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Childhood maltreatment is associated with altered frontolimbic neurobiological activity during wakefulness in adulthood

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Abstract

Childhood maltreatment can disturb brain development and subsequently lead to adverse socioemotional and mental health problems across the life span. The long-term association between childhood maltreatment and resting–wake brain activity during adulthood is unknown and was examined in the current study. Forty-one medically stable and medication-free military veterans ($M = 29.31 \pm 6.01$ years, 78% male) completed a battery of clinical assessments and had [^{18}F]-fluorodeoxyglucose positron emission tomography neuroimaging scans during quiet wakefulness. After statistically adjusting for later-life trauma and mental health problems, childhood maltreatment was negatively associated with brain activity within a priori defined regions that included the left orbital frontal cortex and left hippocampus. Childhood maltreatment was significantly associated with increased and decreased brain activity within six additional whole-brain clusters that included the frontal, parietal–temporal, cerebellar, limbic, and midbrain regions. Childhood maltreatment is associated with altered neural activity in adulthood within regions that are involved in executive functioning and cognitive control, socioemotional processes, autonomic functions, and sleep/wake regulation. This study provides support for taking a life span developmental approach to understanding the effects of early-life maltreatment on later-life neurobiology, socioemotional functioning, and mental health.

Childhood maltreatment has been shown to contribute to a multitude of adverse physical health (Hussey, Chang, & Kotch, 2006), mental health (Edwards, Holden, Felitti, & Anda, 2003), psychosocial (Gilbert et al., 2009), and socioeconomic (Zielinski, 2009) outcomes that persist into adulthood (Cuijpers et al., 2011). Different forms of child maltreatment are independently associated with increased odds for developing psychiatric disorders, drug use, suicide attempts, and worsened sexual health (Norman et al., 2012). Furthermore, an increased number of maltreatment types is associated with increased odds of mental health problems in adulthood (Edwards et al., 2003).

The intersection of child maltreatment and neuroscience research is beginning to emerge. Neuroscience research among child and adult samples who experienced maltreatment during childhood was used to inform the current study. Systematic reviews on the neuroscience of maltreatment during childhood among child and adult samples have cumulatively identified structural and functional abnormalities in brain circuits and regions across the life span that include the limbic system, prefrontal regions, and cerebellar regions (Hanson et al., 2010; Hart & Rubia, 2012; McCrory, De Brito, & Viding, 2011; Teicher et al., 2003; Teicher & Samson, 2013). Among children and adults, a history of childhood maltreatment is consistently associated with the size of, and function in, the frontolimbic (medial prefrontal cortex [mPFC], orbital frontal cortex [OFC], anterior cingulate cortex [ACC], hippocampus, and amygdala) and frontocerebellar areas (mPFC, OFC, ACC, and cerebellum; see review in Hart & Rubia, 2012). Frontolimbic areas are associated with emotional reactions to external stimuli, and modulation of the emotional responses (Hariri, Bookheimer, & Mazziotta, 2000; Phillips, Ladouceur, & Drevets, 2008). The frontocerebellar circuit is associated with nonmotor functions that include cognition, emotion, and the default mode network (Krienen & Buckner, 2009). It is notable that maltreatment-related size and function of the frontal, limbic, and cerebellar regions are not always the same for both children and adults. Adults who experienced childhood maltreatment exhibited a hypoactive mPFC during a functional affective task that was unaffected by mental health status (van Harmelen et al., in press), whereas young adults who experienced

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child emotional maltreatment exhibited increased dorsal mPFC responsivity during a social exclusion task that was also unaffected by mental health status (van Harmelen et al., 2014). Among children and adults who experienced childhood maltreatment, hippocampal volume tends to be smaller among adults (Teicher, Anderson, & Polcari, 2012) but not different in size among children (De Bellis et al., 2002) independent of Axis I disorders. Compared to matched controls, children who experienced maltreatment did not show differences in cerebellar gray matter volumes (De Brito et al., 2013); however, adolescents without Axis I diagnoses exhibited smaller cerebellar gray matter volumes in relation to increased physical and emotional neglect (Edmiston et al., 2011). Differences in child maltreatment-related brain size and function may differ across child and adult samples potentially because of differences in timing of assessment during brain development following maltreatment exposure.

A systematic review of the neuroscience and child maltreatment literature revealed that many previous studies of maltreatment-related neural alterations did not adjust for concurrent psychiatric symptom severity among the child and adult (see discussion in Hart & Rubia, 2012). Thus, neural alterations previously reported may be partially accounted for by concurrent symptomatology, or even adult trauma exposure, rather than reflect the persistent neural impact of childhood adversity. However, there are structural and functional studies among children and adults who experienced maltreatment that did account for Axis I disorders. Adolescents who experienced childhood maltreatment exhibit alterations to their amygdala and hippocampal size that is accounted for by Axis I psychopathology (Whittle et al., 2013). On the contrary, some studies revealed that existing Axis I disorders did not impact brain structure and function. For example, compared to control participants, adults who experienced child emotional maltreatment exhibited reduced medial prefrontal cortex volumes and exhibited mPFC hypoactivation during a functional affective word-processing task regardless of whether they had an Axis I disorder (van Harmelen et al., 2010, 2014). Further, a recent study showed that healthy adults with greater self-reported childhood abuse show less activity in response to a mental stress task within the hypothalamic and limbic forebrain regions, including the amygdala and bed nucleus of the stria terminalis (Banihashemi, Sheu, Midei, & Gianaros, 2014). Childhood adversity is also differentially associated with brain function in healthy individuals. For example, healthy adults who were raised in risky family environments show less amygdala activity in response to negative facial expressions compared to controls (Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006). Without the confounding influences of disorders, studies in healthy individuals may provide insight into how childhood adversity shapes neural pathways for emotional processing and subsequent vulnerability or resilience to affective disorders. Whether Axis I disorders impact the associations between child maltreatment and brain structure and functioning may be dependent on a variety of factors that range from the brain area being studied to the characteristics of the maltreatment type and timing during development.

The majority of neuroimaging studies of child maltreatment were functional neuroimaging, or conducted while children and adults performed tasks that stimulated systems of reward processing, emotion processing, fear conditioning, working memory, and response inhibition (see reviews in Hart & Rubia, 2012; McCrory et al., 2011; Teicher et al., 2003; Teicher & Samson, 2013). Resting-state neuroimaging studies that are conducted while not actively engaged in a task during wakefulness are also important to consider because they reduce task- and performance-related variability that is more likely observed during the respective behavioral or cognitive process. Both functional and resting-state neuroimaging studies can provide clinical insight into a specific condition. For example, verbal and nonverbal recall of traumatic events may account for neural differences observed among adults with posttraumatic stress disorder (PTSD) compared to control participants (Lanius et al., 2004), and resting-state imaging has been shown to perform almost three times better than task-associated imaging in identifying risk factors for Alzheimer disease among adults (Fleisher et al., 2009). Similarly, resting-state neuroimaging paradigms may provide unique insight into the neurobiology that is associated with child maltreatment, which could otherwise potentially be masked by task- and performance-related variability that is associated with functional tasks. Traitlike neurobiological indices of childhood maltreatment may identify risk for later-life vulnerabilities to mental health and psychosocial challenges.

