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Perceived stress is associated with smaller hippocampal volume in adolescence:

Perceived stress effects in adolescent brain

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Abstract

Perceived stress has been associated with decreased hippocampal, amygdala and prefrontal cortex volume, as well as decreased memory and executive functioning performance in adulthood. Parents' perceived stress has been linked to decreased hippocampal volume in young children. However, no studies have investigated the links between self-perceived stress and brain structure or function in adolescents. Additionally, findings from previous research with younger or older samples are inconsistent, likely in part due to inconsistencies in participants' age range. In this study, we investigated the associations among self-perceived stress, family socioeconomic factors (family income, parental education), subcortical (hippocampus, amygdala) volumes, prefrontal cortical thickness and surface area, and memory and executive functioning performance in adolescents. One hundred and forty-three participants (12 – 20 years old) were administered a cognitive battery, a questionnaire to assess perceived stress, and a structural magnetic resonance imaging (MRI) scan. Higher levels of perceived stress were associated with decreased adolescent hippocampal volume. This study provides empirical evidence of how experience may shape brain development in adolescence – a period of plasticity during which it may be possible to intervene and prevent negative developmental outcomes.

Keywords

perceived stress; stress; hippocampus; amygdala; prefrontal cortex; adolescence

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Disclosure

The authors declare no conflict of interest.

Introduction

Although acute stress is an adaptive response to real or perceived threats, chronic exposure to stress may have deleterious effects on brain structure, cognition and mental health (McEwen, 1998b; McEwen, 1999; McEwen, 2006; McEwen, 2001). Among the factors contributing to chronic stress are adverse socioeconomic circumstances, as well as exposure to traumatic events, abuse and neglect (for a review see Blair & Raver, 2016; Tottenham & Sheridan, 2010). Exposure to chronic stress has been associated with physiological and neuroendocrine dysregulation of stress response mechanisms (Evans & Kim, 2007; Lupien, King, Meaney, & McEwen, 2000; Lupien, King, Meaney, & McEwen, 2001; Lupien, Ouellet-Morin, Herba, Juster, & McEwen, 2016; McEwen, 1998a; Whittle, et al., 2011). Higher levels of stress have been related to functional and structural alterations in areas of the brain that regulate stress hormones (Pruessner, et al., 2008), including the hippocampus, amygdala and prefrontal cortex (Blair & Raver, 2016; Hanson, et al., 2015; McEwen & Gianaros, 2010; Romeo, 2017; Tottenham & Sheridan, 2010). Together, this network is considered critical for the functioning of memory (McEwen & Gianaros, 2010) and self-regulation (Gianaros, et al., 2007; McEwen & Gianaros, 2010).

The perception of stress may drive these physiological consequences. Evidence from previous research examining the associations between perceived stress and brain structure varies, depending in part on analysis techniques, brain regions evaluated and the gender and age of the sample. For example, studies with older samples (including postmenopausal women) have reported that higher perceived stress is associated with decreased grey matter volume in the hippocampus (Gianaros, et al., 2007; Lindgren, Bergdahl, & Nyberg, 2016; Pagliaccio, et al., 2014; Zimmerman, et al., 2016), amygdala (Holzel, et al., 2010) and prefrontal cortex (Gianaros, et al., 2007; Moreno, Bruss, & Denburg, 2016), as well as with deleterious effects on cognitive outcomes (Aggarwal, et al., 2014; Korten, Comijs, Penninx, & Deeg, 2016; Munoz, Sliwinski, Scott, & Hofer, 2015; Rubin, et al., 2015). Additionally, stressful life events reported by parents have been associated with decreased hippocampal volume in their children (Luby, et al., 2013; Pagliaccio, et al., 2014), as well as with reductions in children's prefrontal cortical volume (Buss et al., 2010), and reduced performance in executive function measures in childhood (Blair et al., 2011; Merz et al., 2016). However, the link between perceived stress and children's amygdala volume is less clear, with some work reporting that increased perceived stress is associated with *smaller* amygdala volume in children (Pagliaccio et al., 2014), other work reporting that stress is associated with *larger* amygdala volume in children (Tottenham et al., 2010), and still other work finding no association between stress and amygdala volume (Luby, et al., 2013).

