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14. ABSTRACT
The study directly compared the psychotherapy and medication treatments for PTSD considered to have the most evidence for effectiveness. While both SSRI and PE have demonstrated efficacy, there are significant individual differences in clinical responses to both treatments. To achieve best clinical outcomes and to utilize available treatment most effectively, it is critical to examine how PTSD and related psychopathology and functional impairment change with these treatments alone and in combination. Further, in order to inform clinical practice, we examined psychological and neurobiological predictors of response to treatment and mechanisms of change during treatment (pre to post treatment change) based on previously identified predictors, including emotion regulation and processing with fMRI in response to emotional challenge tasks, DNA and mRNA (pre and post treatment), and cortisol response to awakening. The final enrollment numbers were 223 Veterans randomized to treatment which 120 completed both of their assigned treatments, 149 completed the Week 24 primary outcome assessment visit and 139 have completed the Week 52 final study assessment visit. The primary activity and focus this year was data analyses and manuscript preparation with 6 papers published to date and the main results of the study published in JAMA Psychiatry in February 2019.

15. SUBJECT TERMS
PTSD, Treatment, Medication, Therapy, fMRI, Cortisol

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Table of Contents

Page

1. **Background……. 4**
2. **Keywords……. 4**
3. **Overall Project Summary……... 4-8**
4. **Key Research Accomplishments…… 8**
5. **Reportable Outcomes..…… 8-12**
6. **Conclusion…… 12-13**
7. **Bibliography…….……..…..…… 13-16**
8. **References……. 16-17**
9. **Appendices……..... 17-95**

Randomized Controlled Trial of Sertraline, Prolonged Exposure Therapy and their Combination in OEF/OIF Combat Veterans with PTSD (PROGRESS; PI: RAUCH): FINAL REPORT

DATE: 04/26/2019

Background

PTSD is a major public health concern and a growing problem for the VA and the DOD [1,2]. Combat personnel returning from Afghanistan and Iraq show PTSD prevalence between 12 to 20% [3-6] with significant psychological, physical, and economic burdens for sufferers and society as a whole [7,8]. Based on available treatment guidelines [9], the two first line treatments for PTSD include exposure therapy (such as prolonged exposure [PE]) and selective serotonin reuptake inhibitors (SSRIs; such as sertraline [SERT]). Until the PROGRESS study, there were no randomized, direct comparisons of medication, psychotherapy, and combined treatment among veterans or active duty troops. With completion and publication of our main outcomes paper, we provide this critical data in a typical sample of OEF/OIF returnees with significant combat-related PTSD. We examined comprehensive outcome data on acceptability, adherence, compliance, and symptom change in each treatment arm throughout the study period. These results may now be used to address substantial residual symptoms for some PTSD veterans [10,11] even after PE or SSRI treatment are administered. We can provide suggestions for further treatment optimization and individual treatment matching to continue to reduce the substantial personal and social costs. Identifying specific putative mechanisms involved in treatment response takes critical steps toward achieving the goals of treatment optimization and individual treatment matching. Our examination of the proposed mechanisms of change in the primary statement of work papers from this study will now be used to refine and improve effectiveness and efficiency of PTSD treatment, enhance dissemination, and individualize treatment. Our study goals were ambitious; however, we achieved our aims based on the combined expertise of the research group involved, the synergy of the aims, and the efficient design, which offered a unique opportunity to examine multiple processes simultaneously and to obtain the highest quality of critically needed data. At the conclusion of our study, we have been successful in accomplishing all of these aims and will continue to examine additional secondary and post hoc analyses to further illustrate the processes of PTSD treatment change.

KEYWORDS

PTSD, Veterans, Prolonged Exposure, Sertraline, OEF, OIF, OND, treatment, therapy, medication, combination treatment, CBT, trauma focused therapy, fMRI, cortisol

OVERALL PROJECT SUMMARY

This project consisted of seven primary tasks accomplished over the funding period at four sites: Veterans Affairs Ann Arbor Healthcare System (VAAAHS) /University of Michigan (UM), VA San Diego Healthcare System (VASDHS)/University of California San Diego (UCSD), Ralph H. Johnson Veterans Affairs Medical Center (RHJVAMC)/ Medical University of South Carolina (MUSC), and Massachusetts General Hospital (MGH)/Harvard Medical School.

SOW Task 1: Start-up activities and regulatory approvals (COMPLETED)

- Primary site (VAAAHS/UM) obtained full approval at VA Ann Arbor Healthcare System (Dec 2010), University of Michigan (Dec 2010), and HRPO (Jun 2011).
- MGH obtained full approval from MGH (Aug 2011) and HRPO (Sep 2011).

- RHJVAMC/MUSC obtained full approval from the MUSC IRB (Jul 2011), the VA R&D Committee (Aug 2011), and HRPO (Feb 2012).
- VASDHS/UCSD obtained full approval from UCSD IRB (May 2011), the VA R&D Committee (Sep 2011), and HRPO (Apr 2012).
- All sites completed hiring of key positions.
- Payment processes put in place and fulfilled in a timely manner.
- Subawards completed.

SOW Task 2: Training of study faculty and staff (COMPLETED)

- All Psychotherapists, Pharmacotherapists, Independent Evaluators and Fidelity Raters completed required training for their perspective study roles and had regular training calls with the Study Leads.
- Study Coordinators and Research Assistants were trained prior to any patient contact and had ongoing monthly calls with the Lead Study Coordinator.
- The initial study kickoff meeting occurred on 09/19/2011 in Charleston, SC at one of the study sites. At this meeting, study staff were trained in collecting and entering study data in the secure database which was located and overseen by the Michigan Institute for Clinical and Health Research (MICHR) study staff.

SOW Task 3: Set up study forms and refine all procedures (COMPLETED)

- Creation of all study forms was completed.
- Data was entered securely into a Velos eResearch System database by the study sites.
- The Data Coordinating Center (DCC) provided personalized assistance to Study Coordinators to ensure that site staff successfully enrolled and entered data for their first patients.
- DCC study staff was available to provide ongoing assistance with providing access to the database, guidance on use of the data management software (Velos eResearch) and related functions such as the Ad Hoc query and data report tools.
- The eCRF Completion Guidelines were developed to standardize data entry and were regularly enhanced based on input from study staff. This 62-page document included general information on Velos eResearch and specific data entry instructions for every CRF in the study.

SOW Task 4: Recruit and randomly assign Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) returnees with combat related Posttraumatic Stress Disorder (PTSD) to PE+ placebo (PE/PLB), sertraline + enhanced medication management (SERT), or PE + sertraline (PE/SERT) (COMPLETED)

- The final study participant completed the Week 52 assessment visit in May 2017. Our final screening/enrollment numbers are:

Final #	Screened	Consented	Randomized
VAAAHS/UM	487	76	38
MGH	237	76	40
RHJVAMC/MUSC	579	250	100

VASDHS/UCSD	298	70	45
TOTAL	**1601**	**472**	**223**
Combat Controls	N/A	60	29

SOW Task 5: Conduct neurobiological mechanism study including assessment of genetics/genomics, brain function, and hypothalamic–pituitary–adrenal (HPA) axis function (COMPLETED)

- Our final fMRI sub-study enrollment was 66 participants
  - 26 from VAAAHS/UM, 7 from MGH, 25 from RHJVAMC/MUSC, and 8 from VASDHS/UCSD.
  - 66 completed the pre-scan (Intake).
  - 43 completed the post scan (Week 24).
  - 23 dropped out of the fMRI substudy due to time constraints or were lost to follow-up to the main study.
  - 29 Combat Controls completed an intake scan only.
- Analyses of the biological aims for the primary SOW are completed. Results were presented at ADAA (March, 2019) and papers are either under review or in final phase of preparation for (a) fMRI, (b) cortisol, (c) gene expression (mRNA) in whole blood leukocytes, and (d) genetic and neuroimaging genetics analyses.

SOW Task 6: Follow-up of all returnees for one year from treatment initiation (COMPLETED)

- 149 patients completed Week 24 research assessment *
- 146 patients completed Week 36 research assessment*
- 139 patients completed Week 52 research assessment*

*indicates patients who completed the primary outcome measure (CAPS) and are included in primary analyses

SOW Task 7: Data cleaning, initial statistical analyses, and dissemination of results (COMPLETED)

- The baseline and final treatment datasets are completed.
- Primary Statement of Work Papers: All primary statement of work results were presented at the annual meeting of Anxiety and Depression Association of America on March 28-31, 2019 in Chicago, IL.
  - The Methodology paper was published in *Contemporary Clinical Trials* in January 2018 (citation in bibliography).
  - The Main Clinical Outcomes and Comparative Effectiveness paper was published in *JAMA Psychiatry* in February 2019 (citation in bibliography).
  - Three (3) imaging papers (one for each emotion regulation and processing paradigm) are under review or in final preparation for submission.
    - SEAT imaging paper is currently under review.
    - Resting State paper currently under review.
    - Emotional Faces task (EFAT/ERT) will be submitted in May 2019.
- Secondary (Non-Statement of Work) Papers
  - Four (4) baseline papers have also been published (citations in bibliography).

        - "PTSD as a mediator in the relationship between post-concussive symptoms and pain among OEF/OIF/OND veterans" was published in *Military Medicine* in January 2019.
        - "Postconcussive symptoms (PCS) following combat-related traumatic brain injury (TBI) in veterans with posttraumatic stress disorder (PTSD): Influence of TBI, PTSD, and depression on symptoms measured by the Neurobehavioral Symptom Inventory (NSI)" was published in the *Journal of Psychiatric Research* in March 2018.
        - "Trauma related guilt cognitions partially mediate the relationship between PTSD symptom severity and functioning among returning combat veterans" was published in the *Journal of Psychiatric Research* in February 2018.
        - "The loss of a fellow service member: Complicated grief in post-9/11 service members and veterans with combat-related posttraumatic stress disorder" was published in the *Journal of Neuroscience* in May 2017.
    - A manuscript focused on change in PTSD related cognitions has been submitted for publication and is currently under review and was presented at the 52nd Annual Convention of the Association for Behavioral and Cognitive Therapy in Washington DC in November 2018.
    - Baseline paper on PTSD and Major Depression Disorder is currently under review.
    - Secondary analysis paper "Understanding the Impact of Complicated Grief on Combat Related Posttraumatic Stress Disorder, Guilt, Suicide and Functional Impairment in a Clinical Trial of Post-9/11 Service Members and Veterans" accepted for publication by *Depression and Anxiety* April 2019.
- 16 poster/symposium abstracts were presented at annual meetings, including the International Society of Traumatic Stress Studies (ISTSS), Military Health Science Research Symposium (MHSRS), Association for Behavioral and Cognitive Therapy (ABCT) and Anxiety and Depression Association of America (ADAA). Of those, 10 abstracts were presented between November 2018-March 2019.
- Sonalee Joshi M.A. will present on neural activation during reappraisal and assessment of emotion associated with PTSD at the annual Association for Psychological Science in Washington DC in May 2019.
- The Progress study publication policy and procedure continues to be utilized with monthly publication committee meetings to discuss current and new project proposals from the data set.
- Several projects based on cross-sectional baseline, primary and secondary data are ongoing.
- While the PROGRESS study funding is expended, ongoing analysis from the dataset will continue with other funding sources.

DELAYS/CHALLENGES/BARRIERS

Over the course of the study, our biggest obstacle to recruitment was obtaining Veterans willing to have psychotherapy and/or medication who were not currently on an antidepressant. Despite this, and in collaboration with our CDMRP team, we met the requirements for power outlined in our SOW for the primary aims.

KEY RESEARCH ACCOMPLISHMENTS

- Randomized 223 patients to treatment.
- 120 patients completed both of their assigned treatments.
- 139 patients have completed the final study assessment visit (Week 52).
- 29 Combat Controls completed.
- 66 fMRI patients enrolled with 43 completing the post treatment scan.
- Established consistent procedures for the outcome and mechanisms data across sites.
- Collected all neurobiological and symptom data from all sites through the centralized data center.
- Addition and start-up of 3 new recruitment locations: Charleston, SC, Hinesville, GA, and Toledo, OH.
- Implemented VA Clinical Video Telehealth (CVT) to conduct treatment (medication and therapy) visits and research assessments with patients at Community Based Outpatient Clinics (CBOCs). Provisions for PTSD treatment and assessment visits via CVT are now standard of care at the VA.
- Completed 10 Data Safety Monitoring Board meetings over the course of the study.
- Baseline and final treatment datasets completed.
- Primary analyses completed.
- 6 papers published including the Main Outcomes paper published in *JAMA Psychiatry*.
- 16 poster/symposium abstracts were presented at annual meetings, including the International Society of Traumatic Stress Studies (ISTSS), Military Health Science Research Symposium (MHSRS), Association for Behavioral and Cognitive Therapy (ABCT) and Anxiety and Depression Association of America (ADAA). Of those, 10 abstracts were presented between November 2018-March 2019.
- A symposium entitled: What Works and How: Primary Outcomes and Mechanisms of PTSD Treatment in Veterans from the PROGRESS Trial was presented at the 2019 ADAA meeting in March 2019 presenting all of the primary statement of work papers.

