they performed the exam successfully or not. Snacks were always available during the intervention (juice boxes and cookies). Children were not informed about the certificate of participation or the gift package before or during the MRI exam. After the MRI procedure, the children were rewarded by a research assistant and dismissed.

Participants

The Ethical Committee of the School of Medicine—University of São Paulo, approved all experimental protocols. Written informed consent was obtained from the parents or guardians of all participants, and all children provided verbal consent.

All participants were recruited from public schools in the Brazilian cities of São Paulo and Porto Alegre as part of a larger community-based cohort study entitled "High Risk Cohort Study for Psychiatric Disorders" (HRC) [63]. Inclusion criteria for the large study were as follows: (1) children must to be registered in school by a biological parent, who would be able to provide consent as well as complete demographic and behavioral questionnaires about the child's behavior and family environment; (2) age between 6 and 12 years at the recruitment phase; (3) Brazilian Portuguese as the native language; and (4) the child must have remained enrolled in the same school during the assessment year. A total of 9937 volunteers were initially accessed by the application of The Family History Survey (FHS, [84], of whom 2512 children were included in the HRC cohort. Based on the FHS scores of these children, 958 were randomly recruited and another 1554 were selected according to inferred risk for the development of mental disorders. Estimated intelligence quotients (IQs), socioeconomic status (SES), family environment scale scores, and behavioral assessments were obtained in household interviews. Among the HRC-included population of 2512 children, 772 were assigned to complete an MRI scanning session (time interval between interview and scanning, 35.65 ± 6.95 weeks). A hundred and seventeen participants were later excluded due to incomplete MRI sessions, excessive motion (as identified by the MRI system operator), or preprocessing errors (e.g., unacceptable template registration to the Montreal Neurological Institute [MNI]-152 template), resulting in a total of 655 participants with acceptable structural and functional scans.

The 655 children included in this study (312 from Sao Paulo and 343 from Porto Alegre) were scanned with the same acquisition parameters. The IQ was estimated using the vocabulary and block design subtests of the Wechsler Intelligence Scale for Children [83] and the method described by Tellegen and Briggs [75]. SES classifications were very low or low (E and D classes), medium (C and B classes), and comfortable (A class) as per the criteria of the Brazilian socioeconomic scale (Brazilian Association

Table 1 Demographics

Site	Sao Paulo	Porto Alegre	Whole sample
Age (s.d)	10.6 (1.8) y.o.	10.8 (2.0) y.o.	10.7 (1.9) y.o.
Males (%)	179 (57.3%)	167 (48.7%)	346 (52.8%)
IQ (SD)	103.5 (16.7)	101.8 (16.7)	102.6 (16.7)
Right-handed (%)	270 (86.5%)	289 (84.2%)	559 (85.3%)
SES (low/med/high)	(4/66/30)%	(5/68/27)%	(4/67/29)%
CBCL-G (SD)	0.10 (0.48)	0.18 (0.52)	0.05 (0.52)
FES-G (SD)	0.05 (0.78)	0.22 (0.77)	0.14 (0.78)
N	312	343	655

SD standard deviation, *IQ* estimated Intelligence Quotient, *SES* socioeconomic status, *CBCL-G* child behavioral checklist (general factor), *FES-G* Family Environmental Scale (general factor)

of Market Research Institutes; ABIPEME). Demographical information is presented in Table 1.

Family environment and behavioral assessments

One parent (if both parents were available, the primary informant was the parent currently spending more time with the child) filled the Child Behaviour Checklist (CBCL, [1]) and the Family Environment Scale (FES, [55]). A bifactor (general plus specific factors) model was fitted to the CBCL data, whereby the response to each item comprised the additive effect of one general factor (CBCL-G; covariation of all symptoms), two specific factors (internalizing or externalizing), and a random error (individual effect). Similarly, a bifactor model was fitted to the FES family relationship dimension, comprising a general factor (FES-G; quality of the family environment) and two specific factors (cohesion and conflict between family members). This choice was based on the reports of reliability and criterion validity of these factors [31] of the FES scale and reflects the level of support between family members (cohesion) and parents' perceived expression of anger and explicit conflict (conflict) in family interactions. In this manner, higher FES-G values represent a better quality of family environment (i.e., lower conflict and higher cohesion). The bifactor model method is suitable for the conceptualization of the commonality and specificity of symptoms from distinct dimensions [9, 80]. Both CBCL and FES models were fitted using the structural equation package of MPLUS 7.0 (http://www.statmodel.com/). Additional information about this model can be found in the supplementary materials.

