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Association Between Initial Age of Exposure to Childhood Abuse and Cognitive Control: Preliminary Evidence

Kristen L. Mackiewicz Seghete¹, Anne P. DePrince², and Marie T. Banich³

¹Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, Colorado, USA

²Department of Psychology, University of Denver, Denver, Colorado, USA

³Institute for Cognitive Science, Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, Colorado, USA

Abstract

Cognitive control, which relies on the protracted development of frontal-parietal regions into adolescence, is a brain process that may be particularly vulnerable to the impact of child abuse. In this study, we used functional magnetic resonance imaging (fMRI) to examine associations between the age of onset of childhood abuse and alterations to the neural mechanisms supporting cognitive control in early adulthood, which have not been previously examined. During fMRI scanning, participants completed hybrid block/event-related versions of a classic color-word Stroop task as well as emotional Stroop tasks (threat and positive words). Participants were young adult women ($N = 15$; age range: 23–30 years) who had a history of childhood physical or sexual abuse that began prior to 13 years of age. Results indicated that earlier age of at the onset of childhood abuse was robustly associated with increased transient (i.e., event-related) recruitment of medial cognitive control regions in the classic color-word paradigm as well as with less suppression of medial frontal regions that are part of the default mode network, $\beta_s = -.16$ to $-.87$. In comparison, increased activation in dorsolateral prefrontal regions was associated with earlier age of abuse onset under conditions of sustained (i.e., blocked) cognitive control in the emotion word task for blocks of positive distracting words versus fixation, $\beta_s = -.50$ to $-.60$. These results provide preliminary evidence that earlier age of exposure to childhood abuse impacts the functional activation of neural systems involved in cognitive control in adulthood.

Childhood abuse (CA) is associated with alterations to emotional and cognitive brain processes that are observable even into adulthood (for review, see Hart & Rubia, 2012; Pechtel & Pizzagalli, 2011; Teicher & Samson, 2016). Cognitive control is one cognitive process that is altered in adults with a history of CA. Cognitive control involves biasing towards task-relevant responding in the face of distracting information and is supported by activation of an extensive frontal-parietal network, including the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and posterior parietal regions (Banich,

Correspondence concerning this article should be addressed to Kristen Mackiewicz Seghete, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Mailcode: DC7P, Portland, OR, 97239. mackiewi@ohsu.edu.
Kristen L. Mackiewicz Seghete is now at the Department of Psychiatry, Oregon Health & Science University.

2009; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Milham et al., 2001; Miller & Cohen, 2001). Authors of recent studies have found alterations to activation of prefrontal regions, particularly DLPFC, inferior frontal gyrus (IFG), and medial prefrontal cortex, in children and adults with a history of CA when cognitive control is exerted over both emotional and emotionally neutral information (Bremner et al., 2004; Elton et al., 2014; Hart & Rubia, 2012; Herzog et al., 2017; Lim et al., 2015; Mackiewicz Seghete, Kaiser, DePrince, & Banich, 2017; Mueller et al., 2010; Thoames et al., 2012).

The timing of CA has been identified as a critical factor in elucidating both the immediate and downstream impacts CA has on brain development (for review, see Teicher, Samson, Anderson, & Ohashi, 2016). Structural studies have found that volumetric changes to gray matter in specific brain regions and alterations to white matter integrity in specific tracts are related to age of exposure to CA (for review, see Teicher & Samson, 2016). However, no studies to date have examined the association between functional brain activation and the age of exposure to CA. Given that cognitive control has been shown to be altered in adults with a history of CA and that CA often occurs at a time during which brain regions and functional networks related to cognitive control experience heightened neuroplasticity (Andrews-Hanna et al., 2011; Luna, Padmanabhan, & O'Hearn, 2010; Paus, 2005), it is a cognitive process that may be particularly vulnerable to the timing of CA exposure.

The goal of our analyses was to examine associations between initial age of exposure to CA and neural mechanisms of cognitive control over both emotionally neutral and emotionally charged information in adults with a history of CA. We examined cognitive control using a blocked/event-related hybrid Stroop task that comprised an emotionally neutral condition (i.e., the classic color–word Stroop [CST] test; Stroop, 1935) and two emotional conditions (i.e., positive and threat versions of the emotional Stroop task [EST]; Mathews & MacLeod, 1985). A participant's task in the CST is to identify the color in which a word is printed while ignoring the meaning of the word. The participants must exert cognitive control to engage in the less automatic process of ink color identification as compared to the more automatic process of word reading. The need for cognitive control is increased under conditions in which the word (e.g., “red”) and ink color (e.g., blue) are incongruent, as conflict between competing semantic representations as well as the responses to which they lead must be resolved. Like the CST, the EST also requires the maintenance of goal-directed behavior (i.e., ink color identification) in the face of a more automatic process (i.e., word reading). However, unlike the CST, the need for additional control is engendered because the emotional word is salient and captures attention. In the EST, this emotional salience increases the likelihood the participant will engage in word reading, therefore requiring cognitive control to override a distracting, salient emotional word that captures attention as opposed to resolving inherent semantic or response conflict as in the CST.

