Effects of Early Life Stress on Depression, Cognitive Performance, and Brain Morphology

Ayman Saleh, MD [1], Guy G. Potter, PhD [2], Douglas R. McQuoid, MPH [2], Brian Boyd, BS [1], Rachel Turner [1], James R MacFall, PhD [3], Warren D. Taylor, MD, MHSc [1,4]

[1] The Center for Cognitive Medicine, Department of Psychiatry, Vanderbilt University Medical Center, Nashville, TN, 37212;

[2] Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, 27710;

[3] Department of Radiology, Duke University Medical Center, Durham, NC, 27710;

[4] The Geriatric Research, Education, and Clinical Center (GRECC), Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville, TN, 37212, USA

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Correspondence: Warren D. Taylor, MD, MHSc
Vanderbilt University
1601 23rd Avenue South
Nashville, TN 37212
Email: warren.d.taylor@vanderbilt.edu
Telephone: (615) 322-1073
Fax: (615) 875-0686

ABSTRACT:

IMPORTANCE: Childhood early life stress (ELS) increases risk of adult depression and is associated with altered brain structure and function. It is unclear if specific ELSs contribute to depression and have different effects on neurobiology in subjects with and without depression.

OBJECTIVE: To identify ELSs predictive of adult depression and examine their effect on cognitive function and brain structure.

DESIGN, SETTING, and PARTICIPANTS: Cross-sectional study utilizing neuropsychological testing and 3T magnetic resonance imaging. Participants included 64 subjects with Major Depressive Disorder (MDD) and 65 never depressed individuals. Both groups reported a range of ELSs on the Early Life Stress Questionnaire.

MAIN OUTCOME MEASURES: Neuropsychological test performance, z-transformed and consolidated into composite domain variables of episodic memory, working memory, processing speed and executive function. MRI measures included cortical thickness and regional gray matter volumes, with an *a priori* focus on cingulate cortex, orbitofrontal cortex (OFC), amygdala, caudate and hippocampus.

RESULTS: Of 19 ELSs, only emotional abuse, sexual abuse and severe family conflict predicted adulthood MDD diagnosis ("predictive" ELSs). The effect of total ELS exposure differed between depressed and nondepressed groups. Greater ELS exposure was associated with slower processing speed and smaller OFC volumes in depressed subjects, but faster speed and larger OFC volumes in nondepressed subjects. In contrast, exposure to predictive ELSs had similar effects in both groups. Subjects reporting predictive ELSs exhibited poorer processing speed and working memory performance, smaller volumes of the lateral OFC and caudate, and decreased cortical thickness in multiple areas including the insula bilaterally.

The effects of predictive ELS exposure differed between diagnostic groups only in the left hippocampus, in which depressed subjects' ELS exposure was associated with smaller volumes.

CONCLUSION: When broadly defined, greater ELS exposure has different effects on cognition and regional brain morphology between depressed and nondepressed individuals. However, exposure to predictive ELSs is associated with altered cognitive performance and brain structure regardless of diagnosis. Moreover, predictive ELSs are associated with smaller left hippocampal volumes only in depressed individuals, suggesting that trauma resulting in hippocampal changes may be one mechanism by which ELS influences depression.

INTRODUCTION

Childhood stress and trauma significantly influences the development of psychopathology in adulthood. Early life stress (ELS) lowers the threshold for depressive reactions to stressors later in life (1), while the intensity of ELS predicts symptom severity of mood episodes (2, 3). Although stressors in childhood or adolescence may contribute to a wide range of adult psychopathology, some studies associate major depressive disorder (MDD) with exposure to certain types of early trauma including sexual abuse (4), emotional abuse (2), and family conflict (5). Unsurprisingly, such stressors are also associated with functional and structural neural changes.

Poorer cognitive performance is increasingly recognized as an important aspect of MDD, characterized by poor performance on measures of executive function, processing speed and episodic memory (6, 7). Exposure to ELS is associated with poorer adult cognitive function, specifically in memory domains and executive function, in populations with and without psychopathology (8-12). However, not all studies provide a picture of ELS effects across multiple cognitive domains and much of this work focuses on post-traumatic stress disorder. It is unclear whether ELS exposure influences cognitive performance in MDD.