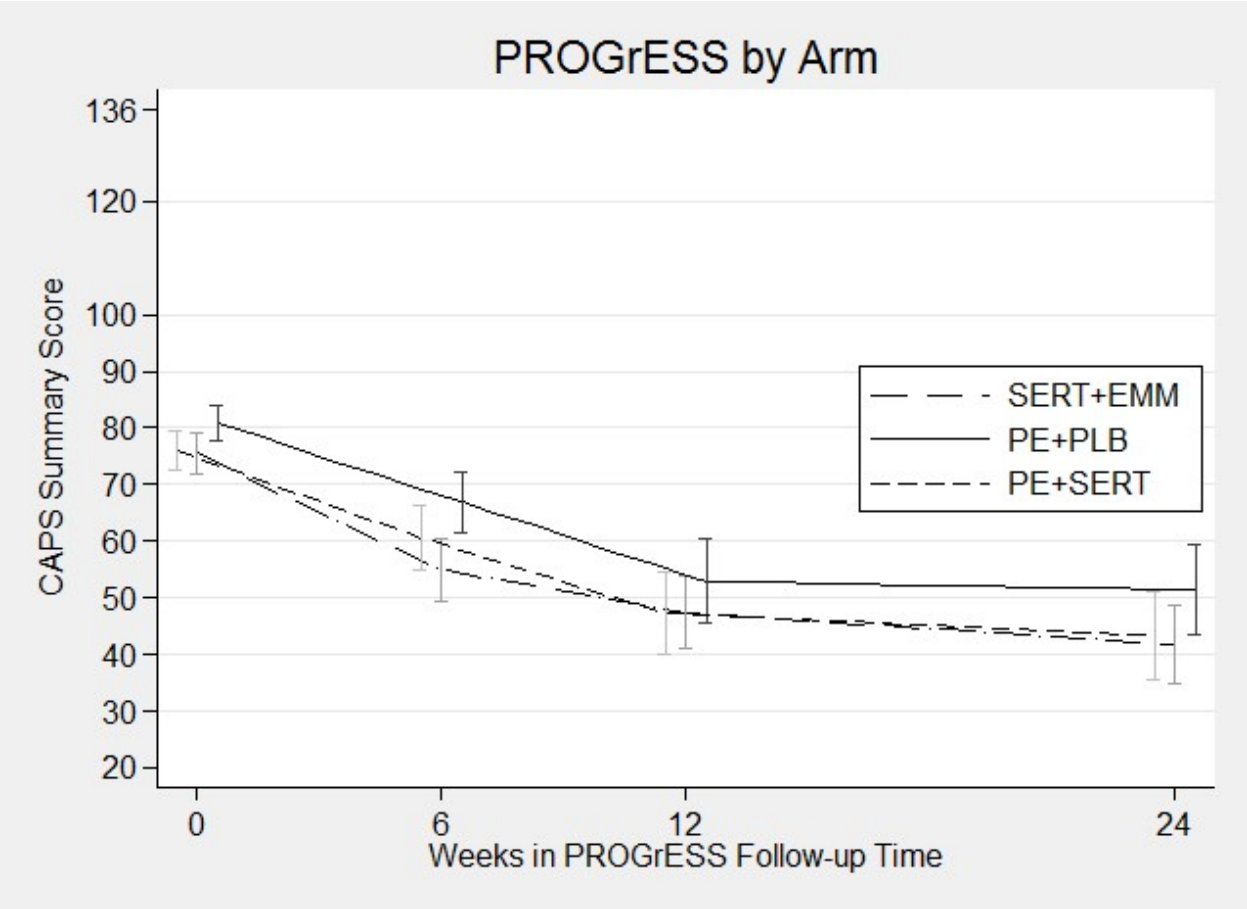
REPORTABLE OUTCOMES

Rauch SAM, Kim HM, Powell C, et al. Efficacy of Prolonged Exposure Therapy, Sertraline Hydrochloride, and Their Combination Among Combat Veterans With Posttraumatic Stress Disorder: A Randomized Clinical Trial. *JAMA Psychiatry.* 2019;76(2):117–126. doi:10.1001/jamapsychiatry.2018.3412

The primary symptom outcome paper provides a head to head comparison of relative effectiveness of: 1) prolonged exposure plus placebo (PE + PLB); 2) PE + sertraline (PE + SERT); and 3) SERT + enhanced medication management (SERT + EMM). At the time of grant submission, we hypothesized larger symptom reductions with PE+SERT than PE+PLB, and larger symptom reductions with PE+PLB than SERT+EMM and that treatment dropout in PE+SERT would be larger than in either SERT+EMM or PE+PLB. Participants across the four sites [VA Ann Arbor Healthcare System (VAAAHS), VA San Diego Healthcare System (VASDHS), Ralph H. Johnson VA Medical Center (RHJVAMC), and Massachusetts General Hospital Home Base Veterans Program (MGH)] completed 24-weeks in the treatment phase and were followed to 52 weeks. Participants completed assessments at weeks 0 (intake), 6, 12, 24, and 52 (Follow-up). Participants and providers were blind to pill condition, and outcome evaluators were blind to assignment. Participants (N = 223) were service members or veterans of Iraq/Afghanistan wars with combat-related PTSD and significant impairment (Clinician Administered PTSD Scale (CAPS) ≥50) of at least three months duration. Participants completed up to thirteen 90-minute sessions of PE by week

24. SERT was titrated over 10 weeks and continued until week 24; medication management was manualized. Primary outcome was past month PTSD symptom severity on Clinician-Administered PTSD Scale (CAPS) at week 24. Of 223 randomized participants, 149 completed the study at 24 weeks. Modified intent-to-treat analysis (n=207) using Mixed Models Repeated Measurement showed that PTSD symptoms decreased significantly during the 24 weeks (p<.001); however, slopes did not differ by treatment arms (p=0.81), and at 24 weeks, the difference between PE+PLB vs. SERT+EMM was 9.1 (p=0.05) and PE+PLB vs. PE+SERT was 6.7 (p=0.16). Both differences are smaller than what would be considered a clinically significant difference on CAPS (10 points[12]). No differences in PTSD symptom change or symptom severity at 24 weeks were found across the three groups (SERT+EMM, PE+PLB, and PE+SERT). None of the dichotomous outcomes [remission (Wk 24 CAPS of 35 or less), response (50% reduction in CAPS at Wk24), or meaningful change (20 or more point reduction in CAPS or less than 35 CAPS at Wk 24)] showed treatment differences. All changes were maintained through 52 weeks. Of note, the magnitude of effect for sertraline in the current sample is larger than found in previous studies among veterans and suggest that the manualized enhanced medication management may have provided increased benefit to patients through psychoeducation, support, and potentially increased compliance. Following publication of the paper, many providers and clinics have requested this manual for use in training their prescribing providers.

Figure 1. Treatment Effect



(Rauch et al, 2019)

Rauch, SAM, King, A.P., Venners, M.V., Kim, H.M., Powell, C., Rajaram, N., Simon, N.M., Hamner, M. Liberzon, I. (In Preparation). Cortisol awakening response in PTSD treatment: Indicator or Mechanism of change.

PTSD is associated with abnormalities in hypothalamic-pituitary-adrenal (HPA) axis activity, specifically enhanced HPA axis negative feedback [13], attenuated cortisol awakening response [14], and attenuated cortisol response to personal trauma script [15,16]. Whether HPA axis function predicts treatment response or treatment related symptom reduction in PTSD remains unclear. In addition, examination of differential treatment effects on HPA axis (i.e., medication and psychotherapy) is warranted. To address this critical gap in knowledge, the PROGRESS study (Rauch et al, 2018) examined cortisol awakening response across treatment in Veterans with chronic PTSD randomized to receive Prolonged Exposure +Placebo (PE + PLB), Sertraline + PE (SERT + PE) or Sertraline + Enhanced Medication Management (SERT + EMM). Salivary cortisol awakening response was collected at baseline, midtreatment (week 6 and 12), posttreatment (week 24) and follow-up (week 36 and 52). Among males at baseline, combat controls showed higher CAR AUCi (*M* = 7.63, *SD*=9.07) than PTSD (*M* = 3.15, *SD*=9.57; *p* = .02) demonstrating combat controls have a more responsive system at baseline. Higher PTSD severity was also related to lower CAR AUCi (*r* = -.52, *p* = .03). Higher intake CAR AUCi is less likely to respond (*z* = -2.06*, p* = .04). Additional examination within condition is ongoing.

Joshi, S., Sheynin, J., Duval, E. R., King, A.P., Angstadt, M., Phan, K.L., Simon, N.M., *Liberzon, I., *Rauch, S.A.M. (In Preparation). Neural Activation during Reappraisal of Emotion and Assessment of Negative Faces Associated with PTSD Symptoms.

Posttraumatic Stress Disorder (PTSD) is a debilitating condition often associated with deficits in regulating emotion and assessment of emotional, and particularly negative, faces. These deficits have been associated with differences in neural activation in emotion processing regions such as the amygdala and regulatory medial and dorsolateral prefrontal cortices. This study assessed neural mechanisms underlying emotion regulation and appraisal in veterans following treatment for PTSD symptoms. Thirty-six veterans with PTSD were assigned to evidence-based treatment groups: Prolonged exposure plus pill placebo (PE + PLB; N = 6), sertraline plus enhanced medication management (SERT + EMM; N = 16), and PE plus sertraline (PE + SERT; N = 14). Participants completed assessments of symptoms in addition to emotion regulation, modulation, and appraisal tasks in an fMRI scanner prior to and following treatment. The Emotional Faces Assessment Task (EFAT) examined neural activation during implicit processing of emotional faces. The Emotion Regulation Task (ERT) assessed neural activation during passive viewing, maintenance of emotional response, and reappraisal of emotional response to distressing images. Greater pre-treatment symptom severity was associated greater activation of the Left Amygdala (β = .45, *p* = .02) and less activation in the Right Amygdala (β = -.55, *p* = .01) for Negative Face trials on the EFAT Task. ERT results for reappraisal of emotion compared to maintenance of emotion yielded less dmPFC activation with greater treatment response with PTSD participants (M = .24, SD = .43) demonstrating greater dmPFC activation compared to controls (M = .04, SD = .38) pre-treatment; t(51.89) = 2.01, p = 0.049. Within the PTSD group, less pre-treatment dmPFC activation was associated with trend-level improvement of symptoms from pre to post treatment (β = -.33, *p* = .09). Decreased amygdala activation (β = -.48, *p* = .04) and increased dlPFC activation (β = .79, *p* = .05) from pre to post treatment for reappraisal compared to maintenance of emotion were also associated with symptom reduction following treatment. This is one of the first studies to examine neural activation across different treatments for PTSD and provides greater insight into emotion regulation and processing in PTSD.

Randomized Controlled Trial of Sertraline, Prolonged Exposure Therapy and their Combination in OEF/OIF Combat Veterans with PTSD (PROGRESS; PI: RAUCH): FINAL REPORT

Sheynin, J., Duval, E. R., King, A.P., Angstadt, M., Phan, K.L., Simon, N.M., *Rauch, S.A.M., *Liberzon, I. (Under Review). Resting-State functional connectivity predicts treatment outcome in patients with PTSD.

Abnormalities in resting-state functional connectivity (rsFC) have been recently demonstrated in posttraumatic stress disorder (PTSD), suggesting they may have relevance for this condition. The current study examined pre to post treatment changes in rsFC in PTSD during the randomized treatment trial. Methods: Sixty-four combat veterans with PTSD were randomly assigned to three treatment groups: Prolonged Exposure plus placebo (PE+PLB), sertraline plus enhanced medication management (SERT+EMM), or the combination (PE+SERT). Twenty-nine combat veterans without PTSD were recruited as a no-treatment control group. Symptom assessment and resting-state MRI scanning occurred before and after treatment. Seed-based and connectome-based approaches were used to analyze rsFC. Results: Before treatment, PTSD was associated with less within-DMN (default-mode network) connectivity, i.e. between PCC, vmPFC and other DMN regions (both $p < .050$; FWE corrected), replicating prior findings. PCC and vmPFC, as well as the insula (salience-network (SN) seed), had also greater connectivity with regions within the dorsal-attention network (DAN) in patients, suggesting cross-network desegregation in PTSD (all $p < .050$; FWE corrected). Patients with more than a 50% improvement in PTSD symptoms with treatment (i.e., "high responders") had less pre-treatment amygdala-PCC connectivity ($p = .011$), suggesting the pivotal role of SN-DMN segregation in predicting treatment response. In addition, these patients had lower global centrality ($p = .042$), suggesting that global topological features may also be related to PTSD treatment response. Conclusions: These findings replicate and extend our knowledge of network-level abnormalities in PTSD, and importantly, suggest potential neural biomarkers of PTSD treatment response.

Duval, E. R., Sheynin, J., King, A.P., Phan, K.L., Simon, N.M., Martis, B., Porter, K. E., Norman, S.B., *Liberzon, I., *Rauch, S.A.M., and the PROGrESS Study Team (Under Review). Neural function during emotion processing and modulation associated with treatment response in posttraumatic stress disorder.

Posttraumatic stress disorder (PTSD) has been associated with exaggerated threat processing and deficits in emotion modulation circuitry. We examined activation in and connectivity between key emotion processing (amygdala, insula, dorsal anterior cingulate cortex) and modulation regions (dorsolateral prefrontal cortex, medial prefrontal cortex), hypothesizing they would differ between PTSD and controls, and would be predictive of PTSD treatment response. Fifty-eight military Veterans with PTSD were randomly assigned to one of three evidence-based treatments (Prolonged exposure, sertraline, and PE plus sertraline) in a clinical trial ("PROGrESS").[1] Twenty-seven combat-exposed controls (CCs) served as a comparison group. Before and after PTSD treatment, functional magnetic resonance imaging was used to assess brain activation and connectivity during the validated Shifted Attention Emotion Appraisal Task.[2,3] Activation in emotion processing (insula) and modulation (prefrontal cortex) regions at pre-treatment, and connectivity between attentional control (dorsolateral prefrontal cortex and superior parietal cortex) and emotion processing (amygdala) regions were associated with PTSD symptom improvement. This study is one of the first to examine task-based activation and functional connectivity in a PTSD treatment trial, and provides evidence suggesting that activation in and connectivity between emotion processing and modulation regions are important predictors of treatment response.

King, A.P., Sheynin, J., Tagett, R., Rajaram, M., Duval, E.R., Phan, K.L., Simon, N.M., Martis, B., Porter, K., Norman, S.B., Stein, M.B., *Liberzon, I., *Rauch, S.A.M. (In preparation). Changes in Whole-blood Leukocyte Gene Expression in Epigenetic Pathways Associated with Treatment for Combat PTSD in OEF/OIF Combat Veterans.

