



# HHS Public Access

Author manuscript

*Biol Psychiatry Cogn Neurosci Neuroimaging*. Author manuscript; available in PMC 2025 July 01.

Published in final edited form as:

*Biol Psychiatry Cogn Neurosci Neuroimaging*. 2024 July ; 9(7): 668–680. doi:10.1016/j.bpsc.2024.03.002.

## Sex differences in response inhibition-related neural predictors of PTSD in recent trauma-exposed civilians

Bibian Borst<sup>1,2</sup>, Tanja Jovanovic, PhD<sup>3</sup>, Stacey L. House, MD, PhD<sup>4</sup>, Steven E. Bruce, PhD<sup>5</sup>, Nathaniel G. Harnett, PhD<sup>6,7</sup>, Alyssa R. Roeckner<sup>1</sup>, Timothy D. Ely BA<sup>1</sup>, Lauren A M. Lebois, PhD<sup>8,9</sup>, Dmitri Young, PhD<sup>10</sup>, Francesca L. Beaudoin, MD, PhD<sup>11,12</sup>, Xinming An, PhD<sup>13</sup>, Thomas C. Neylan, MD<sup>14</sup>, Gari D. Clifford, DPhil<sup>15,16</sup>, Sarah D. Linnstaedt, PhD<sup>13</sup>, Laura T. Germine, PhD<sup>17,18,7</sup>, Kenneth A. Bollen, PhD<sup>19</sup>, Scott L. Rauch, MD<sup>17,20,7</sup>, John P. Haran, MD, PhD<sup>21</sup>, Alan B. Storrow, MD<sup>22</sup>, Christopher Lewandowski, MD<sup>23</sup>, Paul I. Muesy Jr., MD<sup>24</sup>, Phyllis L. Hendry, MD<sup>25</sup>, Sophia Sheikh, MD<sup>25</sup>, Christopher W. Jones, MD<sup>26</sup>, Brittany E. PUNCHES, PhD, RN<sup>27,28</sup>, Lauren A. Hudak, MD, MPH<sup>29</sup>, Jose L. Pascual, MD, PhD<sup>30,31</sup>, Mark J. Seamon, MD<sup>32,31</sup>, Elizabeth M. Datner, MD<sup>33,34</sup>, Claire Pearson, MD<sup>35</sup>, David A. Peak, MD<sup>36</sup>, Robert M. Domeier, MD<sup>37</sup>, Niels K. Rathlev, MD<sup>38</sup>, Brian J. O'Neil, MD<sup>39</sup>, Paulina Sergot, MD<sup>40</sup>, Leon D. Sanchez, MD, MPH<sup>41,42</sup>, Steven E. Harte, PhD<sup>43,44</sup>, Karestan C. Koenen, PhD<sup>45</sup>, Ronald C. Kessler, PhD<sup>46</sup>, Samuel A. McLean, MD, MPH<sup>47,48</sup>, Kerry J. Ressler, MD, PhD<sup>6,7</sup>, Jennifer S. Stevens, PhD<sup>1</sup>, Sanne J H. van Rooij, PhD<sup>1</sup>

<sup>1</sup>Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

<sup>2</sup>Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

<sup>3</sup>Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI, USA

<sup>4</sup>Department of Emergency Medicine, Washington University School of Medicine, St. Louis, MO, USA

<sup>5</sup>Department of Psychological Sciences, University of Missouri - St. Louis, St. Louis, MO, USA

<sup>6</sup>Division of Depression and Anxiety, McLean Hospital, Belmont, MA, USA

<sup>7</sup>Department of Psychiatry, Harvard Medical School, Boston, MA, USA

<sup>8</sup>Division of Depression and Anxiety, McLean Hospital, Belmont, MA

<sup>9</sup>Department of Psychiatry, Harvard Medical School, Boston, MA

<sup>10</sup>University of California San Francisco, San Francisco, CA, USA

<sup>11</sup>Department of Epidemiology, Brown University, Providence, RI, USA

Corresponding Author(s): Sanne J.H. van Rooij, PhD, 69 Jesse Hill Jr Dr SE B22, Atlanta GA 30303, sanne.van.rooij@emory.edu.

Other authors report no biomedical financial interests or potential conflicts of interest.

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

- <sup>12</sup>Department of Emergency Medicine, Brown University, Providence, RI
- <sup>13</sup>Institute for Trauma Recovery, Department of Anesthesiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
- <sup>14</sup>Departments of Psychiatry and Neurology, University of California San Francisco, San Francisco, CA, USA
- <sup>15</sup>Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA, USA
- <sup>16</sup>Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA, USA
- <sup>17</sup>Institute for Technology in Psychiatry, McLean Hospital, Belmont, MA, USA
- <sup>18</sup>The Many Brains Project, Belmont, MA, USA
- <sup>19</sup>Department of Psychology and Neuroscience & Department of Sociology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
- <sup>20</sup>Department of Psychiatry, McLean Hospital, Belmont, MA, USA
- <sup>21</sup>Department of Emergency Medicine, University of Massachusetts Chan Medical School, Worcester, MA, USA
- <sup>22</sup>Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
- <sup>23</sup>Department of Emergency Medicine, Henry Ford Health System, Detroit, MI, USA
- <sup>24</sup>Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN, USA
- <sup>25</sup>Department of Emergency Medicine, University of Florida College of Medicine -Jacksonville, Jacksonville, FL, USA
- <sup>26</sup>Department of Emergency Medicine, Cooper Medical School of Rowan University, Camden, NJ, USA
- <sup>27</sup>Department of Emergency Medicine, Ohio State University College of Medicine, Columbus, OH, USA
- <sup>28</sup>Ohio State University College of Nursing, Columbus, OH, USA
- <sup>29</sup>Department of Emergency Medicine, Emory University School of Medicine, Atlanta, GA, USA
- <sup>30</sup>Department of Surgery, Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA, USA
- <sup>31</sup>Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
- <sup>32</sup>Department of Surgery, Division of Traumatology, Surgical Critical Care and Emergency Surgery, University of Pennsylvania, Philadelphia, PA, USA
- <sup>33</sup>Department of Emergency Medicine, Jefferson Einstein hospital, Jefferson Health, Philadelphia, PA, USA
- <sup>34</sup>Department of Emergency Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

<sup>35</sup>Department of Emergency Medicine, Wayne State University, Ascension St. John Hospital, Detroit, MI, USA

<sup>36</sup>Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA, USA

<sup>37</sup>Department of Emergency Medicine, Trinity Health-Ann Arbor, Ypsilanti, MI, USA

<sup>38</sup>Department of Emergency Medicine, University of Massachusetts Medical School-Baystate, Springfield, MA, USA

<sup>39</sup>Department of Emergency Medicine, Wayne State University, Detroit Receiving Hospital, Detroit, MI, USA

<sup>40</sup>Department of Emergency Medicine, McGovern Medical School at UTHealth, Houston, TX, USA

<sup>41</sup>Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA, USA

<sup>42</sup>Department of Emergency Medicine, Harvard Medical School, Boston, MA, USA

<sup>43</sup>Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, MI, USA

<sup>44</sup>Department of Internal Medicine-Rheumatology, University of Michigan Medical School, Ann Arbor, MI, USA

<sup>45</sup>Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, USA

<sup>46</sup>Department of Health Care Policy, Harvard Medical School, Boston, MA, USA

<sup>47</sup>Department of Emergency Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

<sup>48</sup>Institute for Trauma Recovery, Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

## Abstract

**Background**—Females are more likely to develop posttraumatic stress disorder (PTSD) than males. Impaired inhibition has been identified as mechanism for PTSD development, but studies on the potential sex differences of this neurobiological mechanism and how it relates to PTSD severity and progression are sparse. Here we examined sex differences in neural activation during response inhibition and PTSD following recent trauma.

**Methods**—Participants (N= 205, 138 female sex assigned at birth) were recruited from emergency departments within 72 hours of a traumatic event. PTSD symptoms were assessed 2-weeks and 6-months post-trauma. A Go/NoGo task was performed 2-weeks post-trauma in a 3T MRI scanner to measure neural activity during response inhibition in the ventromedial prefrontal cortex (vmPFC), right inferior frontal gyrus (rIFG), and the bilateral hippocampus. General Linear models were used to examine the interaction effect of sex on the relationship between our regions of interest (ROIs) and the whole brain, and PTSD symptoms at 6-months, and symptom progression between 2-weeks and 6-months.

**Results**—Lower response-inhibition-related vmPFC activation 2-weeks post-trauma predicted more PTSD symptoms at 6-months in females but not in males, while greater response-inhibition-related rIFG activation predicted lower PTSD symptom progression in males but not females. Whole brain interaction effects were observed in the medial temporal gyrus and left precentral gyrus.

**Conclusions**—There are sex differences in the relationship between inhibition-related brain activation and PTSD symptom severity and progression. These findings suggest that sex differences should be assessed in future PTSD studies and reveal potential targets for sex-specific interventions.

### Keywords

Posttraumatic stress disorder (PTSD); sex differences; response inhibition; functional Magnetic Resonance Imaging (fMRI); ventromedial prefrontal cortex (vmPFC); right inferior frontal gyrus (rIFG)

---

## INTRODUCTION

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder one can develop after a traumatic experience that disproportionately affects females, with the lifetime prevalence of PTSD in females at least twofold that of males (1–5). This sex difference in PTSD prevalence cannot be fully attributed to the level of trauma exposure or the type of trauma experienced (5–7). There could, therefore, be neurobiological risk factors that increase the likelihood of developing PTSD in females. Consequently, it is necessary to identify these potential neurobiological risk (or protective) factors for the development of PTSD and how they vary between males and females.

One important putative neurobiological mechanism mediating the development of PTSD is impaired inhibition of fear (8). A hallmark symptom of PTSD is an exaggerated fear response to stimuli that reminds one of their trauma, even in a safe context (8–11). Two brain regions that have been linked to impaired fear inhibition in individuals with PTSD are the ventromedial prefrontal cortex (vmPFC) and the hippocampus. The vmPFC is thought to regulate the fear response by inhibiting the amygdala, which is associated with fear expression (12,13), whereas the hippocampus provides contextual information and, if needed, activates the vmPFC (14,15). Reduced recruitment of these regions during fear inhibition has been demonstrated in individuals with PTSD (16,17).

