

Research Article

COGNITION–CHILDHOOD MALTREATMENT INTERACTIONS IN THE PREDICTION OF ANTIDEPRESSANT OUTCOMES IN MAJOR DEPRESSIVE DISORDER PATIENTS: RESULTS FROM THE iSPOT-D TRIAL

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Background: *Childhood maltreatment (CM) history has been associated with poor treatment response in major depressive disorder (MDD), but the mechanisms underlying this relationship remain opaque. Dysfunction in the neural circuits for executive cognition is a putative neurobiological consequence of CM that may contribute importantly to adverse clinical outcomes. We used behavioral and neuroimaging measures of executive functioning to assess their contribution to the relationship between CM and antidepressant response in MDD patients.* **Methods:** *Ninety eight medication-free MDD outpatients participating in the International Study to Predict Optimized Treatment in Depression were assessed at baseline on behavioral neurocognitive measures and functional magnetic resonance imaging during tasks probing working memory (continuous performance task, CPT) and inhibition (Go/No-go). Seventy seven patients completed 8 weeks of antidepressant treatment. Baseline behavioral and neuroimaging measures were assessed in relation to CM (history of childhood physical, sexual, and/or emotional abuse) and posttreatment depression outcomes.* **Results:** *Patients with maltreatment exhibited decreased modulation of right dorsolateral prefrontal cortex (DLPFC) activity during working memory updating on the CPT, and a corresponding impairment in CPT behavioral performance outside the scanner.*

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No between-group differences were found for imaging or behavior on the Go/No-go test of inhibition. Greater DLPFC activity during CPT significantly predicted posttreatment symptom improvement in patients without maltreatment, whereas the relationship between DLPFC activity and symptom change was nonsignificant, and in the opposite direction, in patients with maltreatment. Conclusions: The effect of CM on prefrontal circuitry involved in executive function is a potential predictor of antidepressant outcomes. Depression and Anxiety 32:594–604, 2015. © 2015 Wiley Periodicals, Inc.

Key words: executive function; stress; depression; neuroimaging; prefrontal cortex; treatment outcome

INTRODUCTION

An extensive literature supports childhood maltreatment (CM) as a robust predictor of adverse outcomes in adults with major depressive disorder (MDD).^[1–3] CM has been associated with more chronic and persistent MDD course^[1–3] and poorer response to MDD treatments.^[1,3] Nevertheless, the neurobiological mechanisms underlying these poorer outcomes remain incompletely understood. Animal and human studies have associated early life stress with abnormal stress-induced reactivity of the hypothalamic–pituitary–adrenal (HPA) axis,^[4] leading investigators to hypothesize that early stress may trigger a cascade of physiological changes that alter the course of neurodevelopment, increasing vulnerability to psychopathology.^[4]

Evidence of abnormal brain function in adults with CM broadly supports this hypothesis.^[3] Functional magnetic resonance imaging (fMRI) studies have associated early trauma history with abnormal functioning in frontal and limbic regions including dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex, and hippocampus, across diverse clinical and nonclinical populations and in both cognitive and emotion processing tasks.^[5–14] The involvement of these brain regions in core executive functions,^[15] combined with behavioral data associating CM with neurocognitive impairment,^[16,17] suggests executive dysfunction may be a consequence of CM that cuts across psychiatric diagnosis, and potentially explains the general vulnerability to psychopathology associated with childhood trauma.

Executive function impairments are also commonly demonstrated in MDD patients, both behaviorally (e.g., impaired performance on tasks probing working memory, inhibition, and planning),^[18] and neurally (e.g., abnormal prefrontal activation during cognitive task performance).^[19,20] Moreover, normalization of prefrontal activity may be a mechanism of action of depression treatments,^[21] and baseline measures of frontal activation may serve as important predictors of MDD treatment response.^[22–25]

Thus, both executive control circuitry functioning and CM have been shown, independently, to relate to MDD outcomes. However, the extent to which the interplay

between executive cognition and CM may influence antidepressant response is not well understood. The concept of biomarker \times early life stress interactions predicting clinical outcomes is gaining attention, particularly with respect to genetic biomarkers.^[26] Interactions between behavioral/neural biomarkers and early life stress, while relatively unexamined to date, may prove similarly robust in elucidating which patients are more or less likely to respond to certain treatments.