Posttraumatic stress disorder (PTSD) is associated with a number of aberrations in neuroendocrine and neuroimmune processes, including increased circulating catecholamines, increased inflammatory cytokines, and altered HPA axis, including hypocortisolemia and hyper-responsive glucocorticoid feedback. Recent studies have also seen evidence of transcriptional dysregulation in PTSD, including leukocyte gene expression related to cytokine, innate immunity, and type I interferon pathways. Such transcriptional dysregulations in leukocytes could play dynamic roles in the expression and maintenance of pathophysiological processes in the syndrome of PTSD. Successful treatment of PTSD might also involve normalization of transcriptional dysregulation, which might point to novel treatment targets. We collected whole blood from OEF/OIF combat-exposed veterans without history of PTSD, and in PTSD patients seeking treatment the week before evidence-based treatment (pre-treatment), and 24 weeks later (post-treatment). Leukocyte RNA was purified and transcriptome-wide gene expression analyzed using RNA sequencing (RNASeq). Transcriptome libraries were prepared from RNA with RIN values >7.0 using Illumina poly(A) capture and HiSeq4000 single-end 50nt sequencing. RNASeq data were processed using our standard RNASeq processing pipeline and QC, and reads were aligned to transcriptome. Reads per transcript were quantified and normalized for differential expression analyses. Comparison of PTSD patients (N=46) to Combat Controls (N=26) at intake (EdgeR with TMM normalization) found 56 genes that were differentially expressed (DE) in leukocytes that met transcriptome-wide threshold for significance, including voltage-gated sodium channels (SCN2A, SCN5A) and PRDM12 , and significant enrichment in adrenergic signaling, complement and coagulation, endocrine regulation, and sensory pathways, consistent with previous findings. Comparison of PTSD patients (N=25) with pre- and post-treatment (week 24) blood found 261 DE genes in the treatment responders (N=14, >20 pt reduction in CAPS), but no DE genes in treatment non-responders (N=11). DE genes were highly connected (PPI enrichment p-value=0.009) and enriched with genes for epigenetic influences. Hub genes include KDMA (histone demethylase), HDAC9, (histone deacetylase), and Ash1 (Histone methyltransferase). These data suggest PTSD is associated with DE genes in adrenergic pathways, and PTSD treatment response may be associated with DE genes involved in epigenetic pathways.

CONCLUSION

Both sertraline and Prolonged Exposure are effective treatments for PTSD in Veterans and Service members with chronic PTSD. Combining the two from treatment onset does not appear to have benefit over monotherapy. Based on this study and current VA/DOD clinical practice guideline recommendations, it seems that the best course of action for first line treatment would be to discuss with patients the treatment options available, including psychotherapy and SSRIs, and then allow the patient to make an informed choice. This will allow the future addition of the alternate option should remission not occur with the first course of care.

Mechanisms of change in psychotherapy may be impacted by the presence of a “pill.” Replication of the current findings and extension to determine how/why this may occur once replicated is warranted.

Recruitment is more difficult in studies that include both medication and psychotherapy because patients who are amenable to medication are already receiving it and are not eligible without a significant washout period, which carries with it associated risk and ethical issues if the medication were

effective. In addition to not being on medication currently, participants must be willing to be randomized and engage in regular psychotherapy sessions as well. The resulting patient sample in such trials, like the PROGRESS study, does not represent the significant group of patients who are unwilling to take a medication or those unwilling or unable to commit the time to participate in psychotherapy. Additional analyses comparing the outcomes with a parallel sample in a PE alone study recruited over the same time period at one of the sites in the study will examine how the patient samples and outcomes compare.

Biological measures of leukocyte gene expression collected in this study suggest PTSD may be associated with differential expression in genes in adrenergic and immune pathways, consistent with other recent work, and that PTSD treatment response may be associated with differential expression genes involved in epigenetic pathways.

Dissemination of best practices for medication management is warranted to ensure that patients are maximizing possible benefits from this intervention. Variability in response may be partially due to patients not staying on medication long enough to obtain full response.

With advances in imaging analytic technology, studies with larger samples that combine patients across scanners in more generalizable paradigms (like resting state) may provide the analytic power to more fully determine treatment specific mechanism of change in brain function and structure to inform treatment refinement.

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Published Manuscripts

1. Rauch SAM, Kim HM, Powell C, et al. Efficacy of Prolonged Exposure Therapy, Sertraline Hydrochloride, and Their Combination Among Combat Veterans With Posttraumatic Stress Disorder: A Randomized Clinical Trial. *JAMA Psychiatry.* 2019;76(2):117–126. doi:10.1001/jamapsychiatry.2018.3412.
2. Avallone K.M., Smith E.R., Ma S., Gargan S., Porter K.E., Authier C.C., Martis B., Liberzon I., Rauch S.A.M. PTSD as a mediator in the relationship between post-concussive symptoms and pain among OEF/OIF/OND veterans. *Military Medicine.* 2019; 184(1-2): e118-e123. doi: 10.1093/milmed/usy225.
3. Porter, K.E., Stein, M.B., Martis, B., Avallone, K.M., McSweeney, L.B., Smith, E.R., Simon, N.M., Gargan, S., Liberzon, I., Hoge, C. W., Rauch, S.A.M. Postconcussive symptoms (PCS) following combat-related traumatic brain injury (TBI) in veterans with posttraumatic stress disorder (PTSD): Influence of TBI, PTSD, and depression on symptoms measured by the Neurobehavioral Symptom Inventory (NSI). *Journal of Psychiatric Research. 2018;* 102:8-13. doi: 10.1016/j.jpsychires.2018.03.004
4. Norman, S.B., Haller, M., Kim, H.M., Allard, C.B., Porter, K.E., Stein, M.B, Venners, M.R., Authier, C.C., Rauch, S.A.M. & the PROGrESS Team. Trauma related guilt cognitions partially mediate the relationship between PTSD symptom severity and functioning among returning combat veterans. *Journal of Psychiatric Research.* 2018; 100:56-62. doi: 10.1016/j.jpsychires.2018.02.003.
5. Rauch, S. A. M., Simon, N. M., Kim, H. M., Acierno, R., King, A. P., Norman, S. B., Venners, M.R., Porter, K., Phan, K.L., Tuerk, P.W., Allard, C., Liberzon, I., Rothbaum, B.O., Martis, B., Stein, M.B.

& Hoge, C. W. Integrating biological treatment mechanisms into randomized clinical trials: Design of PROGrESS (PROlonGed ExpoSure and Sertraline Trial). *Contemporary Clinical Trials*. 2018; 64:128-138. doi: 10.1016/j.cct.2017.10.013.

6. Simon N. M., O'Day E. B., Hellberg S. N., Hoeppner S. S., Charney M. E., Robinaugh D. J., Bui T. H., Goetter E. M., Baker A. W., Rogers A. H., Nadal-Vincens M., Venners M., Kim H. M., & Rauch S. A. M. The loss of a fellow service member: Complicated grief in post-9/11 service members and veterans with combat-related posttraumatic stress disorder. *Journal of Neuroscience Research*. 2018; 96(1):5-15. doi: 10.1002/jnr.24094.

Manuscripts Accepted for Publication

1. Simon, N.M, Hoeppner, S.S., Lubin R.E., Robinaugh D.J., Malgaroli, M, Norman, S.B., Acierno, R, Goetter, E.M., Hellberg, S.N., Charney, M.E., Bui, E, Baker, A.W., Smith, E, Kim, H.M., Rauch, S.A.M. (Accepted for Publication). Understanding the Impact of Complicated Grief on Combat Related Posttraumatic Stress Disorder, Guilt, Suicide and Functional Impairment in a Clinical Trial of Post-9/11 Service Members and Veterans.

Manuscripts under Review

1. Rauch, S.A.M., Kim, H.M., Venners, M.R., Porter, K., Norman, S.B., Simon, N.M., Rothbaum, B.O., Tuerk, P.W., Acierno, R., Bui, E., Powell, C., Smith, E.R., Goetter, E., McSweeney, L. (Under Review). Examination of change in negative PTSD-related thoughts with SSRI, Prolonged Exposure +SSRI, and Prolonged Exposure + Placebo: Do thoughts drive change when pills are involved?
2. Sheynin, J., Duval, E. R., King, A.P., Angstadt, M., Phan, K.L., Simon, N.M., *Rauch, S.A.M., *Liberzon, I. (Under Review). Resting-State functional connectivity predicts treatment outcome in patients with PTSD.
3. Duval, E. R., Sheynin, J., King, A.P., Phan, K.L., Simon, N.M., Martis, B., Porter, K. E., Norman, S.B., *Liberzon, I., *Rauch, S.A.M., and the PROGrESS Study Team (Under Review). Neural function during emotion processing and modulation associated with treatment response in posttraumatic stress disorder.
4. Goetter, E. M., Hoeppner, S., Khan A., Charney, M. E., Wieman, S., Venners, M. Avallone, K., Rauch S. A. M., & Simon, N. M. (Under Review). Combat PTSD and comorbid major depression in Iraq and Afghanistan veterans: The role of deployment cycle adversity and social support.

Manuscripts in Preparation

1. Rauch, SAM, King, A.P., Venners, M.V., Kim, H.M., Powell, C., Rajaram, N., Simon, N.M., Hamner, M. Liberzon, I. (In Preparation). Cortisol awakening response in PTSD treatment: Indicator or Mechanism of change.
2. Joshi, S., Sheynin, J., Duval, E. R., King, A.P., Angstadt, M., Phan, K.L., Simon, N.M., *Liberzon, I., *Rauch, S.A.M. (In Preparation). Neural Activation during Reappraisal of Emotion and Assessment of Negative Faces Associated with PTSD Symptoms.
3. Allard, C.B.; Strauss, E.; Norman, S.B.; Kim, M; Stein, M.B., Simon, N., & Rauch, S.A.M. (In Preparation). Understanding the Impact of Guilt Related to Combat Trauma on PTSD Treatment Outcomes, and its response to PTSD treatment.

Abstract Presentations

1. Rauch, S.A.M. (2019, March). Randomized Controlled Trial of Prolonged Exposure, Sertraline and Their Combination in Combat Veterans with PTSD. In S. Rauch (chair), What Works and How: Primary Outcomes and Mechanisms of PTSD Treatment in Veterans from the PROGRESS Trial. Symposium presented at the Anxiety and Depression Association of America Annual Meeting, Chicago, IL.
2. King, A.P. (2019, March). Changes in Whole-blood Leukocyte Gene Expression in Epigenetic Pathways Associated with Treatment Response in Combat PTSD Patients In S. Rauch (chair), What Works and How: Primary Outcomes and Mechanisms of PTSD Treatment in Veterans from the PROGRESS Trial. Symposium presented at the Anxiety and Depression Association of America Annual Meeting, Chicago, IL.
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5. Sheynin, J. (2019, March). Resting-State Functional Connectivity Predicts Treatment Outcome in PTSD Patients. In S. Rauch (chair), What Works and How: Primary Outcomes and Mechanisms of PTSD Treatment in Veterans from the PROGRESS Trial. Symposium presented at the Anxiety and Depression Association of America Annual Meeting, Chicago, IL.
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7. Sheynin, J., Duval, E.R., King, A.P., Angstadt, M., Phan, K.L., Stein, M.B., Simon, N.M., *Rauch, S.A.M., *Liberzon, I. (2018, November). Resting-State Functional Connectivity is Associated with Treatment Outcome in PTSD Patients. Scientific abstract presented at the 48th annual meeting for the Society for Neuroscience, San Diego, CA.
8. Goetter E. M., Hoeppner S. S., Hellberg S. N., Acierno R., Rauch S. A. M., & Simon N. M. Understanding the Impact of Complicated Grief on Posttraumatic Stress Disorder Outcomes in Post-9/11 Service Members and Veterans. (2018, November). Symposium presented at the 34th Annual International Society for Traumatic Stress Studies Meeting, Washington D.C.
9. Goetter E. M., Charney M., Hoeppner S. S., Khan A. J., Wieman S. T., Venners M., Avallone K., Rauch S. A. M., & Simon N. M. (2018, November). Understanding the relationship between PTSD and comorbid major depression: The role of pre, peri-, and post-deployment adversity and social support. Poster presented at the 34th Annual International Society for Traumatic Stress Studies Meeting, Washington, D.C.
10. Duval, E.R., Sheynin, J., King, A.P., Phan, K.L., Simon, N.M., Martis, B., Porter, K., Norman, S.B., Stein, M.B., Rauch, S.A.M.*, Liberzon, I.* (2018, November). Activation in Pre-Treatment Emotion Modulation Circuitry is Associated with Treatment Response in PTSD. In B. Liddell (chair), Advancing

Neural Models of Posttraumatic Stress Disorder. Symposium presented at the International Society for Traumatic Stress Studies Annual Meeting, Washington, DC.

11. Porter, K.E., Stein, M.B., Martis, B., Avallone, K.M., McSweeney, L.B., Smith, E.R., Simon, N.M., Gargan, S., Liberzon, I., & Rauch, S.A.M. (2017, November). An Examination of the Relationship between PTSD, Depression, and Postconcussive Symptoms Measured by the NSI. Poster presented at the 33rd Annual International Society for Traumatic Stress Studies Meeting, Chicago, IL.
12. Avallone, K.M., Smith, E.R., Ma, S., Gargan, S., Porter, K.E., Authier, C.C., Martis, B., Liberzon, I., Rauch, S.A.M. & the PROGrESS Team. (2017, November) PTSD as a mediator in the relationship between TBI symptoms and pain among OIF/OEF Veterans. Poster presented at the 33rd Annual International Society for Traumatic Stress Studies Meeting, Chicago, IL.
13. Avallone, K.M., Smith, E.R., Ma, S., Gargan, S., Porter, K.E., Authier, C.C., Martis, B., Liberzon, I., & Rauch, S.A.M and the PROGRESS Team. (2017, April). Examining the Relationship between TBI Symptoms and Pain among OIF/OEF Veterans with PTSD. Poster presented at the 2017 meeting for the Anxiety and Depression Association of America, San Francisco, CA.
14. Simon, N., Rogers, A., Kim, M., Charney, M., Bui, E., Goetter, E., Nadal, M., Robinaugh, D., Venners, M., Rauch, S.A.M., & the PROGRESS Team. (2016, August). Complicated grief and the impact of loss of a fellow service member in post 9/11 service members and Veterans with combat related PTSD. Poster presented at the Annual Military Health System Research Symposium Meeting, Kissimmee, FL.
15. Liberzon, I., Sripada, R., Heffernan, J., Ma, S., Rauch, S.A.M., & the PROGrESS Team (2015, December). Increased within-network and cross-network functional connectivity in returning Veterans with posttraumatic stress disorder. Poster presented at the 54th Annual Meeting of the American College of Neuropsychopharmacology, Hollywood, FL.
16. Rauch, S.A.M., Venners, M., Tuerk, P., Simon, N., King, T., Liberzon, I., Kim, M., Phan, K.L., Allard, C., & Norman, S. (2015, November). Designing a combined effectiveness and mechanisms randomized trial in PTSD: Finding a balance. Symposium presented at the 31st Annual International Society for Traumatic Stress Studies Meeting, New Orleans, LA.