Inhibition can also occur in relation to cognition and behavior, such as altering one's behavior in response to unexpected events, which is known as response inhibition (18). Studies targeting response inhibition often use a Go/NoGo task to measure withholding responses to a NoGo signal (19). It is suggested that overlapping neural circuits involved in both fear and response-inhibition are impaired in PTSD (20). For example, women who met PTSD criteria showed lower vmPFC activation during a response inhibition task than women without PTSD (21) which in turn negatively correlated with safety signal learning and fear extinction. Furthermore, patients with PTSD demonstrated lower prefrontal (22,23) and lower hippocampal activation (24) during inhibitory trials of these Go/NoGo

tasks compared to controls. Additionally, reduced response-inhibition-related hippocampal activity measured shortly after trauma predicted PTSD symptoms three and 6-months later (25). The right inferior frontal gyrus (rIFG) is another region known to be involved in response inhibition as it plays a role in attention regulation and executive control (26,27). There is recent evidence for reduced inhibition-related rIFG activation predicting PTSD (23), though findings are mixed (25), suggesting that further research into the role of the rIFG and PTSD is needed.

An important unknown is if there are sex differences in the relationship between the neurocircuitry of response inhibition and PTSD development, though there are several studies suggesting the likelihood of sex-specific effects. A prospective study found evidence for sex-differences in the predictability of brain volume and PTSD symptom severity at 6-months, namely that right anterior cingulate cortex thickness, an area with some overlap with the vmPFC, was related to higher PTSD scores in women, but not in men (28). Furthermore, sex-based differences were observed in the neural activation related to a threat, such that men with PTSD showed greater activation in the hippocampus compared to women with PTSD (29), while another study found that women had greater threat-elicited activation in the PFC compared to men (30). Additionally, neural activation during response inhibition is shown to be sex-specific in healthy individuals, with females showing increased activation of the response inhibition network (which included the rIFG) compared to males, as well as increased amygdala activation (31). These studies suggest that there are sex-specific effects in the recruitment of these brain regions during response inhibition. However, no studies to date have looked at sex differences of the neurocircuitry of response inhibition and its relationship to the PTSD symptoms severity and progression following recent trauma.

The current study aimed to examine sex differences in the neurobiology of PTSD during response inhibition. In this manuscript, we will refer to males and females and sex differences. For the purposes of the manuscript, these terms are used as reference to the sex assigned at birth and identified by participants at the time of enrollment in the study. This does not reflect gender identification.

In this large Emergency Department (ED) study (32), participants were recruited within 72 hours of experiencing a traumatic event. fMRI data were collected 2-weeks later using a Go/NoGo task, and PTSD severity was assessed 2-weeks and 6-months after trauma. Our main research question was whether sex moderates the relationship between inhibition-related activation in the vmPFC, hippocampus, and rIFG 2-weeks after trauma and PTSD symptom severity and progression 6-months after trauma. We hypothesized that less inhibition-related activation in our ROIs, i.e., the vmPFC, bilateral hippocampus, and rIFG, is associated with more PTSD symptoms 6-months post-trauma (PTSD severity) and that biological sex moderates this relationship, such that females demonstrate stronger negative relationships between brain activation and PTSD outcome than males. Secondly, we hypothesized that less inhibition-related activation in our ROIs is related to less symptom reduction from 2-weeks to 6-months post-trauma (PTSD progression), and that biological sex moderates this relationship, such that females demonstrate stronger negative relationships between brain

activation and PTSD outcome than males. Finally, whole brain analyses were performed to identify associations outside our predefined ROIs.

## METHODS AND MATERIALS

### Participants

Participants were recruited from multiple EDs across the United States as part of the large, longitudinal AURORA study (Advancing Understanding of RecOvery afterR traumA) within 72 hours of experiencing a traumatic event (further details in (32)). Participants who sought care in the ED after experiencing physical and sexual assault, motor vehicle collision, > three-meter falls, or mass casualty incidents automatically qualified for study enrollment. Participants with other kinds of traumatic events (such as falls < three meters, burns or poisoning) were screened to see whether a) they experienced the event as involving actual or threatening serious injury, sexual violence, or death by either directly experiencing it themselves, witnessing it, or learning about the trauma and b) the exposure was qualified as a reasonable qualifying event by the research assistant.

A subgroup of participants was recruited for in-person sessions for “deep phenotyping” including a functional MRI 2-weeks after the traumatic event. The AURORA “Freeze 4” psychometric release included N=429 participants who had functional MRI data of the response inhibition task collected at this 2-week visit. Final MRI data were available for N=330 participants after excluding data with benign anatomical abnormalities (N=7), excessive motion (N=33), technical problems with, e.g., stimulus display or response recording (N=14), or poor behavioral performance (N=45) on the task (<70% correct Go trials (N=41) or <70% correct NoGo trials, low accuracy is indicative of the person not paying attention to the task, because generally the task is performed at >90% accuracy). Out of those participants, N=205 (138 females, 67%) provided data on PTSD symptoms at 2-weeks and 6-months and were used in the data analysis of this study. Two studies have used data from the same Go/NoGo task. Stevens et al included the Go/NoGo task and the same ROIs to identify biotypes for post-trauma risk (33). Van Rooij et al defined a resilience factor across all psychological outcome measures (including PTSD symptoms) and determined the predictive role of neuroimaging correlates including response inhibition (34). The Institutional Review Board (IRB) of the University of North Carolina (UNC) approved the study protocol, and other sites created either reliance agreements or parallel IRBs. All participants provided written informed consent.

### Demographics and clinical data collection

Demographic data were collected at the EDs and included, amongst others, age, sex assigned at birth, race, trauma type, and highest completed levels of education. Item-level clinical data were collected with self-reported surveys in the ED, and follow-up surveys were assessed at 2-weeks, eight weeks, three months, 6-months, and 12-months after trauma. Current gender identification was the same as the assigned sex at birth for all participants included in the study. PTSD symptoms were assessed using the PTSD Symptom Checklist for DSM-5 (PCL-5), a 20-item questionnaire in which participants self-reported the presence and severity of posttraumatic stress symptoms. Our primary analysis focused on PTSD

symptoms at 2-weeks to measure early post-trauma symptoms, during which fMRI data were also acquired, and follow-up assessment of symptoms 6-months post-trauma to align with prior studies (23,25,28) and following previous research showing a divergence of risk and resilient groups around 6-months post-trauma (35). Additionally, our secondary ROI analysis assessed PTSD symptoms at 12-months to analyze potential relationships over a longer time period (Supplementary materials S3). To measure the change in PTSD symptoms over time, the PCL-5 scores from 2-weeks were subtracted from the PCL-5 scores at 6-months or 12 months.

## Functional MRI

**Response inhibition task**—Response inhibition was measured with a Go/NoGo task following our prior work (21). Either an X or an O was displayed to the participants. Each trial began with a 500-millisecond appearance of a white fixation cross on a black background, followed by either an X or an O on the screen for 1000 milliseconds (Go Trials). Participants were required to respond as quickly as possible with a 1 for an X sign and a 2 for an O sign. In a third of the trials, the background turned red (NoGo trials), and participants had to refrain from responding. This was followed by a blank screen for 750 milliseconds. There was no jitter in the intertrial interval, which was always 750 milliseconds. The task was divided into four runs, with each run consisting of 26 Go trials, 13 NoGo trials, and 14 blank trials randomly distributed, separated by three 20-second breaks. On average, 106 Go trials (min 104, max. 109) and 48 NoGo trials (min 45, max 50) were performed. A blood oxygen level-dependent (BOLD) contrast for NoGo > Go trials was created to measure response-inhibition activation. (See Figure S1)

**Brain imaging acquisition and analysis**—Participants were screened for MRI ineligibility or other exclusion criteria. fMRI scans were performed with 3T scanners at five different sites, i.e., Emory University, McLean Hospital, Temple University, Wayne State University, and Washington State University in St. Louis. We collected T1-weighted structural scans using a multi-echo magnetization prepared rapid acquisition gradient echo (ME-MPRAGE) technique with consistent parameters for a 1mm isotropic resolution across sites. Functional scans were also collected using the same parameters, but the scan time varied slightly between the scanners at the five sites (see Supplementary Table S1). For further details about the scan parameters, see (33,36). Scanner site was included as a covariate for all analyses using dummy variables.

**ROI analyses**—The BOLD contrast estimates for correct NoGo>Go were extracted for the bilateral hippocampus, rIFG, and the vmPFC as the regions of interest (ROI) following prior studies. The vmPFC was anatomically defined based on previous study findings (6mm sphere around  $-4, 44, -4$ ; (21), and the bilateral hippocampus was anatomically defined based on the Hammers atlas (37), and the rIFG was anatomically defined (Automated Anatomical Labeling Atlas) (25).

To test our hypothesis that less inhibition-related activation in our ROIs is associated with more PTSD symptoms 6-months after trauma, we created a general linear model with all three ROIs as independent variables, age, sex assigned at birth, and scanner

site as covariates, and PTSD symptoms at 6-months as the dependent variable. Age and sex were added as covariates to the first model, as both have been found to influence neural activation during response inhibition (38,39). To test our second hypothesis that sex moderates the relationship between ROI activation and PTSD symptoms, we introduced sex as a moderator for each ROI (interaction term) in a second model. If a significant effect was observed, sensitivity analyses for effects of trauma were performed by including trauma type, childhood trauma, and baseline PTSD (2-weeks post-trauma) as covariates. Then, post-hoc correlation analyses for individual ROIs were conducted with age and site again as covariates. Secondly, similar GLM analyses were used to test the hypothesis that less activation in our ROIs was associated with a smaller improvement in PTSD symptoms from 2-weeks to 6-months. All models were tested on the assumption of collinearity, and it was indicated that multicollinearity was not a concern ( $VIF < 2.5$  for all variables in the models). Similar supplementary analyses were performed for PTSD symptoms 2-weeks and 12-month post-trauma (Results in Supplementary Material S2-S4).