Results of prior neuroimaging studies of women with CA-related posttraumatic stress disorder (PTSD) have found altered activation of medial (Bremner et al., 2004; Herzog et al., 2017) and lateral prefrontal (Herzog et al., 2017) brain regions during both the EST (compared to CA-exposed controls) and the CST (compared to controls with no history of trauma; Thomaes et al., 2012). Although prior studies by Bremner et al. (2004) and Herzog et al. (2017) directly compared the EST to the CST, both studies included a block design and

focused only on negative (including trauma-specific) words. Therefore, in a prior publication that used the same sample of women with a history of CA as is presented in the current study (Mackiewicz Seghete et al., 2017), we used a hybrid blocked/event-related Stroop design that included the CST as well as two versions of the EST, one with threat words and one with positive words. The hybrid blocked/event-related design allows for differentiation of two modes of cognitive control: sustained control that involves proactive maintenance of a task-set, and transient control that involves in-the-moment recruitment of additional resources in the face of dynamic information that cannot be anticipated in a proactive or sustained manner. We assessed the former through comparisons between blocks of trials and the latter through activation on a trial-by-trial basis within a block of trials. Sustained and transient cognitive control rely on overlapping, yet differential, neural mechanisms because of different demands (Braver, 2012), and the clinical sequela of CA may differentially affect these two types of cognitive control. For example, hypervigilance involves proactive surveillance of the environment. If this surveillance results in the detection of information that is perceived to be threatening in the moment, additional resources may be recruited to maintain or heighten vigilance in the moment.

In our prior study, women with a history of CA demonstrated both blunted activation of dorsal prefrontal regions (e.g., DLPFC) and heightened activation of right inferior frontal gyrus (rIFG) when proactive maintenance of cognitive control was required during the CST and both positive and threat versions of the EST. Additionally, compared to women with no history of trauma, women with a history of CA demonstrated greater activation in medial prefrontal brain regions (e.g., ventral medial prefrontal cortex) that are part of the default mode network linked to inner mentation and thought (Andrews-Hanna, Smallwood, & Sprenger, 2014) as well as in subcortical regions when transient cognitive control was required, but only during the threat version of the EST. Our research extends prior findings by showing alterations to cognitive control, regardless of the type of the distractor, for sustained (and not transient) control only. In contrast, alterations in brain activation transiently were shown more in the regions involved in internal mentation.

Whereas our prior publication with this sample focused mainly on group differences in brain activation between women with a history of CA and a control group of women with no history of trauma, the current study focused more specifically on just the sample of women with a history of CA. Here, we focused on examining how age of onset of CA affects neural engagement of cognitive control within only the group of women with a history of CA. Therefore, the presented analyses represent our examination of a separate construct related to a heterogeneous characteristic of the abuse itself—the age of onset—as opposed to an effort to understand group differences.

Although we predicted that an earlier age of CA onset would be associated with greater alterations to activation in brain regions involved in cognitive control, we could not predict the direction of that effect. On one hand, if development of prefrontal regions has been compromised, it might be that an earlier age of onset of abuse could be associated with less activation because the neural substrate to support activation has been compromised. On the other hand, it might be that an earlier age of abuse is associated with greater activation of

these regions because they must be engaged to a greater degree to attain the same level of control.

Method

Participants

Participants with full data were 15 young adult women between the ages of 23 and 30 years ($M = 25.93$, $SD = 2.28$) from an urban area who had experienced physical and/or sexual abuse prior to 13 years of age. There were initially 17 participants who completed all study visits, including the magnetic resonance imaging (MRI) session, but data from two participants had to be removed from analyses due to excessive movement. Participants were right-handed, native English speakers; additionally, they reported no history of brain injury, neurological disease, or psychotic symptoms; no current interpersonal trauma; and no magnetic resonance (MR) contraindications. All participants gave informed written consent and were compensated monetarily. The study was approved by the Colorado Multiple Institutional Review Board at the University of Colorado. This sample was part of a larger study, described in a previous publication (Mackiewicz Seghete et al., 2017).

Procedure

During an initial eligibility session, a clinician administered a trauma interview, self-report measure of trauma history, and a measure of IQ. Then, the participant completed a computerized battery of self-report questionnaires detailed below. Additional computerized cognitive tasks (e.g., digit span) were also completed, but are not detailed here as they are not relevant to these analyses.

Participants completed a second session that included MRI scanning. After an anatomical scan, they completed the Stroop task during fMRI scanning. All responses were made using a button box. The Stroop task consisted of one functional scan with 400 volumes. Stimuli were programmed using E-Prime software (Psychology Software Tools, Sharpsburg, PA) and presented via a pair of stereoscopic, MRI-compatible goggles. Participants were given earplugs to dampen scanner noise, and head movement was restricted through the use of an air pillow conformed to each participant's head.