Even in psychiatrically healthy individuals, neuroimaging studies associate ELS exposure with volumetric and functional alterations in brain regions including the anterior cingulate cortex (ACC) (13, 14), medial prefrontal cortex (15, 16), caudate (17) and insula (18). In contrast, depressed patients who were exposed to ELS exhibit smaller volumes of the orbitofrontal and prefrontal cortexes (19) and hippocampus (17, 19, 20). Jointly, these findings suggest that the effects of ELS exposure on brain structure may differ between healthy and depressed populations. Although it is challenging to disentangle the effects of ELS versus the effects of depression itself, such population-specific findings may provide clues related to depression vulnerability or resilience.

We hypothesized that specific ELSs are associated with a diagnosis of MDD in adulthood. We further hypothesized that those ELSs associated with MDD would also be associated with poorer performance on cognitive tests and structural alterations in brain regions involved in mood regulation. However, as those ELSs by definition would increase the risk of MDD, we also tested for statistical interactions between ELS and MDD diagnosis to determine whether the effect of ELS exposure on cognition and brain structure differed between depressed and nondepressed groups.

METHODS

Subjects

Subjects were between 20 and 50 years of age and enrolled at Duke University (N=112) and Vanderbilt University (N=17) between April 2008 and December 2013. Depressed Subjects had a DSM-IV diagnosis of recurrent MDD, as assessed by the Mini-International Neuropsychiatric Interview (MINI, version 5.0) (21) and interview with a psychiatrist. Additional inclusion criteria included onset of first depressive episode before age 35 years and a Montgomery-Asberg Depression Rating Scale (MADRS) (22) score of 15 or greater. Inclusion criteria specified no antidepressant use in the last month; most subjects reported no antidepressant use for at least three months or longer. Eligible control subjects had neither a history of psychiatric disorders nor a history of psychotropic medication use. Although not an entry criterion, medical comorbidity was quantified using the Cumulative Illness Rating Scale (CIRS) (23).

Exclusion criteria included other lifetime DSM-IV Axis I disorders including substance abuse or dependence. Subjects were excluded for Axis II disorders assessed by the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (24). Additional exclusion criteria included: history of psychosis, acute suicidality, use of illicit

substances in the last month, ECT in the last 6 months, a family history of bipolar disorder, any unstable medical condition, any history of neurological illness or head injury, or MRI contraindications.

Both the Duke University and the Vanderbilt University Institutional Review Boards approved this study. All Subjects provided written informed consent.

Assessment of early life stress

Exposure to childhood stressors was assessed using the self-report Early Life Stress Questionnaire (ELSQ). The ELSQ was developed based on Child Abuse and Trauma Scale (25, 26), which has strong internal consistency, validity, and test-retest reliability. The ELSQ consists of 19 traumatic items answered yes or no occurring during childhood ages 0-17 years (27, 28).

Neuropsychological Testing

Atrained psychometric technician supervised by a licensed neuropsychologist administered neuropsychological testing. Similar to our approach in geriatric depression (29), we created rationally constructed composite domain variables from a broad test battery. To combine tasks, we created Z-scores for each measure based on the performance of all subjects, then averaged the Z-scores for all tests within each domain. Internal consistency for each domain was assessed using Cronbach's coefficient alpha (CoA). This resulted in four composite neuropsychological measures: a) episodic memory (Logical Memory 1 and 2; Benton Visual Retention Test, number correct; Rey's Verbal Learning Test, total I-V and total VII; CoA=0.87); b) executive function (Controlled Oral Word Association test (total score); Trail Making B time (reverse scored time to completion); verbal fluency (total phonological and semantic); Stroop Color-Word interference condition (number completed);

CoA=0.75); c) processing speed (Symbol-Digit Modality (number completed); Trail Making A (reverse scored time to completion); Stroop Color Naming condition (number completed); CoA=0.70); and d) working memory (Digit Span forward (number of trials correctly completed); Digit Span backward (number of trials correctly completed); CoA=0.75).

MRI Acquisition and structural MRI Analyses

Due to differences in MRI manufacturers, only MRI data acquired at Duke University was included in analyses. Regional volumes were calculated using FreeSurfer (version 5.1) software running in a Linux cluster environment. In secondary analyses, we tested for differences in cortical thickness using FreeSurfer's QDEC module. We used a general linear model (GLM) to test for differences in cortical thickness between groups exposed or not exposed to ELSs, including age as a nuisance variable. Correction for multiple comparisons utilized the Monte Carlo simulation method with an initial cluster threshold of $p < 0.01$. Please see eAppendix in the supplement for descriptions of MRI acquisition and analyses.