**Whole brain analyses**—Whole brain regression analyses were performed to examine the correlation between response-inhibition-related activation and PTSD severity and PTSD progression, for our main outcome of 6-months. Scan site, age, and sex were added as covariates in both models. A cluster-defining threshold of  $p < 0.005$  with a cluster-level family-wise error (FWE)-level correction of  $p < 0.05$  was used. Similar to our ROI analyses, in a second step the interaction term with sex was added to the models. When a significant interaction effect was observed, follow-up analyses were performed separately for males and females within the significant cluster (within a mask for the cluster, using  $p < 0.005$ ).

## RESULTS

### Participants

Demographic information and clinical characteristics are presented in Table 1. Most participants experienced a motor vehicle collision (75% of females, 66% of males). Male and female participants in our study were comparable in age, race, income, education level, trauma type, pre-trauma depression rates, and levels of childhood trauma. There were no sex differences in PTSD symptom improvement between 2-weeks and 6-months. Females had higher PTSD symptom severity at 2-weeks and 6-months, and a higher proportion of females met DSM-5 criteria for PTSD at these timepoints.

### Go/NoGo Task behavioral results

The behavioral results for the Go/NoGo task showed high accuracy levels for both males and females (average Go Trials correct: males 93.8% correct, females 95.4% correct; NoGo Trials correct: males 98.5% correct, females 99.1% correct) and no significance difference in performance between males and females was found (Go Trials  $t = 1.410$ ,  $p = 0.159$ ; NoGo  $t = 1.85$ ,  $p = 0.066$ ).

### fMRI ROI analyses

**PTSD symptoms at 6- and 12-months**—The first model using the three ROIs as independent variables and site, sex, and age as covariates significantly predicted PTSD

symptoms at 6-months (Table 2a;  $F_{(9,195)}=2.217$ ,  $R^2=0.093$ ,  $R^2$ . Adj.=0.051,  $p=0.023$ ). However, no individual ROI significantly contributed to the model, and only the main effect of sex did ( $\beta=-0.429$ ,  $t_{(195)}=-2.867$ ,  $p=0.005$ ), with greater levels of PTSD symptoms in females than males.

The second model (Table 2b), in which interaction terms between sex and the ROI activation were added, again significantly predicted PTSD symptoms (Table 2b;  $F_{(12,192)}=2.449$ ,  $R^2=0.133$ ,  $R^2$ . Adj.=0.109,  $p<0.001$ ), and explained an additional 4% of the variance. The interaction between sex and vmPFC activation contributed significantly to the model ( $\beta=0.386$ ,  $t_{(192)}=2.691$ ,  $p=0.008$ ). This interaction effect persisted when trauma type, childhood trauma (CTQ), and baseline PTSD scores were added as additional covariates to the model ( $\beta=0.378$ ,  $t_{(119)}=2.456$ ,  $p=0.015$ ). Post-hoc correlation analyses (Figure 1) showed that lower vmPFC activation correlated significantly with more PTSD symptoms at 6-months in females ( $r=-0.253$ ,  $p=0.004$ ) but not in males ( $r=-0.061$ ,  $p=0.650$ ). The bilateral hippocampus and the rIFG were not significantly correlated with PTSD symptoms at 6-months for either sex (Supplementary Figure S5).

The model predicting PTSD symptoms at 12-months (see Supplementary Results S3) also showed a significant interaction between vmPFC activation and sex, while the overall model was not significant.

**Progression in PTSD symptoms**—The first model using the three ROIs as independent variables and site, sex, and age as covariates did not predict PTSD symptom change from 2-weeks to 6-months (Table 3a; ( $F_{(9,177)}=0.955$ ,  $R^2=0.018$ ,  $R^2$ -adj.= $-0.0323$ ,  $p=0.955$ ).

The second model (Table 3b), in which interaction terms between sex and the ROI activation were added, did again not significantly predict PTSD symptom change ( $F_{(12,174)}=1.502$ ,  $R^2=0.094$ ,  $R^2$ -adj.=0.031,  $p=0.127$ ), but both the interaction between sex and rIFG activation ( $\beta=-0.483$ ,  $t_{(174)}=-3.079$ ,  $p=0.002$ ) and between sex and vmPFC activation ( $\beta=0.340$ ,  $t_{(174)}=-2.212$ ,  $p=0.028$ ) significantly contributed to the model. The interaction effect between sex and rIFG activation persisted when trauma type and childhood trauma were added to the model ( $\beta=-0.435$ ,  $t_{(165)}=-2.765$ ,  $p=0.006$ ), whereas this was not the case for the interaction between sex and vmPFC activation ( $\beta=0.276$ ,  $t_{(165)}=-1.181$ ,  $p=0.072$ ). Post-hoc correlation analyses per ROI (Figure 2) showed that greater rIFG activation correlated significantly with more improvement in PTSD symptoms in males ( $r=-0.338$ ,  $p=0.013$ ), but not in females ( $r=0.109$ ,  $p=0.230$ ). No significant correlations between activation in the vmPFC or hippocampus and PTSD symptom change were found in either sex (Supplementary Figure S6). No significant interactions were found in the 12-month model (Supplementary Results S3)

## Whole brain analyses

**PTSD symptoms at 6-months**—The first model for PTSD severity showed no significant main results. Notably, a preliminary negative main effect ( $p<0.005$ ,  $k=133$ ) was observed in one of the ROIs, the rIFG. However, this finding did not survive cluster-level FWE-correction (Table 4).

The second model, in which sex was added as an interaction term, showed a significant interactive effect of sex in the right middle temporal gyrus (rMTG;  $p < 0.005$ ,  $k = 194$ ; cluster-level  $p_{FWE} = 0.033$ ; Table 4; Figure 3a). Follow-up analyses within the significant cluster separately for males and females showed a significant cluster with a negative correlation for males, but not females. To visualize the direction of the interaction effect, individual contrast estimates for the rMTG cluster were extracted and showed that greater rMTG activation in males but lower activation in females was associated with greater PTSD severity (Figure 3b).

**Progression in PTSD symptoms**—The model for PTSD progression showed no significant main results, but two preliminary negative associations in the left precentral gyrus ( $p < 0.005$ ,  $k = 100$ ), and rIFG ( $p < 0.005$ ,  $k = 148$ ) that did not survive cluster-level FWE correction were observed (Table 5).

The second model, in which sex was added as an interaction term, showed a significant interactive effect of sex in the left precentral gyrus ( $p < 0.005$ ,  $k = 231$ , cluster-level  $p_{FWE} = 0.009$ ; Table 5, Figure 4a). Follow-up analyses within the significant cluster separately for males and females showed a significant cluster with a negative correlation for males, but not females. To visualize the direction of the interaction effect, individual contrast estimates for the left precentral gyrus were extracted and showed that less negative left precentral gyrus activation was correlated with more improvement in PTSD symptoms in males but not in females (Figure 4b).

## DISCUSSION

This prospective fMRI study examined sex differences in the neurobiology of PTSD severity and progression in recently trauma-exposed civilians, specifically focusing on measuring these differences during response inhibition. We demonstrated the moderating role of sex by showing that lower response-inhibition-related vmPFC activation 2-weeks post-trauma predicted greater PTSD symptoms at 6-months in females but not in males, while greater response-inhibition-related rIFG activation predicted more improvement of PTSD symptoms over 6-months in males but not in females. Whole brain analyses further showed the moderative effect of sex, with more rMTG activation predicting greater 6-month PTSD severity in males with an opposite pattern in females. Furthermore, less negative activation of left precentral gyrus predicted more improvement of PTSD symptoms in males with no association observed in females. Response inhibition-related activation of the hippocampus and rIFG 2-weeks post-trauma did not predict PTSD symptoms at 6-months, nor did vmPFC or hippocampal activation predict change in PTSD symptoms over 6-months. This large prospective study supports earlier findings that hypoactivation of vmPFC and rIFG during response inhibition may help identify individuals at risk of developing PTSD (21,23) and is the first to show the importance of sex in the predictability of these relationships between brain activation and PTSD outcomes.

Our findings that lower activation of the vmPFC during a response inhibition task was related to increased severity of PTSD symptoms 6-months post-trauma in females supports our hypothesis and is in line with previous findings that individuals with PTSD show decreased activation in prefrontal regions during Go/NoGo tasks (21,22). Female sex and

lower vmPFC activation were already related to higher PTSD symptoms soon after trauma at 2-weeks (in Supplementary Materials S2), whereas we did not observe a difference in vmPFC activation between males and females. Even after correcting for this baseline difference, our findings suggest that, specifically, women with lower vmPFC activation are at greater risk of PTSD. Furthermore, women with PTSD showed impaired vmPFC activation (21) or mPFC activation (40) during response inhibition and decreased functional connectivity between the vmPFC and amygdala when processing emotional stimuli (41). Interestingly, a study by Powers and colleagues found similar results that impaired vmPFC activation during reactive inhibition may predict PTSD symptom severity at 6-months, but these findings did not hold after controlling for sex (23). However, van Rooij et al. did not observe an association between vmPFC and the development of PTSD, using the same Go-No task in an ED study (25). An explanation for this could be the smaller sample size (N=31), which did not allow for analyses of sex differences.

Prior research has suggested sex differences in the role of the vmPFC or rACC in PTSD. In an ED study, Roeckner et al. showed that rACC thickness was positively correlated with PTSD severity and avoidance symptoms 6-months post-trauma in females (28), and several studies linking the vmPFC to PTSD included only women (21,40,41). A possible explanation for sex differences in the neural activation in the (fear) inhibition networks is sex-specific hormones. Rodent studies found that estradiol, a primary female sex hormone, plays a role in dendritic growth in the vmPFC and the projections to the amygdala (42,43). Another study in rats found that the administration of estradiol facilitated extinction recall and increased c-Fos (a marker for cellular activity) expression in the vmPFC (44), suggesting that upregulation of the vmPFC through estradiol might have a protective function. Furthermore, hormone fluctuations in women are also thought to modulate vmPFC activation during both response inhibition (45) and fear extinction and could potentially play a role in PTSD symptom severity (44,46,47). These hormonal differences and their role in the (fear) inhibitory network could explain why men and women process fear differently, why women are at an increased risk of developing PTSD, and how the vmPFC may play a critical role. Future trauma studies could aim to upregulate the vmPFC in females to see if the beneficial results found in rodents can be replicated in humans and if this could be a potential sex-specific target for interventions.

