The imprint of childhood adversity on emotional processing in high functioning young adults

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Abstract
Adverse childhood experiences (ACEs) have been acknowledged as risk factors for increased mental health complications in adulthood, specifically increasing susceptibility to developing psychopathology upon exposure to trauma. Yet, little is known regarding the impact of mild ACEs on highly functioning population. In this study forty participants were selected from a group of 366 highly selected military parachute trainees using the self-report “childhood trauma questionnaire,” and classified into two groups of 20 each, with and without ACEs. Behavioral measurements were obtained before and at the peak of an intensive combat training period, including anxiety, depression and executive function assessment. Functional MRI including a negative emotional face perception task was conducted at the first time point. Psychometric and cognitive measurements revealed higher levels of anxiety and depressive symptoms, and more difficulties in executive functioning in the ACE group at baseline. Slower reaction time to emotional faces presentation was found in the ACE group. Lower activation in response to negative emotional faces stimuli was found in this group in bilateral secondary visual areas, left anterior insula, left parietal cortex and left primary motor and sensory regions. In contrast, higher activation in the ACE group was found in the right ventral lateral prefrontal cortex (Vlpfc). No significant differences between groups were detected in the amygdala. To conclude, mild adverse childhood experiences produce long-term sequelae on psychological wellbeing and neurocircuitry even in high functioning population. Brain regions modulated by childhood trauma may instigate avoidance mechanisms dampening the emotional and cognitive effects of intensive stress.

KEYWORDS
adverse childhood experiences, functional MRI, avoidance, PTSD, trauma

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1 | INTRODUCTION

Combat military service engenders unique hazards and stressors and is a major risk factor for negative emotional and behavioral outcomes (e.g., PTSD, Depression, and Suicide) (Aversa, Lemmer, Nunnink, McLay, & Baker, 2014; Fear et al., 2010; Katon et al., 2015; Milliken, Auerchtlonie, & Hodge, 2007; Riddle et al., 2007; Sareen et al., 2013; Sofko, Currier, & Drescher, 2016; Xue et al., 2015). Predeployment attributes have also been shown to contribute to the mental health outcome of deployment (Cabrera, Hoge, Bliese, Castro, & Messer, 2007; Michel, Lundin, & Larsson, 2005). Particularly, maltreatment-related adverse childhood experiences (ACEs; e.g., sexual abuse, physical abuse, neglect) have been widely acknowledged as risk factors for producing emotional and physical health problems in adulthood (Affifi et al., 2008; Felitti, 2009; Li, D’Arcy, & Meng, 2016; McLaughlin et al., 2017; Teicher, Samson, Anderson, & Ohashi, 2016; Wang et al., 2018; Xue et al., 2015), specifically contributing to the vulnerability to the toxic effects of deployment stress (Clancy et al., 2006; Dedert et al., 2009; Xue et al., 2015; Youssef et al., 2013).

The compelling association between childhood maltreatment and psychopathology led to continuous research efforts aimed at revealing neurocognitive mechanisms that may embed latent vulnerability to psychiatric disorders (McCrory, Gerin, & Viding, 2017). Imaging studies have provided clues as to the potential effects of childhood adverse events upon brain structure, function and connectivity in adults with and without psychopathology. These brain modifications have been shown to effect the sensory systems and circuits involved in threat detection, emotional regulation and reward anticipation (Teicher et al., 2016) as well as executive control (McCrory et al., 2017). Strong evidence supports alterations in limbic and frontal areas, two regions involved in socioemotional processing (Hein & Monk, 2017). Specifically, deficits have been observed in the amygdala when viewing emotional faces (Dannlowski et al., 2011; Teicher et al., 2016; van Harmelen et al., 2013), thought to reflect threat hypervigilance or avoidance (McCrory et al., 2017), and in the striatum when anticipating reward (Teicher et al., 2016). Studies on emotion regulation report increased activation of the anterior cingulate cortex (ACC) during active emotion regulation, possibly reflecting greater effortful processing (McCrory et al., 2017). Studies of executive control report increased dorsal ACC activity during error monitoring and inhibition (McCrory et al., 2017). The emotion processing meta-analysis of Hein & Monk (2017) reviewing neural response to threat stimuli, found child maltreatment to be related also to hyper activation of the para-hippocampal gyri, right insula, and right superior temporal gyrus (Hein & Monk, 2017).

