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Association between spontaneous activity of the default mode network hubs and leukocyte telomere length in late childhood and early adolescence

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ABSTRACT

The impact of early life stress on mental health and telomere length shortening have been reported. Changes in brain default mode network (DMN) were found to be related to a myriad of psychiatric conditions in which stress may play a role. In this context, family environment and adverse childhood experiences (ACEs) are potential causes of stress. This is a hypothesis-driven study focused on testing two hypotheses: (i) there is an association between telomere length and the function of two main hubs of DMN: the posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC); (ii) this association is modulated by family environment and/or ACEs. To the best of our knowledge, this is the first study investigating these hypotheses. Resting-state functional magnetic resonance imaging data and blood sample were collected from 389 subjects (6–15 age range). We assessed DMN fractional amplitude of low-frequency fluctuations (fALFF) and leukocyte telomere length (LTL). We fitted general linear models to test the main effects of LTL on DMN hubs and the interaction effects with Family Environment Scale (FES) and ACEs. The results did not survive a strict Bonferroni correction. However, uncorrected *p*-values suggest that LTL was positively correlated with fALFF in PCC and a FES interaction between FES and LTL at mPFC. Although marginal, our results encourage further research on the interaction between DMN hubs, telomere length and family environment, which may play a role on the biological embedding of stress.

1. Introduction

Previous studies showed that the maturation of the human brain is deeply influenced by environmental conditions [44]. The brain default mode network (DMN) is one of the most studied functional brain networks [6,41]. The posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC) have been shown to be two main hubs of the DMN [6,29,60,66] being the most explored regions of this network. Although the activity of two regions is frequently correlated, the PCC activity is more related to tasks that involve autobiographical memory and self-referential processes [7] and mPFC is frequently associated with social cognitive processes linked to self and others [2].

The participation of both nodes in DMN can be detected at different ages, it was already detectable by the age of 10 [53]. In contrast, the PCC maturation is expected to take place around 7–9 years old ([15]/[16,46]) while mPFC only completes maturation during young

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adulthood [53,62]. Thus, different stages of maturation of DMN may help explain why it becomes more functionally integrated during later development [21]. This long development might also explain its sensitivity to environmental exposure [20] as it shows to be highly vulnerable to early-life stress [22,31,52,69]. Stressful conditions related to developing countries around the world constitute the environment in which millions of children are growing up [59].

Furthermore, it was also identified an association between DMN activity and systemic inflammation under stressful conditions [30], detected by changes in the peripheral physiology [24,28]. Stress exposure is frequently investigated by exploring the environmental factors and an individual's psychological and physiological responses over time [35,57]. In this regard, changes in DMN nodes were found to be related to a myriad of mental disorders [6,23,27,39,50,63,70] in which chronic stress or repeated exposure to adverse experiences are involved [42,49,51].

In parallel, the enduring outcomes from the exposure to adverse conditions have been examined through the physiological responses to environmental demands [34]. A promising biomarker for measuring the impact of early-life stress on cellular functioning is accelerated telomere shortening [13,48]. Telomeres are DNA-protein structures that cap the ends of chromosomes and are essential for cellular stability during replication [4,26,67]. Given its continuous shortening with each cell division through the lifespan, telomere length has been proposed as a marker of biological aging [4] and also as a measure of disease risk related to aging, such as cardiovascular disease and diabetes [68]. Recent studies identified differences in telomere length in early age [12,54] and in adulthood [58] which are associated with early-life stress. Others authors investigating life-span [5], suggest that accelerated telomere shortening might be as a physiological measure of stress [40]. However, the exact stress mechanisms causing telomere shortening remain unknown, since there are other factors such as immune dysregulation and oxidative stress imbalances [14,25]. This is especially considered when stress exposure occurs during sensitive periods such as childhood and adolescence [9,34] which could affect peripheral blood cells, particularly leukocytes.

Recent studies suggest that adverse childhood experiences (ACEs) and family environment may be associated with accelerated telomere shortening, particularly: witnessing maternal domestic violence [47], lower educational parental level [17,33], marital conflict of the parents [43], lower socioeconomic status [38] and lower levels of parental support/responsiveness [3,56]. Moreover, children in these conditions usually have to deal with family conflicts for a prolonged time until reaching adulthood, thus characterizing chronic exposure to those stressors.