Accepted Abstracts

1. Joshi, S. Duval, E.R., Sheynin J., Phan, K.L., King, A.P., Martis, B., Porter, K., Stein, M.B., *Liberzon, *Rauch, S.A.M. (2019, May). Neural Activation during Reappraisal and Assessment of Emotion Associated with PTSD Poster accepted for presentation at the 31st Annual Convention of the Association of Psychological Science, Washington DC.

Invited Presentations

1. Duval, E. R. (2018, September). Shifting attention: The role of cognitive control and emotion regulation neurocircuits in PTSD. Invited presentation for the William S. Middleton Memorial Veterans Hospital Journal Club, Madison, WI.

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APPENDICES

Published Manuscripts

1. Rauch SAM, Kim HM, Powell C, et al. Efficacy of Prolonged Exposure Therapy, Sertraline Hydrochloride, and Their Combination Among Combat Veterans With Posttraumatic Stress Disorder: A Randomized Clinical Trial. *JAMA Psychiatry.* 2019;76(2):117–126. doi:10.1001/jamapsychiatry.2018.3412.

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19. Avallone, K.M., Smith, E.R., Ma, S., Gargan, S., Porter, K.E., Authier, C.C., Martis, B., Liberzon, I., & Rauch, S.A.M and the PROGRESS Team. (2017, April). Examining the Relationship between TBI Symptoms and Pain among OIF/OEF Veterans with PTSD. Poster presented at the 2017 meeting for the Anxiety and Depression Association of America, San Francisco, CA.
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21. Liberzon, I., Sripada, R., Heffernan, J., Ma, S., Rauch, S.A.M., & the PROGrESS Team (2015, December). Increased within-network and cross-network functional connectivity in returning

Veterans with posttraumatic stress disorder. Poster presented at the 54th Annual Meeting of the American College of Neuropsychopharmacology, Hollywood, FL.

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Listing of personnel receiving pay from research effort

23. See attached PDF file

JAMA Psychiatry | Original Investigation

Efficacy of Prolonged Exposure Therapy, Sertraline Hydrochloride, and Their Combination Among Combat Veterans With Posttraumatic Stress Disorder
A Randomized Clinical Trial

Sheila A. M. Rauch, PhD; H. Myra Kim, ScD; Corey Powell, PhD; Peter W. Tuerk, PhD; Naomi M. Simon, MD; Ron Acierno, PhD; Carolyn B. Allard, PhD; Sonya B. Norman, PhD; Margaret R. Venners, MPH, MSW; Barbara O. Rothbaum, PhD; Murray B. Stein, MD, MPH; Katherine Porter, PhD; Brian Martis, MD; Anthony P. King, PhD; Israel Liberzon, MD; K. Luan Phan, MD; Charles W. Hoge, MD

IMPORTANCE Meta-analyses of treatments for posttraumatic stress disorder (PTSD) suggest that trauma-focused psychotherapies produce greater benefits than antidepressant medications alone.

OBJECTIVE To determine the relative efficacy of prolonged exposure therapy plus placebo, prolonged exposure therapy plus sertraline hydrochloride, and sertraline plus enhanced medication management in the treatment of PTSD.

DESIGN, SETTING, AND PARTICIPANTS The Prolonged Exposure and Sertraline Trial was a randomized, multisite, 24-week clinical trial conducted at the Veterans Affairs Ann Arbor Healthcare System, Veterans Affairs San Diego Healthcare System, Ralph H. Johnson Veterans Affairs Medical Center, and Massachusetts General Hospital Home Base Veterans Program between January 26, 2012, and May 9, 2016. Participants and clinicians were blinded to pill condition, and outcome evaluators were blinded to assignment. Participants completed assessments at weeks 0 (intake), 6, 12, 24, and 52 (follow-up). Participants (N = 223) were service members or veterans of the Iraq and/or Afghanistan wars with combat-related PTSD and significant impairment (Clinician-Administered PTSD Scale score, ≥50) of at least 3 months' duration. Analyses were on an intent-to-treat basis.

INTERVENTION Participants completed up to thirteen 90-minute sessions of prolonged exposure therapy by week 24. Sertraline dosage was titrated during a 10-week period and continued until week 24; medication management was manualized.

MAIN OUTCOMES AND MEASURES The primary outcome was symptom severity of PTSD in the past month as assessed by the Clinician-Administered PTSD Scale score at week 24.

RESULTS Of 223 randomized participants, 149 completed the study at 24 weeks, and 207 (180 men and 27 women; mean [SD] age, 34.5 [8.3 years]) were included in the intent-to-treat analysis. Modified intent-to-treat analysis using a mixed model of repeated measures showed that PTSD symptoms decreased significantly during the 24 weeks (sertraline plus enhanced medication management, 33.8 points; prolonged exposure therapy plus sertraline, 32.7 points; and prolonged exposure therapy plus placebo, 29.4 points; β,–9.39; 95% CI, –11.62 to –7.16; $P < .001$); however, slopes did not differ by treatment group (prolonged exposure therapy plus placebo group, –9.39; sertraline plus enhanced medication management group, –10.37; and prolonged exposure therapy plus sertraline group, –9.99; $P = .81$).

CONCLUSIONS AND RELEVANCE No difference in change in PTSD symptoms or symptom severity at 24 weeks was found between sertraline plus enhanced medication management, prolonged exposure therapy plus placebo, and prolonged exposure therapy plus sertraline.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01524133

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Editorial page 109

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 117

Author Affiliations: Author affiliations are listed at the end of this article.

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Clinical practice guidelines for posttraumatic stress disorder (PTSD) have presented both trauma-focused psychotherapies and selective serotonin reuptake inhibitors (SSRIs) as effective, strongly recommended treatments.[1-3] The American Psychological Association[4] and the Veterans Affairs (VA) and Department of Defense recommended trauma-focused psychotherapy vs medication for the treatment of PTSD[1] based on meta-analyses comparing effect sizes across studies that rarely involved direct head-to-head comparisons of psychotherapy vs medication.[5,6] Without direct comparisons, effect sizes across studies may not accurately reflect efficacy, owing to differences in study designs and comparators. Furthermore, although combined medication and psychotherapy is the most common treatment practice for veterans with PTSD,[7] current guidelines are unable to make specific recommendations.[8] The few extant comparisons of trauma-focused psychotherapy vs SSRIs or combined treatment have significant limitations in design or generalizability or have focused on refractory conditions or augmentation strategies.[9-14]

The present study was designed to address these critical gaps in guidance for clinicians, especially those who serve military service members and veterans. The study provides a comparison of 2 effective treatments for PTSD—prolonged exposure therapy and sertraline hydrochloride—and whether their combination enhances either treatment alone. Prolonged exposure therapy was selected owing to the abundance of research supporting its efficacy.[1,15] Of the 2 SSRIs approved by the US Food and Drug Administration for the treatment of PTSD,[1] sertraline is generally tolerated better than paroxetine hydrochloride and has more robust data on long-term efficacy.[5,16] To control for placebo effects and nonspecific effects of therapy (eg, therapist alliance or consistency of administration), prolonged exposure therapy was combined with pill placebo or sertraline (double-blinded), and sertraline was administered using a manualized enhanced medication management protocol.[17] In this context, sertraline and prolonged exposure therapy plus sertraline were administered under matched conditions, with psychotherapists and pharmacotherapists administering treatment modalities according to manualized protocols, under expert supervision. We examined the relative efficacy of prolonged exposure therapy plus placebo, prolonged exposure therapy plus sertraline, and sertraline plus enhanced medication management among 223 veterans with combat-related PTSD on our primary outcome of PTSD severity as assessed by blinded clinicians[18] and on our secondary outcomes of clinically meaningful change, remission, response, and self-reported PTSD.[19]

Based on previous studies,[20] we hypothesized that larger reductions in symptom severity would be achieved with prolonged exposure therapy plus sertraline than with prolonged exposure therapy plus placebo and that larger reductions in symptom severity would be achieved with prolonged exposure therapy plus placebo than with sertraline plus enhanced medication management. Finally, based on concerns that sertraline might interfere with learning and reducing symptom severity using prolonged exposure therapy, we hypothesized that treatment dropout in the group treated with prolonged exposure therapy plus sertraline would be greater than in either the group treated with sertraline plus enhanced medication management or the group treated with prolonged exposure therapy plus placebo.

Key Points

Question How do prolonged exposure therapy, sertraline hydrochloride, and their combination compare with regard to reducing the severity of posttraumatic stress disorder symptoms during 24 weeks of treatment?

Findings This randomized clinical trial showed that, in a modified intent-to-treat analysis (n = 207) using a mixed model of repeated measures, the severity of posttraumatic stress disorder symptoms decreased significantly during the 24 weeks of treatment; however, slopes did not differ by treatment arms and at 24 weeks.

Meaning No difference in change in posttraumatic stress disorder symptoms or symptom severity at 24 weeks was found across the 3 groups of sertraline plus enhanced medication management, prolonged exposure plus placebo, and prolonged exposure plus sertraline.

Methods

Design

The Prolonged Exposure and Sertraline Trial (PROGrESS) is a randomized clinical trial approved by the institutional review boards at the Veterans Affairs Ann Arbor Healthcare System, the Veterans Affairs San Diego Healthcare System, the Ralph H. Johnson Veterans Affairs Medical Center, and the Massachusetts General Hospital Home Base Veterans Program and the Department of Defense Human Research Protection Office. The study is registered at ClinicalTrials.gov, and the trial protocol is available in Supplement 1. A data safety and monitoring board reviewed the conduct of the study. Participants provided written informed consent before enrollment. Participants and clinicians were blinded to pill condition through week 24, and independent evaluators were blinded to treatment assignments for the duration of the study.

Participants

Participants were recruited from the following 4 sites: the Veterans Affairs Ann Arbor Healthcare System, the Veterans Affairs San Diego Healthcare System, the Ralph H. Johnson Veterans Affairs Medical Center, and the Massachusetts General Hospital Home Base Veterans Program. Inclusion criteria were service members or veterans of the Iraq or Afghanistan wars with combat-related PTSD and significant impairment (Clinicians-Administered PTSD Scale [CAPS][5] score, ≥50) of at least 3 months' duration. Exclusion criteria were the following: (1) current, imminent risk of suicide; (2) active psychosis; (3) alcohol or substance dependence (in the past 8 weeks); (4) inability to attend weekly appointments for the treatment period; (5) prior intolerance to or failure of adequate trial of prolonged exposure therapy or sertraline; (6) medical illness likely to result in imminent hospitalization or contraindication to study treatments; (7) serious cognitive impairment

(eg, confusion or inability to track discussion); and (8) concurrent use of antidepressants or antipsychotics, benzodiazepines, prazosin hydrochloride, and sleep agents (eg, zolpidem tartrate), which were allowed if the dosage was stable for 2 weeks by baseline. Veterans with mild traumatic brain injury were not excluded.

Procedures

Full details of the study methods, selection of participants, randomization, blinding, and outcome assessments are published elsewhere.[17] Key procedures are reviewed here. Veterans and service members recruited between January 26, 2012, and May 9, 2016, were assessed with a review of their medical records, CAPS,[5] and the Mini International Neuropsychiatric Interview.[21] Once eligibility was determined, randomization (with masked allocation) occurred using a secure centralized interactive web-based application (Treatment Assignment Tool; University of Michigan). Randomization was stratified by site with treatment assignments randomly permuted in varying block sizes within the site.

Maintenance of the blinding was prioritized. All pills were encapsulated to protect the blinding. All evaluators were blinded to both medication and therapy assignments. Only 19 unblinding incidents occurred, with an alternate evaluator assigned for those cases. Independent evaluators completed training and achieved 90% or more agreement on CAPS prior to conducting assessments. Interrater reliability was conducted throughout the study period on 20% of randomly selected taped CAPS and Mini International Neuropsychiatric Interview assessments. Correlations on the CAPS ranged from 0.98 to 0.99, and the percentage agreement for Mini International Neuropsychiatric Interview diagnostic outcomes was 85% to 100%, with a κ coefficient of 0.86 for major depressive episode and 0.85 for generalized anxiety disorder. All raters attended fidelity calls to ensure consistency of rating across sites and over time. Calls occurred bimonthly for CAPS and annually for the Mini International Neuropsychiatric Interview. After completion of week 24 outcome measures, patients and clinicians were unblinded, and participants were offered open prolonged exposure therapy and/or sertraline or treatment outside of the study. Participants received $50 per assessment for weeks 0 (intake), 6, 12, 24, and 52.

Measures

Self-report and clinician-administered clinical measures occurred at weeks 0 (intake), 6, 12, 24, 36, and 52. Blinding was broken at week 24.

The primary outcome was severity of PTSD symptoms in the past month measured by the CAPS,[5] a clinician interview assessing symptom severity and diagnostic status. Current severity of PTSD symptoms was assessed in relation to targeting the most distressing war zone trauma. The *DSM IV-TR* CAPS version[22] was used, as the *DSM-5*[23] was not available at study initiation.

The secondary outcome was self-reported symptoms of PTSD (PTSD Checklist [PCL] Specific Stressor Version),[19] clinically meaningful change, response, and remission. Clinically meaningful change was defined as a reduction of 20 points or more in the CAPS score or a CAPS score of 35 or less, response was defined as a reduction of 50% or more in CAPS score, and remission was defined as a CAPS score of 35 or less; all definitions are based on week 24 or last observed CAPS score up to week 24.