A study in the animal literature described relationships between early-life stress and later brain metabolic function. Adult rhesus monkeys who underwent repeated maternal separation during early life also exhibited altered brain glucose metabolism during a mild stressor within the frontolimbic brain regions, including increased metabolism in the superior temporal sulcus, putamen, thalamus, and inferotemporal cortex, as well as decreased metabolism in the OFC (Parr et al., 2012). To our knowledge, only one human study has used functional neuroimaging to examine the associations between whole-brain resting metabolic activity and child maltreatment. In that study, children (8.8 years old) from Romanian orphanages who experienced extreme emotional and physical neglect completed [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) neuroimaging scans during quiet wakefulness (Chugani et al., 2001). Compared to a group of nonmaltreated children with focal epilepsy (10.7 years old) and a group of normal nonmaltreated adults (27.6 years old), maltreated children exhibited lower relative cerebral glucose metabolism in the frontolimbic brain regions. This hypometabolic profile may be specific to early-life adversity that can be generalized across species, because it has been observed among nonhuman primates. These studies provide translational support that childhood maltreatment may lead to neurobiological alterations that may persist into adulthood within the frontolimbic brain regions, especially the OFC, temporal structures, and brain stem areas. These

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brain regions are also implicated in adult mood disorders (Liao et al., 2012); therefore, early and lasting neural changes in these areas may contribute to heightened vulnerability for poor psychosocial functioning and psychiatric disorders across the life span (e.g., Cicchetti & Cannon, 1999; Ganzel, Kim, Gilmore, Tottenham, & Temple, 2013; Juster et al., 2011; Pollak, 2005; Sanchez, Ladd, & Plotsky, 2001). However, the correlates between child maltreatment and resting-state brain function that is independent of later-life trauma and mental health problems are unknown.

This study is a secondary data analysis from a parent project that examined the neurobiology of a sleep treatment among returning military veterans. Baseline data from this well-characterized sample provided a unique opportunity to examine the associations between childhood maltreatment and regional cerebral metabolic rate of glucose (rCMRglc) measured with FDG PET. The study objective was to examine how childhood maltreatment is associated with resting-state neurobiological alterations among military veterans: these associations were examined independent of later-life trauma and mental health problems. The first aim was to examine the association between childhood maltreatment and rCMRglc in the frontolimbic brain regions. We chose to examine these specific brain regions (i.e., mPFC, OFC, ACC, hippocampus, and amygdala) because they are commonly implicated in studies that examine the associations among child maltreatment with brain structure and function and would likely also be associated with resting-state rCMRglc. Our a priori hypothesis was that childhood maltreatment would be associated with altered rCMRglc in the mPFC, OFC, ACC, hippocampus, and amygdala. The second aim was to further examine the associations between childhood maltreatment and rCMRglc using a whole-brain, network-based, data-driven approach to provide a comprehensive examination of the associations between childhood maltreatment and resting-state rCMRglc (Ashburner & Friston, 2000).

Method

This study is a secondary analysis of a convenience sample from a parent project (W81XWH-08-1-0637) that was approved by the institutional review board at the University of Pittsburgh and the Human Research Protection Office of the Department of Defense as relevant (PT073961). Written, informed consent was obtained from all participants prior to the study procedures.

Participants

Participants were military veterans from Operation Enduring Freedom or Operation Iraqi Freedom who were healthy, medication free, and head-trauma free. Participants were recruited through word of mouth and from community advertisements (e.g., local television commercials, radio commercials, bus signs, list-serves, and flyers). Participants ($N = 49$) were between the ages of 18 and 50. Our exclusion criteria were lifetime psychotic or bipolar disorder, current diagnosis of depression as indicated by the Structured Clinical Interview for DSM-IV, current substance or alcohol abuse (past 3 months), and current sleep disorders (e.g., obstructive sleep apnea) except insomnia or nightmares related to PTSD. Participants were excluded from the current study if they did not complete all clinical measures of interest ($n = 4$), or if their PET imaging data was inadequate ($n = 4$) due to excessive head movement during their PET scan. For the current study, 41 participants were used from the larger sample. All were medication free for at least 6 weeks prior to study entry.

Clinical measures

Child Trauma Questionnaire (CTQ). The CTQ was used to retrospectively identify childhood maltreatment (Bernstein et al., 1994). The CTQ contains five trauma subscales (emotional abuse, physical abuse, sexual abuse, emotional and physical neglect, minimization/denial of abuse), rated on scales of 5 (*less trauma*) to 25 (*more trauma*), as well as a minimization/denial subscale rated on a scale of 0 (*desirable*) to 3 (*exaggerated*). The five trauma-related subscales are summed to create a total score to broadly indicate childhood maltreatment. The CTQ has high internal consistency ($\alpha =$ 0.79–0.94) and good test–retest reliability (intraclass correlation = 0.88; Bernstein et al., 1994).

Clinician-Administered PTSD Scale (CAPS). The CAPS was used to determine PTSD symptomatology (Blake et al., 1990). The CAPS is a structured interview that can be used to identify frequency and intensity of core PTSD symptoms, and is used to identify the presence, absence, and severity of PTSD symptomatology. The CAPS can be scored to indicate PTSD symptom severity and diagnosis during the past month, or the lifetime, of PTSD symptoms. Current PTSD diagnosis and symptomatology was determined with the CAPS (Blake et al., 1990) according to the 1–2 scoring rules (Weathers, Ruscio, & Keane, 1999) and DSM-IV criteria (i.e., 1 = *reexperiencing*, 2 = *avoidance*, 3 = *hyperarousal symptoms*).

Combat Exposure Scale (CES). The CES was used to determine combat exposure severity (Keane et al., 1989). The CES is a self-report measure that comprises seven Likert items that describe severity of combat experience, each scaled from 1 (*none*) to 5 (*≥51 times*). The total CES score can range from 0 (*less combat exposure*) to 41(*more combat exposure*). The CES has good internal consistency (Cronbach $\alpha = 0.85$) and test–retest reliability ($r = .97$), and previously discriminated ($p <$ .005) between PTSD and non-PTSD combat-exposed veterans.