Similar to the 6-month outcome, a sex by vmPFC interaction was observed in model predicting 12-month PTSD symptoms, with lower vmPFC activation predicting greater PTSD symptoms in females but not males. However, unlike the 6-month model, the overall model was not statistically significant in predicting PTSD severity or progression. One explanation could be the smaller sample size for the 12-month analysis, resulting in lower statistical power. Additionally, it is possible that the brain correlates are less indicative of more chronic PTSD, as symptoms at 12 months might represent a more clinically stable representation of PTSD (7,48). Lastly, there may be unknown confounding variables that affect PTSD symptoms in the months between the two timepoints, such as participants seeking treatment or experiencing a new traumatic event.

The rIFG has less frequently been implicated in PTSD. However, our finding that greater rIFG activation during response inhibition predicted lower PTSD progression (or more

PTSD symptom improvement) in males but not in females supports some prior research. Dysfunction of the rIFG region has been linked to both emotional and cognitive processing deficits in PTSD patients (49). Veterans with PTSD showed lower rIFG activation during inhibition task with contextual cues than veterans and civilians without PTSD (50). Another study with predominantly (65%) male participants demonstrated that greater rIFG activation during a response inhibition task predicted less PTSD symptoms at 6-months (23). An important recent study on emotional processing showed that greater rIFG activation 1-month after trauma predicted more improvement in PTSD symptoms 14-months later (51), which aligns with our current findings. Greater rIFG activation was specific to the progression but not the severity of symptoms. Given its role in emotional and response regulation(52,53), it can be postulated that greater rIFG activation indicates better overall regulation, which could be beneficial for recovery after trauma exposure and therefore specifically associated with lower progression of symptoms. These studies suggest that the rIFG, as both a cognitive and emotional control region, might be implicated in PTSD resilience and with a more robust association effect in men. There is, however, limited research on the sex-specific role of the rIFG in individuals with PTSD. Only one study showed a sex-specific effect on inhibitory control, and the rIFG in which trauma-exposed males showed greater rIFG activation and better inhibitory control than trauma-exposed females (54). This suggests that greater IFG activation may play a particular role in preserving inhibitory control in traumatized males, which aligns with the findings of this study.

The whole brain analyses further show the moderative effects of sex in the left precentral gyrus and rMTG. The left precentral gyrus is part of the premotor cortex and has been inferred with both response inhibition (27,55,56) and PTSD symptoms (57,58). The MTG is known to play a role in action-feedback monitoring, an essential part of response inhibition, (59), and white-matter alterations have been found in individuals with PTSD (58)(60). There are known sex differences in the recruitment of the response inhibition or “stopping” network, specifically in the areas that are responsible for motor control, which includes both the rMTG and precentral gyrus, such that females exhibit greater levels of activation (31). Our results suggest that these sex-specific differences play a role in the progression and severity of PTSD symptoms, but more research is needed to understand this relationship specific to these brain regions.

We did not find evidence of hippocampal activation predicting PTSD symptom severity or improvement of symptoms over time. This was contrary to our hypothesis as lower hippocampal activation during a Go/NoGo task was found in several studies in individuals with PTSD and predicted PTSD outcomes three and 6-months post-trauma (24,25). One notable difference between these prior studies and the current study is the comparatively low levels of childhood trauma. This is particularly relevant as prior research has shown an association between greater levels of childhood trauma and decreased inhibition-related activation in the hippocampus (in COMT genotype Met carriers) (24). Furthermore, childhood trauma has consistently been linked to lower hippocampal volumes (61–63) and has been associated with altered hippocampal functioning (61,64,65). It is, therefore, possible that greater levels of childhood trauma explain the association with the development of PTSD in earlier ED studies but not in the current study. Evidently, more research is

needed to fully understand the effects of childhood trauma on this association. Importantly, our other findings remained significant after controlling for childhood trauma.

An important strength of this study is the large sample size, which allowed us to test the interaction of sex, and examine males and females separately in post-hoc analyses while maintaining power. Prior studies showed the predictive role of the ROIs across the sample, whereas we only observed effects for either females or males. The scatterplots showed absence of associations in the opposite sex thereby increasing variability and washing out a significant association. Notably, most prior studies were conducted in (predominantly) male or female samples, which is the most plausible explanation for our lack of showing findings across the sample. A possible explanation for this sex-specific risk is hormonal differences between males and females (42,47,66). A limitation of our study is that we did not have sufficient hormonal data available to test if the moderative effect of sex remained after adding the hormonal status as a covariate. It would, therefore, be of interest to examine this in future research. Another aspect of the study, which is both a limitation and a strength, is that there is not much variation in the type of trauma. Women are known to experience more interpersonal trauma than men, and this type of trauma is known to have a high prevalence of development of PTSD compared to other types of trauma (67–69). In our study, only around ten percent of the experienced trauma was interpersonal and was not different between males and females (Table 1). It would, therefore, be interesting to replicate this study in a population with a higher rate of interpersonal trauma. Lastly, as our ROIs have also been linked to other cognitive processes, for instance, vmPFC and rIFG activation during an emotional regulation task predicted symptom change after treatment (70). Further investigation of brain activation during emotion regulation and sex-specific effects in predicting PTSD progression is of great interest. Also, the use of other inhibition tasks, which would allow for investigation of correct (vs incorrect) responses or use of contextual information during inhibition (proactive inhibition) (23) could provide a more detailed assessment of response inhibition-related neural predictors and potential sex differences.

In conclusion, this study identified sex differences in neural predictors for PTSD symptom severity and progression during a response-inhibition task. Our study showed the importance of considering sex in future PTSD research, as sex differences on a neurobiological level are still poorly understood. Using our knowledge of how brain activity relates to the development of PTSD symptoms separately for males and females can further enhance our search for neurobiological indicators of PTSD after traumatic experiences. This may lead to a better understanding of which individuals are at a higher risk of developing PTSD after trauma exposure and could lead to better, and potentially, sex-specific treatment or prevention.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGMENTS

The investigators wish to thank the trauma survivors participating in the AURORA Study. Their time and effort during a challenging period of their lives make our efforts to improve recovery for future trauma survivors possible.

This project was supported by NIMH under U01MH110925 and K01MH121653, the US Army MRMC, One Mind, and The Mayday Fund. The content is solely responsibility of the authors and does not necessarily represent the official views of any of the funders.

Data and/or research tools used in the preparation of this manuscript were obtained from the National Institute of Mental Health (NIMH) Data Archive (NDA). NDA is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in mental health. Dataset identifier(s): [NIMH Data Archive Collection ID(s) or NIMH Data Archive Digital Object Identifier (DOI)]. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or of the Submitters submitting original data to NDA.

## FINANCIAL DISCLOSURES

Dr. Lebois reports unpaid membership on the Scientific Committee for the International Society for the Study of Trauma and Dissociation (ISSTD). ISSTD was not involved in the analysis or preparation of the manuscript.

Dr. Neylan has received consulting income from Jazz Pharmaceuticals.

In the last three years Dr Clifford has received unrestricted donations from AliveCor Inc, Amazon Research, the Center for Discovery, the Gates Foundation, Google, the Gordon and Betty Moore Foundation, MathWorks, Microsoft Research, Nextsense Inc, One Mind Foundation, the Rett Research Foundation, and Samsung Research. Dr Clifford has financial interest in AliveCor Inc and Nextsense Inc. He also is the CTO of MindChild Medical and CSO of LifeBell AI and has ownership in both companies. These relationships are unconnected to the current work.

Dr. Germine is on the board of the Many Brains Project. Her family also has equity in Intelrad Medical Systems, Inc.

Dr. Rauch reported serving as secretary of the Society of Biological Psychiatry; serving as a board member of Community Psychiatry and Mindpath Health; serving as a board member of National Association of Behavioral Healthcare; serving as secretary and a board member for the Anxiety and Depression Association of America; serving as a board member of the National Network of Depression Centers; receiving royalties from Oxford University Press, American Psychiatric Publishing Inc, and Springer Publishing; and receiving personal fees from the Society of Biological Psychiatry, Community Psychiatry and Mindpath Health, and National Association of Behavioral Healthcare outside the submitted work.

Dr. Sheikh has received funding from the Florida Medical Malpractice Joint Underwriter's Association Dr. Alvin E. Smith Safety of Healthcare Services Grant; Allergan Foundation; the NIH/NIA-funded Jacksonville Aging Studies Center (JAX-ASCENT; R33AG05654); and the Substance Abuse and Mental Health Services Administration (1H79TI083101-01); and the Florida Blue Foundation.

Dr. Jones has no competing interests related to this work, though he has been an investigator on studies funded by AstraZeneca, Vapotherm, Abbott, and Ophirex.

Dr. Datner serves as Medical Advisor and on the Board of Directors for Cayaba Care.

Dr. Harte has no competing interest related to this work, though in the last three years he has received research funding from Aptinix and Arbor Medical Innovations, and consulting payments from Aptinix.

Dr. Koenen's research has been supported by the Robert Wood Johnson Foundation, the Kaiser Family Foundation, the Harvard Center on the Developing Child, Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, the National Institutes of Health, One Mind, the Anonymous Foundation, and Cohen Veterans Bioscience. She has been a paid consultant for Baker Hostetler, Discovery Vitality, and the Department of Justice. She has been a paid external reviewer for the Chan Zuckerberg Foundation, the University of Cape Town, and Capita Ireland. She has had paid speaking engagements in the last three years with the American Psychological Association, European Central Bank, Sigmund Freud University – Milan, Cambridge Health Alliance, and Coverys. She receives royalties from Guilford Press and Oxford University Press.

In the past 3 years, Dr. Kessler was a consultant for Cambridge Health Alliance, Canandaigua VA Medical Center, Holmusk, Partners Healthcare, Inc., RallyPoint Networks, Inc., and Sage Therapeutics. He has stock options in Cerebral Inc., Mirah, PYM, and Roga Sciences.