Statistical Analyses

All analyses were conducted using SAS 9.4 (Cary, NC). We tested for univariate differences between diagnostic groups in demographic and clinical variables using chi-square tests for categorical variables and two-tailed t-tests for continuous variables. Initial tests for differences in the report of early life stressors between depressed and nondepressed cohorts were conducted using chi-square tests, or Fisher's exact test when cell sizes were low.

ELSs that differed between groups in univariate tests were incorporated into general linear models predicting diagnosis (MDD or nondepressed) while controlling for age, sex, education and medical morbidity (CIRS score). Retaining these demographic variables, we conducted backward regression to develop a parsimonious model, removing each ELS item

based on its statistical significance. The remaining ELS items that subsequently predicted a MDD diagnosis were termed "predictive ELSs".

We next planned a hypothesis-driven analytic approach to reduce the number of comparisons. For neuropsychological analyses, we consolidated individual test results into domain scores as described above. For MRI analyses, we selected *a priori* regions associated with ELS in existent literature: the ACC (14), OFC (19), amygdala (30), hippocampus (31) and caudate (17). For exploratory analyses of ELS effects on other regions identified by FreeSurfer, we controlled for multiple comparisons using FDR (false discovery rate), implemented within SAS.

We first examined the effect of the total ELS exposure (defined as total ELSQ score) on cognitive domains and brain volumes. For models examining cognitive domains, we controlled for diagnosis, age, sex, and education. For models examining MRI variables, we controlled for diagnosis, age, sex, and intracranial volume. A similar approach was used for examining the effects of predictive ELSs on cognition and brain structure, with participants dichotomized as exposed or not exposed.

To determine whether ELS effects differed between diagnostic groups, we added a term coding for an interaction between ELS and diagnosis. This was done for analyses of both total ELSQ score and predictive ELS exposure. If the interaction did not reach statistical significance, this suggested that there was no significant difference in the relationship between ELSs, cognition, and brain morphology between diagnostic groups.

Results:

We examined 129 subjects: 64 with MDD and 65 nondepressed controls. The diagnostic groups differed in age and medical morbidity (**Table 1**), with the depressed group being older, having more medical illnesses, and higher total ELSQ score (range: depressed 0-

11, nondepressed 0-8). In univariate analyses, depressed groups exhibited poorer performance in episodic memory, executive function and processing speed. However, these were no longer statistically significant after controlling for age and education level (**Table 1**).

Early life stressors: Predicting MDD diagnosis

Depressed patients reported significantly higher rates of six ELSs (**Table 2**). While controlling for covariates, we incorporated those ELSs into a model predicting MDD diagnosis. After backwards regression, in the final parsimonious model three ELS variables significantly and independently predicted a diagnosis of MDD: emotional trauma ($F_{1,121}$= 6.79, p= 0.0103), sexual abuse ($F_{1,121}$=6.00, p=0.0157) and severe family conflict ($F_{1,121}$= 7.85, p=0.0059).

We next dichotomized the sample based on whether they reported one or more of those three ELSs: emotional abuse, sexual abuse and severe family conflict ("predictive" ELSs). Forty percent of the study population, approximately 75% of the depressed sample and 33% of the nondepressed sample reported one or more of these predictive ELSs. Women were more highly represented in the group reporting predictive ELSs (78.4%, compared with 53.9% of those denying predictive ELSs; χ^2=8.05, 1df, p=0.0046; Supplement eTable 1).

Effect of ELS on cognition:

We found no significant main effect of total ELSQ score on any cognitive domain. However, we observed an interaction between total ELSQ score and diagnosis on processing speed ($F_{1,122}$=5.28, p=0.0232) and a trend for an effect on working memory ($F_{1,122}$=3.64, p=0.0588), but not episodic memory or executive function. On analyzing the interaction, depressed patients exhibited worsening processing speed with increasing ELSQ score

(**Figure 1**), while nondepressed Subjects exhibited faster processing speed performance with increased ELSQ score.

In contrast, predictive ELSs were associated with poorer performance on working memory ($F_{1,123}$=5.08, p=0.0260) and processing speed ($F_{1,123}$=7.74, p=0.0062), but not executive function or episodic memory. Interaction terms between predictive ELSs and diagnosis were not statistically significant, suggesting these ELSs have comparable effects in both depressed and nondepressed groups. Increasing numbers of predictive ELSs were associated with progressively poorer performance on tests of processing speed and working memory (Supplement eTable 2).