In this study we sought to address these gaps in our knowledge by investigating (1) behavioral and neural measures of executive function as biomarkers distinguishing MDD patients with and without CM history, and (2) potential interactions between these biomarkers and CM in the prediction of antidepressant outcomes. We hypothesized that patients with CM would exhibit evidence of impaired executive function that would, in turn, mediate relationships between maltreatment status and treatment outcomes. Neurocognitive and fMRI data were obtained from patients participating in the first wave of the International Study to Predict Optimized Treatment in Depression (iSPOT-D), using canonical paradigms designed to challenge executive functioning domains that are commonly disrupted in MDD patients.^[18] Results of such analysis may not only advance our understanding of the neurobiological mechanisms by which CM yields poorer outcomes, but also accelerate the development of biomarkers to predict which patients are more or less likely to benefit from particular interventions.

MATERIALS AND METHODS

PARTICIPANTS

Ninety eight MDD patients had baseline fMRI and CM data collected at the Westmead Hospital (University of Sydney, Australia), as part of the iSPOT-D study. Of these 98, 77 completed the week 8 (post-treatment) follow-up visit and were included in treatment outcomes analyses. A comprehensive description of the iSPOT-D study design and protocols has been previously published.^[27,28] Briefly, patients were 18–65 years old with primary diagnosis of nonpsychotic MDD confirmed by Mini-International Neuropsychiatric Interview^[29] and had baseline 17-item Hamilton Depression Rating Scale (HDRS₁₇)^[30] score ≥ 16 . Participants were unmedicated at baseline and randomized to receive flexibly-dosed, open-label escitalopram, sertraline, or

venlafaxine for 8 weeks. This study was approved by the institutional review board, and all participants provided written informed consent.

CHILDHOOD MALTREATMENT ASSESSMENT

CM history was obtained using the Early Life Stress Questionnaire (ELSQ),^[31,32] which assesses content domains equivalent to those assessed by the Childhood Trauma Questionnaire^[33] and Childhood Abuse and Trauma Scale.^[34] ELSQ norms have been established in a large community sample,^[32] while construct validity has been established regarding the prediction of greater depression and anxiety severity, independent of stressful life events in adulthood.^[32] The ELSQ has also been validated using neural correlates, including greater anterior cingulate grey matter loss with greater trauma,^[35,36] and interactions between early life trauma and genetic variation predicting affective network circuit disruptions and the mediation of depression and anxiety symptoms.^[37,38] The ELSQ contains 19 self-report items encompassing diverse categories of early stressors (e.g., abuse, poverty/neglect, medical illness, natural disasters, bullying). For each item, participants indicate whether they experienced the stressor (yes/no) prior to age 18 years. We defined CM as an affirmative response to any of the three abuse questions (“Were you physically abused?”, “Were you sexually abused?”, and “Were you emotionally abused?”), based on an extensive literature supporting these categories of early life stress as robust predictors of risk for adverse psychiatric outcomes.^[3]

BEHAVIORAL ASSESSMENTS

Behavioral assessments were conducted both outside and inside the scanner. Out-of-scanner testing was performed with a computerized neurocognitive battery including nine tests of cognition (and two tests of emotion recognition not included in the present analysis).^[39] These tests assess neurocognitive constructs equivalent to those assessed in traditional paper-and-pencil batteries and have been validated against standard neuropsychological tests,^[40] with established normative data,^[41] test-retest reliability,^[42] and cross-cultural validity.^[43] Reaction time (RT) and accuracy measures from individual tasks were used to calculate composite capacity scores for psychomotor function, attention, cognitive flexibility, decision speed, executive function-maze navigation, information processed speed, response inhibition, verbal memory, and working memory (Table 1). Capacity scores were computed by normalizing test scores to those of a sample of 336 healthy controls enrolled in iSPOT-D, then averaging the normalized RTs and accuracies for each task. This procedure yielded standardized *z*-scores (relative to a mean of 0), with higher scores indicating better performance. In-scanner behavioral measures consisted of RT and accuracy measures from two cognitive fMRI tasks (Go/No-go and continuous performance task) described in further detail below.

fMRI TASK DESIGN

Participants were scanned while performing two cognitive tasks, Go/No-go and continuous performance test (CPT), which are part of standardized imaging protocols with established utility assessing depression.^[44] The protocols were developed originally for scanning at 1.5 T^[45] and applied in treatment studies of related clinical groups.^[46] For Go/No-go, participants were asked to respond as quickly as possible to a “Go” stimulus (the word “press” in green), and to inhibit this response when seeing the “No-go” stimulus (the word “press” in red). A total of 180 Go and 60 No-go stimuli were presented in pseudorandom order for 500 ms each, with an interstimulus interval of 750 ms, in blocks of two Go or two No-go stimuli. The No-go blocks were not repeated more than three times in a row.