Dr. McLean has served as a consultant for Walter Reed Army Institute for Research, Arbor Medical Innovations, and BioXcel Therapeutics, Inc.

Dr. Ressler has performed scientific consultation for Bioxcel, Bionomics, Acer, and Jazz Pharma; serves on Scientific Advisory Boards for Sage, Boehringer Ingelheim, Senseye, and the Brain Research Foundation, and he has received sponsored research support from Alto Neuroscience.

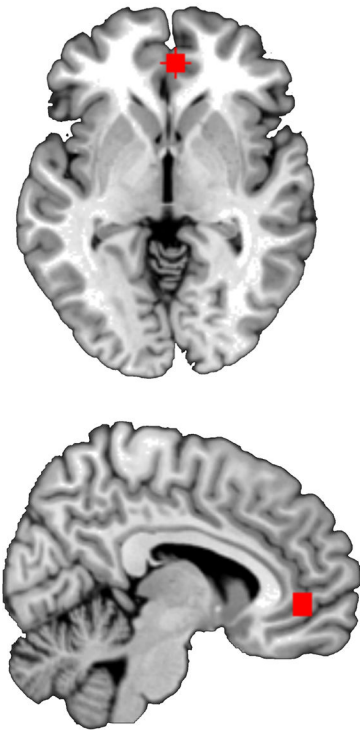
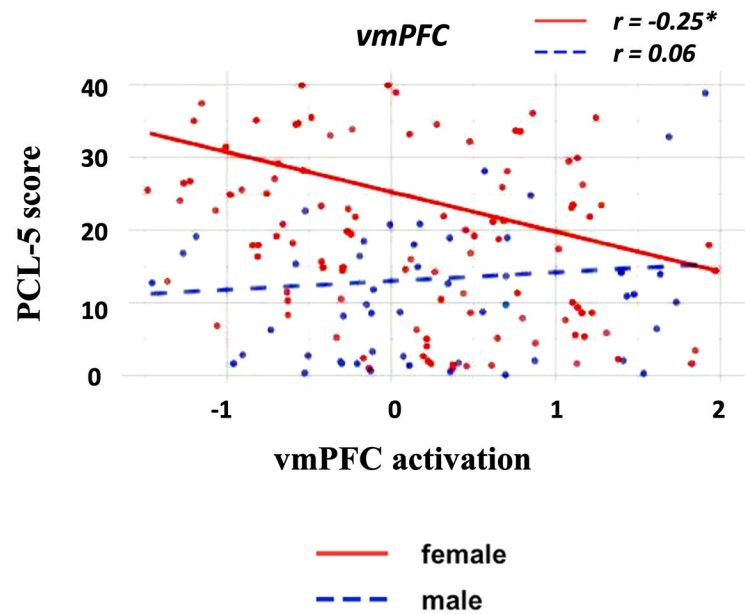
## REFERENCES

1. Christiansen DM, Berke ET (2020): Gender- and Sex-Based Contributors to Sex Differences in PTSD. *Curr Psychiatry Rep* 22: 1–9. [PubMed: 31912372]
2. Seedat S, Scott KM, Angermeyer MC, Berglund P, Bromet EJ, Brugha TS, et al. (2009): Cross-national associations between gender and mental disorders in the World Health Organization World Mental Health Surveys. *Arch Gen Psychiatry* 66: 785–795. [PubMed: 19581570]
3. Shalev AY, Gevonden M, Ratanatharathorn A, Laska E, van der Mei WF, Qi W, et al. (2019): Estimating the risk of PTSD in recent trauma survivors: results of the International Consortium to Predict PTSD (ICPP). *World Psychiatry* 18: 77–87. [PubMed: 30600620]
4. Tolin DF, Foa EB (2008): Sex differences in trauma and posttraumatic stress disorder: A quantitative review of 25 years of research. *Psychol Trauma Theory, Res Pract Policy S*: 37–85.
5. Olf M, Langeland W, Draijer N, Gersons BPR (2007): Gender differences in posttraumatic stress disorder. *Psychol Bull* 133: 183–204. [PubMed: 17338596]
6. Breslau N, Chilcoat HD, Kessler RC, Peterson EL, Lucia VC (1999): Vulnerability to assaultive violence: further specification of the sex difference in posttraumatic stress disorder. *Psychol Med* 29: 813–821. [PubMed: 10473308]
7. Kessler RC (1995): Posttraumatic Stress Disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 52: 1048. [PubMed: 7492257]
8. Jovanovic T, Kazama A, Bachevalier J, Davis M (2012): Impaired safety signal learning may be a biomarker of PTSD. *Neuropharmacology* 62: 695–704. [PubMed: 21377482]
9. Maren S, Phan KL, Liberzon I (2013): The contextual brain: Implications for fear conditioning, extinction and psychopathology. *Nat Rev Neurosci* 14: 417–428. [PubMed: 23635870]
10. Jovanovic T, Norrholm SD, Blanding NQ, Davis M, Duncan E, Bradley B, Ressler KJ (2010): Impaired fear inhibition is a biomarker of PTSD but not depression. *Depress Anxiety* 27: 244–251. [PubMed: 20143428]
11. Jovanovic T, Norrholm SD, Fennell JE, Keyes M, Fiallos AM, Myers KM, et al. (2008): Posttraumatic stress disorder may be associated with impaired fear inhibition: Relation to symptom severity. *Psychiatry Res* 167: 151–160.
12. Corcoran KA, Quirk GJ (2007): Recalling safety: Cooperative functions of the ventromedial prefrontal cortex and the hippocampus in extinction. *CNS Spectr* 12: 200–206. [PubMed: 17329980]
13. Quirk GJ, Beer JS, Byrne JH, Suzuki W (2006): Prefrontal involvement in the regulation of emotion: convergence of rat and human studies This review comes from a themed issue on Neurobiology of behaviour Edited Introduction: definition of emotion regulation. *Curr Opin Neurobiol* 16: 723–727. [PubMed: 17084617]
14. Kalisch R, Korenfeld E, Stephan KE, Weiskopf N, Seymour B, Dolan RJ (2006): Context-Dependent Human Extinction Memory Is Mediated by a Ventromedial Prefrontal and Hippocampal Network. *J Neurosci* 26: 9503–9511. [PubMed: 16971534]
15. Ji J, Maren S (2007): Hippocampal involvement in contextual modulation of fear extinction. *Hippocampus* 17: 749–758. [PubMed: 17604353]
16. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. (2009): Neurobiological Basis of Failure to Recall Extinction Memory in Posttraumatic Stress Disorder. *Biol Psychiatry* 66: 1075–1082. [PubMed: 19748076]
17. Rougemont-Bücking A, Linnman C, Zeffiro TA, Zeidan MA, Lebron-Milad K, Rodriguez-Romaguera J, et al. (2011): Altered processing of contextual information during fear extinction in PTSD: An fMRI study. *CNS Neurosci Ther* 17: 227–236. [PubMed: 20406268]

18. Albert J, López-Martín S, Carretié L (2010): Emotional context modulates response inhibition: Neural and behavioral data. *Neuroimage* 49: 914–921. [PubMed: 19716425]
19. Leibenluft E, Rich BA, Vinton DT, Nelson EE, Fromm SJ, Berghorst LH, et al. (2007): Neural Circuitry Engaged During Unsuccessful Motor Inhibition in Pediatric Bipolar Disorder. *Am J Psychiatry* 164: 52–60. [PubMed: 17202544]
20. van Rooij SJH, Jovanovic T (2019): Impaired inhibition as an intermediate phenotype for PTSD risk and treatment response. *Prog Neuro-Psychopharmacology Biol Psychiatry* 89: 435–445.
21. Jovanovic T, Ely T, Fani N, Glover EM, Gutman D, Tone EB, et al. (2013): Reduced neural activation during an inhibition task is associated with impaired fear inhibition in a traumatized civilian sample. *Cortex* 49: 1884–1891. [PubMed: 23020899]
22. Falconer E, Bryant R, Felmingham KL, Kemp AH, Gordon E, Peduto A, et al. (2008): The neural networks of inhibitory control in posttraumatic stress disorder. *J Psychiatry Neurosci* 33: 413–422. [PubMed: 18787658]
23. Powers A, Hinojosa CA, Stevens JS, Harvey B, Pas P, Rothbaum BO, et al. (2022): Right inferior frontal gyrus and ventromedial prefrontal activation during response inhibition is implicated in the development of PTSD symptoms. *Eur J Psychotraumatol* 13. 10.1080/20008198.2022.2059993
24. van Rooij SJH, Stevens JS, Ely TD, Fani N, Smith AK, Kerley KA, et al. (2016): Childhood trauma and COMT genotype interact to increase hippocampal activation in resilient individuals. *Front Psychiatry* 7: 1–12. [PubMed: 26903886]
25. van Rooij SJH, Stevens JS, Ely TD, Hinrichs R, Michopoulos V, Winters SJ, et al. (2018): The Role of the Hippocampus in Predicting Future Posttraumatic Stress Disorder Symptoms in Recently Traumatized Civilians. *Biol Psychiatry* 84: 106–115. [PubMed: 29110899]
26. Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM (2010): The role of the right inferior frontal gyrus: inhibition and attentional control. *Neuroimage* 50: 1313–1319. [PubMed: 20056157]
27. Van Belle J, Vink M, Durston S, Zandbelt BB (2014): Common and unique neural networks for proactive and reactive response inhibition revealed by independent component analysis of functional MRI data. 10.1016/j.neuroimage.2014.09.014
28. Roeckner AR, Sogani S, Michopoulos V, Hinrichs R, van Rooij SJH, Rothbaum BO, et al. (2022): Sex-dependent risk factors for PTSD: a prospective structural MRI study. *Neuropsychopharmacology* 47: 2213–2220. [PubMed: 36114284]
29. Felmingham K, Williams LM, Kemp AH, Liddell B, Falconer E, Peduto A, Bryant R (2010): Neural responses to masked fear faces: Sex differences and trauma exposure in posttraumatic stress disorder. *J Abnorm Psychol* 119: 241–247. [PubMed: 20141261]
30. Dark HE, Harnett NG, Hurst DR, Wheelock MD, Wood KH, Goodman AM, et al. (2022): Sex-related differences in violence exposure, neural reactivity to threat, and mental health. *Neuropsychopharmacology* 47: 2221–2229. [PubMed: 36030316]
31. Gaillard A, Rossell SL, Carruthers SP, Sumner PJ, Michie PT, Woods W, et al. (2020): Greater activation of the response inhibition network in females compared to males during stop signal task performance. 10.1016/j.bbr.2020.112586
32. McLean SA, Ressler K, Koenen KC, Neylan T, Germine L, Jovanovic T, et al. (2020): The AURORA Study: a longitudinal, multimodal library of brain biology and function after traumatic stress exposure. *Mol Psychiatry* 25: 283–296. [PubMed: 31745239]
33. Stevens JS, Harnett NG, Lebois LAM, Van Rooij SJH, Ely TD, Roeckner A, et al. (2021): Brain-Based Biotypes of Psychiatric Vulnerability in the Acute Aftermath of Trauma. *Am J Psychiatry* 178: 1037–1049. [PubMed: 34645277]
34. Van Rooij S, Santos J, Hinojosa C, Ely T, Harnett N, Hospital M, et al. (n.d.): Rethinking resilience using the r-factor: Neurobiological mechanisms of static and dynamic components of resilience following trauma. 1–20.
35. Galatzer-Levy IR, Ankri Y, Freedman S, Israeli-Shalev Y, Roitman P, Gilad M, Shalev AY (2013): Early PTSD Symptom Trajectories: Persistence, Recovery, and Response to Treatment: Results from the Jerusalem Trauma Outreach and Prevention Study (J-TOPS). 10.1371/journal.pone.0070084