Effect of ELS on brain structure:

The MRI sample included 51 depressed and 53 nondepressed individuals. After controlling for age, sex, and intracranial volume, we found no significant differences between diagnostic groups in *a priori* regions (Supplement eTable 3). We also found no direct effects of total ELSQ score in *a priori* regions. However, we observed an interactive effect between total ELSQ score and diagnosis on the left lateral OFC ($F_{1,97}$=4.05, p=0.0469). Greater numbers of ELSs are associated with increasing OFC volumes in nondepressed Subjects but minimal differences in depressed subjects (**Figure 2**). In exploratory analyses, after controlling for multiple comparisons we did not observe significant direct or interactive effects of total ELSQ score on other brain regions.

Forty percent of the MRI sample (32 depressed and 10 nondepressed subjects) reported one or more predictive ELSs. In analyses of *a priori* regions, predictive ELSs were associated with smaller left lateral OFC ($F_{1,98}$= 5.11, p=0.0260) and smaller right caudate volumes ($F_{1,98}$=6.19, p=0.0145). We found a significant interaction between diagnosis and predictive ELS exposure only for the hippocampus, with predictive ELSs being associated

with smaller left hippocampus volume ($F_{1,98}$=4.98, p=0.0280) and a trend for smaller right hippocampus volume ($F_{1,98}$=3.35, p=0.0705), but only in the depressed group. In exploratory analyses after controlling for multiple comparisons there were no statistically significant findings in other brain regions.

Finally, we finally tested for relationships between predictive ELS exposure and cortical thickness. After controlling for sex and diagnosis, predictive ELS exposure was associated with reduced cortical thickness in several regions, including the bilateral insula, frontal and parietal lobes (**Figure 3** and Supplement eTable 4). In no region was predictive ELS exposure associated with increased thickness.

Discussion:

Similar to past literature (32), depressed individuals report more ELSs than nondepressed individuals. However, only emotional abuse, sexual abuse and severe family conflict significantly predicted adult MDD. When defined broadly, ELS exposure affects processing speed and lateral OFC volumes differently in depressed and nondepressed adults. A different pattern emerged when ELSs were limited to those predictive of depression ("predictive ELSs"). In these analyses, we found effects on cognition and morphology that, aside from findings in the hippocampus, did not differ between diagnostic groups

Childhood trauma has prominent effects on adult mental health (12, 33). Emotional abuse is common in childhood and adversely affects self-esteem, interpersonal skills and personal autonomy and integrity (34). Childhood sexual abuse has a worldwide prevalence of 20% (35) and is associated with multiple psychiatric disorders including MDD, addictions, and increased suicide risk (13, 35). Significant family strife also interferes with normal development and creates a vulnerability to maladjustment and internalizing personal problems (36, 37). Admittedly, while these specific stresses predicted adulthood MDD,

others propose that any significant childhood stress may increase the risk of depression. Such effects may depend on stressor severity and chronicity, age of exposure and positive support (38).

Effects of ELS exposure on cognition

ELS exposure also affected cognitive performance. When defined broadly using the total ELSQ score, ELS exhibited different effects between depressed and nondepressed subjects on processing speed (**Figure 1**). These group differences may reflect different neural responses to or recovery from stress that influences resiliency or vulnerability to depression. In contrast, the effect of predictive ELS exposure on processing speed and working memory was independent of diagnosis.

When considering the relationship between ELS and processing speed, we may be observing an inverted U-shaped curve. In this model, ELS broadly defined is associated with improved processing speed, but exposure to more severe (and potentially more chronic) ELSs results in impaired performance and vulnerability to depression. This is concordant with studies in older adults associating childhood trauma with better processing speed (39). In our nondepressed population, it is possible that less severe stresses result in improved processing speed and contribute to a resiliency mechanism (40). However, subjects predisposed to depression may have pre-existing circuit dysfunction where even milder stresses put strain on the circuit, resulting in poorer cognitive performance.

A similar model may apply to working memory, although we observed a relationship only with the more severe predictive stressors that did not differ between diagnostic groups. Past work supports negative effects of childhood stressors on working memory (10, 12, 41). This may be related to altered function of stress-sensitive systems, as working memory deteriorates with increased allostatic stress load (8).