Treatment

Active treatment began at week 0 and was maintained through week 24. Sertraline therapy was titrated through week 10 and continued until week 24. Early response was defined as 2 consecutive PCL scores below 28. Enhanced medication management elements ended at week 12 or with early response. Previous investigations[24,25] and recent evidence[26] support these criteria, documenting 18% of individuals with military-related PTSD as early responders to prolonged exposure therapy.

Prolonged Exposure Therapy

Participants were scheduled for 13 standard, 90-minute prolonged exposure therapy sessions by week 12 and were allowed to complete all sessions by week 24. Prolonged exposure therapy sessions included recorded sessions and in vivo exposure homework.[27] All study therapists were trained with a Veterans Affairs prolonged exposure therapy 4-day workshop and demonstrated fidelity on at least 2 supervised cases. Prolonged exposure therapy fidelity was ensured via structured weekly supervision telephone calls and independent audio recording of a random 20% of sessions (381 sessions). The therapy staff were 15 certified therapists across 4 study sites (3 from the Veterans Affairs Ann Arbor Healthcare System, 2 from the Veterans Affairs San Diego Healthcare System, 5 from the Ralph H. Johnson Veterans Affairs Medical Center, and 5 from the Massachusetts General Hospital Home Base Veterans Program). The mean (SD) number of prolonged exposure therapy cases per therapist was 8.7 (7.7) (median number, 6; range, 1-30). The analyzed fidelity measure consisted of 22 items per session, assessing prolonged exposure therapy components and therapist behaviors, and components or prescriptions not related to prolonged exposure therapy. All sites achieved a mean fidelity per session of at least 94%.

Pharmacotherapy

Medication doses were flexibly adjusted between 50 and 200 mg/d, with the last dosage increase at week 10 to ensure stable dosing by week 12. Medication was continued until week 24. Medication management (sertraline or placebo) was fully manualized to standardize pharmacotherapy delivery as brief (approximately 15 minutes) medication management, when administered alongside prolonged exposure therapy, or as enhanced medication management. Enhanced medication management was approximately 30 minutes for those randomized to receive sertraline alone to balance time, psychoeducation, and clinician support compared with prolonged exposure therapy conditions.[17] Thus, enhanced medication management added 15 minutes of psychoeducation and/or active listening to the 15-minute routine medical manage-

ment. Both medication management and enhanced medication management included clear instructions to not talk about the trauma details, included elements of exposure, or gave guidance on addressing certain PTSD-specific symptoms, such as avoidance. Prior to participation, pharmacotherapists were trained and certified on the manual and study procedures, and they participated in cross-site monthly supervision. Enhanced medication management and medication management sessions were recorded, and a randomly selected 20% were rated for fidelity and avoidance of proscribed elements of prolonged exposure therapy. Overall adherence across conditions was 96.7%.

Statistical Analysis

The primary analytic cohort is a modified intent-to-treat cohort, excluding veterans who consented but who were not dispensed any medication or placebo. The study design had 82% power to detect a 0.48 standardized effect size (corresponding to a mean [SD] difference of 11.4 [24.0] points in CAPS score) between prolonged exposure therapy plus placebo and sertraline plus enhanced medication management, and between prolonged exposure therapy plus placebo and prolonged exposure therapy plus sertraline at 24 weeks (primary end point) based on 2-sided .025-level tests using a longitudinal data model.[17] The α was chosen at .025 to account for 2 comparisons of interest.

To compare week 24 outcomes and pace of recovery, we used a mixed model of repeated measures with week 0, 6, 12, and 24 assessments as dependent variables, and with indicators for sertraline plus enhanced medication management and for prolonged exposure therapy plus sertraline, ln (time), interactions of ln (time) by indicators for sertraline plus enhanced medication management and for prolonged exposure therapy plus sertraline and study sites (stratification factor) as predictors. In the CAPS model, log-transformed time was used to model nonlinear slopes of time, and the interaction term of ln (time) by group was used to test for treatment effects on the rate of symptom changes over time. The model included random intercepts and slopes with autoregressive covariance structure, and, based on the model, predicted mean CAPS scores at week 24 were compared between 2 pairs of treatment groups. We examined the extent and pattern of missing data and used logistic regression model to evaluate baseline factors predictive of missing week 24 CAPS score and included them as covariates in sensitivity analysis. For the PCL, polynomial terms of time were included to model curvilinear trends. We examined adherence to treatment assignment (retention), with adherence to medication defined as taking medication or placebo at week 24, and adherence to prolonged exposure therapy defined as completing 13 therapy sessions within 24 weeks. Early responders were considered adherent to treatment. Treatment adherence was defined for combination therapy (eg, prolonged exposure therapy plus placebo) as completion of both therapies. Binary outcomes included remission, response, and clinically meaningful change, and they were compared across treatment groups using logistic regression models, adjusting for site, baseline CAPS score, and sex.

Results

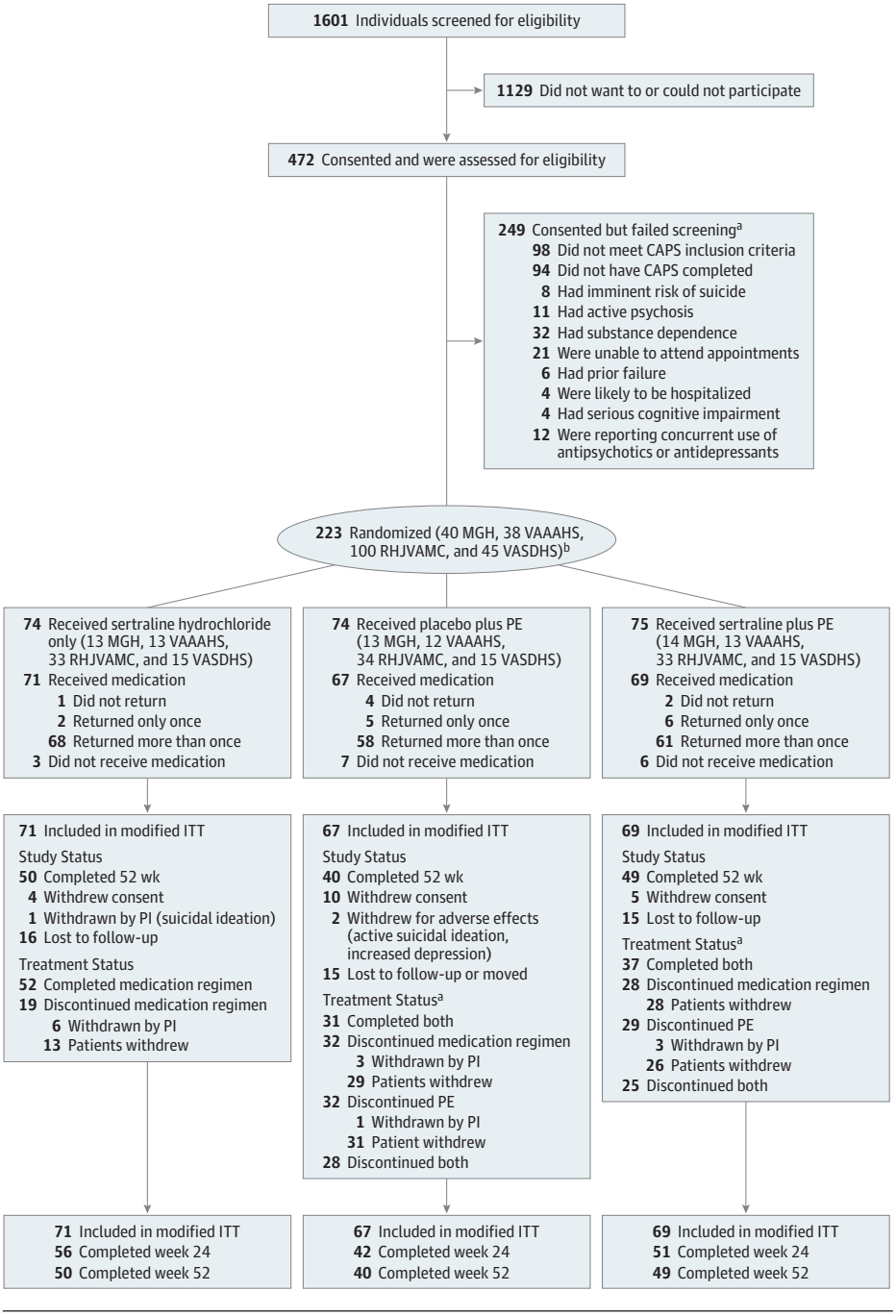
Figure 1 shows the CONSORT diagram; 472 participants underwent eligibility assessments after providing informed consent, 223 were randomized, and 207 participants (33, 34, 95, and 45 at each of the 4 sites) were dispensed medication (primary intent-to-treat cohort). After flexible dosage titration to tolerability and response, the mean (SD) week 12 sertraline hydrochloride dosage was 170.7 (46.9) mg/d for the sertraline plus enhanced medication management group, 171.6 (45.0) mg/d for the sertraline plus prolonged exposure therapy group, and 197.4 (11.3) mg/d for the prolonged exposure therapy plus placebo group ($P < .001$). The week 12 dosage for prolonged exposure therapy plus placebo differed from the 2 sertraline groups combined ($P < .001$). As previously noted, concurrent treatment with antidepressants or antipsychotics, benzodiazepines, prazosin, or sleep agents (eg, zolpidem) was allowed if the dosage was stable for 2 weeks. At baseline, the difference in concomitant psychiatric medications was significant across groups: allowed psychiatric medications at stable dosages were present in 9 of 71 patients (12.7%) in the sertraline plus enhanced medication management group, 20 of 67 patients (29.9%) in the prolonged exposure therapy plus placebo group, and 16 of 69 patients (23.2%) in the sertraline plus prolonged exposure therapy group ($P = .04$).

Modified Intent-to-Treat Cohort

Patient characteristics were comparable across groups, except for sex, marital status, and baseline function (**Table 1**). The prolonged exposure therapy plus sertraline group had fewer men and fewer married participants. Completion of week 24 CAPS did not differ significantly across treatment groups (56 of 71 [78.9%] in the sertraline plus enhanced medication management group, 42 of 67 [62.7%] in the prolonged exposure therapy plus placebo group, and 51 of 69 [73.9%] in the sertraline plus prolonged exposure therapy group; $P = .10$).

Unadjusted descriptive statistics of primary and secondary outcomes are shown in **Table 2**, and unadjusted mean cross-sectional CAPS scores are shown in **Figure 2**. Changes in unadjusted CAPS scores showed significant symptom reductions at week 24 (33.8 points for sertraline plus enhanced medication management [$P < .001$], 32.7 points for prolonged exposure therapy plus sertraline [$P < .001$], and 29.4 points for prolonged exposure therapy plus placebo [$P < .001$]). The primary model of longitudinally assessed CAPS scores showed no significant difference at week 24 between prolonged exposure therapy plus placebo and sertraline plus enhanced medication management (mean [SD] difference in score, 9.11 [4.65]; $P = .05$) or between prolonged exposure therapy plus placebo and prolonged exposure therapy plus sertraline (mean [SD] difference in score, 6.69 [4.77]; $P = .16$) (**Table 3**); the predicted mean scores were 41.9 for the sertraline plus enhanced medication management group, 51.0 for the prolonged exposure therapy plus placebo group, and 44.4 for the prolonged exposure therapy plus sertraline group. The symptoms of PTSD decreased significantly (β, -9.39; 95% CI, −11.62 to −7.16; $P < .001$) over 24 weeks in the prolonged exposure

Figure 1. CONSORT Diagram of Participants in the Prolonged Exposure and Sertraline Trial



CAPS indicates Clinician Administered PTSD Scale; ITT, intent to treat; LTF, lost to follow-up; MGH, Massachusetts General Hospital Home Base Veterans Program; PE, prolonged exposure therapy; PI, principal investigator; PTSD, posttraumatic stress disorder; RHJVAMC, Ralph H. Johnson Veterans Affairs Medical Center; VAAAHS, Veterans Affairs Ann Arbor Healthcare System; and VASDHS, Veterans Affairs San Diego Healthcare System.

[a] Some individuals had more than 1 exclusion.

[b] Groups not mutually exclusive.

therapy plus placebo group, and the rate of the decrease in the CAPS scores did not differ significantly for the sertraline plus enhanced medication management group (β, -0.98; P = .52) or for the prolonged exposure therapy plus sertraline group (β, -0.60; P = .70) (Table 3; Figure 2).

Secondary outcomes of self-reported symptoms of PTSD (PCL) estimated from a mixed model of repeated measures did not differ significantly across groups (eFigure in Supplement 2). The predicted mean difference in PCL scores at week 24 was 0.01 between the prolonged exposure therapy plus placebo group and the sertraline plus enhanced medication management group (P = .99) and 2.6 between the prolonged exposure therapy plus placebo group and the prolonged exposure therapy plus sertraline group 2.6 (P = .28).