36. Tanriverdi B, Gregory DF, Olino TM, Ely TD, Harnett NG, van Rooij SJH, et al. (2022): Hippocampal Threat Reactivity Interacts with Physiological Arousal to Predict PTSD Symptoms. *J Neurosci* 42: 6593–6604. [PubMed: 35879096]
37. Hammers A, Allom R, Koeppe MJ, Free SL, Myers R, Lemieux L, et al. (2003): Three-Dimensional Maximum Probability Atlas of the Human Brain, With Particular Reference to the Temporal Lobe. *Hum Brain Mapp* 19: 224–247. [PubMed: 12874777]
38. Kleerekooper I, van Rooij SJH, van den Wildenberg WPM, de Leeuw M, Kahn RS, Vink M (2016): The effect of aging on fronto-striatal reactive and proactive inhibitory control. *Neuroimage* 132: 51–58. [PubMed: 26899783]
39. Li CR, Huang C, Constable RT, Sinha R (2006): Gender differences in the neural correlates of response inhibition during a stop signal task. *Neuroimage* 32: 1918–1929. [PubMed: 16806976]
40. Aupperle RL, Stillman AN, Simmons AN, Flagan T, Allard CB, Thorp SR, et al. (2016): Intimate Partner Violence PTSD and Neural Correlates of Inhibition. *J Trauma Stress* 29: 33–40. [PubMed: 26748991]
41. Stevens JS, Jovanovic T, Fani N, Ely TD, Glover EM, Bradley B, Ressler KJ (2013): Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder. *J Psychiatr Res* 47: 1469–1478. [PubMed: 23827769]
42. Shansky RM, Morrison JH (2009): Stress-induced dendritic remodeling in the medial prefrontal cortex: Effects of circuit, hormones and rest. *Brain Res* 1293: 108–113. [PubMed: 19361488]
43. Shansky RM, Hamo C, Hof PR, Lou W, McEwen BS, Morrison JH (2010): Estrogen Promotes Stress Sensitivity in a Prefrontal Cortex-Amygdala Pathway. *Cereb Cortex* 20: 2560–2567. [PubMed: 20139149]
44. Zeidan MA, Igoe SA, Linnman C, Vitalo A, Levine JB, Klibanski A, et al. (2011): Estradiol Modulates Medial Prefrontal Cortex and Amygdala Activity During Fear Extinction in Women and Female Rats. *Biol Psychiatry* 70: 920–927. [PubMed: 21762880]
45. Protopescu X, Pan H, Altemus M, Tuescher O, Polanecsky M, McEwen B, et al. (2005): Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle. *Proc Natl Acad Sci* 102: 16060–16065. [PubMed: 16247013]
46. Milad MR, Zeidan MA, Contero A, Pitman RK, Klibanski A, Rauch SL, Goldstein JM (2010): The influence of gonadal hormones on conditioned fear extinction in healthy humans. *Neuroscience* 168: 652–658. [PubMed: 20412837]
47. Glover EM, Jovanovic T, Mercer KB, Kerley K, Bradley B, Ressler KJ, Norrholm SD (2012): Estrogen Levels Are Associated with Extinction Deficits in Women with Posttraumatic Stress Disorder. *Biol Psychiatry* 72: 19–24. [PubMed: 22502987]
48. Ben-Zion Z, Shany O, Admon R, Keynan NJ, Avidris N, Balter SR, et al. (2022): Neural Responsivity to Reward Versus Punishment Shortly After Trauma Predicts Long-Term Development of Posttraumatic Stress Symptoms. *Biol Psychiatry Cogn Neurosci Neuroimaging* 7: 150–161. [PubMed: 34534702]
49. Clausen AN, Francisco AJ, Thelen J, Bruce J, Martin LE, McDowd J, et al. (2017): PTSD and cognitive symptoms relate to inhibition-related prefrontal activation and functional connectivity. *Depress Anxiety* 34: 427–436. [PubMed: 28370684]
50. van Rooij SJH, Rademaker AR, Kennis M, Vink M, Kahn RS, Geuze E (2014): Impaired right inferior frontal gyrus response to contextual cues in male veterans with PTSD during response inhibition. *J Psychiatry Neurosci* 39: 330–338. [PubMed: 24886789]
51. Sheynin J, Lokshina Y, Ahrari S, Nickelsen T, Duval ER, Ben-Zion Z, et al. (2023): Greater Early Post-Trauma Activation in Right Inferior Frontal Gyrus Predicts Recovery from Posttraumatic Stress Disorder Symptoms. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 10.1016/j.bpsc.2023.07.002
52. Viviani R (2013): Emotion regulation, attention to emotion, and the ventral attentional network. *Front Hum Neurosci* 7: 1–24. [PubMed: 23355817]
53. Clausen AN, Francisco AJ, Thelen J, Bruce J, Martin LE, McDowd J, et al. (2017): PTSD and cognitive symptoms relate to inhibition-related prefrontal activation and functional connectivity. *Depress Anxiety* 34: 427–436. [PubMed: 28370684]

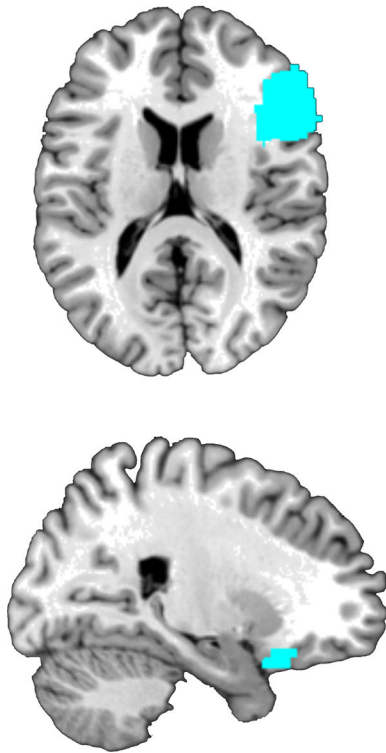
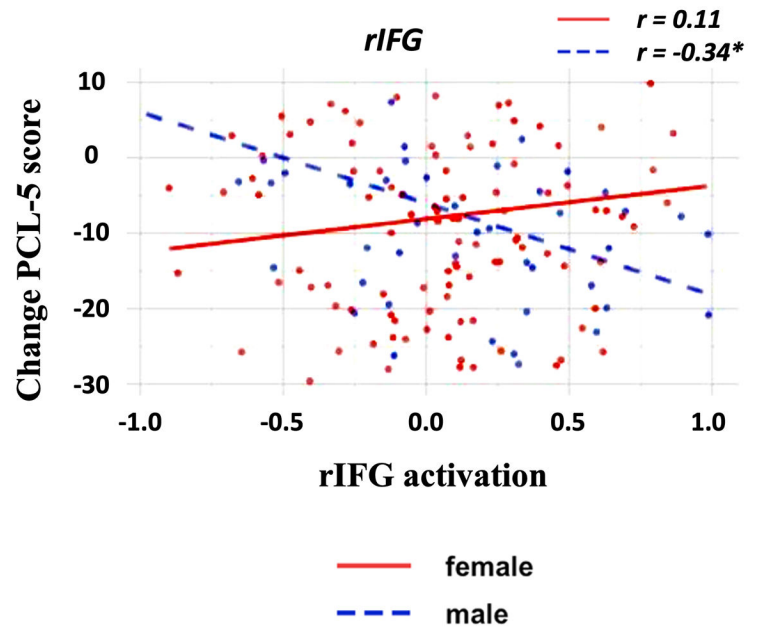
54. Elton A, Tripathi SP, Mletzko T, Young J, Cisler JM, James GA, Kilts CD (2014): Childhood maltreatment is associated with a sex-dependent functional reorganization of a brain inhibitory control network. *Hum Brain Mapp* 35: 1654–1667. [PubMed: 23616424]
55. Zhang R, Geng X, Lee TMC (2017): Large-scale functional neural network correlates of response inhibition: an fMRI meta-analysis. *Brain Struct Funct* 222: 3973–3990. [PubMed: 28551777]
56. Zhang F, Iwaki S (2019): Common neural network for different functions: An investigation of proactive and reactive inhibition. *Front Behav Neurosci* 13: 448834.
57. Van Rooij SJH, Geuze E, Kennis M, Rademaker AR, Vink M (2015): Neural correlates of inhibition and contextual cue processing related to treatment response in PTSD. *Neuropsychopharmacology* 40: 667–675. [PubMed: 25154707]
58. Kunimatsu A, Yasaka K, Akai H, Kunimatsu N, Abe O (2020): MRI findings in posttraumatic stress disorder. *J Magn Reson Imaging* 52: 380–396. [PubMed: 31515885]
59. Van Kemenade BM, Arikan BE, Podranski K, Steinsträter O, Kircher T, Straube B (2019): Distinct Roles for the Cerebellum, Angular Gyrus, and Middle Temporal Gyrus in Action-Feedback Monitoring. *Cereb Cortex* 29: 1520–1531. [PubMed: 29912297]
60. Sun Y, Wang Z, Ding W, Wan J, Zhuang Z, Zhang Y, et al. (2013): Alterations in White Matter Microstructure as Vulnerability Factors and Acquired Signs of Traffic Accident-Induced PTSD (H. Chen, editor). *PLoS One* 8: e83473. [PubMed: 24349515]
61. H van Rooij SJ, Smith RD, Stenson AF, Ely TD, Yang X, Tottenham N, et al. (2020): Increased activation of the fear neurocircuitry in children exposed to violence. *Depress Anxiety* 37: 303–312. [PubMed: 31951308]
62. Douglas Bremner J, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, et al. (2003): Article MRI and PET Study of Deficits in Hippocampal Structure and Function in Women With Childhood Sexual Abuse and Posttraumatic Stress Disorder. *Am J Psychiatry* 160. Retrieved July 31, 2023, from <http://ajp.psychiatryonline.org>
63. Steun MB, Koverola C, Hanna C, Torchia MG, McClarty B (1997): Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med* 27: S0033291797005242.
64. Maheu FS, Dozier M, Guyer AE, Mandell D, Peloso E, Poeth K, et al. (2010): A preliminary study of medial temporal lobe function in youths with a history of caregiver deprivation and emotional neglect. *Cogn Affect Behav Neurosci* 10: 34–49. [PubMed: 20233954]
65. Bremner JD (2002): Neuroimaging of childhood trauma. *Semin Clin Neuropsychiatry* 7: ascnp0070104.
66. Lebron-Milad K, Milad MR (2012): Sex differences, gonadal hormones and the fear extinction network: implications for anxiety disorders. *Biol Mood Anxiety Disord* 2: 1–12. [PubMed: 22738278]
67. Badour CL, Resnick HS, Kilpatrick DG (2017): Associations Between Specific Negative Emotions and DSM-5 PTSD Among a National Sample of Interpersonal Trauma Survivors. *J Interpers Violence* 32: 1620–1641. [PubMed: 26088902]
68. Cowden Hindash AH, Lujan C, Howard M, O'Donovan A, Richards A, Neylan TC, Inslicht SS (2019): Gender Differences in Threat Biases: Trauma Type Matters in Posttraumatic Stress Disorder. *J Trauma Stress* 32: 701–711. [PubMed: 31590206]
69. Kelley LP, Weathers FW, McDevitt-Murphy ME, Eakin DE, Flood AM (2009): A comparison of PTSD symptom patterns in three types of civilian trauma. *J Trauma Stress* 22: 227–235. [PubMed: 19444884]
70. Duval ER, Sheynin J, King AP, Phan KL, Simon NM, Martis B, et al. (2020): Neural function during emotion processing and modulation associated with treatment response in a randomized clinical trial for posttraumatic stress disorder. *Depress Anxiety* 37: 670–681. [PubMed: 32306485]