Effects of ELS exposure on brain structure

ELS exposure was also associated with altered volumes of several regions involved in emotional regulation (42-46). In parallel with our observations on processing speed, we observed diagnostic group differences on the relationship between total ELSQ score and lateral OFC volume (**Figure 2**). A similar inverted U-shaped model may also apply to this relationship. This theory is concordant with a primate study examining early life maternal separation (47). This study associated separation with increased adult OFC volume, a finding thought to be related to stress resiliency by learning extinction of fear through top-down regulation (48, 49).

Exposure to more severe predictive ELSs was associated with smaller OFC and caudate volumes in both cohorts. This is concordant with past work showing that physically and emotionally abused children exhibit smaller volumes of the OFC and middle temporal gyrus (50). Similarly, domestic violence and sexual abuse are associated with smaller caudate volumes in healthy subjects (17). Our results from cortical thickness analyses are in line with a study associating decreased insula thickness with ELS exposure (18). As the insula plays a role in salience network regulation, reported abnormalities may explain deterioration in working memory and processing speed (51, 52).

Smaller hippocampal volumes are reported in MDD (53) and also observed in nondepressed adults exposed to ELS (19, 20, 45). We found that predictive ELSs were associated with hippocampal volume only in depressed individuals. Animal models demonstrate that controlled maternal separation results in decreased hippocampal volumes, however that volumes may normalize in adulthood (54). Extending that finding to our data, we may be observing a vulnerability mechanism wherein subjects who do not experience recovery of hippocampal neurogenesis are at increased risk of adult depression. Conversely,

risk of depression may be increased if there is not recovery of neurogenesis. This theory is concordant with past work demonstrating that depression itself contributes to hippocampal volume reduction (55) while smaller hippocampal volumes are also a risk factor for depression (56). Moreover, our finding is concordant with the hypothesis that left hippocampus could be more sensitive to traumatic events compared with the right hippocampus (19, 57).

Study Limitations and Conclusions

Study weaknesses include using a self-report scale for ELS, which does not measure severity and chronicity of the events. It may also contain a memory bias, although others report consistency between retrospective accounts and documented events (3). Although we report what ELSs are associated with MDD in adulthood, as we did not include other psychiatric disorders it is possible they are also associated with other psychiatric disorders. Our study is cross sectional and does not address longitudinal and developmental effects of ELS on brain volume and cognition. It also does not inform us if the observed cognitive and volumetric differences observed in the MDD population persist with successful depression treatment. Moreover, we defined predictive ELSs based on their relationship with MDD, so our findings should be confirmed in independent populations. However, as we did not observe significant differences in cognitive or MRI measures between groups after controlling for demographic variables (Table 1, eTable 3), the predictive ELSs do not appear to be serving as a surrogate marker for depression diagnosis.

Even if reported more frequently by the MDD population, not all ELSs predict adult MDD. Further, we found a complex relationship between ELSs, cognitive function and regional brain structures that in some cases differed between diagnostic groups. Longitudinal

352 human studies are required to investigate what factors contribute to the cognitive deficits
353 observed with exposure to ELS and to clarify the association with volumetric brain changes.
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Dr. Warren Taylor had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analyses.

All authors deny any conflicts of interest.

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Table 1. Demographics and Cognitive Function

Variable	Depressed (N = 64)	Control (N = 65)	Test Statistic	df	p value
Age (years)	35.1 (8.9)	29.7 (9.2)	t=3.40	127	0.0009
Sex, Women % (n)	60.9% (N=39)	66.2% (N=43)	X^2= 0.38	1	0.5382
Education (years)	15.2 (2.4)	16.0 (1.9)	t=1.94	127	0.0550
CIRS total	0.6 (1.0)	0.022 (0.5)	t=2.89	127	0.0043
MADRS total score	25.1 (4.5)	0.7 (0.9)	t=41.97	64.15	<.0001
ELSQ total score	3.5 (2.7)	1.8 (1.7)	t=4.36	106.13	<.0001
Race, white % (n)	67.2% (N=43)	55.4% (N=36)	X^2=1.89	1	0.1689
Processing Speed	-0.13 (0.73)	0.31 (0.73)	t = 3.41	127	0.0009
• Adjusted			F=3.50	1,125	0.0639
Working memory	-0.09 (0.86)	0.17 (0.95)	t = 1.60	127	0.1123
• Adjusted			F=0.21	1,125	0.6453
Episodic memory	-0.21 (0.82)	0.26 (0.66)	t = 3.55	127	0.0006
• Adjusted			F=2.82	1,125	0.0954
Executive function	-0.06 (0.78)	0.26 (0.70)	t = 2.45	127	0.0158
• Adjusted			F=0.94	1,125	0.3350