Beck Depression Inventory (BDI). The BDI was used to determine depression symptoms within the past week (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). The BDI is a 21-item self-report measure that describes depressive symptoms. BDI items are scaled from 0 (*lower intensity*) to 3 (*higher intensity*). Items are summed to create total scores

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that can range from 0 (*minimal depression*) to 63 (*severe depression*). The BDI can discriminate between depressed and nondepressed samples (Salkind, 1969) and has high internal consistency ($\alpha = 0.80$; Beck et al., 1961).

Procedure and image processing

Participants completed all clinical measures, and completed an initial magnetic resonance (MR) brain scan with a Siemens 3T Trio scanner to acquire structural brain images. A volumetric MPRAGE sequence was acquired in the sagittal plane (echo time/repetition time = 2.98/2300 ms, flip angle = 9°, field of view = 24 × 25.6 cm, 160 slices, 12-mm slices). MR data was transferred to the PET facility over the electronic network and registered with the PET data.

Participants slept in the sleep research laboratory for five consecutive nights; the first two were used for the present analyses. The first night was conducted to rule out the presence of sleep apnea and periodic leg movement disorder. The second night was used as the baseline night, and participants slept undisturbed at their habitual bedtime and rise time. On the following morning, participants completed the wake scan 2–4 hr following their rise time, according to previous validated procedures (Nofzinger et al., 1998; Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997). Prior to the FDG uptake period, participants were given a 15-min accommodation period during which they were instructed to lie supine with their eyes closed and ears open. Following this accommodation period, participants continued to lie awake with their eyes closed while being continuously monitored with electroencephalography to assure that wakefulness was maintained (wakefulness during the uptake period was maintained among all participants). At this time, participants were injected intravenously with FDG through an indwelling catheter (*M* dose = 6.52 ± 1.66 mCi). At approximately 60 min following the initial FDG injection, a 30-min emission scan and a 15-min transmission scan were obtained. PET scans were conducted with a Siemens/CTI ECAT HR + scanner in three-dimensional mode using a wide field of view focused from the brain stem through the forebrain.

PET images were reconstructed using standard commercial software as 63 transaxial slices with approximately 4- to 5-mm full width at half-maximum resolution. Nonbrain tissue was cropped from MR images by setting all nonbrain voxels to zero intensity with ANALYZE software (Biomedical Imaging Resource, Mayo Foundation, Rochester, Minnesota). PET images were coregistered to their corresponding cropped structural magnetic resonance images with Automated Image Registration software (Woods, Cherry, & Mazziotta, 1992). Finally, coregistered images were smoothed with a 10-mm full width at half-maximum Gaussian filter for statistical analyses (2 × 2 × 2 mm voxel size).

Statistical analyses

Descriptive and inferential statistical analyses were calculated with SPSS version 20.0 (SPSS Inc., Chicago); $p < .05$ was considered statistically significant. The Hedge *g* effect sizes for unequal sample sizes were calculated among participants with and without PTSD (small = 0.20–0.30; medium > 0.30–0.80; large > 0.80; Cohen, 1988).

Neuroimaging data analyses were calculated with Statistical Parametric Mapping version 8 (Friston, Ashburner, Kiebel, Nichols, & Penny, 2006) and PickAtlas version 3.0.4 (Maldjian, Laurienti, Kraft, & Burdette, 2003) that were executed through MATLAB software (MathWorks Inc., Natik, MA). For all analyses, both positive and negative correlations were calculated between the CTQ total score and rCMRglc. For all analyses, age, sex, BDI scores, CES scores, and CAPS past-month scores were entered as covariates. Age and sex were entered as a covariate because FDG PET studies have identified age- and sex-related differences in glucose metabolism (Hsieh et al., 2012). BDI, CES, and CAPS past-month scores were entered as covariates because depression symptoms (Baxter et al., 1985), combat exposure (Phan, Britton, Taylor, Fig, & Liberzon, 2006), and posttraumatic stress symptoms (Germain et al., 2013; Hayes, Hayes, & Mikedis, 2012) have been shown to affect brain glucose metabolism. For all analyses, the significance threshold was set at $p < .05$, with familywise error corrections. The atlas-based region of interest (ROI) analyses were focused on five separate a priori defined frontolimbic brain regions that included the bilateral mPFC (Brodmann areas [BAs] 8–10), OFC (BAs 11, 12, and 47), ACC (BAs 24, 32, and 33), hippocampus, and amygdala. For each ROI analysis, we applied a height threshold of $p < .05$ and a small volume correction. Whole-brain voxelwise regression models were computed to assess positive and negative correlations between childhood maltreatment and rCMRglc during wakefulness. Whole-brain analyses were replicated, and reported as supplemental analyses, while only controlling for age, sex, and CES in order to examine whether the inclusion of mental health variables (i.e., BDI and CAPS past-month scores) influenced the results. For the whole-brain analyses, we applied a height threshold of $p < .01$, an extent threshold of 15 contiguous voxels.

Results

Forty-one participants were included in the current study (n = 32 males, age = 29.31 ± 6.09). Participant demographic information, descriptive data, and subsample comparisons are indicated in Table 1. Participants with ($n = 30$) and without (n = 11) PTSD did not significantly differ on sex, ethnicity, child maltreatment, depression, or combat exposure. Participants with PTSD were younger than participants without PTSD.

ROI analyses: Frontolimbic areas

All ROI analyses were conducted while adjusting for age, sex, BDI scores, CES scores, and CAPS past-month scores. For the positive correlation, increased childhood maltreatment was not significantly associated with increased rCMRglc in any of the frontolimbic brain ROIs.

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Table 1. *Demographic information, descriptive data, and comparisons among participants with and without PTSD*

	Total Sample ($N = 41$)	PTSD ($n = 30$)	Non-PTSD ($n = 11$)	Difference
Variable	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	Hedge *g*
Sex: male (%)	78.00	76.70	81.80	$\chi^2 = 0.52$
Ethnicity: White (%)	90.20	90.00	90.90	$\chi^2 = 0.00$
Age	29.31 (6.09)	28.14 (5.41)	32.50 (6.96)	0.73*
CTQ total	34.95 (12.74)	36.87 (13.98)	29.73 (6.47)	0.56
Emotional abuse	7.15 (4.22)	7.33 (4.60)	6.64 (3.08)	0.16
Physical abuse	7.51 (3.58)	8.07 (3.98)	6.00 (1.34)	0.58
Sexual abuse	5.83 (3.29)	6.07 (3.82)	5.18 (0.60)	0.26
Emotional neglect	7.98 (4.15)	8.43 (4.49)	6.73 (2.87)	0.40
Physical neglect	6.49 (2.64)	6.97 (2.93)	5.18 (0.60)	0.69
Minimization/denial	0.61 (1.00)	0.60 (0.93)	0.64 (1.21)	0.04
CAPS past month	47.22 (21.47)	57.37 (14.11)	19.55 (10.69)	2.78***
Combat exposure	16.80 (10.61)	16.53 (11.03)	17.55 (9.82)	0.09
BDI	6.41 (4.6)	7.00 (4.74)	4.82 (3.25)	0.49

Note: PTSD, Posttraumatic stress disorder; CTQ, Child Trauma Questionnaire; CAPS, Clinician-Administered PTSD Scale; BDI, Beck Depression Inventory.
*$p < .05$. **$p < .01$. ***$p < .001$.