In short, we have enough evidence that early-life stress exposure is associated both with telomere length and DMN function. Despite this growing evidence, the association between them has neither been evaluated nor it was checked if this association is modulated by environmental factors. In this current hypothesis-driven study based on a sample of children and adolescents, we aim to test two very specific hypothesis: (i) there is an association between telomere length and the spontaneous activity of the posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC); (ii) this association is modulated by family environment and/or ACEs. A full detailed exploration of the potential mechanism and other variables involved in this association is not in the scope of this study due to two main reasons: (i) to avoid Type I Error inflation due to excessive multiple testing; (ii) we do not have appropriate data to unveil the comprehensive biological mechanisms which might lead to these associations.

2. Materials and methods

2.1. Subjects

This study is based on 665 school-age children (6 to 14 years old), from the '*Brazilian High-Risk Cohort Study (BHRCS) for Psychiatric Disorders in Childhood*'. The *BHRCS*is a population-based sample from 57 Brazilian public schools (35 schools from the city of São Paulo; and 22 schools from the city of Porto Alegre). Further details about this cohort can be found in Salum et al. [45]. For this study, only the data of 389 children are being used, considering the availability of both telomere length and resting state fMRI for these participants. Written informed consent was obtained from all biological parents and verbal assent from participants. All experimental procedures were approved by the local Ethics Committees.

2.2. Telomere length measurement

Leukocyte TL (LTL) was measured from DNA of 4 mL of whole blood, collected in an EDTA tube, by quantitative polymerase chain reaction (qPCR) previously described by Cawthon [8]. This step is fully described in [64] (PMID: 30384090). Briefly, this technique consists of determining the relative ratio (T/S) between the telomere region copy number (T) and a single copy gene (S) using a relative standard curve. We chose albumin gene (*ALB*) as the single-copy gene. The T/S ratio is proportional to the mean leukocyte TL in the peripheral blood of the participant.

2.3. Assessments

The Brazilian socioeconomic scale ABA/ABIPEMI (2010 version, [1]) was used to define the socioeconomic scores (SES). The quantitative SES was calculated for each family, as only one child per family was enrolled in *BHRCS*.

Family environment was assessed using a validated version for the Brazilian linguistic and cultural context [61] of the Family Environment Scale (FES, [36]). For this study, the interpersonal family functioning was evaluated through cohesion (i.e., degree of commitment, help and support of family members to one another) and conflict (i.e., the amount of openly expressed anger and conflict) subscales, which were answered by the children's biological parents (the biological mothers were 87.6% of the informants) in a household interview. Items of both subscales were aggregated to compute a family environment score based on a bifactor model. This model is composed of a general latent factor (general interpersonal family functioning) and specific factors of cohesion and conflict. The general factor represents the commonalities of cohesion and conflict (which are negatively correlated) and was considered as the family environment score. The bifactor model provided a good fit to the data (RMSEA = 0.029, CI90% 0.026 to 0.033; CFI = 0.985, TLI 0.98). Higher scores reflect better quality of the family environment.

The presence of ACEs considering maltreatment (or physical abuse), neglect by parental caregiving, sexual and emotional abuse were assessed by report of the mothers, all occurrences related to children family environment. The possible answers were: no, yes once or twice, yes it occurred or still eventually occurs; and yes, it usually occurs.

2.4. Imaging acquisition

Resting-state functional neuroimaging data were obtained in two 1.5 T MRI GE scanners (São Paulo city: Signa HDX and Porto Alegre city: Signa HD) with identical acquisition parameters. One hundred and eighty whole-brain EPI volumes were obtained for each participant (TR = 2000 ms, TE = 30 ms, slice thickness = 4 mm, gap = 0.5 mm, flip angle = 80°, matrix size = 80 × 80, reconstruction matrix = 128 × 128, 1.875 × 1.875 mm, NEX = 1, slices = 26, total acquisition time of 6 min). Participants were instructed to maintain eyes open and fixate gaze at a painted target. T1-weighted scans (3D FSPGR sequence) were obtained considering up to 160 axial slices (TR = 10.91 ms, TE = in phase 4.2 ms, thickness = 1.2 mm, flip angle = 15°, matrix size = 256 × 192, FOV = 24.0 × 18.0 cm,

NEX = 1).