Data presented as mean (standard deviation) for continuous variables or percentage (N) for categorical variables. Comparison of demographic variables utilized pooled, two-tailed t-tests for continuous measures with equal variances and Satterthwaite's t-tests for unequal variances. Comparison of categorical variables utilized chi-square tests. Cognitive measures were z-transformed and presented both as unadjusted (pooled t-tests) and adjusted for age and education level (general linear models with F-values).

538 CIRS = Cumulative Illness Rating Scale; ELSQ = Early Life Stress Questionnaire; MADRS

539 = Montgomery-Asberg Depression Rating Scale

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Table 2. Reported ELS Exposure between Depressed and Nondepressed Participants

Reported trauma	Depressed (n=64)	Control (n=65)	p value
Emotional Trauma	37.5 % (n=24)	7.7 % (n=5)	< 0.0001
Physical abuse	18.7 % (n=12)	3.0 % (n=2)	0.0045
Sexual abuse	28.1 % (n=18)	4.6 % (n=3)	0.0003
Domestic violence	9.4 % (n=6)	6.1 % (n=4)	0.5305
Severe family conflict	39.1 % (n=25)	12.3 % (n=8)	0.0006
Neglect	15.6 % (n=10)	1.5 % (n=1)	0.0043
Divorce	21.9 % (n=14)	13.9 % (n=9)	0.2581
Separated	18.8 % (n=12)	12.3 % (n=8)	0.3407
Death in family	39.1 % (n=25)	44.6 % (n=29)	0.5227
Major illness in family	28.1 % (n=18)	13.9 % (n=9)	0.0536
Fire destroyed home	3.1 % (n=2)	1.5 % (n=1)	0.6191
War	3.1 % (n=2)	3.1 % (n=2)	1.0000
Natural disaster	1.6 % (n=1)	3.1 % (n=2)	1.0000
Major personal illness	6.3 % (n=4)	7.7 % (n=5)	1.0000
Hospitalization/surgery	21.9 % (n=14)	18.5 % (n=12)	0.6290
Bullied	37.5 % (n=24)	13.9 % (n=9)	0.0025
Premature birth	10.9 % (n=7)	3.1 % (n=2)	0.0958
Adoption	1.6 % (n=1)	1.5 % (n=1)	1.0000
Other events	9.4 % (n=6)	6.2 % (n=4)	0.5305

Percentile (number) of subjects exposed to each trauma type. Due to small cell sizes, ELSs were compared using Fisher`s exact test except chi-square tests were used for death in family ($x2 = 0.41$, 1df) and hospitalization/surgery ($x2=0.23$, 1df).

Figure 1. Relationship of ELSQ total score with processing speed

While increased number of ELSs resulted in progressively poorer performance in the z-transformed process speed domain in depressed patients, greater numbers of ELSs is associated with better process speed performance in nondepressed controls.

Figure 2. Relationship of ELSQ total score with left hemisphere lateral OFC volume

With increasing ELS exposure, nondepressed subjects showed relative increases in OFC volume. Conversely, depressed subjects exhibited a slight decline in OFC volume with increasing ELS exposure.

Figure 3. Cortical thickness differences related to predictive ELS exposure

Whole brain vertex-wise display shows the direct effect of reported predictive ELSs (emotional abuse, sexual abuse, or severe family strife) on cortical thickness. Analyses controlled for diagnosis (MDD or nondepressed) and sex. Lighter blue color reflects areas where ELS exposure is associated with thinner cortex. ELS exposure was not significantly associated with increased cortical thickness in any region.