The CPT task incorporated a modified one-back design, in which participants were instructed to press a button when the same yellow letter appeared twice in a row, while ignoring any white letters.^[47] A

series of 120 letters (B, C, D, and G) were presented in yellow or white for 200 ms each, with an interstimulus interval of 2300 ms. Stimuli consisted of 60 letters in the “working memory updating” condition (yellow letters not appearing twice in a row), 20 “target” letters (yellow letters appearing twice in a row), and 40 “perceptual baseline” letters (white letters).

IMAGE ACQUISITION

MRI scans were obtained on a 3T GE Signa HDx scanner (GE Healthcare, Milwaukee, Wisconsin) using an 8-channel head coil. Functional images were acquired using echo planar imaging MR sequence (40 contiguous axial/oblique slices, 3.5 mm slice thickness; 64 × 64 matrix; 24 cm FOV; TR = 2500 ms; TE = 27.5 ms; flip angle = 90°). For each task, 120 volumes were collected, with a scan time of 5 min, 8 s. Three dummy scans were acquired at the start of each task. Additionally, 3D T1-weighted structural images were acquired in the sagittal plane using 3D spoiled gradient echo sequence (180 contiguous 1 mm slices; 256 × 256 matrix with in-plane resolution of 1 × 1 mm; TR = 8.3 ms; TE = 3.2 ms; flip angle = 11°; TI = 500 ms; NEX = 1; ASSET = 1.5; frequency direction: S/I), for use in normalization of fMRI data to standard space.

DATA ANALYSIS

Statistical analyses were conducted in SPSS 21.0 (IBM Corporation, New York). Multivariate ANOVA was used to analyze between-group differences in behavioral performance, measured as composite capacity scores across nine neurocognitive tests. The model included the 9 capacity scores as dependent variables, and CM as the independent variable. Post hoc between-group tests were performed to assess differences on individual neurocognitive tests.

fMRI data were preprocessed and analyzed with SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>) implemented in Matlab (MathWorks, Inc., Natick, Massachusetts). Motion correction was performed by realigning fMRI images to the first image of each task run. A boundary-based registration technique^[48] was used to generate a mean image for the fMRI time series and normalize it to the T1-weighted structural scan. T1-weighted data were normalized to standard MNI space using the FMRIB nonlinear registration tool.^[49] Normalization warps from these two steps were stored for use in functional-to-standard space transformations. Global signal was estimated with a mask within the ventricles and white matter and was removed from the motion-corrected fMRI time series. fMRI data were smoothed using an 8 mm Gaussian kernel and high-pass filtered using a cut-off period of 128 s.

In first-level analysis, the primary contrasts of interest were: for CPT, “working memory updating” minus “perceptual baseline,” to evaluate brain function during working memory updating, subtracting out effects of passive letter viewing; and for Go/No-go, “No-go” minus “Go,” to evaluate brain function during response inhibition.

Second-level analyses involved unpaired *t*-tests comparing BOLD activations in the contrasts of interest in patients with versus without CM. The search area was restricted a priori to a mask combining regions of interest (ROIs) from the AAL library^[50] that cover lateral and medial prefrontal cortex, insula, and amygdala (corresponding to ROIs defined as “frontal lobe,” “cingulate gyrus,” “insula,” and “amygdala” in the AAL library^[50]). This search area was based on previous literature associating CM with functional abnormalities in these regions during tasks probing executive and emotional functioning.^[5–7,11,12] Significant regions were identified at a threshold of $P < .05$, using family-wise error (FWE) correction at the cluster level (cluster-forming threshold was $P = 0.01$, uncorrected). For each significant cluster, beta values were extracted from a 10 mm radius sphere centered around the peak voxel, for visualization purposes and follow-up analyses. Exploratory,

TABLE 1. Cognitive tests and corresponding capacity scores included in the computerized test battery