Image acquisition

Prior to scanning, all subjects engaged in recreational activities for desensitization. Image acquisition was performed using a 1.5-T MRI scanner (GE, Signa HDX and HD). Anatomical T1-weighted scans [repetition time (TR) = 10.916 ms, echo time (TE) = 4.2 ms, slice thickness = 1.2 mm, flip angle = 15°, matrix size = 256 × 192, field of view (FOV) = 245 mm, number of excitations (NEX) = 1, bandwidth = 122.109, number of slices up to 156 for whole brain coverage] were obtained for spatial normalization and segmentation purposes. fMRI data were acquired during a resting state protocol (with the subject's eyes open and focused on a fixation point (180 volumes, TR = 2000 ms, TE = 30 ms, slice thickness = 4 mm, gap = 0.5 mm, flip angle = 80°, matrix size = 80 × 80, FOV = 240 mm, reconstruction matrix = 128 × 128, NEX = 1, number of slices = 26).

Image preprocessing

A resting-state fMRI preprocessing pipeline was applied using AFNI v. 2011 [13] and FMRIB Software Library (FSL) software v.5 [38]. The following steps were performed (routines from http://www.nitrc.org/projects/fcon_1000): discarding the first four volumes; head-motion correction; despiking; linear detrending; spatial smoothing (full width at half maximum = 8 mm); and rigid-body registration to the respective anatomical (T1) volume. Anatomical images were skull-stripped and nonlinearly registered to the MNI-152 template standard space.

From the resultant images, fALFF values (in 0.01–0.1 Hz frequency range) [93] were calculated for each voxel. This measure is robust against head motion artifacts [88, 89] and physiological (cardiac and respiratory) noise [94]. Moreover, a previous study from our group demonstrated the utility of fALFF for investigating spontaneous activity in the DMN as well as its relationship to brain maturation and psychopathology [68]. Single-subject fALFF maps were transformed to z scores across the whole brain and registered to the standard space using anatomical data. Mean frame displacement across scans (Eq. 9 of [89] was computed as a representation of the amount of head motion for each subject.

Statistical analysis

Effects of SES and gender on CBCL-G and FES-G scores were assessed using one-way analysis of variance tests (ANOVAs). Correlations between head motion (mean frame displacement) and CBCL-G and FES-G scores were tested using Spearman correlation coefficients.

In order to build group-level brain maps of regions where fALFF was correlated with FES-G scores, we used a whole-brain voxel-wise general linear model (GLM) with fALFF as the dependent variable, FES-G scores as the main regressor, and age, gender, and site as nuisance variables. The significance level was adjusted for family-wise error (FWE; random fields theory) and set to a cluster level of < 0.05 (clustering forming p voxel < 0.001). Note that FWE adjustment is a conservative choice when compared to false-discovery-rate (FDR), reinforcing our commitment to avoid Type I Error. Mean fALFF values of significant clusters were then extracted. Alternative models were also fitted including SES classification or frame-displacement as covariates, since these are well-recognized confounding variables. Including the respective interaction term with FES-G scores tested moderation effects of age.

The association between fALFF in identified brain regions (clusters) and the level of behavioral and emotional problems were subsequently examined using a GLM with CBCL-G scores as the dependent variable, fALFF (in separate models for each region) as the main regressor, and age,

gender, and site as nuisance variables. Including the respective interaction term in the model tested moderation effects of age on the association between fALFF and CBCL scores.

Finally, we carried out a mediation analysis by using the PROCESS package [35]. For each cluster, analyses were conducted considering FES-G score as the input variable, mean fALFF as a mediator, CBCL-G score as the output, and age as a covariate. Confidence intervals for mediation effects were obtaining using 5000 bootstrap samples. Unless otherwise stated, values represent the mean ± standard deviation.