For the negative correlation, increased childhood maltreatment was significantly associated with decreased rCMRglc in a peak-level voxel within the left OFC and left hippocampus. Decreased rCMRglc in a peak-level voxel within the left ACC was not significant at $p < .05$ (i.e., $p = .06$). Negative correlations within these ROIs are depicted in Table 2 and Figure 1a–c.

Whole-brain analyses

All whole-brain analyses were conducted while adjusting for age, sex, BDI scores, CES scores, and CAPS past month scores.[1] Childhood maltreatment was positively associated with rCMRglc during wakefulness in three discrete clusters (Table 2 and Figure 2a–c). The first cluster included the bilateral medial (BA 10) and superior medial frontal gyri (BA 9). The second cluster included the bilateral caudate, putamen (i.e., dorsal striatum), and rostral ACC (BA 32). The third cluster included the bilateral cerebellar vermis that extended from the dorsal culmen through the declive, folium, and tuber.

Childhood maltreatment was negatively associated with rCMRglc during wakefulness in three discrete clusters (Table 2 and Figure 3a–c). The first cluster included bilateral regions that spanned the parietal lobe, occipitotemporal area, cuneus, precuneus, and primary visual and extrastriate visual cortical areas (BAs 7, 17, 18, 19, 37, 39, and 40). The second cluster included the left central lobule of the cerebellum, superior aspect of the left cerebellar hemisphere, inferior semilunar lobule of the right posterior cerebellum, superior and inferior colliculus, midbrain and bilateral thalamus, and bilateral hippocampus. The third cluster included the bilateral orbital frontal gyrus (BAs 11, 12, and 47) and the subgenual region of the ACC (sACC; BA 25).

Supplemental analyses

All positive and negative whole-brain analyses were recalculated while adjusting for age, sex, and CES scores; BDI and CAPS past-month scores were not adjusted for in the models. Childhood maltreatment was positively associated with rCMRglc during wakefulness in three discrete clusters (online-only supplemental Table S.1 and supplemental Figure S.1a–c). Childhood maltreatment was negatively associated with rCMRglc during wakefulness in two discrete clusters (supplemental Table S.1 and supplemental Figure S.1d–e). Significant clusters identified by the positive and negative correlations included the regions identified in the whole-brain analyses while statistically adjusting for all variables.

Discussion

To our knowledge, this is the first study to report associations between childhood maltreatment and rCMRglc during quiet wakefulness in adults, after adjusting for age, sex, depression symptoms, adult combat exposure, and current PTSD symptom severity. The results suggest that childhood maltreatment is associated with later-life increased neural activity in regions involved in executive functioning and cognitive control, reward and decision making, emotional self-control, and cognition and emotion expression; and reduced activity in regions that subserve social and emotional processing, cognitive and emotional functioning, autonomic functions, sleep/wake regulation, and mood disorders. Accordingly, we re-

1. Whole-brain results did not change when also statistically adjusting for the number of discrete traumatic events experienced after the age of 18 as identified by the Trauma History Questionnaire (Green, 1996).

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Table 2. *Statistics depicting significant results for positive and negative ROI and whole-brain correlation analyses between regional cerebral metabolic rate of glucose and childhood maltreatment*

Analysis and Cluster	MNI Coordinates of Max Voxel in Cluster			Cluster Size	Z	$P_{FWE-corr}$
	X	Y	Z			
+ROI frontolimbic areas						*ns*
–ROI frontolimbic areas						
Left OFC	−8	52	−20	757 k_E	4.14	.02
Left hippocampus	−26	−38	−4	58 k_E	3.29	.02
Left ACC[a]	−8	26	26	268 k_E	3.58	.06
+Whole brain						
Cluster 1	2	64	30	1,876 k_E	3.54	.02
Cluster 2	−22	18	22	1,841 k_E	4.22	.02
Cluster 3	−6	−50	−2	1,725 k_E	4.24	.02
–Whole brain						
Cluster 1	60	−50	38	10,281 k_E	4.38	<.001
Cluster 2	42	−66	−50	4,243 k_E	4.37	<.001
Cluster 3	−8	50	−22	2,880 k_E	4.19	.001

Note: Adjustments were made for age, sex, Beck Depression Inventory scores, Combat Exposure Scale scores, and Clinician-Administered PTSD Scale past month scores. Brain regions within each cluster are described in the Results section. ROI, Region of interest; MNI, Montreal Neurological Institute and Hospital; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; FWE-corr, family-wise error corrected; k_E, voxel number within cluster; PTSD, posttraumatic stress disorder.
[a]The correlation was not $p < .05$.

ported in our previous works that early-life trauma exposure impacts biological processes that extend into adulthood, which include neural responses to threat (Herringa, Phillips, Fournier, Kronhaus, & Germain, 2013) and sleep physiology (Insana, Kolko, & Germain, 2012). In addition, we previously demonstrated that military veterans differed on rCMRglc during sleep as a function of PTSD diagnosis (Germain et al., 2013). The current study extends these findings and provides further support for taking a life span developmental approach to understanding the effects of early-life trauma on brain activity in later life. More specifically, this study provides rationale for including early-life experiences to our previously proposed model that describes the neural interactions with sleep that are involved in adult PTSD (Germain, 2013; Germain, Buysse, & Nofzinger, 2008). The associations between child maltreatment and rCMRglc in specific brain regions identified in this study may underlie resilience or vulnerabilities to psychosocial and mental health challenges faced by survivors of child maltreatment. Speculation about how the associations between child maltreatment and rCMRglc in specific brain regions relate to specific functional outcomes is beyond the scope of the current work; however, these results may provide groundwork for future investigations to implement specific functional tasks to investigate these processes.