In adolescents, we have the unusual ability to inquire about the individual's *own* perception of stress relatively early in life. However, the effects of self-perceived stress on the structure of the adolescent brain are largely unknown. This represents a key gap in the literature, as stress response mechanisms are still undergoing development during the adolescent period (Hollenstein, McNeely, Eastabrook, Mackey, & Flynn, 2012; Romeo, 2010) and may result in different neural consequences during adolescence as compared to other life stages (Lupien, McEwen, Gunnar, & Heim, 2009). Due to pubertal changes in gonadal hormones and sensitivity of the hypothalamic-pituitary axis (HPA), adolescents are highly vulnerable

to the consequences of stress that can persist into adulthood as potentiation or incubation effects (Lupien, Ouellet-Morin, Herba, Juster, & McEwen, 2016). Moreover, adolescence is marked by intense neurobiological and cognitive changes related to the maturational alterations in the brain structure (Spear, 2000), representing an important opportunity to intervene and prevent negative developmental outcomes.

In this study, we asked whether adolescents' own perception of stress would be associated with brain structure and memory and executive functioning performance. We investigated the associations among perceived stress, family socioeconomic factors (family income, parental education), subcortical volumes (hippocampus, amygdala), prefrontal cortical thickness and surface area, and memory and executive functioning performance in adolescents. Based on previous research with younger (Luby, et al., 2013; Pagliaccio, et al., 2014) and older participants (Aggarwal, et al., 2014; Gianaros, et al., 2007; Holzel, et al., 2010; Lindgren, Bergdahl, & Nyberg, 2016; Moreno, Bruss, & Denburg, 2016; Munoz, Sliwinski, Scott, & Hofer, 2015; Pagliaccio, et al., 2014; Zimmerman, et al., 2016), we hypothesized that higher perceived stress in adolescence would be associated with reductions in hippocampal volume, amygdala volume, prefrontal cortical thickness and surface area, and memory and executive functioning performance. Finally, we explored whether socioeconomic factors may moderate these associations, given that socioeconomic circumstance has been related to stress (Blair & Raver, 2016; Tottenham & Sheridan, 2010) and may moderate links with brain structure and function (Brito, Piccolo & Noble, 2017; Noble, McCandliss & Farah, 2007; Noble et al., 2012; Piccolo, Merz, He, Sowell & Noble, 2016).

Method

Participants

This study included 143 participants from the multi-site Pediatric Imaging, Neurocognition, and Genetics (PING) study (<http://ping.chd.ucsd.edu>). Participants were included if they had complete data available for the following measures: Perceived Stress Scale, parental education, family income, age, gender, genetic ancestry factor (GAF), scanner serial number, hippocampus volume, amygdala volume, prefrontal cortex morphometry (including volume, surface area and cortical thickness of inferior frontal gyrus [IFG], middle frontal gyrus [MFG], and anterior cingulate cortex [ACC], as well as executive functioning measures (see Table 1 for sample demographics). Participants from the PING study were recruited at nine university-based data collection sites in the cities of Los Angeles, Davis, New Haven, Sacramento, San Diego, Boston, Baltimore, Honolulu, and New York. Exclusion criteria involved report of history of neurological, psychiatric, medical, or developmental disorders. All participants and their parents gave their informed written consent/assent to participate in all study procedures. Each data collection site's Office of Protection of Research Subjects and Institutional Review Board approved the study.

Instruments and Procedures

Perceived Stress Scale (PSS-10)—This self-administered scale was used to measure an individual's level of perceived stress has been widely used to measure chronic stress (Cohen,

Kamarck, & Mermelstein, 1983). The Perceived Stress Scale includes 10 questions about the person's feelings and thoughts during the past month. The response options for each feeling or thought indicate the frequency with which it occurred: 0 = never; 1 = almost never; 2 = sometimes; 3 = fairly often; and 4 = very often, with higher scores indicating higher levels of chronic stress (in this sample $M = 15.25$, $SD = 6.26$). Although not designed to be a diagnostic instrument, the scale has good reliability and validity and has been used in many settings.

Socioeconomic status—Parents reported the total yearly family income and their level of educational attainment. Parental education was measured by averaging maternal and paternal years of education. Both parental education and family income data were collected in bins, which were recoded as the means of the bins for analysis (Noble, et al., 2015). Family income was natural log-transformed, as it was positively skewed. Parent education and income were highly correlated ($r = .525$, $p < .001$).