Results

The relation between family environment, symptoms, head motion and SES

Participant demographic information is summarized in Fig. 1; histograms of CBCL-G and FES-G data as well as box-plots of SES and gender data are shown. We observed that FES-G scores were skewed to right while CBCL-G scores were skewed to the left, as was expected from data of a community sample. Furthermore, CBCL-G and FES-G scores were moderately negatively correlated (Spearman's rho = − 0.39; $p < 0.001$), expressing the expected association between more conflictive/less cohesive family environments and increased burden of behavioral and emotional problems. Additionally, socioeconomic status was positively associated with FES-G scores (ANOVA, $p = 0.003$) but was not significantly associated with CBCL-G scores (ANOVA, $p = 0.241$). No gender differences were observed according to FES-G (ANOVA, $p = 0.164$) or CBCL-G scores (ANOVA, $p = 0.615$). Mean head motion across subjects (mean frame-displacement across scans) was 0.16 ± 0.23 mm (95% percentile, 0.45 mm), and no correlations were found between head motion and CBCL-G ($p = 0.224$) or FES-G scores ($p = 0.902$).

Neural correlates of FES-G

Figure 2 depicts statistical parametric maps (GLM) at the group-level for regions with positive and negative correlations between FES-G scores and fALFF (with age, gender,

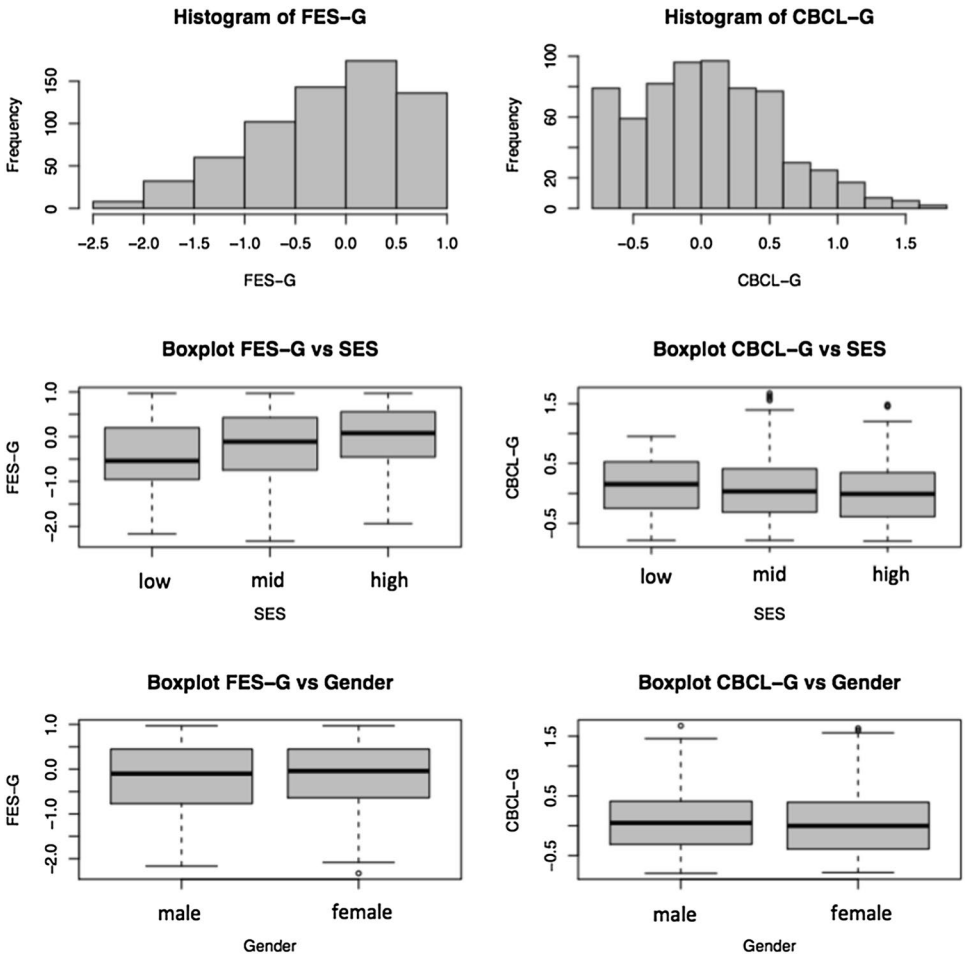

Fig. 1 Histograms of CBCL-G and FES-G values and box-plots of socioeconomic status and gender