**A vmPFC activation****B Correlation PTSD symptoms at six months per sex**

**Figure 1: vmPFC activation predicts PTSD symptoms at 6-months in females.**

**A)** The vmPFC is displayed as a region of interest in red. **B)** Correlation between vmPFC activation and PTSD symptoms (PCL-5 scores) at 6-months per sex while controlling for age and scanner site. Lower vmPFC activation significantly correlates with more PTSD symptoms at 6-months in females ( $r=-0.25$ ,  $p=0.004$ ) but not in males ( $r=0.06$ ,  $p=0.65$ ).

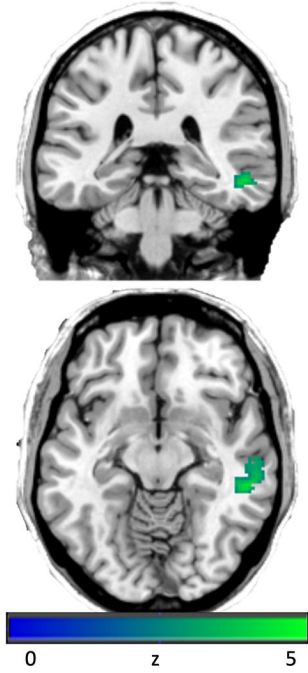
\*Significant correlation  $p<0.05$

**A rIFG activation****B Correlation PTSD improvement per sex**

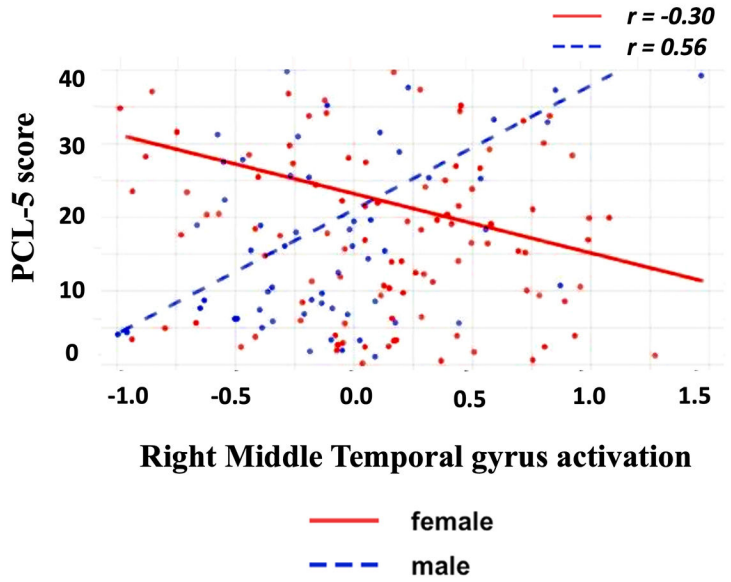
**Figure 2: rIFG activation predicts PTSD symptom change over 6 months in males.**

**A)** The rIFG is displayed as a region of interest in blue. **B)** Correlation between rIFG activation and change in PTSD symptoms (PCL-5 scores 6-months – 2-weeks) over 6-months per sex, while controlling for age and scanner site. Higher rIFG activation significantly correlates with more PTSD symptom improvement in males ( $r=-0.34$ ,  $p=0.01$ ), but not in females ( $r = 0.11$ ,  $p=0.23$ ). \*Significant correlation  $p<0.05$

### A Right Middle Temporal Gyrus activation



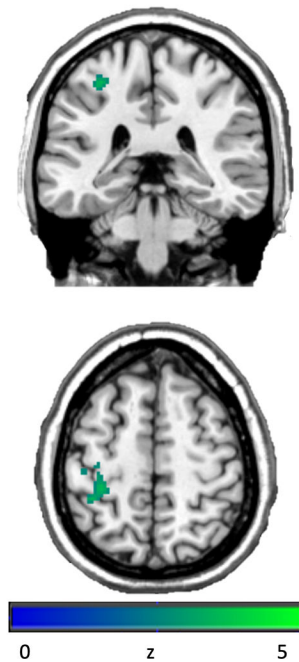
### B Correlation PTSD symptoms at 6 months per sex



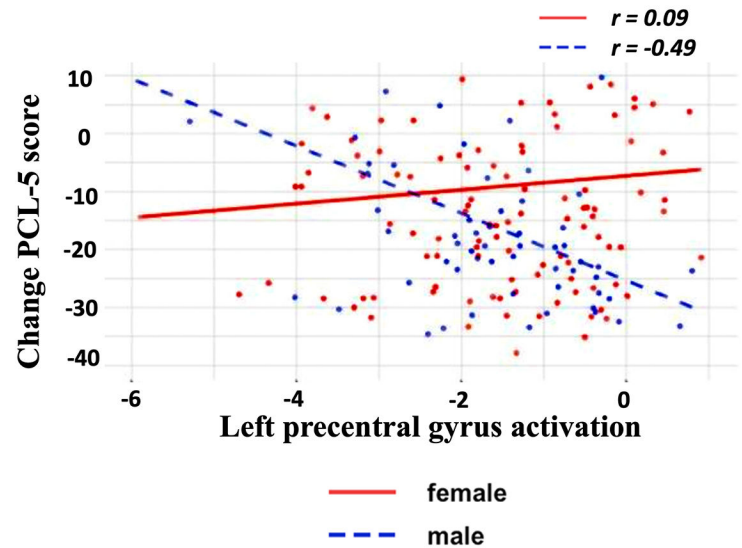
**Figure 3: Whole brain correlation analyses with PTSD severity**

A) The significant cluster for the interaction between sex and PTSD severity at 6-months in the right middle temporal gyrus (rMTG;  $p < 0.005$ , FWE-corrected cluster threshold,  $k=194$ ) is extracted and visualized with MRICron. B) Correlation between rMTG activation (contrast values extracted and averaged for the cluster displayed in A) and PTSD symptoms at 6-months per sex, while controlling for age and scanner site is displayed. Lower rMTG activation correlates with more PTSD symptoms at 6-months in females (correlation with extracted mean:  $r = -0.30$ ,  $p < 0.001$ ) whereas lower rMTG activation significantly correlates with less PTSD symptoms in males (correlation with extracted mean,  $r = 0.56$ ,  $p < 0.001$ ).

### A Left Precentral Gyrus activation



### B Correlation PTSD improvement per sex



**Figure 4: Whole brain correlation analyses with PTSD progression**

A) The significant cluster for the interaction between sex and PTSD progression between 2-weeks and 6-months in the left precentral gyrus ( $p < 0.005$ , FWE-corrected cluster threshold,  $k = 231$ ) is extracted and visualized with MRICron. B) Correlation between left precentral gyrus activation (contrast values extracted and averaged for the cluster displayed in A) and PTSD progression between 2-weeks and 6-months per sex, while controlling for age and scanner site is displayed. Less negative precentral gyrus activation correlated with lower PTSD progression (or: more improvement) in males (correlation with extracted mean,  $r = -0.34$ ,  $p = 0.01$ ), but no association in females was observed.