Functional images were acquired with a General Electric (Waukesha, Wisconsin) Signa 3T MRI scanner with a T2*-weighted gradient-echo, echo-planar imaging, repetition time [TR] = 2000 msec, echo time [TE] = 32 msec, flip angle = 77° , 29 axial slices, thickness = 4 mm, gap = 0 mm, $64\text{m} \times 64\text{m}$ in-plane resolution, in-plane FOV = 22 cm. A high-resolution T1-weighted spoiled gradient recalled echo (SPGR) anatomical scan was collected for each participant to localize functional activity, TR = 9 msec, TE = 2 msec, flip angle = 10° , 124 coronal slices, thickness = 1.7 mm, $0.87\text{m} \times 0.87\text{m}$ in-plane resolution, in-plane FOV = 220 mm.

Measures

Trauma history—We took a two-part approach to determine the nature and extent of trauma history. First, participants were administered the Trauma History Questionnaire

(THQ; Green, 1996), which is a 24-question measure that assesses a respondent's history of various interpersonal and noninterpersonal traumas, at what ages these events occurred, and the number of incidents. It has been found to demonstrate adequate reliability and validity (Hooper, Stockton, Krupnick, & Green, 2011). In addition to any interpersonal traumatic events, participants could endorse having experienced a potential noninterpersonal trauma (e.g., car accident, natural disaster). However, individuals who endorsed a potential noninterpersonal traumatic event were only eligible if they did not endorse that the noninterpersonal event was traumatic, as defined by meeting *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association [APA], 2000) Criteria A for PTSD. The questionnaire was administered verbally by a clinician, as opposed to self-report, so that direct follow-up could be done to determine if any noninterpersonal events met Criteria A for PTSD.

Second, we obtained more detailed information about interpersonal trauma using a two-stage interview strategy adapted from the National Crime Victims Survey (NCVS; Fisher & Cullen, 2000). The NCVS is used annually by the U.S. Census Bureau to assess for crime, including sexual and physical assault, and has been used specifically in young adult women to assess for sexual victimization (Fisher & Cullen, 2000). In the first stage, participants were asked a series of behaviorally defined screening questions designed to cue memory for relevant incidents. The initial screening questions, with subsequent follow up, used to assess childhood physical or sexual abuse included: being attacked or threatened, including attempted or complete rape; and being attacked or threatened by someone you know. In the second stage, participants who answered "yes" to any screening questions were asked a series of detailed questions about the incident(s), including whether physical force or weapons were used, the ages at which the incidents occurred, and the participant's relationship to the perpetrator. The NCVS was used as an additional survey measure to confirm that the incidents reported in the THQ were physical or sexual abuse and to provide additional details on those incidents. Any discrepancies between measures were clarified during the interview. Age of CA onset was defined as the earliest reported age of exposure to physical or sexual abuse, categorized by whole years. The last age of exposure to CA and the duration of CA were also extracted. Age of last exposure to CA was similarly categorized by whole years. Discrete duration, as opposed to cumulative time between first and last exposure, was categorized as follows: 1 month or less (primarily single events); 1–12 months; or more than 12 months. Duration was defined categorically instead of continuously because some participants could not give an exact duration of the experienced CA.

PTSD—To determine the degree to which participants met diagnostic criteria for PTSD, all participants completed the Posttraumatic Diagnostic Scale (PDS; Foa, Cashman, Jaycox, & Perry, 1997), a 49-item self-report measure based on *DSM-IV* criteria for PTSD. It assesses for the presence and severity of all 17 possible *DSM-IV* PTSD symptoms. Severity ratings are made from 0 (*not at all or only one time*) to 3 (*5 or more times a week/almost always*). Continuous symptom severity and a categorical diagnosis of PTSD (Foa et al., 1997) were calculated and determined for each participant. The reliability of total PTSD symptom severity on the PDS was good (Cronbach's $\alpha = .83$).

Depression—All participants also completed the self-report Beck Depression Inventory–II (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II provides a measure of depressive symptoms that the participant has experienced over the past 2 weeks. The reliability of the BDI-II was high (Cronbach's $\alpha = .93$).

Demographic information, socioeconomic status, and IQ—Participants provided information on their age, race, occupation, and education. Current socioeconomic status (SES) was determined using education and occupation information in order to calculate the Hollingshead Index of Social Position (ISP; Hollingshead, 1975). We measured IQ using the Wechsler Abbreviated Scale of Intelligence (WASI; Psychology Corporation, 1999), two-subtest format.

fMRI task—While in the scanner, participants performed a manual-response version of the Stroop task (Stroop, 1935). On all trials, participants pressed a button to respond to the ink color in which a word was printed. Practice trials (variable length strings of “X”s) were completed during the anatomical scan that preceded the Stroop task in order to reinforce the color-mapping with the button box used in the Stroop task. The Stroop task included four types of trials defined by the type of word: incongruent, neutral, threat, and positive. Neutral trials consisted of neutral, noncolor words; incongruent trials consisted of color words in a different color ink (e.g., the word “blue” written in red ink); threat words consisted of threat-specific words (e.g., abuse, hit); and positive words consisted of happy words not related to physical or emotional safety (e.g., joy, happy). The four ink colors (red, blue, green, yellow) served as the incongruent words. Threat words were selected from a previous study that used abuse-related threat words (Bremner et al., 2001). Positive words were selected from the normed words on the Affective Norms for English Words (ANEW; Bradley & Lang, 1999) and matched the threat words in arousal, to the degree possible. It was also confirmed that the valence of positive words, threat words, neutral words, and incongruent words were within positive, negative, and neutral ranges, respectively. Words across type were matched in length. Given that many of the emotional words, especially the threat words, are not used with the same frequency as color words and neutral words, it was not possible to match words across type on frequency.