Sensitivity Analysis

Missing data for the week 24 CAPS scores occurred for 15 of 71 participants (21.1%) in the sertraline plus enhanced medication management group, 25 of 67 participants (37.3%) in the prolonged exposure therapy plus placebo group, and 18 of 69

Table 1. Baseline Demographic Characteristics of Enrolled Intent-to-Treat Cohort

Characteristic	Participants With PTSD, No. (%)			
	Sertraline Hydrochloride (n = 71)	PE Plus Placebo (n = 67)	PE Plus Sertraline (n = 69)	Total (N = 207)
Age, mean (SD), y	33.7 (8.2)	34.7 (8.3)	35.1 (8.5)	34.5 (8.3)
Male sex	66 (93.0)	59 (88.1)	55 (79.7)	180 (87.0)
Race				
White	43 (60.6)	36 (53.7)	40 (58.0)	119 (57.5)
Black	20 (28.2)	20 (29.9)	22 (31.9)	62 (30.0)
Other	8 (11.3)	11 (16.4)	7 (10.1)	26 (12.6)
Hispanic or Latino ethnicity	14 (19.7)	7 (10.4)	10 (14.5)	31 (15.0)
Marital status[a]				
Married	42 (59.2)	36 (53.7)	30 (43.5)	108 (52.1)
Never married	19 (26.8)	11 (16.4)	15 (21.7)	45 (21.7)
Divorced	8 (11.3)	14 (20.9)	17 (24.6)	39 (18.8)
Separated	1 (1.4)	6 (9.0)	7 (10.1)	14 (6.8)
Educational level				
High school (or equivalent)	31 (43.7)	23 (34.3)	22 (31.9)	76 (36.7)
Some college (13-15 y)	32 (45.1)	27 (40.3)	34 (49.3)	93 (44.9)
Bachelor's degree or above (≥16 y)	8 (11.3)	17 (25.4)	13 (18.8)	38 (18.4)
Work status				
Full time	36 (50.7)	34 (50.7)	36 (52.2)	106 (51.2)
Part time	6 (8.5)	9 (13.4)	8 (11.6)	23 (11.1)
Not working	29 (40.8)	24 (35.8)	25 (36.2)	78 (37.7)
Served in Iraq	56 (78.9)	53 (79.1)	58 (84.1)	167 (80.7)
Served in Afghanistan[b]	32 (45.1)	36 (53.7)	30 (43.5)	98 (47.3)
CAPS score, mean (SD)[c]	75.5 (15.0)	80.9 (13.2)	76.0 (14.2)	77.4 (14.3)
CAPS subscale B score, mean (SD)	19.6 (6.0)	20.6 (7.2)	18.8 (6.7)	19.6 (6.6)
CAPS subscale C score, mean (SD)	29.0 (8.2)	32.1 (7.1)	29.9 (7.4)	30.3 (7.7)
CAPS subscale D score, mean (SD)	27.0 (5.0)	28.2 (4.6)	27.4 (4.8)	27.5 (4.8)
Major depressive disorder	43 (60.5)	52 (77.6)	48 (69.6)	143 (69.1)
Panic disorder	9 (12.7)	7 (10.4)	6 (8.7)	22 (10.7)
Agoraphobia	16 (22.5)	14 (20.9)	11 (15.9)	41 (19.8)
Alcohol abuse[a]	7 (9.9)	8 (12.9)	6 (8.7)	21 (10.1)
Substance abuse[d]	2 (2.8)	1 (1.5)	2 (2.9)	5 (2.4)

Abbreviations: CAPS, Clinician-Administered PTSD Scale; PE, prolonged exposure therapy; PTSD posttraumatic stress disorder.

[a] Does not include alcohol dependence because that was an exclusion criterion. Two patients from sertraline hydrochloride group have missing data. Percentages were calculated from a denominator of 207.

[b] One participant had an unknown marital status, and 1 participant had an unknown Afghan war status. Percentages were calculated from a denominator of 207.

[c] Total CAPS score from 17 items for the past month.

[d] Does not include substance dependence because that was an exclusion criterion.

participants (26.1%) in the prolonged exposure therapy plus sertraline group. Missing data were associated with race/ethnicity and marital status, and the primary model of CAPS, adjusting for marital status and race/ethnicity, did not show a difference in the week 24 outcomes by treatment groups. The dropout rate from the blinded study medication was 26.8% (19 of 71) for the sertraline plus enhanced medication management group, 47.8% (32 of 67) for the prolonged exposure therapy plus placebo group, and 40.6% (28 of 69) for the prolonged exposure therapy plus sertraline group, with a median time of discontinuation of therapy of 12 weeks for the sertraline plus enhanced medication management group, 5 weeks for the prolonged exposure therapy plus placebo group, and 5 weeks for the prolonged exposure therapy plus sertraline group. The dropout rate was 47.8% (32 of 67) in the prolonged exposure therapy plus placebo group and 42.0% (29 of 69) in the prolonged exposure therapy plus sertraline group, with a median time of discontinuation of prolonged exposure therapy of 5 weeks in both groups. Adherence (retention) to the entire treatment condition (ie, both the prolonged exposure therapy and the pill for the prolonged exposure therapy plus placebo group and the prolonged exposure therapy plus sertraline group) differed across groups whether unadjusted or adjusted, with the highest rate of adherence in the sertraline plus enhanced medication management group (52 of 71 [73.2%]), and the lower rates of adherence in the prolonged exposure therapy plus placebo group (31 of 67 [46.3%]) and the prolonged exposure therapy plus sertraline group (37 of 69 [53.6%]) (unadjusted $P = .005$ and adjusted $P = .006$). Similar to the primary modified intent-to-treat analysis, sensitivity analysis examining the adherent subset found no differences in CAPS scores by treatment group.

Clinically Meaningful Change, Response, and Remission Outcomes

None of the dichotomized response ($\chi^2 = 2.07$; $P = .36$), clinical response ($\chi^2 = 1.37$; $P = .50$), and remission ($\chi^2 = 3.43$;

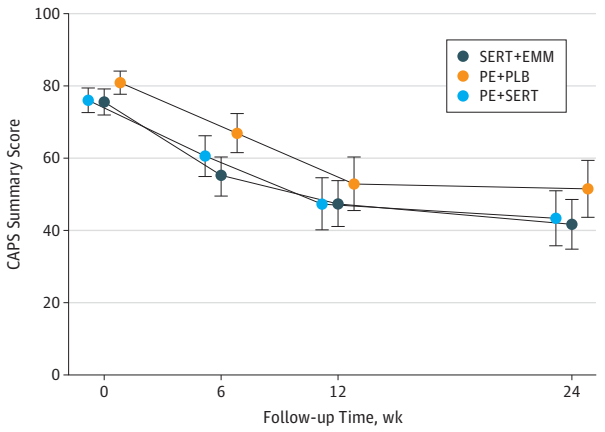
Table 2. Unadjusted Summary Statistics of Primary Outcome and Secondary Outcomes During 24 Weeks

Outcome	Sertraline Hydrochloride Plus EMM (n = 71)	PE Plus Placebo (n = 67)	PE Plus Sertraline (n = 69)
Total CAPS score, mean (SD)			
Week 0 (n = 207)	75.5 (15.0)	80.9 (13.2)	76.0 (14.2)
Week 6 (n = 172)	54.9 (21.9)	66.9 (19.2)	60.6 (20.9)
Week 12 (n = 159)	47.4 (24.4)	52.9 (24.9)	47.3 (26.4)
Week 24 (n = 149)	41.7 (25.7)	51.5 (25.3)	43.3 (27.2)
Total PCL score, mean (SD)			
Week 0 (n = 207)	56.2 (10.0)	59.6 (9.6)	56.6 (11.6)
Week 6 (n = 168)	48.1 (14.4)	51.5 (13.6)	46.9 (16.2)
Week 12 (n = 154)	42.8 (15.5)	43.0 (14.7)	40.5 (17.7)
Week 24 (n = 146)	41.5 (16.6)	42.3 (13.9)	40.5 (19.2)
Remission[a]			
No.	28	14	26
% (95% CI)	39.4 (28.0 to −51.7)	20.9 (11.9 to 32.6)	37.7 (26.3 to 50.2)
Response[a]			
No.	29	18	26
% (95% CI)	40.8 (29.3 to 53.2)	26.9 (16.8 to 39.2)	37.7 (26.3 to 50.2)
Clinically meaningful change[a]			
No.	44	35	39
% (95% CI)	62.0 (49.7 to 73.2)	52.2 (39.7 to 64.6)	56.5 (44.0 to 68.4)

Abbreviations: CAPS, Clinician-Administered PTSD Scale; EMM, enhanced medication management; PCL, PTSD checklist; PE, prolonged exposure therapy; PTSD, posttraumatic stress disorder.

[a] Remission is defined as a CAPS score of 35 or less, response is defined as 50% or higher reduction in CAPS score from baseline, and clinically meaningful change is defined as a reduction of 20 points or more in the CAPS score from baseline or a CAPS score of 35 or less. All definitions are based on week 24 CAPS scores or the last observed CAPS scores if week 24 scores are missing, and participants were considered nonremitted, not responsive, and without clinically meaningful change if all follow-up CAPS scores were missing.

Figure 2. Cross-sectional Mean Scores of Clinician-Administered PTSD Scale (CAPS) Showing Change in Posttraumatic Stress Disorder Symptoms During Treatment



PE indicates prolonged exposure therapy; PLB, placebo; PTSD, posttraumatic stress disorder; and SERT, sertraline hydrochloride. Error bars represent 95% CIs.

P = .18) outcomes differed significantly by treatment group (Table 2) after adjusting for site, baseline CAPS score, and sex.

Discussion

This head-to-head randomized clinical trial comparing sertraline plus enhanced medication management, prolonged exposure therapy plus placebo, and prolonged exposure therapy plus sertraline was initiated to answer fundamental questions about the efficacy of these treatments alone or in combination in a population of veterans. All treatments led to significant reductions in the severity of PTSD symptoms. However, contrary to our hypotheses and findings in meta-analyses, no significant differences were observed across the 3 study groups in severity of PTSD symptoms for either clinician-assessed measures or self-report measures. These results are unlikely to be the result of type II error because the study was well powered for these comparisons. The high rates of clinically meaningful change observed among veterans in this trial (eg, ranging from 52% to 62%) are noteworthy, given the proportion of participants with chronic treatment-resistant PTSD. There were no significant differences in response rates or remission rates across treatment groups.

Although we hypothesized greater effects for combination treatment than for either treatment alone and greater effects for prolonged exposure therapy plus placebo than for sertraline plus enhanced medication management, the results that we observed were not entirely unexpected. A previous randomized clinical trial of eye movement desensitization and reprocessing vs fluoxetine showed no differences 12 weeks after treatment,[12] and a study comparing a hybrid trauma-focused exposure-based acceptance and commitment therapy and medical management (sertraline supplemented with a sleep aid), or their combination, showed no significant differences after treatment.[9] Finally, prolonged exposure therapy resulted in statistically higher rates of remission of PTSD compared with paroxetine, but the combination of prolonged exposure therapy and paroxetine did not differentiate from either alone.[11]

Importantly, this study was designed to deliver sertraline and prolonged exposure therapy plus sertraline under matched conditions that included rigorous training and ongoing supervision of psychotherapists and pharmacotherapists. To balance clinical attention and expectations, the group receiving sertraline without prolonged exposure therapy received 30

Table 3. Mixed-Effects Model of Primary Outcome (CAPS 17-Item Total Score) Using Follow-up Data at Weeks 6, 12, and 24 and Marginal Mean Scores at Week 24 Estimated Based on the Model[a]

Model	Coefficient (SE)	*z* Score	*P* Value	95% CI
Constant	80.76 (2.96)	27.26	<.001	74.95 to 86.57
Study arm (with PE plus placebo as reference)				
Sertraline hydrochloride plus EMM	−5.95 (2.60)	−2.29	.02	−11.04 to −0.87
PE plus sertraline	−4.74 (2.62)	−1.81	.07	−9.87 to 0.38
Study site (with site 1 as reference)				
Site 2	0.84 (3.48)	0.24	.81	−5.98 to 7.66
Site 3	1.19 (2.88)	0.41	.68	−4.46 to 6.83
Site 4	−0.81 (3.26)	−0.25	.80	−7.21 to 5.58
ln (time + 1) (with PE plus placebo as reference)[b]	−9.39 (1.14)	−8.25	<.001	−11.62 to −7.16
ln (time + 1) by sertraline plus EMM	−0.98 (1.52)	−0.64	.52	−3.96 to 2.00
ln (time + 1) by PE plus sertraline	−0.60 (1.56)	−0.39	.70	−3.66 to 2.45
Marginal CAPS mean score at week 24				
PE plus placebo	51.04 (3.49)	14.64	<.001	44.20 to 57.87
Sertraline plus EMM	41.93 (3.07)	13.66	<.001	35.91 to 47.94
PE plus sertraline	44.35 (3.26)	13.62	<.001	44.20 to 57.87
Comparison between groups at week 24 (primary contrasts)[c]				
PE plus placebo vs sertraline plus EMM	9.11 (4.65)	1.96	.05	0.01 to 18.22
PE plus placebo vs PE plus sertraline	6.69 (4.77)	1.40	.16	−2.66 to 16.04

Abbreviations: CAPS, Clinician-Administered PTSD Scale; EMM, enhanced medication management; PE, prolonged exposure therapy; PTSD, posttraumatic stress disorder.

[a] The model is based on CAPS scores at weeks 0, 6, 12, and 24 and had random intercepts and slopes with autoregressive covariance structure. The CAPS score was also evaluated using longer-term data by including weeks 36 and 52 and no differences in slope were found across groups ($P = .83$).

[b] Time is in weeks and log-transformed to depict the pattern of decreasing symptoms at a decreasing rate seen in Figure 2. Coefficients of ln (time + 1) estimate the treatment effect as changes in symptom scores, and they do not differ between sertraline hydrochloride plus EMM vs PE plus placebo ($P = .52$) and between PE plus sertraline vs PE plus placebo ($P = .70$).