Structural magnetic resonance imaging (MRI)—Detailed information about the standardized structural MRI protocol administered in each site and the pre- and post-processing techniques were reported previously (Fjell, et al., 2012). In this study, the MRI protocol was performed at six different sites: Los Angeles ($N = 20$), San Diego ($N = 44$), Honolulu ($N = 29$), New Haven ($N = 14$), New York ($N = 26$), and Baltimore ($N = 10$). High-resolution structural MRI included a three-dimensional T1-weighted scan. A modified Freesurfer software suite (<http://surfer.nmr.mgh.harvard.edu/>) was used to analyze the images and obtain the measures of cortical and subcortical volume, and vertex-wise cortical thickness and surface area. Subcortical structures were labeled using an automated, atlas-based, volumetric segmentation procedure (Fischl et al., 2002). Volumes in mm^3 were calculated for each structure. All MRI data passed a standardized quality-image check (see Jernigan, et al., 2016 for details).

Genetic ancestry factor (GAF)—A complete description of the genetic ancestry of the PING sample is presented elsewhere (Akshoomoff et al., 2014; Fjell, et al., 2012). Briefly, saliva samples were analyzed in the Scripps Translational Research Institute (STRi). Genomic DNA was genotyped with Illumina Human660W-Quad BeadChip and replication and quality control filters (sample call rate >99 , call rates $>95\%$, minor allele frequency $>5\%$) were performed (Bakken, et al., 2012). A supervised clustering approach implemented in the ADMIXTURE software was used to assess genetic ancestry and admixture proportions in the PING participants (Alexander & Lange, 2011). Through this approach, a GAF was developed for each participant, representing the proportion of ancestral descent for each of six major continental populations: African, Central Asian, East Asian, European, Native American and Oceanic.

Cognitive measures: Performance on episodic memory, working memory, inhibition and cognitive flexibility tasks were evaluated using NIH Toolbox® Cognitive Function Battery (Weintraub et al., 2013), as described below.

Picture Sequence Memory Test: The task evaluated episodic memory and involved recalling increasingly lengthy series of illustrated objects and activities that were presented

one at a time in the center of the computer screen. The stimuli were presented in a fixed order, with corresponding audio-recorded brief definitions of its contents. The participants were asked to recall the sequence of pictures, by moving each picture from the center to its correct location to replicate the correct sequence. Three test trials were administered to each participant with the level of difficulty adjusted for different age ranges. One point was computed for each adjacent pair of pictures correctly placed. Final scores corresponded to the number of correct adjacent pairs reproduced (Akshoomoff et al., 2014) (in this sample $M = 33.17$, $SD = 8.34$).

List sorting working memory test: This test requires immediate recall and sequencing of different pictures of different foods and animals displayed on the computer screen visually (object) and orally (spoken name), one at a time. Participants were asked to order stimuli by size, from smallest to largest (Tulsky et al., 2013). The test was divided into the one-list (one category) and two-list conditions (two categories). In one-list condition, all stimuli come from one category (food or animals) and in two-list condition, stimuli are presented from two categories (food and animals, mixed). The participant must report first all stimuli from one category, then from the other, in order of size within each. Working memory scores consisted of combined total items correct on both one-list and two-list conditions, with a maximum of 28 points (in this sample $M = 21.08$, $SD = 2.63$).

Flanker inhibitory control test: This test required the participant to focus on a given stimulus while inhibiting attention to stimuli flanking it. The test consisted of a block of 25 fish trials and a block of 25 arrow trials, with 16 congruent and 9 incongruent trials in each block, presented in pseudorandom order on the center of a computer screen. On congruent trials, all the stimuli were pointing in the same direction. On the incongruent trials, the flanker fish/arrow was pointing in the opposite direction of the central fish/arrow. Congruent and incongruent trials were intermixed in the block of standard trials. The accuracy score was based on performance on both congruent and incongruent trials. A two-vector method was used that incorporated both accuracy and reaction time (RT) for participants who maintained a high level of accuracy (>80% correct), and accuracy only for those who did not meet these criteria. Each vector score ranged from 0 to 5, for a maximum total score of 10 (in this sample $M = 8.78$, $SD = .58$).