Although the connection between maltreatment and comprised mental health is strongly supported, linking specific brain changes to precise ACEs and definite psychiatric disorders seems to be more complicated (Teicher et al., 2016). Current evidence displays a variety of multiple chaining factors (e.g., strong social networks) in addition to the neurophysiological ones, which play a mediator role between toxic stressors early in life and future negative expression (Nurul, Green, Logan-Greene, & Borja, 2015). Adding to this complexity; only a minority of studies have focused on mild versions of ACE attempting to distinguish their potential impact from that of severe trauma (Vai et al., 2018). Alongside with their markedly negative impact on adult well-being (Repetti, Robles, & Reynolds, 2011), mild ACEs have been suggested to engender potential adaptive mechanisms such as enhancement of social cognition capacity (Schweizer et al., 2015), or an increase in neural efficacy during affective theory of mind (Vai et al., 2018). Moreover in some cases it has even been suggested that exposure to childhood adversity of all sorts can lead to post traumatic growth and resilience (Cicchetti, 2010; Woodward & Joseph, 2003).

In light of the data presented above, we examined a group of carefully selected young healthy male elite paratrooper unit volunteers with and without mild ACE at baseline and while undergoing high intensity combat simulation. In a recently submitted manuscript (Kalla et al; submitted) we report elevated baseline anxiety and depressive symptoms as well as poorer executive functions in the subgroup of mild ACE paratroopers compared with their non-ACE peers. Interestingly, the negative effect of combat-simulation training upon these measures was lower in the ACE subgroup compared to their non-ACE counterparts.

In the current study we report brain neural correlates of this unique cohort. We sought differences in neural circuitry between the ACE and non-ACE paratroopers parallel to their emotional and cognitive dissimilarities. This is in line with previous efforts seeking brain alterations after childhood adversity, reflecting toxic effects of early-life stress, or potentially adaptive modifications (Belsky & Pluess, 2013; Moreno-López et al., 2020; Rutter, 2012; Teicher et al., 2016). We also sought an association between baseline brain neurocircuitry and behavioral self-reporting effects of exposure to extreme stressful conditions. To the best of our knowledge, no previous study has examined brain circuitry of such high functioning selected population with and without premorbid childhood adversity, and its putative association with resilience or vulnerability to stress.

2 | METHODS

2.1 | Subjects and procedure

Three hundred and sixty-six highly selected IDF combat parachute trainees were screened for exposure to childhood adversity using the self-report “Childhood trauma questionnaire” CTQ (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997; Bernstein et al., 2003) scale (range: 27–135). Participants were then classified into two groups, comprising 86 subjects, (43 per group) based on the severity of their childhood trauma: An ACE group, the study group, scoring 37 (a score denoting significant childhood adversity) or higher on the CTQ, and a non-ACE group, the control group, scoring 27 on the CTQ (denoting no childhood adversity). All participants were male, aged 18–21, completed 12 years of school, and did not suffer from any psychiatric disorders, determined by the Structured Clinical Interview (SCID) (First, Spitzer, Gibbon, & Williams, 1997). Behavioral measurements were
obtained at two time points, approximately two-month apart, within a 6 month closely monitored combat training period: before (time 1) and at the peak of the intensive combat training period (e.g., war simulation condition, time 2). The war simulation condition is the culmination of the training period, and includes an entire week of extreme physiological and psychological stress supervised by trained army social workers and psychologists. Performance requirements are competitive, and a considerable part of perceived real-life stress results from fear of failing to pass training and consequent certification required for continuing service in the elite unit. The behavioral results of this cohort have been recently submitted for publication (Kalla et al, 2020).

In the current study we use functional MRI (fMRI) to compare neural circuitry between the ACE and control groups, in relation to their emotional and cognitive function at rest and while undergoing high intensity combat simulation. Due to time constraints of the military training schedule, this part of the study comprised only 20 participants per group. These were randomly selected from the larger cohort described above. No difference in behavioral measurement scores was noted between the subgroup of soldiers that participated in this part of the study and whole subject group from which they were randomly selected (for both ACE and non-ACE participants) and Behavioral data at time 2 was collected from 36 soldiers (17 non-ACE, 19 ACE) since four soldiers dropped out at this stage. No difference in behavioral measurement scores between the dropouts and their respective group mates was evident at time 1.