2.5. Image processing

The images were processed using scripts (from http://www.nitrc.org) based on routines from AFNI (version 2011_12_21_1014) and FSL (version 5.0). Data of each participant were preprocessed by the following steps: the first four volumes were discarded, head motion correction, skull-stripping and despiking, linear detrending, spatial smoothing (Gaussian kernel, FWHM = 6 mm) and grand-mean scaling. Fractional amplitude of low-frequency fluctuations (fALFF) [71] was calculated for each intracranial voxel in the frequency range from 0.01 to 0.1 Hz. The fALFF maps were then normalized to z-scores considering the whole brain. Finally, the normalized fALFF maps were spatially normalized to standard space using a non-linear transform, the individual T1 image and the Montreal Neurological Institute (MNI152) template.

The mean fALFF were extracted from PCC/Precuneus and MPFC, as regions of interest (ROIs, spherical, 4 mm diameter), according to the coordinates of Fox et al. [18].

2.6. Statistical analysis

First it is important to remind that this is a hypothesis-driven study to test associations and not to unveil the biological processes driving this relation. Thus, to avoid excessive multiple comparisons resulting in the inflation of Type I Error, the statistical analyses were very focused. For each region-of-interest (PCC and mPFC), associations between fALFF and LTL were tested using the general linear model (GLM), considering the fALFF as the dependent variable. The model was composed of main effects of LTL and FES, the respective interaction effect, and the following covariates: age, sex, site of acquisition and amount of head motion (mean displacement, FD; [65]). The same analyses were repeated by using the number of ACEs (assuming linearity of the responses) instead of FES. Thus, a total of four separately GLM were fitted (two brain regions and two environmental variables) for statistical assessment. The main parameter of interest was the interaction effect (the null hypothesis is that it is equal to zero). If this parameter is not statistically significant, we then analyze the main effect of LTL. No further statistical analyses were conducted. The type I Error was set at 5% without multiple comparisons adjustment, since Bonferroni correction for four multiple comparisons did not yielded significant results.

Yan et al. [65] have shown that fALFF is relatively robust against head motion artifacts when compared to other resting state fMRI features. This is one of the main reasons for using fALFF in this study. However, we preferred to be conservative and also included mean frame-displacement as covariate at group level analysis, in order to control the findings for this potential confounder.

3. Results

The demographic characteristics of the children and adolescents participating in this study are presented in Table 1. The mean age of the sample was 10.82 (s.d. = 1.88) years old and 54% (n = 212) were male. Moreover, Table 2 highlights that almost 50% of the participants were exposed at least to one ACE.

Table 1
Demographical characteristics of the sample.

Sociodemographics (whole sample)	n	Mean (SD)	Range
Age, y	389	10.82 (1.88)	6.96–15.01
LTL (T/S Ratio)		1.15 (0.17)	0.68–1.91
Family environment scale (FES)		−0.17 (0.78)	−2.17–0.97
Socioeconomic status (SES)		20.08 (4.50)	6–39
Sex (male)	212 (54%)		

Abbreviations: y = years, SD = standard deviation.

Table 2
Distribution of Adverse Childhood Experiences (ACEs).

ACEs	Total
None	174 (44.7%)
One	133 (34.2%)
Two	43 (11.0%)
Three	14 (3.6%)
More than three	4(1.0%)
Missing	21 (5.4%)

Table 3
Results of GLM analyses for LTL and interpersonal family function (FES). The statistical significant associations are highlighted in bold. Abbreviations - mPFC: medial prefrontal cortex; PCC: posterior cingulate; FES: family environment scale; LTL: leukocyte telomere length; GLM: general linear model.

Dependent variable	Independent variables	Beta	p-value
mPFC	FES	−0.439	0.038
	LTL	0.004	0.977
	FES*LTL	0.369	0.040
PCC	FES	0.033	0.872
	LTL	0.336	0.022
	FES*LTL	−0.027	0.876

Table 3 summarizes the results of the main GLM analyses of this study. Strictly, our results did not confirm our hypothesis, since the results did not survive a Bonferroni correction for four multiple comparisons. But considering the potential contribution of these findings to the field and the novelty in testing these hypotheses, we present the findings based on uncorrected p-values, which were statistically significant.

As hypothesized, the FES*LTL interaction effect on mPFC was marginally significant (uncorrected-p = .040). Thus, the better the quality of the family environment, the stronger is the association between mPFC fALFF and LTL. In contrast, at PCC, no significant interaction effect FES*LTL was found. However, we found a main effect of LTL (uncorrected-p = .022).

In contrast, we found no significant interaction effect between the number of ACEs and LTL for either MPFC or PCC.