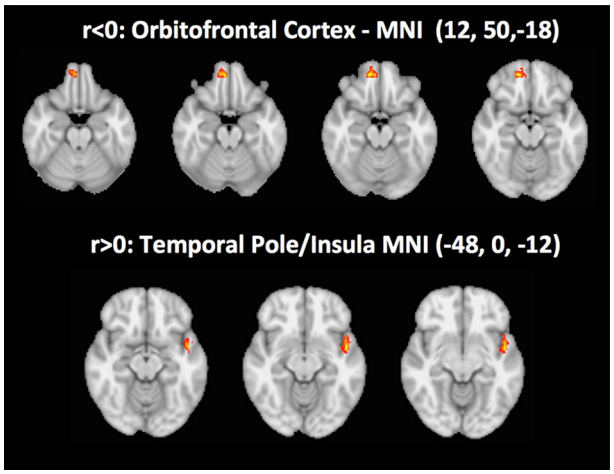

Fig. 2 Group-level brain maps of the association between fALFF and FES-G (cluster level $p < 0.05$; p voxel < 0.001; with age, gender, and site as covariates). Maps are in radiological notation. The color of the voxels within the identified clusters (from red to white), represent the z value of each voxel

and site as covariates). fALFF in the right orbito-frontal cortex (r-OFC; local maxima MNI coordinates: $x = 12$, $y = 50$, $z = -18$) was negatively correlated with FES-G scores. Conversely, fALFF in a cluster covering the left temporal pole and the anterior portion of the superior temporal gyrus (l-TP; local maxima MNI coordinates: $x = -48$, $y = 0$, $z = -12$) was positively correlated with FES-G scores.

We next extracted mean fALFF values across voxels within clusters that were mapped in the previous analysis. We considered mean fALFF within a cluster as the dependent variable and used the same independent variables as those in the previous analysis (FES-G score, age, gender, and site) to fit a GLM. Despite the fact that data were from a cohort of children, we did not identify an effect of age on fALFF values ($p = 0.288$ and 0.200 for the l-TP and r-OFC, respectively). However, and as expected, FES-G scores were significantly associated with fALFF in the l-TP (beta $= -0.079$, $p = 0.017$) and r-OFC (beta $= 0.09$, $p = 0.015$). Regarding possible confounders, all findings were still significant when SES classification was included as a covariate ($p < 0.001$ for both regions), and we did not identify an effect of SES classification on fALFF ($p = 0.341$ and 0.402, respectively). It is important to highlight that when including nuisance covariates such as head motion (and CBCL-G) at group level analyses, the findings remain statistically significant ($p < 0.001$ for both regions).

Moderation effects of age on correlation between FES-G scores and fALFF were not statistically significant ($p = 0.145$ and 0.638, respectively), suggesting that these correlations are not age-dependent.

Table 2 GLM coefficients with CBCL-G as the response variable, fALFF as the main regressor, and age, gender, and site as covariates

Brain region	Coefficient	Beta	SE	p value
Temporal pole	Intercept	0.360	0.144	0.013
	fALFF	− 0.079	0.033	**0.017**
	Gender	− 0.046	0.039	0.239
	Age	0.011	0.010	0.288
	Site	− 0.279	0.039	< 0.001
Orbitofrontal cortex	Intercept	0.355	0.145	0.015
	fALFF	0.091	0.037	**0.015**
	Gender	− 0.045	0.039	0.253
	Age	0.013	0.010	0.200
	Site	− 0.263	0.040	< 0.001

fALFF was significantly correlated with CBCL-G in both regions
The values in bold highlight the p values < 0.05

Associations between fALFF and CBCL dimensions

Interestingly, a significant positive correlation was found between CBCL-G scores and fALFF values in the r-OFC, while a significant negative correlation was found between CBCL-G scores and fALFF in the l-TP (Table 2). These associations were still significant when SES classification ($p = 0.022$ and 0.020) and frame-displacement ($p = 0.017$ and 0.016) were included as covariates.

Then, we tested the moderation effects of age on the correlation between fALFF and CBCL-G scores by including interaction terms in the model. Interaction was significant in the l-TP (beta $= 0.053$, $p = 0.003$) but not in the r-OFC ($p = 0.356$). Thus, there is evidence that the correlation between l-TP fALFF and CBCL-G scores is age-dependent. Since the beta coefficient of fALFF at the temporal pole was negative (Table 2) and the interaction beta coefficient (age × fALFF) was positive, the correlation between fALFF and CBCL-G scores became more positive (less negative) as children grew older. In other words, the relationship between higher fALFF in l-TP and fewer behavioral problems seems to be stronger in younger children.

Mediation analyses

Given the identification of significant associations among FES-G scores, fALFF, and CBCL-G scores, a hypothesis-driven mediation analysis was a natural next step. Thus, we tested the mediation analysis in a FES-G-to-fALFF-to-CBCL-G model. However, no statistically significant results were identified. The bootstrap 95% confidence interval for indirect effects contained 0 for the temporal pole (− 0.0110; 0.0069) and for the OFC (− 0.0190; 0.0006). This lack of a mediation effect is discussed below.