Capacity score name	Test	Construct	Outcome measures	Test description	Tests assessing equivalent construct
Psychomotor function	Motor tapping	Psychomotor function	Number and variability of taps	Tapping index finger as fast as possible for 30 s; assessing sensorimotor response speed	Finger tapping
Attention	Continuous performance test	Sustained attention working memory	Accuracy (total, false-positive, false-negative errors), RT, variability of RT	Sustained attention to series of letters (D,C,G, or T). Identify when same letter is 1-back. Requires working memory updating	Conners CPT, TOVA
Cognitive flexibility	Verbal interference (color-word Stroop)	Cognitive control	Accuracy (errors), RT	Respond to the name of color word (ignore color) and then color word presented in (ignore name); assessing suppression of automatic responses	Stroop
Decision speed	Choice reaction time	Simple decision RT	Average RT, variability of RT	Respond to one of four circles as they light up; assesses decision-related reaction time. Assessing sensorimotor coordination and speed	Corsi blocks
Executive function-maze navigation	Executive maze	Executive function	Accuracy (total, overrun errors), completion time	Discover (by trial and error) a maze path; reflecting planning, monitoring feedback and error correction	Austin maze
Information processed speed	Switching of attention	Information processing speed – executive function	Accuracy (switching errors), completion time, connection time	Connect a sequence of alternating numbers and letters; assesses information processing efficiency	Trails A and B (paper and pencil)
Response inhibition	Go/No-Go	Response inhibition	Accuracy (total, false positive, false negative errors), RT, variability of RT	Press response pad as quickly as possible to "Go" (green) trials, and withhold to "No-Go" (red) trials. Assessing impulsivity versus inhibition	
Verbal memory	Memory recall	Declarative verbal memory	Accuracy (recall, intrusion errors), learning rate	Learn and then recall lists of 12 words; assesses learning, memory recall.	Rey Auditory Verbal Learning Test, California Verbal Learning Test
Working memory	Digit span	Working memory	Accuracy (total recall, maximum recall span)	Repeat a series of digits in forward and backward order; assessing working memory	Digit span

CPT, continuous performance test; TOVA, test of variables of attention; RT, reaction time.

uncorrected ($P < 0.01$) whole-brain analyses were also conducted (results in Supporting Information Table S1).

In the next phase of analysis, only those brain regions that significantly differed in patients with, versus without, CM were analyzed with respect to treatment outcome, with the goal of identifying significant interaction effects with CM. Similar analyses were conducted with the behavioral measures that significantly differed according to CM status.

The treatment outcomes of interest included HDRS₁₇ response (50% improvement from baseline), HDRS₁₇ remission (posttreatment score < 7), and HDRS₁₇ percent change. Binary logistic regression analyses were used to assess HDRS₁₇ response or remission as a function of behavior/ROI, CM, and behavior/ROI \times CM. Analogous linear regression analyses were used to assess HDRS₁₇ percent change as the dependent variable.

RESULTS

SAMPLE CHARACTERISTICS

Among 98 MDD participants (48% female, mean \pm SD age 33.6 ± 13.1 years), 43 reported a history of CM (defined as history of childhood physical, sexual, and/or emotional abuse), while 55 reported no such history. Of the 43 participants with CM, physical abuse was endorsed by 49%, sexual abuse by 28%, and emotional abuse by 88%, with 44% reporting multiple types of abuse. Participants with CM were more likely to be

female, but were otherwise demographically similar to those without maltreatment. Both groups had similar baseline HDRS₁₇ scores, but the CM group had higher baseline quick inventory of depressive symptomatology self-rated (QIDS-SR) score (Table 2). Among 77 participants included in the treatment outcomes analyses, 36 endorsed CM, while 41 reported no CM. Patients in this subset had no between-group differences in baseline demographic and illness characteristics.

BEHAVIORAL RESULTS

Out-of-scanner behavioral data across nine neurocognitive domains were available for 91 participants, 41 with and 50 without CM (Fig. 1). There was a significant overall main effect of CM on behavioral performance (Wilks' lambda = 0.814, $F = 2.050$, $df = 9$, $P = 0.044$, partial eta squared = 0.186). The group reporting CM performed more poorly across domains, with significant between-subjects effects specifically for attention ($F = 12.780$, $df = 1$, $P = 0.001$), cognitive flexibility ($F = 5.502$, $df = 1$, $P = 0.021$), and working memory ($F = 6.595$, $df = 1$, $P = 0.012$). However, after controlling for potential confounds of gender and baseline QIDS-SR score, the main effect of CM on behavioral performance became

TABLE 2. Pretreatment baseline participant characteristics

	MDD with childhood maltreatment ($N = 43$) mean \pm SD or %	MDD without childhood maltreatment ($N = 55$) mean \pm SD or %	<i>P</i> -value
Age at first visit	34.0 \pm 13.7 years	33.3 \pm 12.6 years	0.813
Gender	62.8% Female 37.2% male	36.4% Female 63.6% male	0.014*
Marital status	56.1% Single 29.3% married/cohabitating 12.2% divorced/separated 2.4% widowed 4.7% missing data	68.0% Single 24.0% married/cohabitating 8.0% divorced/separated 0.0% widowed 9.1% missing data	0.500
Race/ethnicity	62.8% White 0.0% Hispanic 2.3% mixed 30.2% other 4.7% unknown/missing	50.9% White 1.8% Hispanic 1.8% mixed 34.5% other 10.9% unknown/missing	0.699
Employment	25.6% Employed 39.5% students 16.3% retired 0.0% unemployed 18.6% other/unknown/missing	29.1% Employed 32.7% students 7.3% retired 12.7% unemployed 18.2% other/unknown/missing	0.087
Education	13.6 \pm 2.9 years	14.7 \pm 2.8 years	0.061
Age at MDD onset	21.2 \pm 12.3 years	23.0 \pm 12.3 years	0.481
Illness duration	12.3 \pm 12.7 years	9.8 \pm 10.3 years	0.292
Number of lifetime MDD episodes	13.4 \pm 23.0	11.8 \pm 20.0	0.701
Comorbid anxiety diagnosis ^a	55.8%	54.5%	1.000
Baseline HDRS _{17/52}	21.7 \pm 3.8	20.7 \pm 3.9	0.210
Baseline QIDS-SR ₁₆ score/27	14.5 \pm 3.5	12.7 \pm 3.3	0.012*