ROI analyses: Frontolimbic areas

Our first study aim was to examine the association between childhood maltreatment and rCMRglc in the frontolimbic brain regions. Child maltreatment was not associated with increased activity within our ROIs. However, the results partially supported our hypothesis that childhood maltreatment would be associated with decreased activity within the mPFC, OFC, ACC, hippocampus, and amygdala. Childhood maltreatment was associated with decreased activity within the left OFC and left hippocampus; although not significant, a trend was observed within the left ACC ($p = .06$). These findings corroborate with a body of adult and pediatric research that describes the associations between child maltreatment and neural structure and functioning within the frontolimbic brain network (Dannlowski et al., 2012; Hart & Rubia, 2012; Mead, Beauchaine, & Shannon, 2010; van Harmelen et al., 2010), and parallel the decreased activity patterns observed with FDG PET in the OFC and hippocampus among maltreated children (Chugani et al., 2001). The frontolimbic brain network is implicated in mood disorders (Adler, DelBello, & Strakowski, 2006; Price & Drevets, 2012; Rigucci, Serafini, Pompili, Kotzalidis, & Tatarelli, 2010), and neural activity in the left frontolimbic brain regions are involved in the cognitive control of emotions (Ochsner & Gross, 2005; Ochsner et al., 2004). Furthermore, brain regions that are implicated in decreasing response to threat exhibited lower rCMRglc in association with increased childhood maltreatment. The present results demonstrate that childhood maltreatment is associated with increased activity in the frontolimbic brain network during resting wakefulness during adulthood. Alterations within these regions may be involved in childhood maltreatment-related altered threat responses and their accompanied psychosocial and mental health problems that are commonly observed in later life.

Contrary to previous work that identified a negative association between childhood maltreatment and rCMRglc in the amygdala and the mPFC among children during rest (Chugani

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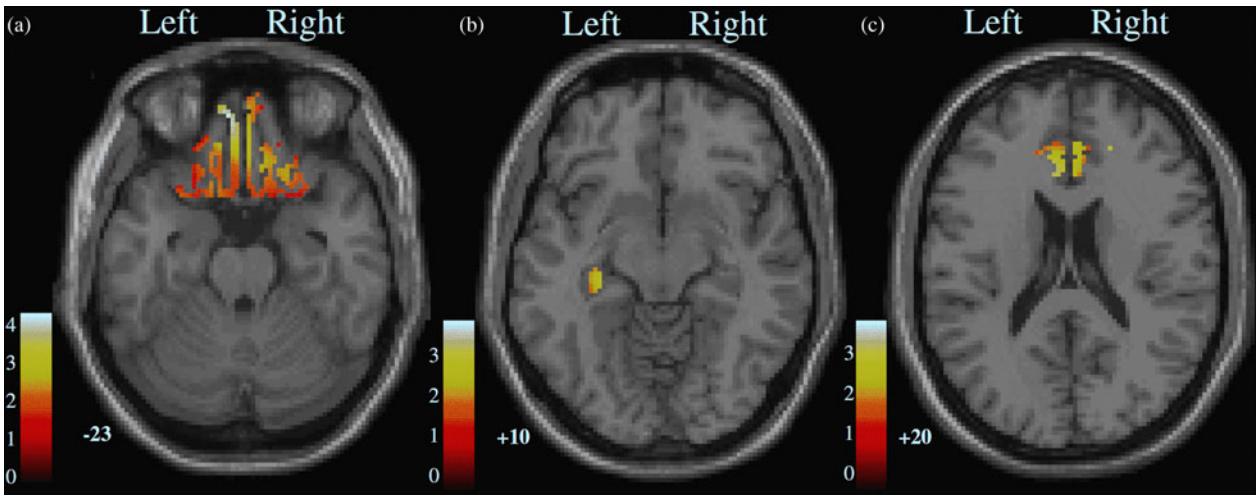

Figure 1. (Color online) Region of interest analyses for the negative correlation between child maltreatment and rCMRglc in (a) bilateral orbital prefrontal cortex, (b) left hippocampus, and (c) bilateral anterior cingulated. The figures are depicted in an axial view. The T-bars and slice display coordinates are indicated at the bottom left of the slice.

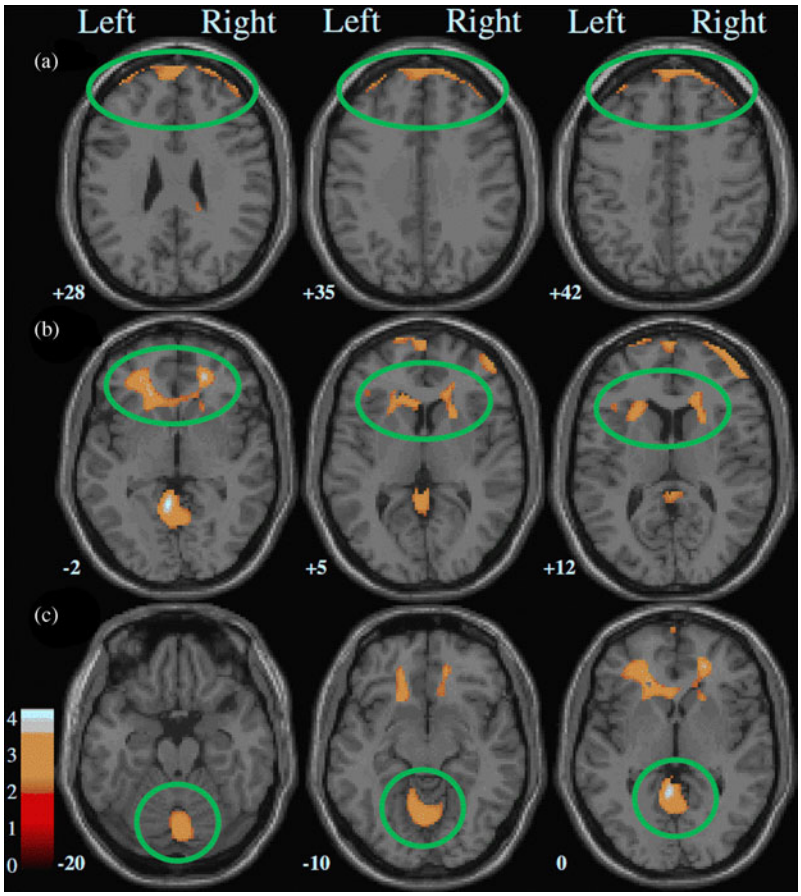

Figure 2. (Color online) Whole-brain analyses for the positive correlation between child maltreatment and rCMRglc depicted by significant clusters: (a) bilateral medial and superior medial frontal gyri; (b) middle frontal gyrus and bilateral anterior cingulate; and (c) bilateral cerebellar vermis, including the culmen and declive. The figures are depicted in an axial view. The T-bar is indicated at the bottom left of the figure, and slice display coordinates are indicated at the bottom left of each slice.