**Table 1.**

## Demographics and Clinical Characteristics

Characteristic	Females (N=138)	Males (N=67)	Statistic	p value
Age, years	34.8 ± 12.4	34.4 ± 12.9	t = 0.24	.80
Race			c <sup>2</sup> = 1.67	.64
Black	68/138 (49)	28/67 (41)		
White	49/138 (36)	25/67 (37)		
Hispanic	15/138 (11)	11/67 (16)		
Other	6/138 (4)	3/67 (4)		
Income			c <sup>2</sup> = 3.73	.32
£ \$19,000	35/138 (25)	13/67 (19)		
%19,001 – \$35,000	49/138(36)	27/67 (40)		
\$35,001 – \$ 50,000	22/138 (16)	8/67 (12)		
\$50,001 – \$75,000	15/138 (11)	4/67(6)		
\$75,001 – \$100,000	9/138 (7)	6/67 (9)		
>\$100,000	8/138 (6)	9/67 (13)		
Highest education (completed)			c <sup>2</sup> = 4.50	.61
No high school education	2/138 (1)	0/67 (0)		
Some high school (no degree)	7/138 (5)	6/67 (9)		
High school	38/138 (28)	16/67 (24)		
Associate degree, some college	53/138 (38)	27/67 (40)		
Bachelor's degree	28/138 (17)	12/67 (18)		
Master's degree	10/138 (5)	5/67 (7)		
Doctoral degree	0/138 (0)	1/67 (1)		
Broad trauma type			c <sup>2</sup> = 4.44	.62
Motor vehicle collision	103/138 (75)	44/67 (66)		
Non-motorized collision	3/138 (2)	4/67 (6)		
Fall:	10/138 (7)	7/67 (10)		
Physical assault	13/138 (10)	7/67 (10)		
Sexual assault	2/138 (1)	0/67 (0)		
Animal related	4/138 (3)	3/67 (4)		
Other	3/138 (2)	2/67 (3)		
Child trauma (CTQ, scale 0–44)	9.7 ± 9.6	7.7 ± 8.3	t = 1.45	.15
<b>Depression</b> 30 days Pre-Trauma (PROMIS)	18/138 (13)	10/67 (15)	c <sup>2</sup> = 1.135	.71
Clinical characteristics				
PTSD Symptoms (PCL-5, scale 0–80) at 2-weeks	31.1 ± 16.1	24.8 ± 16.0	t = 2.51	.01
Meet DSM-5 criteria <sup>*</sup>	69/129 (53)	20/58 (34)	c <sup>2</sup> = 5.79	.02
PTSD Symptoms (PCL-5, scale 0–80) at 6-months	24.1 ± 18.6	15.9 ± 14.9	t = 3.15	.002

Characteristic	Females (N=138)	Males (N=67)	Statistic	p value
Meet DSM-5 criteria *	46/138 (33)	11/67 (16)	$\chi^2 = 6.43$	.01
Change in PCL-5 score (6-months minus 2-weeks)	$-8.2 \pm 16.8$	$-8.7 \pm 16.0$	$t = 0.21$	0.84

Demographics and clinical characteristics: Values shown are mean  $\pm$  SD or n/total n (%). Independent T-tests were performed to compare the mean scores between men and women, whereas chi-square tests were used to compare the proportions of both groups. CTQ: Childhood Trauma Questionnaire; PROMIS: PTSD: posttraumatic stress disorder, PCL-5: PTSD Symptom Checklist for DSM-5; DSM IV: Diagnostic and Statistical Manual of Mental Disorders version five.

\* DSM -5 criteria were met when a participant had a PCL-5 score of 30 or more.

**Table 2.**

ROI analyses for PTSD severity at 6-months

*A. Model without interaction with sex*

	F	df	P	R <sup>2</sup>	R <sup>2</sup> Adj.
<b>Model</b>	2.217	9	0.023	0.093	0.051
Site	0.588	4	0.671		
Age	1.121	1	0.291		
Sex	8.218	1	<b>0.005**</b>		
B_hipp	0.096	1	0.757		
rIFG	3.168	1	0.077		
vmPFC	2.418	1	0.122		

*B. Model with interaction with sex*

	F	df	P	R <sup>2</sup>	R <sup>2</sup> Adj.
<b>Model</b>	2.449	12	.005	0.133	0.078
Site	0.933	4	0.446		
Age	1.263	1	0.263		
Sex	8.921	1	<b>0.003**</b>		
B_hipp	0.010	1	0.753		
rIFG	3.103	1	0.080		
vmPFC	1.004	1	0.318		
Sex * B_hipp	0.431	1	0.512		
Sex * r_IFG	1.928	1	0.167		
Sex * vmPFC	7.239	1	<b>0.008**</b>		

\*\*  
p<0.01

Results from General Linear Models predicting PTSD symptoms at 6-months with the ROIs as independent variables and PTSD symptoms at 6-months as the dependent variable. *A.* shows the model including site, age, and sex as covariates. *B.* shows the model including the interaction with sex, and site and age as covariates. B\_hipp, bilateral hippocampus; rIFG, right inferior frontal gyrus; vmPFC, ventromedial prefrontal cortex.

**Table 3.**

ROI analyses for PTSD progression from 2-weeks to 6-months.

<i>A. Model without interaction with sex</i>					
	<b>F</b>	<b>df</b>	<b>P</b>	<b>R<sup>2</sup></b>	<b>R<sup>2</sup> Adj.</b>
Model	0.353	9	0.955	0.017	-0.032
Site	0.188	4	0.944		
Age	0.134	1	0.715		
Sex	0.001	1	0.975		
B_hipp	0.032	1	0.859		
rIFG	0.924	1	0.338		
vmPFC	1.352	1	0.246		
<i>B. Model with interaction with sex</i>					
	<b>F</b>	<b>df</b>	<b>P</b>	<b>R<sup>2</sup></b>	<b>R<sup>2</sup> Adj.</b>
Model	1.502	12	.127	0.094	0.0314
Site	0.616	4	0.652		
Age	0.223	1	0.638		
Sex	0.003	1	0.956		
B_hipp	0.407	1	0.524		
rIFG	1.836	1	0.177		
vmPFC	3.019	1	0.084		
Sex * B_hipp	1.005	1	0.318		
Sex * r_IFG	9.478	1	<b>0.002</b> **		
Sex * vmPFC	4.895	1	<b>0.028</b> *		

\*  
p<0.05\*\*  
p<0.01

Results from General Linear Models predicting PTSD symptoms change over 6-months with the ROIs as independent variables and site, age, and sex as covariates and PTSD symptom change from 2-weeks to 6-months as the dependent variable. *A.* shows the model including site, age, and sex as covariates. *B.* shows the model including the interaction with sex, and site and age as covariates., B\_hipp, bilateral hippocampus; rIFG, right inferior frontal gyrus; vmPFC, ventromedial prefrontal cortex.

**Table 4:**

Whole brain analyses for PTSD severity at 6-months.

PTSD_6mo		Cluster-level			MNI coordinates			Brain region	
		P <sub>FWE</sub>	k	p <sub>Uncorr</sub>	z-score	X	Y		Z
Main effect	<i>positive</i>	-	-	-	-	-	-	-	
	<i>negative</i>	0.172	133	0.002	4.14	44	18	38	rIFG
Interaction with sex		<b>0.033</b>	<b>194</b>	<b>&lt;0.001</b>	<b>4.40</b>	<b>54</b>	<b>-32</b>	<b>-10</b>	<b>rMTG</b>
		0.294	133	0.005	3.62	68	-8	2	rMTG
		0.231	125	0.003	3.64	-32	-22	54	left precentral gyrus
Males only <sup>#</sup>		0.600	79	0.009	4.18	58	-30	-12	rMTG
Females only <sup>#</sup>		1.000	23	0.139	3.53	54	-34	-8	rMTG
		1.000	24	0.131	3.48	62	-22	-12	rMTG

Whole brain correlation analyses using  $p < 0.005$  with PTSD symptoms as the independent variable, and sex, age and scan site as covariates and second analysis with sex as a moderator. Clusters  $k > 100$  are displayed for the main and interaction effect and findings surviving cluster-level FWE correction are shown in **bold**.

<sup>#</sup> A mask for the cluster with significant interaction is used for males only and females only and clusters surviving  $p < 0.005$  are shown. rIFG, right inferior frontal gyrus; rMTG, right middle temporal gyrus.

**Table 5:**

Whole brain analyses for PTSD progression from 2-weeks to 6-months.

PTSD_6mo		Cluster-level			MNI coordinates			Brain region	
		P <sub>FWE</sub>	k	P <sub>Uncorr</sub>	z-score	X	Y		Z
Main effect	<i>positive</i>	-	-	-	-	-	-	-	
	<i>negative</i>	0.365	100	0.006	4.20	-38	-16	60	left precentral gyrus
Interaction with sex		0.092	148	0.001	4.29	44	18	38	rIFG
		<b>0.009</b>	<b>231</b>	<b>&lt;0.001</b>	<b>3.71</b>	-32	-30	60	<b>left precentral gyrus</b>
		0.225	117	0.003	4.1	58	-30	-12	rMTG
Males only <sup>#</sup>		<b>0.022</b>	<b>186</b>	<b>&lt;0.001</b>	4.10	-40	-20	62	<b>left precentral gyrus</b>
Females only <sup>#</sup>		-	-	-	-	-	-	-	

Whole brain correlation analyses using  $p < 0.005$  with PTSD symptom progression from 2-weeks to 6-months as the independent variable, and sex, age and scan site as covariates and second analysis with sex as a moderator. Clusters  $k > 100$  are displayed for the main and interaction effect and findings surviving cluster-level FWE correction are shown in **bold**.

<sup>#</sup>A mask for the cluster with significant interaction is used for males only and females only and clusters surviving  $p < 0.005$  are shown. rIFG, right inferior frontal gyrus; rMTG, right medial temporal gyrus.