MDD, major depressive disorder; HDRS₁₇, 17-item Hamilton depression rating scale; QIDS-SR₁₆, 16-item quick inventory of depressive symptomatology self-rated.

*Significant at α level of 0.05, two-tailed.

^aDiagnoses include generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, and simple phobia

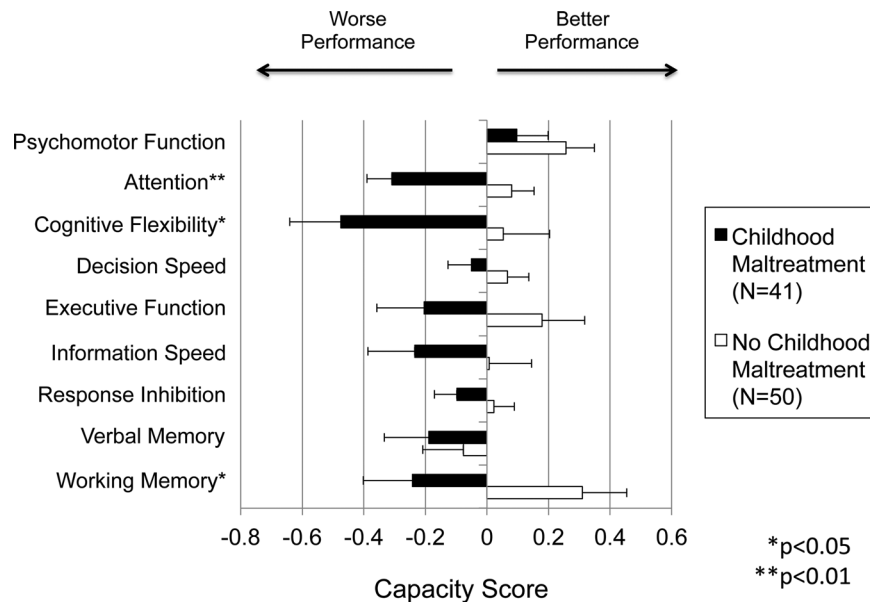


Figure 1. Behavioral results for participants with and without childhood maltreatment. Black and white bars represent estimated marginal means of individual capacity scores for patients with and without childhood maltreatment, respectively. Error bars indicate standard error. The omnibus test statistic was significant for an overall effect of childhood maltreatment status on behavioral performance (Wilks' lambda = 0.814, $F = 2.050$, $df = 9$, $P = 0.044$). Individual between-subjects effects were significant for attention, cognitive flexibility, and working memory.

nonsignificant (Wilks' lambda = 0.857, $F = 1.447$, $df = 9$, $P = 0.183$, partial eta squared = 0.143). Main effects of gender (Wilks' lambda = 0.837, $F = 1.685$, $df = 9$, $P = 0.107$, partial eta squared = 0.163) and baseline QIDS-SR score (Wilks' lambda = 0.930, $F = 0.657$, $df = 9$, $P = 0.745$, partial eta squared = 0.070) were also nonsignificant. In-scanner performance on Go/No-go and CPT did not significantly differ as a function of CM.

IMAGING RESULTS

In cluster-wise analyses with FWE correction, patients with compared to without CM significantly differed with respect to right DLPFC activation during working memory updating on CPT ($x = 42$, $y = 26$, $z = 42$, FWE-corrected $P = 0.046$; Fig. 2). There were no significant between-group differences for the Go/No-go task.

The CPT contrast of interest, consistent with prior research,^[44] reflected the difference in neural activation between two task conditions, "working memory updating" minus "perceptual baseline" (i.e., passive letter viewing). Both groups exhibited a pattern of relatively less right DLPFC activity during the "working memory updating" compared to "perceptual baseline" condition (Fig. 3A), though the between-condition difference was smaller in the CM group (Fig. 3B).