[c] The standardized effect sizes based the between-group difference in CAPS scores are 0.38 (9.11/23.7) for PE plus placebo vs sertraline plus EMM and 0.28 (6.69/23.7) for PE plus placebo vs PE plus sertraline, where 23.7 is the common SD of the changes in CAPS score from baseline to week 24.

minutes of enhanced medication management, with sertraline expected to support medication adherence.[1] These enhancements may have contributed to the somewhat larger effect size obtained for the sertraline plus enhanced medication management condition compared with previous medication-only trials. The present study did not include a prolonged exposure therapy without a pill condition, which resulted in increased patient burden during prolonged exposure therapy in clinical practice. Thus, the quality of the prolonged exposure therapy provided was high, but the overall effect may have been affected by the placebo. Moreover, we used 24 weeks as our primary outcome, with high levels of adherence to medication and a graded 10-week titration schedule to minimize adverse effects. This longer duration of medication management may have allowed participants to achieve greater benefit from sertraline compared with shorter trials, as previous studies have shown.[28]

Contrary to our hypotheses, while sertraline plus enhanced medication management performed better than expected, in the purist effectiveness comparison of prolonged exposure therapy plus sertraline vs prolonged exposure therapy plus placebo, there was no evidence for added benefit for active medication. It is possible that participants in both the prolonged exposure therapy plus placebo group and the prolonged exposure therapy plus sertraline group attributed changes to the pill, reducing motivation for exposure components. The combined prolonged exposure therapy treatments had a greater burden for participants owing to the requirement to attend 2 different appointments and more time required per week in addition to homework, which may have contributed to the higher attrition among the participants who received prolonged exposure therapy compared with the participants who received sertraline alone. The present study design allowed for early response, and the prolonged exposure therapy plus sertraline group did show significantly more early responders (13 of 69 [18.8%]) than did the other 2 groups (6 of 67 participants [9.0%] in the prolonged exposure therapy plus placebo group and 4 of 71 participants [5.6%] in the sertraline plus enhanced medication management group were early responders). However, the overall slopes of change and the results of the intent-to-treat analysis did not differ. There were significant differences in rates of adherence, with adherence being lower in both the prolonged exposure therapy plus sertraline group and the prolonged exposure therapy plus placebo group.

Limitations

Although our results are informative, limitations are apparent. Based on study design, only combat veterans were included, suggesting that an extension to other trauma populations and demographic groups that are not represented is necessary. In addition, only participants who were not currently taking an SSRI and were willing to receive prolonged exposure therapy and/or sertraline could be randomized. This restriction made recruitment challenging because many veterans with PTSD were already receiving an SSRI,[7] and many

veterans are unwilling to take psychotropic medication. Despite this fact, the retention rate (ranging from 46.3% [31 of 67] to 73.2% [52 of 71]) was similar to that seen in other studies of PTSD in veterans. Nonetheless, additional research needs to focus on enhancing treatment retention, including delivering prolonged exposure therapy over compressed time frames.[29] Third, the enhanced medication management protocol is not standard medication management but does show excellent results. This protocol may provide a possible guide to enhance routine medication treatment and achieve the magnitude of effect found in this study.

Conclusions

In this first direct comparison of 2 of the most commonly administered treatments of PTSD (sertraline and prolonged exposure therapy) and their combination (sertraline plus prolonged exposure therapy) for veterans, we found no significant differences between the 3 treatment groups. These results require additional replication and may suggest changes to future clinical guidelines, particularly when SSRIs are administered under similar conditions to this study.

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PTSD as a Mediator in the Relationship Between Post-Concussive Symptoms and Pain Among OEF/OIF/OND Veterans

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ABSTRACT Introduction: Traumatic brain injury (TBI), pain, and post-traumatic stress disorder (PTSD) commonly co-occur in Veteran populations, particularly among Veterans returning from the recent conflicts in Iraq and Afghanistan. Extant research indicates that both TBI and PTSD can negatively impact pain broadly; however, less is known about how these variables impact one another. The current study examines the impact of self-reported post-concussive symptoms on both pain severity and pain interference among Veterans with PTSD who screened positive for a possible TBI, and subsequently, evaluates the potential mediating role of PTSD in these relationships. Materials and Methods: Participants were 126 combat Veterans that served in Operation Enduring Freedom, Operation Iraqi Freedom, or Operation New Dawn who were being evaluated for participation in a multisite treatment outcomes study. As part of an initial evaluation for inclusion in the study, participants completed several self-report measures and interviews, including the Brief Traumatic Brain Injury Screen, Neurobehavioral Symptom Inventory, Brief Pain Inventory, and the Clinician Administered PTSD Scale, which were utilized in these analyses. Results: For pain severity, greater post-concussive symptoms significantly predicted increased pain severity with a significant indirect effect of post-concussive symptoms on pain severity through PTSD (indirect effect = 0.03; 95% confidence interval = 0.0094–0.0526). Similar results were found for pain interference (indirect effect = 0.03; 95% confidence interval = 0.0075–0.0471). Conclusions: These findings replicate and extend previous findings regarding the relationship between TBI, pain, and PTSD. Self-reported post-concussive symptoms negatively impact both pain severity and pain interference among Veterans with probable TBI, and PTSD serves as a mediator in these relationships. Clinically, these results highlight the importance of fully assessing for PTSD symptoms in Veterans with a history of TBI presenting with pain. Further, it is possible that providing effective PTSD treatment to reduce PTSD severity may provide some benefit in reducing post-concussive and pain symptoms.

INTRODUCTION

Extant research indicates that pain is the most common physical complaint among Veterans who served in Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF),[1] or Operation New Dawn (OND) and pain symptomology commonly co-occurs with post-traumatic stress disorder (PTSD).[2,3] The co-occurrence between PTSD and pain in this Veteran population is well documented, with estimates ranging between 10% and 50%.[4,5] Not surprisingly, this comorbidity has a greater negative impact on symptoms, quality of life, and overall functioning compared with either disorder alone. For example, individuals diagnosed with PTSD reported more severe pain and poorer quality of life than those who reported only chronic pain with no diagnosis of PTSD.[6] In addition, Veterans with chronic pain report higher rates of PTSD than the general population[2] and Veterans with both pain and PTSD report increased severity of pain, greater disability related to pain, and greater disruption in normal functioning.[2,7,8]

Traumatic brain injury (TBI) is another common concern among the OEF/OIF/OND population and has been referred to as the "signature injury" of the conflicts in Iraq and Afghanistan. One common cause of TBI is blast exposure, which accounts for approximately 65% of all injuries from these conflicts.[9] Pain is frequently reported among Veterans with TBI and can also be a consequence of TBI.[9] In the OEF/OIF/OND population, almost half of combat troops receiving care for headaches have a history of TBI.[10]

Characteristics of the current conflicts, such as number of deployments and length of conflicts, may contribute to the high rates of injury and pain. For instance, most service members report multiple deployments and wear and tear on the body is common in these intense deployed environments. This combination of factors places service members at an increased risk for exposure to injuries and situations that could result in the development of pain or TBI. Sherman and colleagues postulated that injury-related events as well as

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changes to the brain's cognitive and perceptual functions play a role in the association between TBI and pain, but that it is likely that there are also other factors which impact this relationship.[11] One factor which complicates treatment and assessment of comorbid pain and TBI is the presence of psychiatric disorders as altered emotional states can impact both subjective experience of pain and cognitive functioning.[12]

OEF/OIF/OND Veterans who have experienced a TBI frequently meet criteria for one or more psychiatric disorders, with PTSD being one of the most common psychiatric conditions seen in OEF/OIF/OND Veterans with TBI.[13] Similar to findings for comorbid pain and PTSD, Veterans with comorbid PTSD and TBI experience greater symptomology, including re-experiencing symptoms, emotional reactivity, hyperarousal, avoidance, and sleep disturbances, compared with those with PTSD alone.[14] Moreover, there is some evidence that individuals with both PTSD and TBI perform more poorly on neuropsychological measures than those with either diagnosis separately.[15] Similarly, a recent study found that the co-occurrence of PTSD and TBI had a more detrimental impact on functional outcome than either diagnosis alone.[16]

Research in recent years has found that pain, PTSD, and TBI frequently co-occur together as a group among OEF/OIF/OND Veterans[5,17] This combination has been referred to as the "polytrauma clinical triad."[17,18] While the exact reasons for this co-occurring triad are unknown, Otis and colleagues contend that a variety of factors specific to the OEF/OIF/OND conflicts contribute to the polytrauma triad, including increased length of tours and multiple deployments, increased exposure to physical and psychological stressors, increased exposure to physical trauma (e.g., blasts, explosions), and a greater ability to survive injuries due to advances in gear (e.g., body armor) and medical care.[19] They suggest that this combination of factors places individuals at an increased risk for stress-related mental health issues (e.g., PTSD), as well as physical injuries and complaints (e.g., TBI, post-concussive symptoms, pain).

These issues interact with increasing negative effects of each on the other, thus it is critical to better understand the interplay between them. Both TBI and PTSD negatively impact pain,[2,6,7,11,12] but less is known about the relationship between TBI, PTSD, and pain. With the co-occurrence of TBI and PTSD, it seems likely that factors involved in the development and maintenance of one may influence the other. Some research examining the impact of TBI and PTSD on pain suggests that Veterans with comorbid TBI and PTSD report higher levels of subjective pain compared to those with only one of these disorders.[17] Further, Stojanovic and colleagues[17] found a significant association between perceived pain and functional impairment. While existing research has identified that both TBI and PTSD can negatively impact pain broadly, less is known about the impact of post-concussive symptoms following a probable TBI on pain severity and interference (i.e., difficulties with movement or work) above and beyond the effects of PTSD. Additionally, given the negative impact emotional distress can have on both cognitive functioning and perceived pain, it is important to understand the role of PTSD in the relationship between post-concussive symptoms and pain severity and interference. Thus, the aims of the current study were to replicate and extend prior research findings by (1) examining the impact of post-concussive symptoms on both pain severity and pain interference among OEF/OIF/OND Veterans with PTSD and probable TBI, and if a significant relationship exists, to (2) evaluate the potential mediating role of PTSD in this relationship.

METHOD

Participants

Participants were comprised of 126 combat OEF/OIF/OND Veterans, evaluated between 2011 and 2016 as part of a larger multisite randomized control trial funded by the Department of Defense (PROlonGed ExpoSure Sertraline: Randomized Controlled Trial of Sertraline, Prolonged Exposure Therapy and Their Combination of OEF/OIF with PTSD; PROGrESS). Details regarding the larger study are published elsewhere.[20] Data for the current study were obtained during the initial baseline evaluation for inclusion into the larger study and represents all participants who applied, including combat controls and those who were ineligible for inclusion in the treatment portion of the study. However, only participants who were positive on the TBI screener[21] (The Brief Traumatic Brain Injury Screen [BTBIS]) were included in the analyses for this study. During the evaluation, participants completed self-report measures and structured diagnostic interviews that assessed for a range of symptoms and conditions including PTSD, self-reported post-concussive symptoms, and pain, which were used in these analyses.

The resulting sample was 97.6% male, primarily Caucasian (73.8%), and was an average age of 35.02 (SD = 10.92). Participants reported an average of 2.79 deployments, served predominately in Iraq (81%), and were primarily from the regular armed services (i.e., Air Force, Army, Marines, Navy; 84.1%). See Table I for full descriptive characteristics of this sample.

Measures

Brief Pain Inventory-Short Form

The Brief Pain Inventory-Short Form (BPI) is a self-report measure of pain that evaluates both pain severity (0: no pain through 10: pain as bad as you can imagine) and impairment related to pain (0: does not interfere through 10: interferes completely).[22] A separate score for pain severity and impairment from pain was calculated. Data on the psychometric properties of the measure have shown that it has good internal consistency, test–retest reliability, and validity.[23,24] The participants' average pain severity (range: 0–40) and overall interference score (range 0–70) were utilized in the current analyses.

The Brief Traumatic Brain Injury Screen

The Brief Traumatic Brain Injury Screen (BTBIS), which is also known as The 3 Question DVBIC TBI Screening Tool, is a three-item questionnaire used to screen Veterans and Service Members for potential mild traumatic brain injuries that they may have endured during their service.[21] The questions assess for the presence of an event that could have caused a TBI and resulted in injury (e.g., blast exposure), the experience of TBI symptoms around the time of the event (e.g., loss of consciousness), and current symptoms that may be related (e.g., headache, memory problems). While an official TBI diagnosis cannot be made from this screener, if the person endorses the first two aspects, it is considered a positive TBI screen. In the current study, participants were included in the sample if they screened positive on this measure and deemed as having a "probable TBI."

Clinician Administered PTSD Scale

The Clinician Administered PTSD Scale (CAPS) is a semi-structured diagnostic interview for PTSD, which assesses the frequency and intensity of PTSD symptoms.[25] Scores range from 0 to 136, with greater scores indicating greater frequency and/or intensity of symptoms. It has been shown to be a psychometrically strong instrument with test–retest reliabilities between 0.90 and 0.98 and internal consistency of 0.94 for total score.[26] Based on the timeframe of this study, the original CAPS based on criteria from DSM-IV-TR were used. The current study used the total score for the past month in the analyses.

TABLE I. Descriptive Statistics and Sample Characteristics (N = 126)

	Mean (SD) or N (%)
Age (years)	35.02 (10.92)
Gender (male)	123 (97.6%)
Race	
White	93 (73.8%)
Black	22 (17.5%)
Other	11 (8.8%)
Hispanic ethnicity	17 (13.5%)
Marital status	
Married or remarried	60 (47.6%)
Separated or divorced	30 (23.8%)
Never married	36 (28.6%)
Education (years)	13.84 (1.92)
Military history	
Regular armed services	106 (84.1%)
National Guard	18 (14.3%)
Reserve	1 (0.8%)
Number of deployments[a]	2.79 (3.1)
Deployed to Iraq	102 (81%)
Deployed to Afghanistan	56 (44.4%)
CAPS	70.16 (27.34)
NSI	34.16 (17.20)
BPI severity	4 (2.63)
BPI interference	3.56 (2.85)

Note. All percentages are valid percents, these may not equal 100% due to rounding. CAPS = Clinician Administered PTSD Scale; NSI = Neurobehavioral Symptom Inventory; BPI = Brief Pain Inventory.
[a]Total deployments over military career.

Neurobehavioral Symptom Inventory

The Neurobehavioral Symptom Inventory (NSI) is a self-report questionnaire that is commonly used within the VA to assess for neurobehavioral symptoms that are purported to represent post-concussive, mild TBI symptoms.[27] The measure consists of 22 items that assesses symptoms from the past 2 weeks on a 0 (none) to 4 (very severe) scale, where higher scores indicate greater severity of symptoms (range: 0–88). Previous findings have demonstrated that the measure has good internal consistency (0.95 for total score) and is a valid measure, although data also demonstrated that results are strongly influenced by aspects of psychological distress.[28]

Analytic Plan

Bivariate correlations were computed to assess the relationships between the primary dependent variables (i.e., BPI pain severity, BPI interference from pain), independent variable (NSI), and proposed mediator (CAPS total score). The mediation analyses for this study were conducted using PROCESS in SPSS in order to obtain the total, direct, and indirect effects of post-concussive symptoms on pain severity and interference through PTSD severity.[29–31] Separate mediation analyses were conducted for each of the dependent variables. Ordinary least squares (OLS) regressions using 10,000 bias-corrected bootstrapped samples were conducted to estimate all models and effects.