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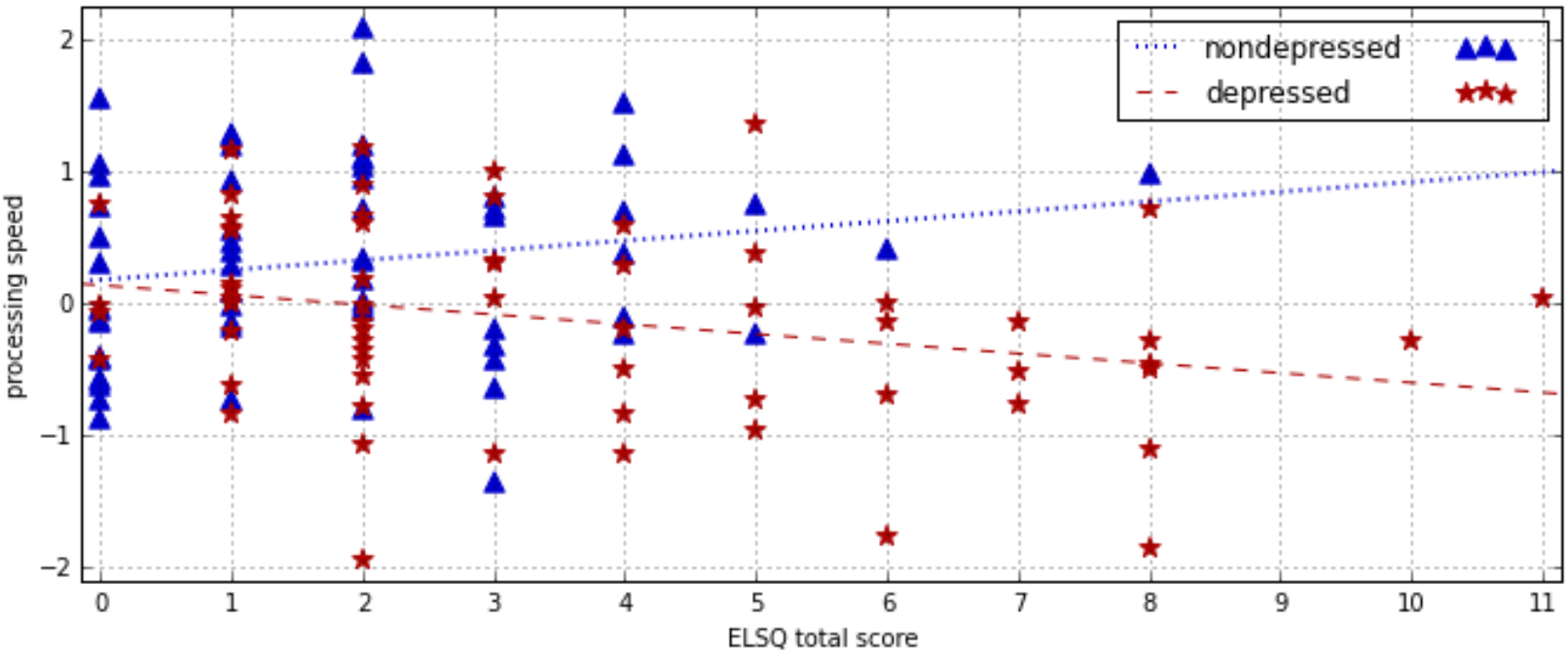
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processing speed
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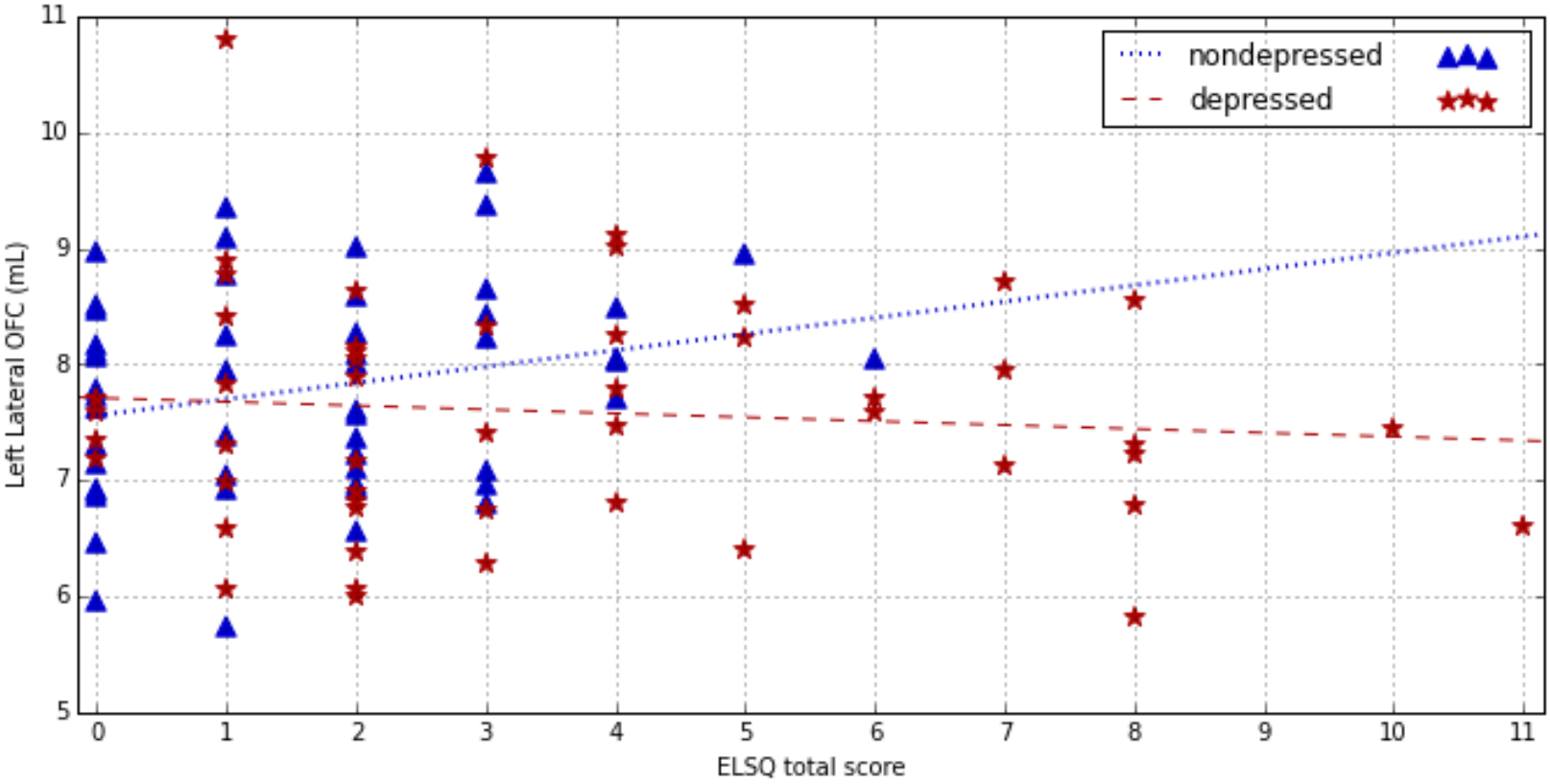