4. Discussion

Previous literature findings suggest that chronic stress is associated both with telomere length [48] and DMN functioning in adults [28]. In this brief report, based on a large sample of children and adolescents, we tested whether the telomere length is associated with DMN spontaneous activity (fALFF) at mPFC and PCC, the two main hubs of this network. Moreover, we also tested whether this hypothesized association was modulated by the quality of the family environment and the number of ACEs in a large sample of individuals from a developing country.

When adjusting for multiple comparisons our results were not significant. However, we have indeed found interesting marginal findings. Given the novelty of the study and the potential contributions to the debate on the topic of interactions between brain, genetics and environment, we present a discussion based on these marginal findings (uncorrected p-values). As hypothesized, we found a positive correlation between LTL and PCC fALFF, and a positive correlation with mPFC fALFF and LTL modulated by the quality of the family environment (i.e., interaction effect of FES*LTL). To the best of our knowledge, these findings are the first to demonstrate these associations. In line with our hypothesis, family environment quality, which is a potential source of stress, modulates the association between DMN function and telomere

length. The significant interaction effect found in FES*LTL but not in ACE*LTL raises many questions on the dynamics between these two factors. Possibly, the family environment may play the role of buffer to ACE effects but testing this hypothesis was not in the scope of the current study. Alternatively, it could simply mean that adverse experience effects over LTL are late-emerging [57] but longitudinal approach on further studies are necessary to assess this hypothesis.

Nevertheless, our results suggest that it is worth considering the telomere length as a physiological measure of stress in association with brain activity, beyond the behavioral aspects. The comprehension of the risks to health development could help us prevent or treat the consequences of these early experiences [55]. A systematic review concluded that adversities in childhood (such as violence, low socioeconomic status, maternal depression, family disruption, and institutionalization) have an impact on TL, suggesting that exposed individuals show signs of accelerated erosion of telomere ends even at an early age [9]. Important changes in the immune system are detected when an individual is exposed to stressful conditions, particularly in the tissues where leukocytes are produced [30], and can affect the LTL. Furthermore, the association of the LTL with fALFF of PCC might be a potential avenue to elucidate the neurobiological pathways linking cellular aging with physical and psychiatric biological distress. Despite the unknown mechanisms, this association may suggest that the child experiences with their family affect their peripheral markers and also their brain. This is in line with the hypotheses of a “biological embedding” of their social environment [11,32].

Considering that better parental care and involvement leads to a greater emotional, behavioral, physical and psychological well-being [10], the quality of family environment is fundamental to a healthy development child. We conjecture that the children's perception of their environmental conditions is associated with the DMN [19,37], which may represent an internalization of early experiences [32].

4.1. Limitations and future directions

Some limitations of this study should be considered. First, it is important to mention that this was a hypothesis-driven study with a very limited scope. The cohort investigated are very rich in psychiatric and cognitive variables. However, the exploratory association analyses among LTL, DMN function, and environmental factors with these other variables were not conducted and are out of the scope of this study. Second, we emphasize that the *p*-values of the effects found ($p = .040$ and 0.022) did not survive Bonferroni correction (four multiple comparisons), but they may contribute to the progress in this interdisciplinary field. In addition, it is important to bear in mind that the cross-sectional design of this study does not allow any inference on causal relation between the associations found. Thus, a deeper comprehension of the long-lasting detrimental effects of environmental variables (such as chronic exposure) cannot be achieved. Finally, we have obtained environmental information based only on parental report but not by children self-report of the family environment which is their subjective perception of stressful events. In future studies, environmental measures and ratings objectively assessed by investigators, such as rating the interaction between children and their parents in observed behavioral paradigms, could be useful to assess family conflict.

5. Conclusion

To the best of our knowledge, this is the first study to evaluate the associations among telomere length, family environment and DMN function during childhood and early adolescence. Although the results were marginal, the findings encourage further studies on these association.

Declaration of Competing Interest

Luis Augusto Rohde has received grant or research support from, served as a consultant to, and served on the speakers' bureau of Eli Lilly and Co., Janssen, Medice, Novartis and Shire. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by Dr. Rohde have received unrestricted educational and research support from the following pharmaceutical companies: Eli Lilly and Co., Janssen, and Novartis. Dr. Rohde has received authorship royalties from Oxford Press and ArtMed and travel grants from Shire to take part in the 2018 APA annual meeting and from Novartis to take part in the 2016 AACAP annual meeting.

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