Dimensional change card sort cognitive flexibility task (DCCS): The DCCS is a measure of cognitive flexibility. Two target pictures were presented, one on each side of the screen, and vary along two dimensions (e.g., shape and color). Participants were asked to match a series of bivalent test pictures (e.g., yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g., color) and then, after a number of trials, according to the other dimension (e.g., shape). In the “switch” trials, the participant must change the dimension being matched. Scoring is based on a combination of accuracy and reaction time for participants who maintained a high level of accuracy (>80% correct), and accuracy only for those who did not meet this criterion. Each vector score ranged from 0 to 5, for a maximum total score of 10 (in this sample $M = 8.59$, $SD = .64$).

Statistical analyses

Descriptive statistics (Table 1) and Pearson correlations (Table 2) were analyzed to describe the sample and to explore the relationship between the variables. Linear multiple regressions were used to investigate the associations between perceived stress; socioeconomic factors (family income and parental education); left and right hippocampus; left and right amygdala; IFG, MFG, and ACC structure (volumes, surface area and cortical thickness); and cognitive measures, controlling for age, age squared, sex, scanner site, and GAF. In the models using hippocampus or amygdala volumes as outcomes, whole brain volume was additionally included as a covariate. The regression models were performed by adding all control variables in a first step and then adding perceived stress to the models. Scanner site, sex and GAF were entered as dummy variables. Analyses were performed using SPSS version 23 and moderation models were tested using PROCESS (Hayes, 2015). Multiple comparisons were verified using False Discovery Rate (FDR) analyses.

Results

Bivariate correlations

Bivariate correlations (see Table 2) showed that perceived stress was not correlated with socioeconomic factors, brain structure or cognitive measures. Family income was positively correlated with left hippocampus ($r = .18, p = .029$), left amygdala ($r = .18, p = .028$), right amygdala ($r = .18, p = .033$), and ACC volume ($r = .17, p = .04$). Family income ($r = .22, p = .007$) and parental education ($r = .24, p = .004$) were correlated with working memory task performance.

Perceived stress associated with hippocampal volume

Greater perceived stress was associated with smaller total hippocampal ($\beta = -.17, p = .017, Adj. R^2 = .45$) and left hippocampal size ($\beta = -.22, p = .003, Adj. R^2 = .41$), controlling for age, age squared, sex, GAF, scanner site, and whole brain volume (Figure 1). This relationship remained significant when controlling for parental education (total hippocampal volume: $\beta = -.18, p = .014, Adj. R^2 = .45$; left hippocampus: $\beta = -.23, p = .003, Adj. R^2 = .41$) or family income (total hippocampal volume: $\beta = -.17, p = .018, Adj. R^2 = .45$; left hippocampus: $\beta = -.22, p = .004, Adj. R^2 = .41$). No statistically significant association was found between perceived stress and right hippocampus volume, left/right amygdala volume, IFG, MFG or ACC cortical thickness or surface area. Perceived stress was not significantly associated with any socioeconomic factors or cognitive measures. Socioeconomic factors did not moderate the association between perceived stress and brain structures.

Discussion

Several recent studies in adults have reported that higher perceived stress levels are associated with smaller hippocampal volumes (Gianaros, et al., 2007; Lindgren, Bergdahl, & Nyberg, 2016; Romeo, 2017; Zimmerman, et al., 2016), a structure sensitive to the experience of stress (McEwen, 2001). Similarly, recent work has reported that increased parental perceptions of stress are associated with smaller hippocampal volumes in young children (Luby, et al., 2013; Pagliaccio, et al., 2014). This study extends this work, by

examining the association between perceived stress and brain structures earlier in development – specifically, during adolescence, a unique time-period in which we can reliably investigate an individual's *own* perception of stress relatively early in life. Because adolescence is marked by intense hormonal, neurobiological and cognitive changes, adolescents are highly vulnerable to the consequences of stress (Lupien et al., 2016).

Previous research into the associations among perceived stress, SES and brain structure and function have been mixed, depending in part on the sample age range and gender, analysis method, brain measures, and control variables. Our findings are in accordance with results from some previous findings, but contrary to others. We discuss these differences below.