A hybrid blocked/event-related design, which was adapted from a previous study and shown to be sensitive to detecting differences between clinical and control populations (Banich et al., 2009), allowed us to examine both sustained and transient neural responses. The hybrid design consisted of blocks of trials (measure of sustained activity) and event-related trials within these blocks (measure of transient activity). Each block consisted of block-specific trials (threat, positive, or incongruent) and a set of neutral frequent trials that occurred in all blocks. In all the blocks, block-specific and neutral frequent trials were presented for 2 sec. There were 4 repetitions of each block type (threat, positive, incongruent) for a total of 12 Stroop blocks and 11 blocks of fixation interspersed between target blocks. Each block contained eight target trials and eight neutral frequent trials randomly distributed across the block, resulting in a total of 32 trials for each trial type. All block types, including fixation, had a 32-sec duration. Block order was randomly distributed, and first block type was

counterbalanced within the group. There were 20 sec of fixation baseline at the beginning of the scan.

fMRI preprocessing—We conducted fMRI preprocessing with the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMIRB) Software Library (FSL; <http://www.fmrib.ox.ac.uk/fsl/index.html>). Images were motion-corrected with Motion Correction using FMIRB's Linear Registration Tool (MCFLIRT), and brain tissue was extracted with Brain Extraction Tool (BET) to remove all nonbrain tissue from the images. Prior to statistical analysis, images were spatially smoothed with a Gaussian kernel (FWHM = 8 mm), mean-based intensity normalized, high-pass temporal filtered with a cutoff period of 100 sec to remove low-frequency noise, slice-time corrected, and intensity-normalized to allow valid analyses across participants. Seven volumes (all fixations) were dropped from the beginning of each functional run to ensure steady-state magnetization. Analyses only included participants with less than 2.5 mm of root mean square (RMS) movement across all six movement parameters.

Data Analysis

Statistical analyses were conducted with FMIRB's improved linear model. Analyses on the blood oxygen level-dependent (BOLD) time series were run separately for each participant, using separate blocked and event-related analyses. Time series were convolved using a double-gamma hemodynamic response function. For comparisons across individuals, parameter and variance estimates for each participant were registered to Montreal Neurological Institute standard stereotaxic space (MNI152), with the two-stage registration procedure implemented in FMIRB's Linear Image Registration Tool. To enable them to be more easily differentiated, blocked regressors and effects are denoted by upper-case labels (e.g., Threat), whereas event-related regressors and effects are denoted by lower-case labels (e.g., threat).

Separate general linear models (GLM) were modeled for the blocked and event-related data. For the blocked analyses, separate regressors for each block type (Incongruent, Positive, and Threat) were modeled in a single GLM with the onset of each initial correct trial in a string of correct trials. Additionally, three separate regressors were modeled to account for error trials within each block type. In order to ensure that blocked effects were independent of these error trials, each blocked regressor was orthogonalized with respect to the corresponding error regressor. For the event-related analyses, seven regressors corresponding to the trial types were modeled in a single GLM: incongruent trials, neutral trials within incongruent blocks, positive trials, neutral trials within positive blocks, threat trials, neutral trials within threat blocks, and error trials. For each regressor, a double-gamma response function was convolved at the onset of each trial.

Within FLAME1+2, age of CA onset was regressed on activation for contrasts of interest (Block: Incongruent > Fixation, Positive > Fixation, and Threat > Fixation; Event-related: incongruent > neutral within incongruent block, positive > neutral within positive block, and threat > neutral within threat block). FLAME automatically controls for outliers in the whole-brain analysis. To take advantage of spatial neighborhood information, while

moderately controlling for Type I error (given the restricted sample size and a priori hypotheses), threshold-free cluster enhancement (TFCE; Smith & Nichols, 2009) was implemented in FSL randomise (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) with permutation performed in a voxel-wise manner. We applied TFCE transformation to all voxels in the brain before permutation, and a grey matter mask was applied (Woo, Krishnan, & Wager, 2014). Images were thresholded at $p < .005$ (uncorrected). This uncorrected peak threshold was selected based on evidence that permutation testing with peak thresholding up to $p < .01$ is robust to false positives (Eklund, Nichols, & Knutsson, 2016) and based on our prior experience with similar sample sizes and clinical groups. For ease of interpretation, only clusters with greater than 10 voxels are presented.