TREATMENT OUTCOME RESULTS

Among 77 study completers, CM was not independently associated with treatment outcome differences.

Childhood Maltreatment > No Childhood Maltreatment

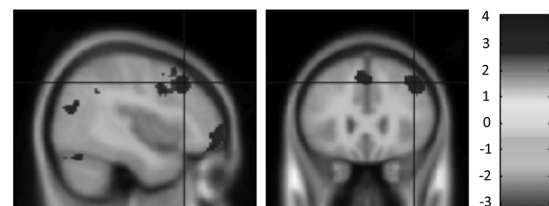


Figure 2. Patients with childhood maltreatment, compared to those without maltreatment, had significantly greater right dorsolateral prefrontal cortex activation during working memory updating on a continuous performance task (crosshairs at $x = 42$, $y = 26$, $z = 42$, clusterwise FWE-corrected $P = 0.046$). The contrast for this task represents neural activation to the "working memory updating" condition (i.e., holding the current letter in mind) minus the "perceptual baseline" condition (i.e., passive letter viewing).

Thus, MDD patients with and without CM had similar rates of HDRS₁₇ response and remission (63.9 and 61.0% for response [Chi-square = 0.069, $df = 1$, $P = 0.818$], and 44.4 and 51.2% for remission [Chi-square = 0.352, $df = 1$, $P = 0.649$], respectively), and similar pre- to posttreatment change in HDRS₁₇ score (-57.9 and -55.6% [$t = 0.389$, $df = 77$, $P = 0.698$], respectively).

None of the significant between-group differences in behavior (i.e., attention, cognitive flexibility, and working memory) interacted with CM status to predict treatment outcomes.

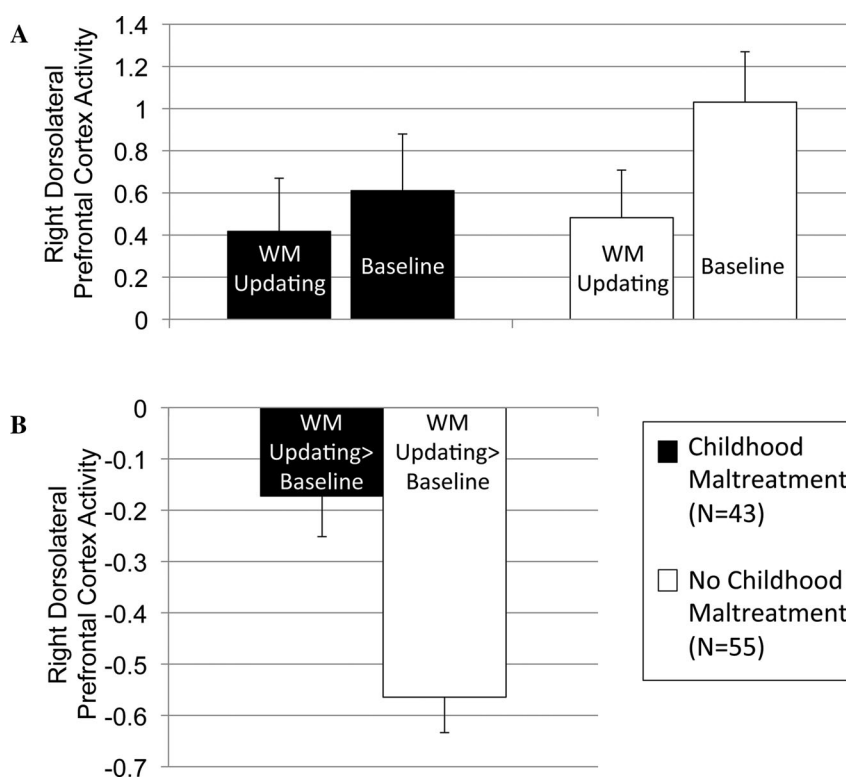


Figure 3. (A) Chart shows right dorsolateral prefrontal cortex (DLPFC) activity for the “working memory (WM) updating” and “perceptual baseline” conditions on the continuous performance task (extracted from 10 mm sphere around $x = 42, y = 26, z = 42$) in patients with childhood maltreatment (black bars) and patients without childhood maltreatment (white bars); bars represent estimated marginal means controlling for gender. Error bars indicate standard error. (B) Chart shows right DLPFC activity for the “working memory (WM) updating” minus “perceptual baseline” contrast on the continuous performance task (extracted from a 10 mm sphere around $x = 42, y = 26, z = 42$). Black and white bars represent estimated marginal means of extracted beta values for patients with and without childhood maltreatment, respectively, controlling for gender. Error bars indicate standard error.