Discussion

Here we report associations between the quality of family environment, spontaneous local functional oscillations in specific frontal and temporal heteromodal brain regions, and the manifestation of behavioral and emotional problems in children. We found that a lower quality of family environment (i.e., with less cohesion and more conflict) was associated with reduced amplitude of spontaneous activity in the left temporal pole (l-TP) and increased amplitude in the right orbitofrontal cortex (r-OFC). Moreover, the amplitude of activity in these areas was inversely related to the expression of behavioral and emotional problems. Remarkably, higher amplitudes of spontaneous activity in the r-OFC were associated with higher levels of behavioral and emotional problems, whereas higher amplitudes in the l-TP were associated with fewer problems. Hence, spontaneous activity of these areas is meaningfully associated with both the level of family cohesion/conflict and the manifestation of behavioral and emotional problems in children. Moreover, we found a significant moderation effect of age on the association between l-TP fALFF values and behavioral problems, suggesting that a potential effect of environmental factors on brain function mediating vulnerability to behavioral problems may be at least partially dependent on the exposure timing. More specifically, the patterns observed in l-TP fALFF seem to be more pronounced in younger children, as usually observed in developmentally sensitive periods.

The growing evidence of the effects of environmental factors on the development of brain structural and large-scale functional networks points to larger effects on frontal and temporal heteromodal areas. Our results are indeed consistent with the results of studies addressing the effects of environmental factors on brain development [42, 57, 58, 69]. Noble et al. [58], for instance, reported that parental education and family income status were associated with the surface area of both the temporal pole and the OFC, and that the surface area of these regions mediated the relationship between family income and cognitive performance. Also, such heteromodal areas that comprise large-scale networks instantiating higher order cognition (e.g., DMN and attentional networks) exhibit a protracted structural and functional developmental trajectory when compared with sensorimotor networks. In fact, the DMN achieves stability and mature features later in adolescence, which arguably makes them more susceptible to environmental factors during development [29, 60, 78]. Furthermore, delayed maturation of these networks, particularly of the DMN, was reported to be related with an increased incidence of mental symptoms and disorders [40, 66–68].

Functionally, the temporal pole is a node of the mediofrontal component of the DMN and is thought to be involved in the monitoring of one's own mental state as well as that of others [3]. The OFC, although classically implicated in inhibitory control, is considered to play a general role in constructing and maintaining a cognitive map that defines the current task space [74]. Interestingly, both the temporal pole and the OFC were identified as parts of a common neural substrate for psychiatric conditions in a meta-analysis of six major mental disorders [26]. Executive dysfunction and impaired perception of one's own mental state and/or that of others has been posited as the basis of a common psychopathological substrate [26]. These impairments can be reasonably associated with altered functionality in both the OFC and the temporal pole. We speculate that the pattern observed in the relationships between family environment, fALFF in the temporal pole, and behavioral problems is consistent with the hypothesis that higher spontaneous activity in the temporal pole is associated with improved social cognition and self-referential processes [3]. The symmetrically inverse pattern observed in the OFC, in contrast, is consistent with the observation that increased fALFF in the right OFC is associated with impaired cognitive well-being [43] as well as with a myriad of mental disorders such as attention deficit hyperactivity disorder [46, 91], depression [48, 87], obsessive–compulsive disorder [37], and post-traumatic stress disorder [90]. Together, these findings suggest that decreased fALFF in l-TP and, especially, increased fALFF in r-OFC might represent vulnerability factors for mental disorders in general. Furthermore, it also suggests that these factors could be prone to modulation by the early environment.

It is important to emphasize that the hypothesis of a common neural substrate for mental disorders does not invalidate clinical categorical distinctions. Rather, our findings highlight one aspect of a complex chain of events involving genetic and environmental susceptibility factors that might lead to psychopathological manifestations. In fact, environmental effects on neurodevelopmental trajectories may result in distinct outcomes later in life [17, 65]. Furthermore, a potential bidirectional interaction between behavioral and emotional problems in children and the quality of the family environment deserves further consideration [33, 34].