Percent signal change values were extracted from significant regions of interest (ROI; 5 mm sphere around peak). Scatter plots for each region were visually inspected. Robust regression (implemented in SPSS using the R plug-in) was used to quantify the associations for display purposes, as there were concerns about the potential impact of outliers. Post hoc robust regressions were completed, including depressive symptoms (total BDI-II score) and severity of PTSD symptoms (total PDS severity score). A similar pattern of results was observed, for the most part, with both models. Therefore, the more parsimonious model with only age of onset of CA was included in the final analyses. See Supplemental Table 1 for the standardized beta coefficients for both models.

All behavioral data were analyzed using IBM SPSS (Version 24) and used an alpha value of .05. Correct trial reaction time (RT) was calculated separately for each trial type. To account for individual variation in mean reaction time, Stroop interference scores were calculated for each condition as a percentage of RT on block-specific neutral trials; for example, (mean target correct trial RT – mean within target block neutral correct trial RT)/mean within target neutral correct trial RT. There were no missing data.

Results

Participant Characteristics

Participant demographics, group characteristics, and CA characteristics are presented in Table 1. Potentially traumatic interpersonal events were endorsed by 20% of participants, and all participants denied *DSM-IV-TR* (APA, 2000) Criteria A for PTSD for these events. All interpersonal events reflected natural disasters (e.g., earthquake) or car accidents. Approximately 68% of participants met criteria for PTSD, based on the PDS. See Table 1 for clinical characteristics.

The age of CA onset was not significantly associated with the age of last exposure to CA, $r = -.19$, $p = .503$, nor was it significantly different between categories of duration of CA, $F(2, 14) = 0.76$, $p = .491$. Additionally, age of CA onset was not significantly associated with IQ, $r = -.19$, $p = .492$; depressive symptoms, $r = .13$, $p = .638$; or PTSD symptom severity, $r = -.32$, $p = .244$.

Behavioral Stroop Results

A repeated-measures analysis of variance (ANOVAs) with the factor of Block (Incongruent, Positive, Threat) was performed for interference. There was a main effect of Trial, $F(2, 13) = 34.74$, $p < .001$, with participants demonstrating more interference on incongruent ($M = 0.218$, $SE = 0.025$) trials than on positive trials ($M = 0.008$, $SE = 0.021$) or threat trials ($M = 0.034$, $SE = 0.016$), all $ps < .001$. There was no difference between interference on the positive and threat trials, $p = .331$. A repeated-measures ANOVA with factors of Block (Incongruent, Positive, Threat) and Trial (Target, Neutral) revealed no significant main effects or interactions for accuracy, $ps = .257$ to $.865$. Age of CA onset was not significantly associated with interference, $ps = .176$ to $.845$, or accuracy, $ps = .258$ to $.897$.

Sustained Cognitive Control (Blocked Analyses)

Younger age of CA onset was associated with less activation of left brain stem and temporal pole during the Incongruent blocks, compared to Fixation blocks. For the Positive blocks, compared to Fixation blocks, younger age of CA onset was associated with greater activation of left superior mid-DLPFC and right posterior DLPFC (BA 6; see Table 2).

Transient Cognitive Control (Event-Related Analyses)

For the contrast of incongruent trials versus neutral trials within the incongruent blocks, younger age of CA onset was robustly associated with more activation across a large number of brain areas, including ventral medial prefrontal cortex (vmPFC), dorsal medial prefrontal cortex (dmPFC), dACC, ventral anterior cingulate cortex (vACC), middle frontal gyrus (MFG), and IFG. Additionally, younger age of CA onset was associated with higher levels of activation of bilateral insula and multiple bilateral parietal, temporal, and occipital regions (see Table 2 and Figure 1). For the contrast of positive trials versus neutral trials within the positive block, younger age of CA onset was associated with less activation of dACC. We found no other associations within the emotional trials (see Table 2).

Discussion

This was the first study to demonstrate an association between younger age of CA onset and alterations in neural activation when a participant was required to implement cognitive control. The most robust associations between brain activation and age of CA onset were observed for transient cognitive control during the CST in the face of directly conflicting, emotionally neutral information. In contrast, associations with cognitive control of emotional information during the EST were limited. Although these results might seem counterintuitive in that one would expect more disruption from emotional distractors in this population, in our sample, as in others (e.g., Compton et al., 2003), greater behavioral interference was induced by distracting color words in the CST as compared to emotional words during the EST. This pattern is not surprising, as the CST requires resolving direct conflict in order to override prepotent responding as opposed to ignoring distracting, salient information that captures attention (Williams, Mathews, & Rauch, 1996). As such, it may be that the heightened cognitive control demands in the CST made that task more sensitive to age of CA onset than the EST.