The association between higher levels of perceived stress and decreased total hippocampal volume is broadly consistent with the literature (Lindgren, Bergdahl, & Nyberg, 2016; Luby, et al., 2013; Zimmerman, et al., 2016). However, while studies in young children must rely either on parental report of stress or physiological measures (e.g., Luby, et al., 2013), here we found that higher levels of adolescents' self-perceived stress were associated with reduced hippocampal volume. This finding suggests that the effect of perceived stress on brain structure may be similar to physiological stress effects.

Animal research has consistently demonstrated that the wear-and-tear produced by repeated stressful situations may result in damage to the hypothalamic-pituitary-adrenal (HPA) axis and resultant reductions in hippocampal volume (McEwen, 2001; McEwen, Nasca, & Gray, 2016; Romeo, 2017). However, the extent to which this effect is lateralized is controversial. In line with our findings, one other study found a specific association between stressful life events (reported by the parents) and decreased left (but not right) hippocampal volume in young children (Luby, et al., 2013). Another study reported a link between perceived stress and left hippocampal size, but only for individuals with certain genetic profiles (Pagliaccio, et al., 2014). On the other hand, Gianaros and colleagues (2007) found that higher perceived stress was associated with a smaller right (but not left) hippocampal volume in postmenopausal women. Variations in the age range and sex of participants across these studies may have driven these differences. Additionally, Gianaros and colleagues (2007) speculated that the morphology of the right hippocampus and networked brain areas may be more closely related than left hippocampus areas to indicators of *moderate* perceived stress. In supplementary analyses, the same authors reported a reduction in left hippocampal grey matter volume as a function of *high* levels of perceived stress (Gianaros et al., 2007). In fact, adolescents participating in our research reported relatively high mean scores of perceived stress ($M=15.25$, $SD=6.26$) when compared to the mean scores from Gianaros and colleagues' (2007) study ($M=8.75$; $SD=2.44$), and similar mean scores when compared to the PSS-10 original studies (Cohen et al., 1983; Cohen & Janicki-Deverts, 2012) ($M=14.54$; $SD=5.95$), supporting Gianaros' hypotheses.

We did not find associations between adolescents' perceived stress and amygdala or prefrontal cortical volumes in this sample, similar to some previous research findings (Luby, et al., 2013; Pagliaccio, et al., 2014), but in contrast to others (Gianaros, et al., 2007; Holzel, et al., 2010; Moreno, Bruss, & Denburg, 2016). These disparities may reflect differences in analysis techniques, e.g., evaluating amygdala gray matter density rather than volume

(Holzel, et al., 2010), or studying postmenopausal women or older adults rather than adolescents (Gianaros, et al., 2007; Moreno, Bruss, & Denburg, 2016). We additionally did not find associations between perceived stress and cognitive measures, similar to some previous research (Ronnlund, Sundstrom A Fau - Sorman, Sorman De Fau - Nilsson, & Nilsson, 2013; Zimmerman, et al., 2016), but distinct from other work (Aggarwal, et al., 2014; Boals & Banks, 2012; Korten, Comijs, Penninx, & Deeg, 2016; Munoz, Sliwinski, Scott, & Hofer, 2015; Rubin, et al., 2015). Each of these studies examined adults or elderly individuals; none included adolescents in the sample.

In the present study, although family income was positively correlated with hippocampal, amygdala and ACC volumes, we did not find a significant link between socioeconomic factors and adolescents' perceived stress. Previous work has shown that socioeconomically disadvantaged children are more likely to be exposed to stressful environments (Blair & Raver, 2016; Evans, 2004), and are more likely to exhibit dysregulation of physiological and neuroendocrine mechanisms responsible for stress response modulation (Evans & Kim, 2007; Hair, Hanson, Wolfe, & Pollak, 2015; Lupien et al., 2000; Lupien et al., 2001; Lupien et al., 2016; Sripada, Swain, Evans, Welsh, & Liberzon, 2014). However, socioeconomic disparities in parental reports of perceived stress have been mixed (Ursache, Merz, Meyer, & Noble, 2017; Ursache, Noble, & Blair, 2015). One possibility is that adolescents' perception of their stressful experiences may reflect relationships with peers or teachers that are not captured by the family-level socioeconomic indicators used in this study.