Participants gave informed written consent before taking part in the study. Study was approved by the Hadassah Hebrew University Medical Center and the IDF Ethical committees.

### 2.2 | Behavioral measurements

The following questionnaires were administered at both time points.

- **Beck Depression Inventory (BDI)** (Beck, Steer, & Carbin, 1988) - Self-report questionnaire designed to rate depression severity focusing on affective, behavioral, somatic and cognitive dimensions of depression. Sum raw Scores of 10 to 15 reflect mild depression; 16 to 23 reflect moderate depression and scores of 24 or above indicate severe depression.

- **Spielberger State and Trait Anxiety Inventory (STAI)** (Spielberger, 1983) - Self-report 40 item instrument, measuring two types of anxiety: state anxiety – anxiety about an event, and trait anxiety – anxiety level as a personal characteristic. Higher raw scores are positively correlated with higher levels of anxiety.

- **Behavior Rating Inventory of Executive Function - Adult (BRIEF-A)** (Waid-Ebbs, Wen, Heaton, Donovan, & Velozo, 2012). A standardized instrument that measures adult’s executive functions in everyday environment. It consists of 75 items within nine non overlapping theoretically and empirically derived clinical scales; Inhibit, Self-Monitor, Plan/Organize, Shift, Initiate, Task Monitor, Emotional Control, Working Memory, and Organization of Materials. We used the Global Executive Composite (GEC) which is a summary raw score that incorporates all nine clinical scales.

### 2.3 | fMRI data acquisition

MRI Scans were performed using a 3 T Siemens Skyra scanner (Siemens Healthcare GmbH, Erlangen, Germany) in the Edmond & Lily Safra Center for Brain Sciences Neuroimaging unit. Anatomical MRI sequences included high-resolution T1-weighted images (minimum echo time [TE], repetition time [TR] = 2,300 milliseconds, voxel size of 1 x 1 x 1 mm). Blood oxygenation level dependent (BOLD) fMRI measurements were obtained with a gradient-echo echo-planar imaging sequence using TR = 2 s, TE = 41.8 ms, flip angle = 78°, inplane resolution 2*2 mm, imaging matrix = 96x96, FOV = 192*192 mm, 72 slices, 2 mm each and 163 repetitions.

### 2.4 | fMRI paradigm

We used the “negative emotional face-matching” task (Hariri, Ca, & Mazziotta, 2000): A block-design paradigm consisting of five blocks of a perceptual face-processing task interspersed with six blocks of a sensorimotor control task. We used angry and fearful facial expressions as in Hariri’s original task. Each emotion block had three trials of anger as the target emotion and three trials of fear as the target emotion. During the emotion blocks (faces condition), a target face was presented at the top of the screen and subjects were instructed to select one of two faces presented at the bottom matching the emotional expression as the target face. During the sensory motor blocks (shapes condition), a target ellipse was presented at the top of the screen and subjects were instructed to select one of two ellipses presented at the bottom which was at the same orientation as the target ellipse.

### 2.5 | fMRI data analysis

All functional data analysis was performed using the BrainVoyager QX software package (Brain Innovation). After preprocessing, the functional data sets were spatially normalized into the Montreal Neurological Institute (MNI) template. Data were analyzed by means of a General Linear Model (GLM). Amygdala region of interest (ROI) was defined functionally using whole brain GLM contrast between “faces” and “shapes” condition beyond ACE variable subdivision. The Amygdala location was confirmed by the MNI Yale atlas tool location (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html).

In order to examine entire brain pattern differences between groups, data was spatially smoothed in order to increase Signal to Noise Ratio and support averaging between subjects (spatial Gaussian smoothing, FWHM = 8 mm). Then a whole brain analysis of variance (ANOVA) was performed: group (ACE/non-ACE) X condition (faces/
shapes) interaction. Maps were thresholded using a $p$-value of .01. In order to correct for multiple comparisons, cluster-size threshold (729 mm), based on Monte Carlo simulation ($p < .05$) was used. Beta parameters were extracted from GLM analysis for both conditions ("faces" and "shapes") in the amygdala’s ROI, and in the significant clusters of the whole brain ANOVA analysis. These measures were used for further statistical analysis together with the behavior measurements.