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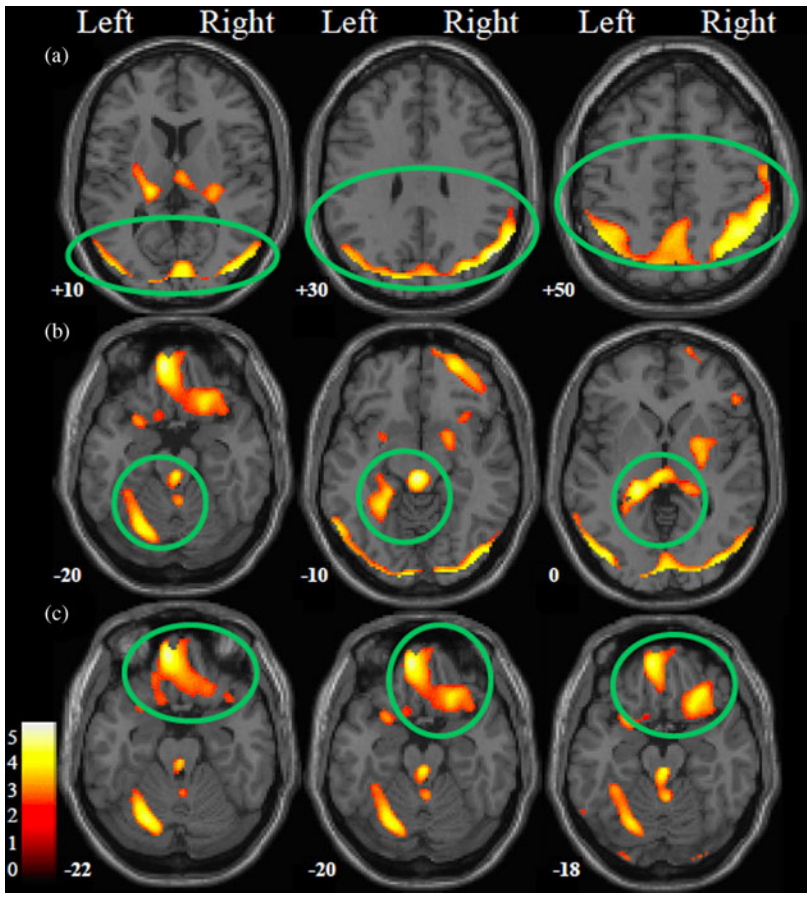

Figure 3. (Color online) Whole-brain analyses for the negative correlation between child maltreatment and rCMRglc depicted by significant clusters: (a) bilateral parietal lobe, middle temporal gyri, cuneus, precuneus, and primary visual cortex; (b) inferior semilunar lobule of the right posterior cerebellum, cerebellar tonsil, midbrain, bilateral hippocampus, and bilateral thalamus; and (c) bilateral orbital frontal gyrus. The figures are depicted in an axial view. The T-bar is indicated at the bottom left of the figure, and slice display coordinates are indicated at the bottom left of each slice.

et al., 2001), we did not find these associations among adults. Our results could be discrepant with this previous finding due to the difference between the time elapsed since the maltreatment experienced by the child and adult samples, cultural or other differences between samples, clinical differences, analytical techniques, or the differences in maltreatment types experienced among the samples (Teicher, Samson, Polcari, & McGreenery, 2006). In addition, the amygdala and prefrontal cortex are more developed among adults compared to children (see Andersen & Teicher, 2008), and these differences may differentially modulate amygdala functioning and the corresponding differences in rCMRglc between the two groups. As evidenced by functional neuroimaging studies, maltreatment-related alterations within the amygdala and mPFC may be evoked in response to threat stimuli (McCrory et al., 2011; Tottenham et al., 2011).

Whole-brain analyses

Our second study aim was to examine the association between childhood maltreatment and whole-brain rCMRglc. We found that increased childhood maltreatment was associated with altered metabolic patterns in the frontocerebellar regions.

Whole-brain analyses: Positive correlations. Child maltreatment was associated with increased rCMRglc in three distinct clusters. One cluster included areas in the medial and superior medial frontal gyri. These cortical regions are broadly associated with executive function (Funahashi, 2001), and the cognitive control and interpretation of emotion (Miller & Cohen, 2001; Ochsner & Gross, 2005). These regions are diffusely connected to a series of neural networks and circuitry that are responsible for various functions (Ongur & Price, 2000), such as the downregulatory control of subcortical limbic structures, which in turn leads to an appropriate contextual response to emotion-evoking stimuli such as threat (Davidson, 2002; Kim et al., 2011; Quirk, Likhtik, Pelletier, & Pare, 2003; Sotres-Bayon, Bush, & LeDoux, 2004). The prefrontal cortex goes through pronounced changes throughout early life and adolescence with increases in myelination and synaptogenesis (Thompson & Nelson, 2001). This pro-

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nounced neural development is sensitive to stress, which may result in adult structural and functional differences that are associated with child maltreatment. Adults who were maltreated as children have smaller mPFC volumes compared to nonmaltreated adults (van Harmelen et al., 2010), and adults who experienced harsh parenting during childhood exhibit dysregulated mPFC and amygdala circuits in response to fearful/angry face stimuli (Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006). The mPFC–amygdala circuit is implicated in anxiety, PTSD, and depression that result from child maltreatment (Heim, Shugart, Craighead, & Nemeroff, 2010; McCrory et al., 2011l Teicher et al., 2003; Teicher & Samson, 2013). Our results extend these structural and functional findings and demonstrate that child maltreatment is associated with increased activity within executive prefrontal regions during resting wakefulness, but decreased activity in more automatic fear regulatory areas including the mPFC and hippocampus. Subregions of the hippocampus are associated with contextual fear conditions via connections to the mPFC and other limbic forebrain regions (Gewirtz, McNish, & Davis, 2000; Maren, Phan, & Liberzon, 2013).

Childhood maltreatment was associated with increased metabolic activity within the dorsal striatum and the rostral ACC. These areas are broadly implicated in decision making and reward processing (Balleine, Delgado, & Hikosaka, 2007), and emotional self-control (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001; Bush, Luu, & Posner, 2000; Posner, Rothbart, Sheese, & Tang, 2007), respectively. The rostral ACC is anatomically connected to the OFC and limbic regions, and is responsible for autonomic functions, conditioned emotional learning, and assigning emotional valence to stimuli (see Yucel et al., 2003). The ACC is implicated in various cognitive and emotional functions, as well as psychiatric conditions. Among adults, a history of childhood maltreatment is associated with reduced ACC volume (Dannlowski et al., 2012) and dorsal ACC reactivity to emotional threat (Herringa, Brin, et al., 2013). The dorsal striatum is implicated in reward processing and goal-directed decision making that can involve emotional information (Balleine et al., 2007); consequently, the ACC is also involved in selective response to negative rewards (Liu, Hairston, Schrier, & Fan, 2011). The current results demonstrate that childhood maltreatment may influence dorsal stratum and ACC functioning during resting wakefulness, and supports further work to investigate how altered reward functioning and emotion may be involved in child maltreatment-related psychosocial problems that are present across the life span.