In contrast, there was a significant interaction between right DLPFC activity during CPT and CM status predicting HDRS₁₇ percent change ($B = -0.344, SE = 0.151, P = 0.026$, controlling for gender, baseline QIDS-SR, and baseline HDRS₁₇; Fig. 4) but not HDRS₁₇ response or remission. Follow-up within-group regressions indicated the effect of DLPFC activation on HDRS₁₇ change was significant for patients without CM, with greater DLPFC activation predicting improvement in depression ($B = 14.608, SE = 7.115, P = 0.047$, controlling for baseline HDRS₁₇), but was non-significant (and numerically in the opposite direction) for patients with CM ($B = -17.304, SE = 12.691, P = 0.182$, controlling for baseline HDRS₁₇). These results suggest the DLPFC \times CM interaction effect was likely driven by (1) the relationship between DLPFC activity and HDRS₁₇ change in the non-CM group, and (2) the between-group difference in the direction of the relationship.

DISCUSSION

In this study, we investigated whether behavioral and neuroimaging measures of executive function differed

in MDD patients with and without CM history, and whether such between-group differences interacted with CM to predict treatment outcomes. Our behavioral results suggest that CM history may be associated with impairment across a range of executive functions. Neurally, we demonstrated a differential pattern of activation within an executive control circuitry region during a working memory task, which moreover interacted with CM to predict posttreatment change in depression severity. Our results thus extend previous literature associating early life stress with executive network dysfunction, by demonstrating the potential clinical relevance of neural differences for predicting treatment response in MDD patients.

We found that patients with compared to without CM performed more poorly across multiple neurocognitive domains, with more pronounced deficits in attention, cognitive flexibility, and working memory. Although the effect of CM on neurocognitive performance failed to achieve significance when controlling for potential confounds, possibly due to power limitations, our overall pattern of results was consistent with previous studies associating early life stress with executive functioning impairments.^[16,17] While there are data to

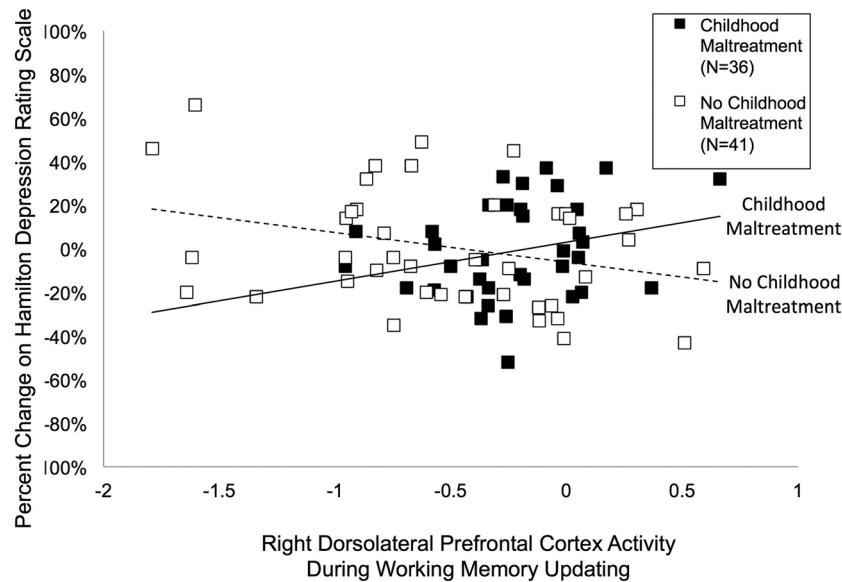


Figure 4. Right dorsolateral prefrontal cortex (DLPFC) activation differentially predicts improvement on the 17-item Hamilton Depression Rating Scale (HDRS17) as a function of childhood maltreatment status (significant right DLPFC \times childhood maltreatment interaction, $P = 0.026$). Scatter plot shows percent change in HDRS17 score (controlling for gender and baseline QIDS-SR and HDRS17 scores) in relation to right DLPFC activity during working memory updating on a continuous performance task. Trend lines are shown for patients with childhood maltreatment (solid line) and without childhood maltreatment (dashed line).

suggest that neurocognitive impairment and early life stress may independently predict poorer antidepressant response among MDD patients,^[1,51] studies to date have not examined the impact of cognition \times early life stress interactions on clinical outcomes. In our study, neurocognitive performance did not interact with CM to differentially predict antidepressant response. Nevertheless, further studies with larger samples may help to clarify the impact of cognition \times early life stress interactions upon MDD treatment outcomes.