In an alternative but not mutually exclusive functional anatomy perspective, both the OFC and the temporal pole are cytoarchitectually classified as limbic cortical areas and characterized as having the simplest laminar structure in the neocortex [4]. Recently, laminar structure was hypothesized to determine the directional flow of sensory predictions, with predictive signals flowing from less laminated cortices to more laminated ones [5]. The cytoarchitectual properties of the temporal pole and the OFC, along with the functional anatomy of these highly interconnected limbic cortical areas, suggest a privileged position in a hierarchical generative

model of interoceptive and exteroceptive predictions [10]. Accordingly, these limbic cortical areas might be considered as a core substrate for a variety of mental symptoms involving cognitive, affective, and social domains. Impaired functionality in these areas might be associated with vulnerability to a wide variety of mental symptoms and disorders, consistent with the propose of a general substrate for most mental disorders.

We argue that efforts to untangle the complex role of family environment on psychopathological trajectories might be better informed by clarifying the effects of childhood experiences on developing large-scale functional networks. Such approaches are relevant, as family environment can be considered as a modifiable target for mental health promotion [8, 49]. Convincing evidence exists for a significant effect of early childhood interventions that address family environment on mental health outcomes. Such interventions include programs to improve caretaker responsiveness and sensitivity [41, 56, 86]. Future studies should directly address fALFF as a tool to investigate the biological mechanisms of susceptibility to and protection from mental disorders, especially in disadvantaged populations.

Mediation effects were not identified when we considered family environment as the input, fALFF as a mediator, and behavioral and emotional problems as the output. However, it is important to note that fALFF is a measurable feature of neural systems rather than a direct measure of processing or functionality. That is, fALFF is a proxy variable for the complex latent brain processes that putatively underlie behavior. Thus, while our data reinforce the utility of fALFF values as potential indicators of vulnerability to mental disorders, they do not permit inferences about cause-effect relationships. Moreover, measurement error in the mediator variable is a relevant obstacle in mediation analyses, since the analysis itself is based on the strength of the correlations between the input, mediator, and output. Correlations may have been strongly affected by small measurement errors that are common in fMRI and specifically related to the use of 1.5-T scanners.

The present study had several other limitations that should also be considered in parallel with its conclusions. Unequivocally, time spent with family is an important missing variable in this context. However, because the items in the questionnaire were more focused on conflict and cohesion within the family, time spent with family was not assessed. Meanwhile, time spent with family is expected to be positively correlated with cohesion, which alleviates concern regarding the lack of this variable. Moreover, assessment tools were completed by the parents—usually the biological mother. Thus, a second limitation is a possible gender effect in regard to the informant (father or mother) who completed the questionnaires. First, it is important to mention that the majority of the responders were mothers (94.9%). In addition, it is important to underscore that if both parents were available to answer the questions, the primary informant was the one spending more time with the child in the days prior.

Conclusion

In summary, increased amplitudes of spontaneous oscillatory activity in the orbitofrontal cortex and decreased amplitudes in the temporal pole were associated with both lower quality of the family environment and increased incidence of behavioral and emotional problems in children. Our findings illustrate how conflictive and non-cohesive family environments influence spontaneous oscillatory brain activity during development. Future investigations should clarify the relevance of these findings as markers of vulnerability to mental disorder later in life [18, 19, 68].

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Compliance with ethical standards

Conflict of interest Dr. Luis Augusto Rohde has been on the speakers' bureau/advisory board and/or acted as a consultant for Eli-Lilly, Janssen-Cilag, Novartis, and Shire in the last 3 years. The ADHD and Juvenile Bipolar Disorder Outpatient programs chaired by Dr. Rhode have also received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Eli-Lilly, Janssen-Cilag, Novartis, and Shire. Dr. Rohde has also received travel grants from Shire for participation in the 2014 American Physiological Association and 2015 World Federation of ADHD congresses. Finally, he receives authorship royalties from Oxford Press and ArtMed. Dr. Rodrigo Affonseca Bressan has been on the speakers' bureau/advisory board of AstraZeneca, Bristol, Janssen, and Lundbeck. Dr. Bressan has also received research grants from Janssen, Eli-Lilly, Lundbeck, Novartis, Roche, FAPESP, CNPq, CAPES, Fundação E.J. Safra, and Fundação ABAHDS. He is also a shareholder in Biomolecular Technology Ltd. Dr. Edson Amaro Jr. has received research grants from FAPESP, CNPq, CAPES, Fundação E.J. Safra, and Fundação ABAHDS. Dr. Pedro Pan received a PhD Scholarship from CNPq.

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