### 2.6 Statistical analysis

All behavioral and imaging statistical analyses were carried out with SPSS 11.01. Two-tailed t tests, comparing between group differences in self-reporting mood and cognition behavioral questionnaires at both time points was conducted. To investigate the effect of ACE, combat training, and their interaction, we conducted a two way MANOVA with repeated measures at two points followed by 2-way ANOVA to explore their effects and interactions.

Response latency and accuracy during fMRI task for each condition were extracted and group differences were analyzed with between-subjects MANOVA.

In order to detect direction of imaging significant effects, post-hoc two-tailed t tests, comparing "faces"—"shapes" for ACEs relative to non-ACEs group were performed. In order to examine a significant contribution of the ACE group variable beyond subjects’ mood levels at rest, on fMRI activation, separate regressions were performed for each of the betas of "faces"—"shapes" of each significant brain cluster found in the whole brain ANOVA interaction analysis. We entered variables into a Hierarchical linear modeling (HLM) by blocks as follows: (a) self-reporting mood assessments (b) ACE group variable. In addition multiple regressions were used to examine relationships between the betas ("faces"—"shapes") of each significant brain cluster found in the whole brain ANOVA interaction analysis and subject’s depression, anxiety and executive functions’ questionnaire scores measured at time 1 and 2. False discovery rate (FDR) was used to correct for multiple comparisons.

### 3 | RESULTS

#### 3.1 Patients’ psychological characteristics

All participants were male, aged 18–21. No significant age differences were found between groups $t(38) = 0.77$. 

Table 1 presents participant scores in the CTQ, and between group differences in self-reporting mood and cognition behavioral questionnaires, including the state and trait anxiety assessments (STAI), depression assessment (BDI) and executive functions assessment (BRIEF-A), taken at time 1 and time 2.

The MANOVA comprising all variables showed a significant difference between the two groups $F(1, 31) = 2.79$, $p < .05$ and a significant effect of combat training (time condition) $F(1, 31) = 9.07$, $p < .001)$. The follow up ANOVA revealed increase at time 2 in state anxiety $F(1, 34) = 33.01$, $p < .001), and in executive functions’ difficulties $F(1, 34) = 5.79$, $p < .05)$. No interaction between group and time was found, yet in state anxiety ANOVA interaction effect was close to significance $F(1,34) = 3.84$, $p = .058$, indicating a lower increase in state anxiety during combat training on the ACE group compared to non ACE’s.

#### 3.2 Group differences in response-latency and accuracy

A between-subjects MANOVA of response-latency and accuracy in "shapes" and "faces" conditions was not significant, yet a further ANOVA revealed significantly slower reaction time in the ACE group

|          | Non ACE |               | ACE        |               | t(df) | p    |
|----------|---------|---------------|------------|---------------|-------|------|
|          | Mean    | SD            | Mean       | SD            |       |      |
| CTQ      | 27      | 0             | 46.54      | 8.37          | 10.38 | .01  |
| BDI      | 4.45    | 3.34          | 10.95      | 8.96          | 2.95  | .24  |
| S-AI     | 31.65   | 7.32          | 37.85      | 12.84         | 1.87  | n.s. |
| T-AI     | 28.70   | 6.68          | 39.35      | 12.97         | 3.26  | .01  |
| BRIEF-A  | 99.00   | 15.24         | 119.95     | 28.64         | 2.89  | .01  |
| BDI      | 5.71    | 6.05          | 11.58      | 7.86          | 2.49  | .05  |
| S-AI     | 42.76   | 11.69         | 44.32      | 11.26         | .40   | n.s. |
| T-AI     | 35.12   | 24.02         | 41.21      | 12.66         | .97   | n.s. |
| BRIEF-A  | 105.71  | 22.28         | 128.89     | 29.93         | 2.61  | .05  |

Note: CTQ, BDI, BRIEF, S-AI, T-AI-scores represent group average of raw scores.

Abbreviations: BDI, Becks Depression Inventory; BRIEF-A, behavior rating inventory of executive function-adult; CTQ, Childhood trauma questionnaire; n.s., not significant; S-AI, State Anxiety Inventory; SD, Standard Deviation; t (df), t test, degrees of freedom; T-AI, Trait Anxiety Inventory.

*Close to significance $p = .07$. 

**TABLE 1** Psychometric self-report questionnaires at time 1 and time 2
in the “faces” condition ("faces" RT mean; F(1, 39) = 4.437, p < .05). No other significant main or interaction effects were found (Table 2).