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Left Lateral OFC (mL)
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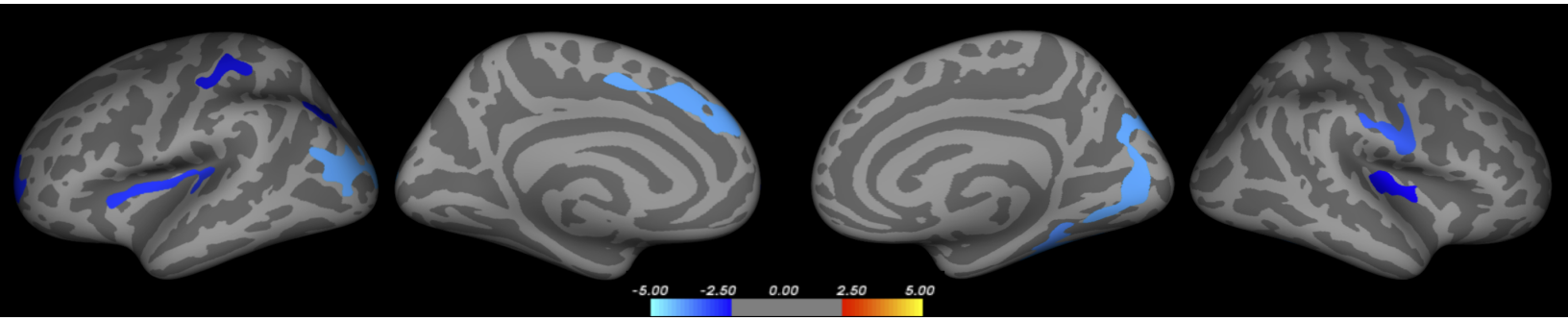
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