We primarily observed significant associations between age of CA onset and activation for the contrast of incongruent trials compared to neutral trials within the incongruent block, which assessed the need for transient cognitive control that arises above and beyond any sustained top-down control. Younger age of CA onset was associated with alterations in activation of a number of medial and lateral prefrontal brain regions. These include the dACC, a region associated with transient aspects of cognitive control, especially those that are response-related (Banich, 2009; Banich et al., 2009; Silton et al., 2010), as well as the posterior DLPFC and IFG, regions important for biasing towards task-relevant processes and goals, respectively (Banich, 2009; Banich & Depue, 2015). In contrast, we found no significant associations between age of CA onset and activation for the contrast of the incongruent block as compared to fixation, which is thought to reflect more sustained aspects of cognitive control.

Notably, this pattern is distinct from that observed in our prior work (Mackiewicz Seghete et al., 2017), in which we compared activation for the same sample of women with a history of CA as was used in the current study to a control group. Results from those analyses showed no group differences for incongruent trials compared to neutral trials within the incongruent block. Rather, women with a history of CA demonstrated less activation of DLPFC than controls across block types, including the incongruent block. This dissociation suggests two separate mechanisms that occur as a result of CA. In general, a history of CA appears to result in decreased recruitment of proactive cognitive control mechanisms. With earlier exposure to CA, more reactive aspects of cognitive control are affected as well.

One possible interpretation of this pattern of decreased reactive control with earlier age of onset is that an earlier onset of CA is associated with a more “immature” mode of cognitive control, as models of neuromaturation suggest medial frontal regions of the brain mature before lateral frontal regions (Paus, 2005). In addition, developmental studies have suggested a reliance mainly on reactive cognitive control mechanisms prior to late adolescence, after which more proactive mechanisms come to greater maturity (Andrews-Hanna et al., 2011). As our entire sample experienced CA onset prior to 13 years of age, our results may be consistent with the idea that lateral frontal regions of the brain undergoing maturation during the time of abuse may have been affected in a manner that has lasting effects, leading to a greater reliance on reactive, medial mechanisms to recruit lateral frontal regions in the moment as opposed to having sufficient proactive recruitment of these frontal regions.

Additionally, younger age of CA onset was associated with more activation of vACC, subgenual ACC, vmPFC, and midline precuneus. Unlike more dorsal medial prefrontal brain regions, these ventral medial regions and midline precuneus are often implicated in the default mode and mind-wandering (Andrews-Hanna, Smallwood, & Spreng, 2014).

Additionally, ventral medial prefrontal brain regions are also implicated in emotion regulation and evaluation (de la Vega, Chang, Banich, Wager, & Yarkoni, 2016). Hence, it may be that earlier age of CA onset is associated with enhanced reliance on the medial frontal brain regions to reactively signal for a transient increase in the need for cognitive control. In support of this idea, earlier age of CA onset was also associated with less activation of visual processing regions and less suppression of default mode regions,

suggesting that these regions are more active even under conditions that do not involve emotional information.

Of note, the pattern of association between transient activation during the CST and age of CA onset within this group differs notably from differences in activation between the presented group and a group of controls (Mackiewicz Seghete et al., 2017). In the previous analysis, we noted group differences in activation for sustained cognitive control across both emotionally neutral and emotionally valenced distractors on the CST and EST, respectively, as well as for transient aspects of cognitive control for emotionally valenced information on the EST. This differential pattern for the group contrast as compared to variation with age of CA onset is not surprising, as such dissociations have been observed with regards to executive control (see Yarkoni & Braver, 2010, for discussion). The results of the current investigation provide preliminary evidence to suggest that age of exposure to CA may impact some brain processes above and beyond exposure to CA more generally. This idea is consistent with the proposal, initially based on structural studies, that there are sensitive periods for exposure to CA for multiple brain regions, including the prefrontal cortex (Teicher & Samson, 2016).

There were several limitations to this study. Given its preliminary nature, interpretation is limited because of the restricted sample size. Additionally, we might have failed to find some significant associations due to power, and we were not able to compare individuals with and without PTSD. Although cumulative duration of exposure to CA may be a potential confound, exploratory analyses revealed duration and age of CA onset were not significantly associated in this sample. Structural changes are another potential factor that might have influenced the results. Given that this study focused on functional activation, as opposed to volumetric or structural differences in brain regions, it is not possible to disentangle the degree to which structural changes may be related to our findings. This will be a particularly important area for future research, as experiencing CA during different sensitive periods of development may result in different structural changes to the brain as well as differential impact on cognitive functions (Anderson et al., 2008; Schalinski, Teicher, Carolus, & Rockstroh, 2017; Teicher et al., 2016).