### 3.3 | Functional imaging results

No significant differences were detected in the bilateral amygdalae ROIs between the ACE and non-ACE groups (right amygdala (β "faces"-β "shapes"; t [35.27] = 0.492, p = .626), left amygdala (β "faces"-β "shapes"; t [35.047] = −1.375, p = .178). Whole brain between groups ANOVA revealed several other clusters that significantly differ between ACE and non-ACE (Table 3). Lower activity in the ACE group was found in bilateral secondary visual regions (Broadman 18, 19), left anterior Insula (Broadman 13), left Parietal cortex (Broadman 40) and in the left primary motor and sensory regions (Broadman 1, 4) (Figure 1). The right ventral lateral prefrontal gyrus (Broadman 44, 47), showed an opposite pattern with higher activity in the ACE group (Figure 2).

### 3.4 | Behavioral and imaging relationships

In order to evaluate the specific impact of childhood trauma on brain activity in the above regions of interest, Hierarchical linear modeling (HLM) analysis of beta values was conducted. Explicitly, we tried to estimate whether ACE contributes to BOLD response beyond depression and anxiety-trait levels measured at baseline. Model included 2 steps: in step 1 trait anxiety and depression scores were entered, and in step 2 ACE variable was added. The variables entered into the model were trait anxiety and depression due to their high correlation with ACE variable, thus potentially suspected to mediate between ACE and brain activity. All regression models (step 1 & 2) were found to be significant indicating that all variables contribute to the BOLD response in each brain region of interest. Interestingly, the ACE variable induced in step 2 was found to significantly contribute to BOLD response beyond mood characteristics contribution in all regions of interest (see Table 4).

Furthermore, in order to examine whether brain activity differences (β faces - β shapes) found in whole brain analysis contribute to behavior- mood and cognition measured at times 1 and 2, multiple regressions were run between all above regions of interest and each questionnaire (time 1 and 2). After applying a 5% false discovery rate (FDR) for time 1, activity level in all brain regions had a significant contribution to all behavioral measurements except state anxiety. In contrast, fMRI signal had no significant contribution to behavioral self-reporting effects measured during exposure to extreme stressful conditions (time 2). Results are presented in detail in Table 5.

### 4 | DISCUSSION

This study demonstrates how mild adverse childhood experiences (ACEs) leave an imprint on brain neuro-circuitry as well as on behavior measurements of carefully selected, young, healthy, high functioning male combat unit volunteers. Despite exposure to mild early life stress, this unique population exhibits a high functioning profile expressed in volunteering to an elite combat unit, passing intensive physical and mental screening tests, and meeting the demanding requirements of an arduous training process. From this perspective our ACE group may be characterized "resilient", previously defined as a positive adaptation (Bonanno, 2004; Cicchetti, 2010; Feder, Nestler, & Charney, 2009), or at least an absence of PTSD (New et al., 2009), in the face of early adversity or various sorts of trauma (Cisler et al., 2013; Rutter, 2012). Nevertheless, the negative impact of early adversity is evident as the self-reporting behavioral baseline assessment results show. Our fMRI results present modulated brain patterns, which we suggest to be part of a neural adaptation mechanism. This mechanism may also be the cause of the between group differences in response to stress reported in the full cohort (Kalla et al, submitted) suggesting less impact of stress on the ACE group.

The fMRI results present relatively lower activity in the ACE group in the extrastriate cortex (BA 18, 19), part of the visual association area. These regions have been previously observed, together with other parts of the visual system to be affected following traumatic events (Esearch & Lanius, 2006; Mueller-Pfeiffer et al., 2013; Teicher et al., 2016). Various interpretations have been offered. In PTSD, reduced activity of the ventral visual system stream has been suggested to reflect a sensory deficits whose origins may be related to dysfunctional attention processes (Mueller-Pfeiffer et al., 2013). Other studies imply that “dissociation” involves dysregulation of the visual and somatosensory modalities (Esearch & Lanius, 2006; Reinders et al., 2003). Moreover reduced activation in the bilateral visual association cortices (as well as in the left anterior insula and left inferior parietal cortex) has been related to an avoidant coping response, as noted in children who experienced maltreatment upon performance of a social rejection-themed emotional Stroop task (Vanessa B. Puetz et al., 2016). Avoidance was also offered in a task similar to the one we applied, when reduced activation was reported.