This study has several limitations. First, this is a cross-sectional and correlational study, and as such we are unable to interpret our findings in terms of the direction of causality. One possibility is that higher levels of perceived stress *cause* reduced hippocampal volume (Conrad, LeDoux, Magarinos, & McEwen, 1999; Isgor, Kabbaj, Akil, & Watson, 2004; Sapolsky, 1996; Tottenham & Sheridan, 2010). Alternatively, smaller hippocampal volume may increase vulnerability for stress perception (Gilbertson, et al., 2002; Kasai, et al., 2008). Indeed, some studies have suggested that smaller hippocampal volume may precede dysfunctional stress responses (Gilbertson, et al., 2002; Kasai, et al., 2008; Kremen, Koenen, Afari, & Lyons, 2012; Lindgren, Bergdahl, & Nyberg, 2016; van Rooij, et al., 2015). Longitudinal studies may answer developmental questions more precisely (Mills & Tamnes, 2014). Additionally, the development of subcortical brain structures depends on other unmeasured biological processes, such as genetic influence (Hibar, et al., 2015). Finally, although restricted to adolescence, the sample's age range was relatively wide. Pubertal status should be considered in future studies, and as such, our results should be interpreted with caution.

Nonetheless, this study contributes to the emerging literature investigating the effects of stress on brain structure and function in adolescence, by providing empirical evidence of how experience may shape brain development. Fortunately, the effects of psychosocial stress on neural processes may be reversible (Liston, McEwen, & Casey, 2009). Nurturing environments may minimize the negative consequences of biologically and psychologically toxic events (Biglan, Flay, Embry, & Sandler, 2012). In this sense, the neural plasticity of adolescence may represent an opportunity to propose interventions focusing on stress reduction in order to promote healthy brain development.

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Figure 1.
Greater perceived stress was associated with smaller total hippocampal (A) and left hippocampal size (B).

Table 1

Sample demographics (N = 143)

	<i>M (SD) or n (%)</i>	Range
Age in years	16.49 (2.24)	12.64 – 20
Sex		
Female	66 (46.2%)	
Male	77 (53.8%)	
SES		
Parental education in years	15.48 (2.40)	6 – 18
Family income in U.S. dollars	97 989.51 (77 007.10)	4 500 – 325 000
Genetic ancestry factor (GAF)		
African	13 (9.1%)	
American Indian	4 (2.8%)	
Central Asian	3 (2.1%)	
East Asian	25 (17.5%)	
European	88 (61.5%)	

Table 2

Bivariate Correlations

	PSS	Income	PED	PSMT	WM	Flanker	DCCS
PSS	1						
Income	.036	1					
PED	.096	.525**	1				
PSMT	-.006	.057	.018	1			
WM	-.015	.224**	.240**	.385**	1		
Flanker	.006	.086	.072	.221**	.143	1	
DCCS	-.046	.107	.104	.270**	.295**	.683**	1
Hippocampus	-.081	.176*	.103	-.019	.208*	.090	.158
Amygdala	-.047	.188*	.085	.040	.158	.102	.172*
R_Hippo	-.038	.155	.121	.007	.200*	.092	.184*
R_Amyg	-.048	.178*	.091	.055	.128	.092	.138
L_Hippo	-.119	.183*	.076	-.043	.198*	.080	.117
L_Amyg	-.042	.184*	.072	.019	.181*	.106	.198*
MFG CT	-.039	-.009	.026	-.094	-.022	-.236**	-.189*
IFG CT	.012	.054	.116	-.022	.036	-.279**	-.175*
ACC CT	-.046	-.006	-.030	-.010	-.090	-.239**	-.173*
MFG SA	.109	.133	.051	-.095	.099	-.049	-.011
IFG SA	.003	.119	.035	-.019	.130	.009	.111
ACC SA	.075	.171	.069	-.016	.191*	.080	.182*

Note.

* $p < .05$;

** $p < .01$;

PSS = Perceived Stress Scale; PED = Parental Education; PSMT = Picture Sequence Memory Test; WM = List sorting working memory test; DCCS = Dimensional change card sort cognitive flexibility task; R_Hippo = Right hippocampus volume; R_Amyg = Right Amygdala volume; L_Hippo = Left hippocampus volume; L_Amyg = Left Amygdala volume; MFG = Medium Frontal Gyrus; IFG = Inferior Frontal Gyrus; ACC = Anterior Cingulate Cortex.