Despite this study's limitations, our results provide initial evidence that timing of exposure to CA is associated with differential functional brain outcomes that persist into adulthood. Replication of these findings and further research into the interaction of timing of exposure to CA and functional brain activation is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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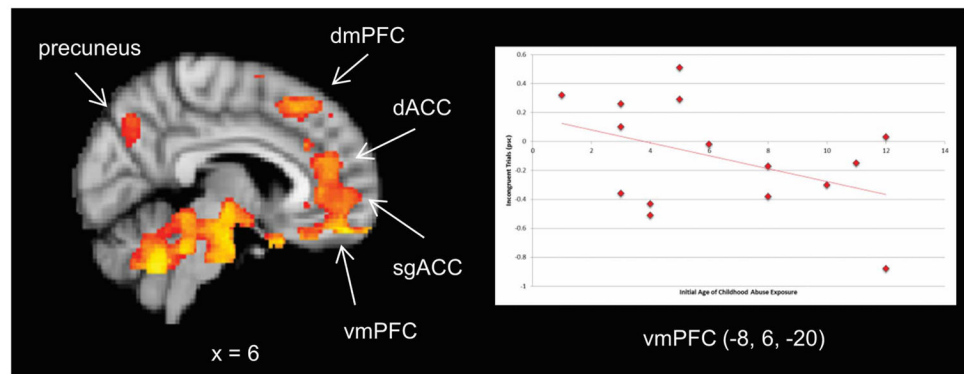


Figure 1.

Whole-brain regression of age of childhood abuse (CA) onset on event-related activation during emotionally neutral Stroop trials. Earlier CA onset is associated with greater activation of bilateral (only right pictured) dorsal medial prefrontal cortex (dmPFC), ventral medial prefrontal cortex (vmPFC), dACC (dorsal anterior cingulate cortex), subgenual anterior cingulate cortex (sgACC), and right precuneus during the incongruent trials than neutral trials within the Incongruent block (shown in red). Graph to the right visually represents relationship from peak in the left vmPFC, with percent signal change during the incongruent trials on the y axis and age of initial CA exposure on the x axis.

Table 1

Group Characteristics

Variable	<i>M</i>	<i>SD</i>	%
Age, years	25.93	2.28	
IQ ^a	119.47	7.46	
SES ^b	42.80	14.04	
Race (% Caucasian)			66.7
Childhood physical abuse only ^c			20.0
Childhood sexual abuse only ^c			26.7
Childhood physical and sexual abuse ^c			53.3
Age of abuse onset	6.33	3.60	
Age of last exposure	13.33	3.24	
Chronic abuse (> 12 months duration)			73.3
BDI-II total score	16.20	10.64	
PTSD ^d			66.7
Total PTSD symptom severity ^d	16.47	10.18	

Notes. *N* = 15. Participants denied posttraumatic stress disorder (PTSD) Criteria A from the *DSM-IV-TR* for noninterpersonal events. IQ = intelligence quotient; SES = socioeconomic status; BDI-II = Beck Depression Inventory-II.

^aMeasured by the Wechsler Abbreviated Scale of Intelligence (WASI).

^bMeasured by the Hollingshead Index of Social Position.

^cChildhood abuse was assessed using the Trauma History Questionnaire (THQ) and the National Crime Victims Survey.

^dPTSD criteria and symptoms were assessed using the Posttraumatic Diagnostic Scale (PDS).

Table 2
Association Between Age of Abuse Onset and Brain Region Activation During the Stroop Task

Region	BA	z	Voxels	x ^a	y ^a	z ^a	β
Blocked activation							
Incongruent > Fixation							
Positive correlations							
Brainstem (L)	--	4.87	73	-10	-10	-24	.74
Temporal pole (L)	28	4.67	34	-24	6	-32	.77
Positive > Fixation							
Negative correlations							
Middle frontal gyrus (L)	8	-3.57	14	-38	36	44	-.50
Middle frontal gyrus (R)	6	-2.67	11	32	18	60	-.60
Event-related activation							
incongruent > neutral							
Negative correlations							
Frontal/Temporal/Parietal (B) ^b	--	--	19,433	--	--	--	--
Medial prefrontal gyrus (L)	25	-6.39	--	-8	6	-20	-.81
Orbital frontal cortex (R)	34	-5.93	--	14	6	-20	-.57
Middle temporal gyrus (R)	21	-5.82	--	68	-28	-10	-.87
Brainstem (R)	--	-5.52	--	24	-28	-34	-.82
Cerebellum (L)	--	-5.39	--	-8	-46	-16	-.78
Temporal pole (R) ^c	38	-5.34	--	48	24	-32	-.63
Superior frontal gyrus (R)	8	-5.31	--	22	24	52	-.83
Lingual gyrus (R)	36	-5.24	--	20	-42	-12	-.67
Cerebellum (L)	--	-4.84	--	-32	-32	-34	-.78
Superior frontal gyrus (L)	8	-4.78	--	-26	20	58	-.51
Medial frontal gyrus (R)	11	-4.73	--	6	32	-24	-.44
Brainstem (L)	--	-4.60	--	-2	-20	-24	-.78
Brainstem (L) ^c	--	-4.54	--	-12	-34	-32	-.69