### TABLE 2 | Both groups average scores of response-latency and accuracy

|       | Latency | Accuracy |
|-------|---------|----------|
|       | Faces M(SD) | Shapes M(SD) | Faces M(SD) | Shapes M(SD) |
| ACE   | 2.40 (0.31) | 1.30 (0.25) | 88% (4.88%) | 95.5% (5.58%) |
| Non ACE | 2.19 (0.33) | 1.19 (0.23) | 88.5% (8.75%) | 96.6% (4.37%) |

Note: Latency—measured in seconds. Accuracy—percentage of success.
Abbreviations: M, mean; SD, standard deviation.
in the visual as well as other several high order cortical regions, in university students with combined experiences of abuse and neglect (Vanessa Bianca Puetz et al., 2019).

The same pattern of relative reduced activity in the ACE group was also noted in the left insula and in the parietal cortex (Brodman 40). The insula is thought to be part of a salience network, and is known to be involved in somatic aspects of emotional state and interoception (i.e., perception of internal bodily state) (Brand & Lanius, 2014) potentially predicting future changes in somatosensory state (Craig, 2009; Critchley, Wiens, Rothsstein, Öhman, & Dolan, 2004). The insula has also been implicated in the processing of aversive emotions such as fear (Etkin & Wager, 2007). Studies on the involvement of the insula in childhood maltreatment reported inconsistent results. For instance, heightened bilateral insular activation to angry faces stimuli was found in victims of family violence (McCrory et al., 2011). In PTSD patients, re-experiencing trauma was positively correlated with activation in the right anterior insula (Brand & Lanius, 2014). In contrary other studies do not find association between insular function and maltreatment (scored using the CTQ) (Heany et al., 2018). Structurally, young people with a history of childhood abuse had significantly reduced cortical thickness in left insula (Lim et al., 2018). In a group of maltreated children, local gyrification deficits were located within the left insula (Kelly et al., 2013).

The parietal cortex (Brodman 40) is known to be involved in recollection of attentional processes (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008) and modulating facial emotions (Surguladze et al., 2010; Zhou et al., 2005). Lower activation was noted in this region in depressed subjects compared with healthy individuals upon

### TABLE 3  Region of interest details according to MNI coordinates, Brodman number and region name.

| Region                               | R/L | BA | X  | Y  | Z  | Voxels | F-value (1,38) |
|--------------------------------------|-----|----|----|----|----|--------|---------------|
| Extrastriate cortex                  | R   | 18 | 19 |   | -86| 32     | 5299          | 10.59         |
| Extrastriate cortex                  | L   | 18 | 19 | -16| -91| 23     | 2533          | 9.7           |
| Ventrolateral prefrontal cortex      | R   | 44 | 53 | 10 | 20 | 973    | 7825          | 8.59          |
| Ventrolateral prefrontal cortex      | R   | 47 | 49 | 23 | -7 | 862    | 10.25         |
| Insula                               | L   | 13 |   | -43| -4 | 1     | 1457          | 9.7           |
| priPrim motor, m sensory             | L   | 4.1| -42| -30| 62 | 4006   | 10.61         |
| Parietal cortex                      | L   | 40 | -47| -33| 37 | 4195   | 10.4          |

Note: This table represents the whole brain analysis of variance (ANOVA): group (ACE/non-ACE) X condition (faces/shapes) interaction. Maps threshold was p-value of .01 and multiple comparisons correction of Monte Carlo simulation (p < .05), cluster-size threshold (729 mm).

Abbreviations: BA, Brodman area; MNI, Montreal Neurological Institute.

### FIGURE 1  Brain clusters showing relative reduced activity in the ACE group. Maps of the five significant whole brain analysis clusters with lower activity in ACE group relative to non-ACE. Each graph presents the β parameters comparing “faces”–“shapes”
exposure to fearful faces stimuli (Surguladze et al., 2010; Zhou et al., 2005). Thus, compromised insular and parietal cortex function, as well as compromised visual association function in response to negative stimuli may reflect distraction and inattentiveness as well as bluntness in emotional perception as part of an "avoidance" mechanism exercised by individuals with a history of ACE to limit negative perceptual input into down-stream processors (Felmingham, Bryant, & Gordon, 2003).