We found not only behavioral but also neuroimaging evidence of cognitive control differences in MDD patients with compared to without CM. Specifically, in a contrast comparing activation during working memory updating with that during passive letter viewing, CM was associated with relatively less difference in right DLPFC activation between the two task conditions. This result is broadly consistent with prior studies associating early life stress with differential patterns of DLPFC activation or connectivity,^[12,14,52,53] and may reflect a diminished capacity in the CM group to modulate DLPFC activity in response to shifting cognitive demands. The DLPFC is an integral component of cognitive control neurocircuitry, involved in higher order cognitive functions such as attention, working memory, and planning and completing tasks.^[54] The DLPFC is also implicated in emotion regulation, via inhibitory effects on limbic regions.^[55] Thus, our finding of diminished DLPFC modulation in patients with maltreatment may yield insight into a potential neural mechanism underlying the adverse cognitive and affective sequelae of CM.

Importantly, we found that right DLPFC activation on the CPT task interacted with CM history to predict differences in antidepressant outcomes. DLPFC hypoactivity has been demonstrated in depressed patients compared to healthy individuals,^[21,44] with DLPFC function potentially normalizing with treatment.^[21] Pre- to posttreatment increase in DLPFC activity, in conjunction with decreased limbic activity, has been proposed as a possible neural mechanism of action of antidepressants.^[21] Consistent with the putative role of the DLPFC in antidepressant response, we found that for patients without CM, greater pretreatment DLPFC activity predicted greater posttreatment improvement in depression. In contrast, for patients with CM, the relationship between pretreatment DLPFC activity and posttreatment change in depression was nonsignificant (and numerically in the opposite direction compared to nonmaltreated patients).

This pattern of findings adds to our evolving understanding of mechanisms underlying the adverse clinical outcomes of early life stress. Previous studies have linked early stress exposure to elevated HPA activity and a potentially neurotoxic environment for early brain development.^[56] It has been postulated that the damaging effects of early trauma on neurodevelopment primarily affect regions involved in the threat response neurocircuitry,^[3] thereby enhancing stress sensitivity and vulnerability to psychiatric sequelae. Prefrontal cortical regions are part of this neurocircuitry, serving to modulate limbic reactivity to potentially threatening stimuli.^[3] Our findings of (1) diminished DLPFC modulation in patients with CM, and (2) a DLPFC \times CM

interaction affecting antidepressant outcomes, suggest the experience of CM may confer a unique signature of neural dysfunction, and hence unique neural mechanisms of illness and treatment response that diverge from those of nonmaltreated patients.

Notably, the present analysis failed to demonstrate a direct relationship between CM and poorer antidepressant outcomes, in contrast to prior literature.^[1,3] In the umbrella sample of 1008 patients for the iSPOT-D trial (from which the present imaging subsample is drawn), childhood abuse was found to predict poorer pharmacotherapy outcomes (DeBattista et al., in preparation), suggesting that power limitations may have contributed to our inability to detect a similar relationship. A recent meta-analysis of ten clinical trials found an effect of CM on depression treatment outcomes in general, yet there was heterogeneity among studies with some demonstrating a negative impact of CM on psychotherapy but not pharmacotherapy response, and others associating CM with poorer pharmacotherapy but not psychotherapy response.^[1] This heterogeneity suggests the relationship between CM and depression outcomes may be complex and multifactorial, potentially involving interaction effects as demonstrated in the current study.

Our study had several limitations. Our early life stress assessment relied upon retrospective self-report and was therefore subject to recall bias. The ELSQ permitted a categorical determination (presence/absence) of CM but did not assess maltreatment severity, thus limiting our ability to evaluate effects of CM as a dimensional rather than dichotomous trait upon behavioral/brain measures and treatment outcomes. The higher prevalence of female patients in the CM group required adjustment for gender in our statistical models, reducing power. Moreover, while the study sample size was adequate to investigate potential predictors of response to antidepressants in general, the within-treatment arm sample sizes were relatively small, yielding insufficient power to examine differential predictors of response to specific antidepressants or medication class.

CONCLUSION

In summary, we found behavioral and neuroimaging evidence of executive control differences in MDD patients as a function of CM history. Our results largely agree with previous reports on neurocognitive and neural correlates of early life stress, many of which involved non-MDD and even nonclinical samples, suggesting executive dysfunction may be a consequence of early life stress in general, irrespective of psychiatric diagnosis. We additionally demonstrated the potential clinical relevance of a neural correlate of CM for treatment response prediction in MDD. Further studies investigating CM \times executive functioning interactions, and the effects of such interactions on clinical outcomes, hold promise to accelerate the development of a comprehensive outcome prediction model for MDD.

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