Region	BA	z	Voxels	χ^2	η^2	β
Brainstem (R)	--	-4.43	--	4	-12	-10 -81
Anterior cingulate cortex (R)	32	-4.42	--	10	42	16 -79
Middle temporal gyrus (R)	21	-4.40	--	66	-16	-18 -41
Medial frontal gyrus (R)	11	-4.37	--	12	52	-20 -79
Anterior cingulate cortex (R)	24	-4.35	--	8	40	-2 -65
Cerebellum (L)	--	-4.20	--	-12	-46	-30 -76
Fusiform gyrus (R)	37	-4.14	--	34	-44	-22 -75
Hippocampus (R)	--	-4.01	--	14	-14	-20 -69
Medial frontal gyrus (R)	10	-3.98	--	12	54	-4 -72
Fusiform gyrus (L)	20	-3.91	--	-42	-16	-28 -46
Cerebellum (R)	--	-3.85	--	12	-42	-28 -72
Fusiform gyrus (L)	37	-3.84	--	-28	-68	-16 -71
Inferior frontal gyrus (R)	47	-3.82	--	34	32	-22 -76
Inferior frontal gyrus (R)	47	-3.81	--	42	18	-20 -56
Anterior cingulate cortex (L)	32	-3.79	--	-10	36	22 -68
Cerebellum (L)	--	-3.76	--	-28	-52	-22 -59
Superior temporal gyrus (L)	38	-3.73	--	-34	4	-28 -16
Orbital frontal cortex (R)	32	-3.69	--	18	34	-16 -73
Cerebellum (L)	--	-3.58	--	-4	-62	-26 -61
Medial frontal cortex (R)	10	-3.57	--	10	64	-20 -25
Parahippocampal gyrus (L)	20	-3.54	--	-30	-16	-30 -62
Parahippocampal gyrus (L)	36	-3.52	--	-40	-24	-12 -70
Inferior frontal gyrus (R)	47	-3.51	--	48	34	-16 -84
Parahippocampal gyrus (R)	27	-3.49	--	-40	-24	-12 -70
Superior frontal gyrus (L)	6	-3.46	--	-12	22	48 -64
Middle temporal gyrus (R) ^c	38	-3.43	--	54	12	-36 -62
Brainstem (L)	--	-3.39	--	-4	-34	-12 -80
Orbital frontal cortex (R)	11	-3.38	--	24	42	-26 -73
Insula (R)	13	-3.35	--	42	40	8 -73
Cerebellum (R)	--	-3.35	--	6	-56	-36 -55
Parahippocampal gyrus (R)	35	-3.28	--	28	-28	-20 -85

Region	BA	z	Voxels	χ^2	y^d	z^d	β
Precentral gyrus (R)	4	-3.26	--	38	-10	62	-.64
Inferior frontal gyrus (R)	45	-3.23	--	54	20	0	-.73
Fusiform gyrus (L) ^c	37	-3.22	--	-46	-62	-16	-.71
Middle temporal gyrus (R)	21	-3.16	--	54	-2	-24	-.71
Middle frontal gyrus (L)	8	-3.11	--	-30	24	42	-.70
Superior parietal lobule (L) ^c	7	-3.74	968	-30	-64	60	-.61
Precuneus (R)	31	-3.14	290	12	-66	30	-.63
Superior occipital gyrus (R) ^c	19	-3.23	202	38	-82	36	-.58
Inferior parietal lobule (R) ^c	40	-2.76	119	52	-44	54	-.52
Middle frontal gyrus (L)	46	-2.58	94	-34	30	18	-.58
Insula (L)	13	-2.95	74	-40	18	0	-.69
Inferior parietal lobule (R)	40	-2.62	69	50	-44	46	-.58
Precuneus (L)	31	-2.64	52	-28	-76	24	-.65
Inferior parietal lobule (L)	40	-3.26	38	-68	-34	30	-.48
Precentral gyrus (L)	6	-2.23	36	-66	0	16	-.62
Middle temporal gyrus (R)	37	-2.65	31	64	-50	-12	-.83
Middle occipital gyrus (L)	19	-2.49	25	-42	-86	14	-.36
Postcentral gyrus (L)	2	-2.19	22	-58	-22	52	-.48
Superior temporal gyrus (R)	22	-2.37	21	64	-14	-4	-.47
Hippocampus (R)	--	-3.26	17	24	-36	6	-.60
Insula (L)	13	-2.40	12	-34	26	12	-.30
Inferior temporal gyrus (L)	20	-2.21	11	-56	-12	-34	-.48
Superior frontal gyrus (L)	10	-2.91	10	-24	50	0	-.61
Superior parietal lobule (R)	7	-2.10	10	38	-58	56	-.56
Lateral occipital cortex (R)	39	-2.00	10	38	-68	34	-.57
positive > neutral							
Positive correlations							
Anterior cingulate cortex (R)	33	2.61	11	2	14	18	.49

Notes. Blocked regressors and effects are denoted by upper-case labels (e.g., Incongruent), whereas event-related regressors and effects are denoted by lower-case labels (e.g., incongruent). R = right; L = left; BA = Brodmann's area.

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Montreal Neurological Institute (MNI) coordinates.
Local maxima indented (> 1,000 voxels).
Results driven by neutral comparison condition.