Childhood maltreatment was associated with both increased and decreased metabolic activity within different areas of the cerebellum. Increased activity was observed throughout the cerebellar vermis from the dorsal culmen through the tuber. The cerebellum is generally associated with vestibular motor control and autonomic functions (Glickstein, 2007), and cognition and emotion expression (Schutter & Van, 2005), and is functionally connected to cortices including the previously discussed prefrontal regions (Allen et al., 2005). More specifically, the anterior portion of the cerebellum is associated with sensorimotor function, whereas the posterior portion is associated with cognition and emotion (Stoodley & Schmahmann, 2009). The cerebellum has been shown to elicit distinct activity patterns in response to specific emotions (happiness, anger, disgust, fear, and sadness; Baumann & Mattingley, 2012), and is implicated in mood and neuropsychiatric disorders (Konarski, McIntyre, Grupp, & Kennedy, 2005; Villanueva, 2012). Within the current study, increased metabolic activity was observed throughout the cerebellar vermis, which is anatomically connected to limbic brain structures (Stoodley & Schmahmann, 2010). The cerebellum is highly plastic throughout the life span, and its development is most pronounced during early life, with volumes peaking in middle to late childhood (Tiemeier et al., 2010). Thus, childhood may be considered a critical window for cerebellar development during which the cerebellum and cerebellar circuitry could be especially sensitive to environmental factors such as stress, which may alter developmental trajectories for psychosocial functioning and resilience toward subsequent stressors. As new knowledge about the cerebellum continues to unfold, more research is needed to describe the impact of child maltreatment on cerebellar development and functioning.

Whole-brain analyses: Negative correlations. Child maltreatment was also associated with decreased rCMRglc in three distinct clusters. These clusters included areas that are generally involved in social and emotional processing, cognitive and emotional functioning, autonomic functioning, sleep/wake regulation, and mood disorders. Decreased activity was also observed in the bilateral OFC and hippocampus as indicated in the ROI analyses described above.

Decreased activity was observed in the cuneus, precuneus, globally throughout the parietal lobe, and within the midtemporal gyri and occipitotemporal regions. The cuneus is associated with visual processing and behavioral inhibition (Crockford, Goodyear, Edwards, Quickfall, & el-Guebaly, 2005), and the precuneus is involved in episodic memory, self-consciousness, and the default mode network (Cavanna & Trimble, 2006). The parietal lobe is generally associated with sensory integration and awareness, and the extrastriate cortex within the occipital lobe is primarily associated with attention to faces and perception of location (Haxby et al., 1994). These areas cumulatively interact to process social and emotional information (Norris, Chen, Zhu, Small, & Cacioppo, 2004). Decreased rCMRglc in these brain areas during resting wakefulness could point to a brain network that is implicated in some of the psychosocial difficulties observed among adults with a history of childhood maltreatment. These diffuse cortical areas, along with the midbrain and thalamic areas discussed below, exhibit decreased activity in relation to child maltreatment and may reflect activity within the corticothalamic network that promotes vigilance (Llinas & Steriade, 2006; Steriade, 1997). These decreased activity patterns during rest may be a compensatory response to in-

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creased threat responses that are common to individuals with a history of maltreatment (Dannlowski et al., 2012).

Increased childhood maltreatment was associated with decreased rCMRglc within the right ventral, left dorsal, and posterior cerebellum. These regions were nonoverlapping with the cerebellar regions observed in the positive correlation maps, but could be implicated in similar cognitive and emotional functioning (Villanueva, 2012). Given the high rates of cerebellar development during early life, this region is particularly sensitive to stressors such as childhood maltreatment. For instance, maltreated children with PTSD have smaller cerebellar volumes than do control children, and these cerebellar volumes are negatively correlated with trauma duration and are positively correlated with age of trauma onset (De Bellis & Kuchibhatla, 2006). Likewise, increased traumatic events experienced during childhood were associated with decreased cerebellar gray matter volume during adulthood (Herringa, Phillips, Almeida, Insana, & Germain, 2012), and adults who were victims of child sexual abuse demonstrated higher resting-state functional magnetic resonance imaging activation within the cerebellum compared to nonvictimized adults (Anderson, Teicher, Polcari, & Renshaw, 2002). Our present work builds upon these previous findings and demonstrates that childhood maltreatment is associated with functional cerebellar alterations during resting wakefulness that extend into adulthood.

Increased childhood maltreatment was also associated with decreased rCMRglc in the midbrain, thalamus, and hippocampus, which are involved in basal autonomic functions and sensory information processing. Child maltreatment can have a long-term and complex dampening effect on the basal autonomic functions that involve the hypothalamic–pituitary–adrenal axis (Tarullo & Gunnar, 2006). The present results further demonstrate that childhood maltreatment may have a long-term effect on the neural control of these autonomic functions. In addition, the thalamus and midbrain are intricately involved in sleep/wake regulation and vigilance (see Brown, Basheer, McKenna, Strecker, & McCarley, 2012). Sleep is commonly disturbed following traumatic events, and sleep is described as the possible hallmark to posttraumatic mental health problems such as PTSD (Germain, 2013). Decreased rCMRglc observed in the midbrain and thalamus regions suggest a possible dysregulation of the sleep/wake system that is tied to child maltreatment. Thus, we are currently investigating the impact of childhood maltreatment on sleep neurobiology.

Finally, decreased rCMRglc was also observed in the sACC, which is well known for being implicated in depression (Mayberg et al., 1997, 2000). A meta-analysis of 55 neuroimaging studies demonstrated that the ACC is involved in emotional recall, imagery, and tasks (Phan, Wager, Taylor, & Liberzon, 2002). Neuroanatomical rat studies demonstrate that the homologous brain region to the human medial prefrontal cortex (i.e., prelimbic and infralimbic cortices) is a preautonomic structure that directly innervates and is synaptically connected to brain stem preganglionic neurons (Rinaman, Levitt, & Card, 2000; Vertes, 2004), and contributes to produce fear extinction (Milad & Quirk, 2012). Brief and prolonged postnatal maternal separation paradigms alter the developmental assembly of preautonomic circuits originating within the mPFC in rats (Card, Levitt, Gluhovsky, & Rinaman, 2005); this work further supports the influence of early-life stress on human sACC development. As reviewed above, childhood maltreatment has long-term effects on psychosocial well-being, including susceptibility to developing mood disorders in later life. The current findings could suggest that the relation between child maltreatment and mental health problems in later life may be mediated through sACC functioning.

Supplemental analyses

The whole-brain analyses were recalculated without current depression and PTSD included in the model to explore whether they had an impact on the association between child maltreatment and rCMRglc. These results revealed neurobiological activity in the same, albeit larger, clusters with a similar location of peak voxel activity compared to when the mental health variables were controlled. These results demonstrate that the associations between child maltreatment and rCMRglc are not grossly underestimated due to removal of covariation between child maltreatment and current depression and PTSD.