Supporting this notion is the relatively higher activity that was found in the ACE group in the right ventrolateral prefrontal gyrus (Brodman 44, 47). This region is involved with impulse control and is responsible for successful inhibition response as demonstrated in healthy adult participants who completed a demanding Go/NoGo task (Steele et al., 2013). Among anxiety disorder patients, enhanced ventrolateral cortex activation has been associated with less anxiety symptoms, suggesting that the vlPFC is part of a compensatory system helping to effectively regulate initial responses to anxiety-provoking stimuli (Monk et al., 2006). The vlPFC is often recruited during reappraisal tasks, in which participants alter their interpretation of a negative stimulus to minimize its emotional impact (McRae et al., 2010; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). In another study, vlPFC activation corresponded with attentional avoidance of threat in subjects with PTSD but not in trauma exposed control individuals (Fani et al., 2012). In yet another study, the right vlPFC was less integrated into the emotion regulation brain network in resilient women (e.g., exposed to early life stress, yet did not develop later depression), suggesting it to serve an adaptive function in optimizing emotion regulation and inhibitory processes (Cisler...
PTSD patients successfully employed neuro-feedback to downregulate amygdala activation upon presentation of emotionally laden content. Activation in the right vlPFC was increased when subjects were instructed to “regulate” amygdala function compared to when they were instructed to merely “view” trauma related words (Nicholson et al., 2017). This may explain both increased activation in vlPFC and similar amygdala function in ACE compared to non-ACE subjects upon exposure to negative emotional faces. Thus, we suggest the enhanced ventrolateral cortex activation in the ACE group to play an inhibitory role in the avoidance mechanism proposed above in order to minimize the emotional impact of negative stimuli.

Behaviorally, slower reaction time was recorded in ACE group while performing the faces trials. This may be a result of the brain avoidance strategy to limit negative perceptual input into downstream processors as suggested above. Such notion is consistent with earlier studies reporting attention bias distracting from threat-related stimuli in PTSD (Pine et al., 2005), or attentional avoidance of fearful facial expressions in early life adversity population (Humphreys, Kircanski, Colich, & Gottlib, 2016). Furthermore, adults with childhood maltreatment exhibit poorer affective picture recognition, even decades following the experience of abuse (Young & Widom, 2014). The slower reaction time matches the reduced activity in the left primary motor region since the response box was located in the subjects’ right side.

The association between brain modulates and the psychological self-reporting results at baseline, which demonstrated more anxiety and depression symptoms in the ACE group, could be also interpreted through avoidance and blunting mechanisms. Blunted neural response (including in the anterior insula) has been previously observed in adolescents with depression symptomatology upon anticipation to aversive cues (Rzepa, Fisk, & McCabe, 2017). Similarly, anxiety patients tend to use control strategies to prevent emotion from being experienced - to attend to cognitive information at the expense of emotional experience, leading emotion to be avoided or blunted (Mennin, Heimberg, Turk, & Fresco, 2002).

Furthermore, the hierarchical linear modeling (HLM) revealed an additional unique impact of childhood trauma on brain activity beyond what is related to mood characteristics (i.e., depression and trait anxiety). This result emphasizes the broader effect of childhood trauma on brain function including mechanisms, which do not relate directly to negative psychological outcome.

In contrary to the baseline correlations between brain activity and behavioral measurements, brain modulates were not able to predict the recurrent behavioral assessment during the stressful event.

Our results are in contrast to previous research in PTSD and ACE population which largely exhibited increased activation of the limbic system, especially the amygdala, and altered activation of the medial prefrontal gyrus (mPFC), during processing threat related facial expression (Dannlowski et al., 2011; Hein & Monk, 2017; van Harmelen, van Tol, Demenescu, et al., 2013). However, a recent meta-analysis reporting on the neural correlates of CTQ scores depicted marked heterogeneity in findings among studies, and recommends further exploration of effect modifiers (Heany et al., 2018). Interestingly, in a recent study examining the long-term effects of ACE on brain function, increased amygdala activation was noted while comparing non-maltreated participants with either abuse maltreated or neglect maltreated subjects, but not when comparing nonmaltreated participants with all maltreated subjects (Vanessa Bianca Puetz et al., 2019). Moreover, in the same study, increased amygdala activation was observed in the angry vs. neutral face contrast, but not in the fearful vs. neutral face contrast. In our study we used the contrast of “negative emotional faces” (e.g., without separating fearful and angry faces), vs “shapes” to compare ACE and non-ACE subjects, without specifying type of adversity, and did not elicit a differential amygdala response between groups. It would therefore appear that the relationship between ACE, emotional processing and amygdala function may be complex and dependent upon diverse variables.