Limitations

There are several limitations to the current study. First, the study was conducted among a convenience sample that included primarily male military veterans with and without current PTSD. The small proportion of female to male participants did not provide adequate power to examine a potential Sex × Maltreatment interaction. Given that all participants are veterans reduces the generalizability of the study. Exposure to combat may represent a potent stressor that could interact with vulnerabilities associated with early adversity in ways that are atypical for the population at large through differential ecophenotypes (Teicher & Samson, 2013). The presence of combat-related PTSD could have influenced the relations between child maltreatment and brain activity; however, child maltreatment can directly lead to mental health problems and posttraumatic stress, which may ultimately contribute to the effects of childhood maltreatment, an issue of multicollinearity. Nevertheless, participants with and without PTSD did not significantly differ on sex, ethnicity, child maltreatment, combat exposure, or depression, and all analyses were calculated while statistically adjusting for age, sex, BDI scores, CES scores, and CAPS past-month scores. The secondary data analysis did not present the opportunity to adjust for childhood and current socioeconomic status, which is known to influence brain structure and function throughout development (Hackman, Farah, & Meaney, 2010). Perception of parental social standing or parental edu-

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cation would be optimal measures to include in future studies (Ginaros et al., 2008, 2011). Second, this secondary data analysis did not have a control group available for use. Without the comparison of a maltreatment versus a nonmaltreatment control group, it is difficult to make inferences about how atypical these resting states are because they are derived from correlations within a single sample. These analyses constrained the interpretation of our study results in regard to whether the resting-state patterns were normal, abnormal, or associated with any kind of psychosocial function. However, these results do provide insight into candidate brain areas to examine in relation to maltreatment-related psychosocial function. Third, the decision to statistically adjust for current symptoms of depression and PTSD in the analyses is only one analytical approach that comes with both costs and benefits. This method reveals the association between child maltreatment and rCMRglc without the influence of current psychopathology. Although justifiable, this method could be considered analogous to comparing only maltreated individuals without psychopathology to nonmaltreated controls, which may in turn underestimate the consequences of exposure to child maltreatment because some of the covariation between child maltreatment and rCMRglc would be removed from the model. To explore whether current depression and PTSD had an impact on the association between child maltreatment and rCMRglc, the analyses were recalculated without these mental health variables retained in the model. An alternative design and analytical approach would be to ascertain rCMRglc differences between maltreated participants and controls, and then ascertain the degree to which depression, anxiety, PTSD, or other factors mediate these differences. Fourth, child maltreatment was broadly defined without an indication of when it occurred during early development, yet different forms of child maltreatment may affect the brain differently during different developmental periods (Lupien, McEwen, Gunnar, & Heim, 2009; Teicher et al., 2006). Animal research has demonstrated that stressor type (Pohl, Olmstead, Wynne-Edwards, Harkness, & Menard, 2007) and timing of exposure during development (Wilkin, Waters, McCormick, & Menard, 2012) each lead to differential anxiety- and depression-like behaviors in later life. Human work among adults has shown that early-life stress experienced between the ages of 8 and 17 years is associated with reduced ACC and insular volumes whereas early-life stress experienced before 7 years of age is not (Baker et al., 2013). Within the current study, the five maltreatment subtypes measured by the CTQ were not examined in relation to positive and negative correlations with rCMRglc because the sample size was limited and the current research design would not support that type of fine-grained analysis. Longitudinal studies designed to examine the neural impacts of specific types of maltreatment, the exposure timing, and exposure duration are necessary to fully identify brain circuits that are more, or less, resilient to early adversity. Fifth, although self-report is an acceptable means to acquire child maltreatment reports (Runyan et al., 2005; Winegar & Lipschitz, 1999), the use of a retrospective child maltreatment report may introduce reporting biases. However, the severity of child maltreatment among the current sample was equivalent to a previous community-based sample without existing psychopathology (Dannlowski et al., 2012). The preselection of individuals exposed to different levels of adversity during childhood is necessary to fully characterize the persistent neurodevelopmental dose-dependent effects of child maltreatment. Sixth, we expected that child maltreatment would be more robustly associated with a number of regions of interest (i.e., bilaterally at cluster-level significance). The null findings are likely a function of the relatively small sample, which is nevertheless within the recommended range for PET studies (i.e., $N = 10–20$; Andreasen et al., 1996).

Significance

Previous work indicated that child maltreatment is associated with functional magnetic resonance imaging based neural activity in regions and circuits that are implicated in emotion (Hart & Rubia, 2012; McCrory et al., 2011; Teicher et al., 2003; Teicher & Samson, 2013). Previous work has also shown that childhood maltreatment is associated with lower resting-state functional connectivity between the hippocampus and subgenual cingulate, right amygdala and bilateral precuneus, left insula and hippocampus and putamen, and dorsal ACC and the precuneus and regions in the prefrontal cortex (Herringa et al., 2013; van der Werff et al., 2013a, 2013b). The current findings contribute to this growing body of work by showing that during resting wakefulness, increased child maltreatment was associated with increased rCMRglc in areas that are involved in executive functioning and cognitive control, emotional self-control, and cognition and emotion expression; as well as decreased rCMRglc in areas that are implicated in social and emotional processing, cognitive and emotional functioning, and autonomic control and sleep/wake regulation. Overall, we interpret these metabolic profiles as increased activity in executive control regions, but less activity in emotion, autonomic, and sleep regulatory regions.

Finally, several brain regions that were associated with childhood maltreatment are also implicated in the modulation of sleep and sleep-dependent learning and memory processes (e.g., midbrain, thalamus, OFC, and hippocampus). Therefore, sleep neuroimaging studies among maltreated children may provide further insights into neural mechanisms of risk and resilience.

Although the study design does not provide insight into the association between child maltreatment and functional cognitive or emotional performance, the results support the need to more proximally examine the extent to which child maltreatment affects various neural systems and resulting behavioral and emotional outcomes. Within this study, increased cerebral metabolic activity in regions involving cognitive and executive functions may reflect a compensatory mechanism mediating resilience, or the inefficient modula-

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tion of other neural processes that confer heightened risk. Similarly, decreased rCMRglc in regions involved in emotion and autonomic regulation may reflect heightened resilience, or reduced capacity to respond to challenges. Prospective studies are required to determine how cerebral metabolic profiles associated with childhood maltreatment relate to heightened vulnerability or resilience to subsequent trauma exposure (e.g., van der Werff et al., 2013a, 2013b), and how they may relate to cognitive and emotional performance.

Supplementary Material

To view the supplementary material for this article, please visit http://dx.doi.org/010.1017/S0954579415000589.

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