Our findings are strikingly similar to those reported by Puetz et al (Vanessa B. Puetz et al., 2016). Reduced activation in the left anterior insula, left inferior parietal cortex and bilateral visual association cortices were noted in a group of 10–14 year old maltreated children while performing an emotional Stroop task compared to a group of healthy controls. The authors propose that this pattern denotes implementation of an avoidant coping style and shallower processing which reflects an adaptive mechanism of functional avoidance. This interpretation is consistent with previous studies finding divergent attention away from threat-related stimuli in PTSD as described above (Fani et al., 2012). This mechanism may be enhanced by hyper activation in the vlPFC, indication coinciding and synchronized attention regulation serving to avoid processing of threatening stimuli. It has further been suggested (Vanessa B. Puetz et al., 2016) that brain activation patterns may change over time, consequent to prolonged stress and resultant alteration in neuroendocrine metabolite environment (McEwen, 2012).

Taken together, our study shows that traces of childhood adversity are perceivable on behavior, emotion, and cognitive function as

### Table 5

| Questionnaire | F(df) | R² | p  | ROI          | β    | p    |
|---------------|-------|----|----|--------------|------|------|
| BDI           | 3.05 (7,32) | .4 | < .05 | L BA 18,19 | -.45 | < .05 |
| T-Al          | 2.95 (6,33) | .35 | < .05 | L BA 18,19 | -.35 | n.s  |
| S-Al          | 1.12 (6,33) | .42 | n.s | –            |      |      |
| BRIEF-A       | 2.68 (6,33) | .33 | < .05 | –            |      |      |

Note: ROI's with exclusive significant contribution to the model are presented. Table presents questionnaires which survived Multiple comparisons correction of 5% false discovery rate (FDR). The left column presents the significance of each regression model, and the right column notes which of the ROI's had a significant exclusive contribution to model significance.

Abbreviations: BDI, Becks Depression Inventory; S-Al, State Anxiety Inventory; T-Al, Trait Anxiety Inventory; BRIEF-A, behavior rating inventory of executive function-adult; BA, Brodman Area; L, left; n.s, not significant.

aClose to significance.
well as upon brain activation in carefully selected young, healthy, high functioning male combat unit volunteers. This is of notice since participants themselves rated the adversity they underwent as mild. We suggest that reduced activation in emotional related areas and relatively enhanced activation in inhibitory related areas reflects avoiding coping style.

The coping style applied by our ACE soldiers may be a double-edged sword: On the one hand, it may contribute to their overall high level of function and their relative resilience to stressful conditions. On the other, it entails some deficiency in emotion and cognitive function. It is as yet unclear as to how will they withstand such truly threatening and intimidating conditions that encountered in true war conditions.

The findings from this study need to be considered in light of the following limitations: Firstly, our study sample includes only high functioning adults who differ by occurrence of childhood trauma, therefore generalization of outcomes to other populations, such as low functioning early trauma soldiers, is limited. Secondly, since we did not perform an fMRI scan during peak stress phase of the war simulation condition, we can only hypothesize as to the mechanism of coping with actual stress.

Thirdly, the definition of “high functioning” was based on acceptance into an elite army unit. Although the selection process is considered reliable and serves the army well, it is not known whether the participants exhibit difficulties in other life domains. The high motivation to volunteer and get accepted to an elite unit may also mask the more unpleasant aspects of exposure to ACE.

At last, the stressful event was a controlled one and not comparable to an actual war situation. However, the increase in state anxiety during conditions that encountered in true war conditions.

To summarize, we have shown that childhood maltreatment leaves long-lasting subjective and objective marks upon affected individuals. Future longitudinal, higher powered research is required to provide an answer to what may be the most essential question in PTSD research and management – the capacity to identify vulnerable individuals before exposure to debilitating stress.

CONFLICT OF INTEREST
All authors report no disclosures.

ETHICS APPROVAL AND PATIENT CONSENT STATEMENT
Participants gave written consent before taking part in the study. Study was approved by the Hadassah Hebrew University Medical Center and the IDF Ethical committees.

DATA AVAILABILITY STATEMENT
Data availability statement: These data can be made available upon request, due to privacy issues. If data is requested, a formal data sharing agreement would be required.

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