RESULTS

Descriptive Data and Bivariate Correlations

Descriptive statistics and sample characteristics are presented in Table I. The associations among the independent variable, dependent variable, and the proposed mediator are presented in Table II. All study variables were significantly positively associated with one another.

TABLE II. Intercorrelations Among Proposed Mediator, Independent, and Dependent Variables

	1	2	3	4
1. CAPS Total	–	0.62**	0.48**	0.49**
2. NSI Total	–	–	0.47**	0.54**
3. BPI Severity	–	–	–	0.79**
4. BPI Interference	–	–	–	–

Note. A double asterisk indicates correlation is significant at 0.01 level.

Mediation Analyses

The following models were estimated using PROCESS in SPSS. In terms of pain severity, Model 1 represents the total effect of self-reported post-concussive symptoms (NSI total score) on pain severity (BPI pain severity score). Results indicated that increased post-concussive symptoms significantly predicted greater perceived pain severity (Table III, Model 1 and Fig. 1 path *c*). Model 2 represents the effect of post-concussive symptoms on PTSD symptom severity (CAPS total score) and results indicated that having greater post-concussive symptoms significantly predicted higher levels of PTSD symptoms (Table III, Model 2 and Fig. 1 path *a*). The direct effect of post-concussive symptoms on pain severity after accounting for the influence of PTSD symptom severity is represented in Model 3. PTSD symptoms were positively associated with pain severity (Table III, Model 3 and Fig. 1 path *b*), and the direct effect of post-concussive symptoms was positively associated with pain severity after accounting for the effect of PTSD symptoms (Table III, Model 3 and Fig. 1 path *c'*). PROCESS directly calculates the indirect effect (by multiplying the path *a* coefficient by the path *b* coefficient obtained from the OLS regression analyses) as well as the corresponding confidence interval. For the current analyses, the indirect effect was calculated as $ab = 1.00 \times 0.03 = 0.03$ and the resulting confidence interval (95% CI = 0.0094–0.0526) did not include zero, suggesting a significant indirect effect of post-concussive symptoms on pain severity through PTSD symptom severity. That is, PTSD symptom severity serves as a partial mediator of the association between perceived post-concussive symptoms and pain severity.

With regard to reported interference from pain, Model 4 represents the total effect of post-concussive symptoms on pain interference (BPI pain interference score). Results indicated that increased post-concussive symptoms significantly predicted greater perceived interference from pain (Table IV, Model 4 and Fig. 2 path *c*). Model 5 represents the effect of post-concussive symptoms on PTSD symptom severity and results indicated that having greater post-concussive symptoms significantly predicted higher levels of PTSD symptoms (Table IV, Model 5 and Fig. 2 path *a*). The direct effect of post-concussive symptoms on pain interference after accounting for the influence of PTSD symptom severity is represented in Model 6. PTSD symptoms were positively associated with pain interference (Table IV, Model 6 and Fig. 2 path *b*), and the direct effect of post-concussive symptoms was positively associated with pain interference after accounting for the effect of PTSD symptoms (Table IV, Model 6 and Fig. 2 path *c'*). The indirect effect was calculated as $ab = 1.00 \times 0.03 = 0.03$ and the resulting confidence interval (95% CI = 0.0075–0.0471) did not include zero, suggesting a significant indirect effect of post-concussive symptoms on reported interference from pain through PTSD symptom severity. That is, PTSD symptom severity serves as a partial

TABLE III. OLS Regression Model Coefficients for BPI Severity

Outcome	Model 1 BPI Severity	Model 2 CAPS	Model 3 BPI Severity
Constant	1.56**	35.94***	0.48
NSI	0.07***	1.00***	0.04**
CAPS			0.03**
R^2	0.21	0.39	0.28

Note. All Models contain unstandardized OLS regression coefficients with OLS R^2.
**$p < 0.01$, ***$p < 0.001$.

TABLE IV. OLS Regression Model Coefficients for BPI Interference

Outcome	Model 4 BPI Interference	Model 5 CAPS	Model 6 BPI Interference
Constant	0.57	35.92***	−0.37
NSI	0.09***	1.00***	0.06***
CAPS			0.03**
R^2	0.29	0.39	0.33

Note. All Models contain unstandardized OLS regression coefficients with OLS R^2.
*$p < 0.05$, **$p < 0.01$.

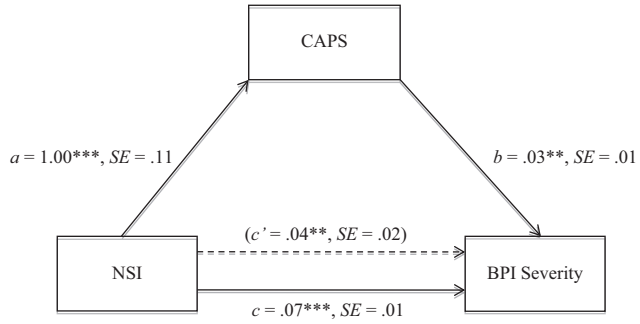

FIGURE 1. Path coefficients for simple mediation analysis on BPI pain severity. Dotted line denotes the effect of self-reported post-concussive symptoms on pain severity when PTSD symptom severity is included as a mediator. *a, b, c*, and *c'* are unstandardized OLS regression coefficients. **$p < 0.01$, ***$p < 0.001$.

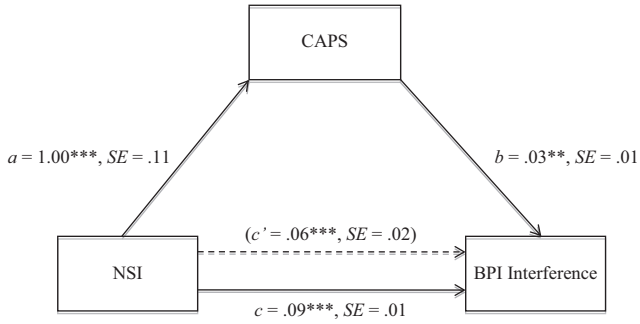

FIGURE 2. Path coefficients for simple mediation analysis on BPI pain interference. Dotted line denotes the effect of self-reported post-concussive symptoms on pain interference when PTSD symptom severity is included as a mediator. *a, b, c*, and *c'* are unstandardized OLS regression coefficients. **$p < 0.01$, ***$p < 0.001$.

mediator of the association between perceived post-concussive symptoms and interference from pain.

DISCUSSION

Extant research clearly documents the co-occurrence of TBI and related post-concussive symptoms, PTSD, and pain among Veterans from the OEF, OIF, and OND conflicts as well as the negative consequences of TBI-related post-concussive symptoms and PTSD on pain generally; however less is known about the impact of these symptoms on specific components related to pain (e.g., pain severity). Further, emotional distress negatively impacts both cognitive functioning and pain, but to date, no research has examined the potential mediating role of PTSD on the relationship between post-concussive symptoms and pain. The purpose of the current study was to examine the impact of self-reported post-concussive symptoms on both pain severity and pain interference among OEF/OIF/OND Veterans with PTSD and probable TBI and to evaluate the potential mediating role of PTSD in this relationship. Results from the current study suggest that greater post-concussive symptoms predict greater intensity of the experience of pain, as well as perceived impairment from pain, which replicates and extends previous research in this area.[17]

Additionally, there was a significant indirect effect of post-concussive symptoms on pain severity and interference through PTSD. In other words, the association between post-concussive symptoms and pain (both severity and interference from pain) appears to be influenced, in part, by PTSD symptoms. Post-concussive symptoms were a significant predictor of PTSD symptoms, which, in turn, significantly predicted greater pain severity or pain interference.

While preliminary, the results of this study provide some insight into the interconnection between these conditions and may have important clinical implications. Previously, Otis et al posited that the high rates of co-occurring TBI, PTSD, and pain in service members from the current conflicts are potentially related to features of the wars that increased exposure to physical and psychological stressors.[19] Although the current study cannot speak to the full range of physical stressors endured, findings lend support for the idea that heightened psychological distress may play a key role in continued pain following exposure to head injuries and blasts in a combat zone.

Clinically, these results highlight the importance of fully assessing for PTSD symptoms in Veterans with a history of TBI presenting with pain. In some cases, patients may initially present with a focus on physical complaints related to both pain and experience of TBI. However, given the high rates of comorbidity and the strength of the correlation between symptoms, it is essential to explore symptoms of psychological distress. Further, based on the finding that PTSD symptoms partially mediate the relationship between post-concussive symptoms and pain, it is possible that providing effective PTSD treatment to reduce PTSD severity may provide some benefit in reducing post-concussive and pain symptoms. Additional research is needed to more closely examine this potential relationship. However, previous randomized control trials have supported that perceived pain is reduced in Prolonged Exposure.[32]

While these results are promising, limitations must be considered. Specifically, post-concussive symptoms were assessed via self-report. While participants reported experiencing an event that may have resulted in a TBI, a full neuropsychological evaluation was not conducted and a confirmation of TBI diagnosis (e.g., via medical record review) or severity (e.g., mild, moderate, severe) was not obtained as part of this study. Additionally, there is some overlap in symptoms included on the NSI and psychological distress.[33] Future research incorporating a full neuropsychological evaluation or confirmation of TBI diagnosis and severity would allow for a better understanding of the role of PTSD in the association between TBI and pain. Further, various factor structures of the NSI have been proposed in previous research with the most favorable being a four-factor model (e.g., affective, cognitive, somatosensory, vestibular).[34,35] Using different factor solutions of the NSI, as well as incorporating a non-TBI comparison group into future studies would help to minimize the potential impact due to overlap of symptoms. It would also be beneficial for future studies to utilize a larger sample size and additional measures of pain, as the current study utilized only one self-report measure of pain. Another limitation of the present study is that it was cross-sectional and, as a result, no conclusions regarding temporal pattern can be made. For example, it cannot be determined if the pain described was a result of traumatic events or TBIs experienced within the combat deployment or possibly due to some prior injury. Future research should examine the timeline of symptoms which would provide additional information about how these symptoms and experiences may impact the development or maintenance of others.

In conclusion, the present findings suggest a significant indirect effect of TBI symptoms on both pain severity and pain interference through PTSD. PTSD may serve as a link in the relationship between TBI symptoms and experience of pain.

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PREVIOUS PRESENTATION

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Postconcussive symptoms (PCS) following combat-related traumatic brain injury (TBI) in Veterans with posttraumatic stress disorder (PTSD): Influence of TBI, PTSD, and depression on symptoms measured by the Neurobehavioral Symptom Inventory (NSI)

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A B S T R A C T

Mild traumatic brain injury (mTBI) is commonly reported in recent combat Veterans. While the majority resolve, some Veterans develop postconcussive symptoms (PCS). Previous research suggests these symptoms are not specific to head injury and are often associated with psychiatric symptoms. The current study examines the relative contributions of posttraumatic stress, depressive symptoms, and TBI on postconcussive symptoms, and explores whether the relationship remains after controlling for symptom overlap. Two hundred eighteen combat Veterans from Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND) provided the data for this study as part of a baseline evaluation for inclusion into larger treatment study for posttraumatic stress disorder (PTSD). Participants completed the Brief Traumatic Brain Injury Screen (BTBIS), Neurobehavioral Symptom Inventory (NSI), PTSD Checklist-Stressor Version (PCL-S), Beck Depression Inventory-II (BDI-II). Significant differences in NSI total score between individuals with and without history of TBI were not found. A series of regression analyses demonstrated that Depression and PTSD were significant predictors of NSI score even after removal of NSI symptoms that overlap with PTSD or depression. TBI status was also a significant predictor of PCS in most models, but its relative contribution was much smaller than that of depression and PTSD. Within PTSD symptoms, hyperarousal cluster was a significant predictor of NSI scores. Findings demonstrate that depression and PTSD are related to PCS beyond similarities in construct. Further, within a primarily PTSD treatment-seeking population, these psychiatric symptoms appear to be a stronger contributor than TBI.

1. Introduction

Traumatic brain injuries have been observed to be common in Veterans who have served in combat operations in Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND). Data from these conflicts suggest approximately 12–23% of service members meet criteria for a Traumatic Brain Injury (TBI), the majority of which are classified as mild traumatic brain injuries (mTBI; e.g., Hoge et al., 2008; Schneiderman et al., 2008; Terrio et al., 2009), also known as concussions. The clinical course of mTBI usually results in complete recovery, but a minority of individuals experience lasting postconcussive symptoms (PCS; Tator et al., 2016;

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Dikmen et al., 2017). Common PCS include concentration and memory problems, dizziness, headaches, irritability, anxiety, and a range of other physical, cognitive, and emotional symptoms. PCS has been shown to be associated with worse health outcomes, increased physical and mental healthcare utilization, and poorer reported quality of life in OIF/OEF/OND Veterans (e.g., King et al., 2014; Schiehser et al., 2015; Williams et al., 2017), pointing to a growing need to better understand these symptoms.

Numerous studies, however, show that PCS lacks a validated clinical case definition. Both ICD-10 and DSM-IV definitions of post-concussion syndrome, based on common symptoms reported after concussion, have been shown to have very poor diagnostic validity, and the diagnosis was eliminated from DSM-5. The research on PCS indicate that these symptoms lack specificity for head injury and are associated with a host of other psychological and physical health conditions (e.g., Hoge et al., 2008; Iverson, 2006; Smith-Seemiller et al., 2003), as well as occurring in high rates in individuals without concussions (e.g., Iverson and Lange, 2003; Wang et al., 2006). In studies of patients seen in emergency room trauma centers, pre-injury psychiatric conditions, such as depression, anxiety, and acute posttraumatic stress disorder (PTSD) symptoms were found to be significant predictors of PCS, while the presence or absence of mTBI was not a consistent predictor (Meares et al., 2011; Ponsford et al., 2012). Similarly, in a study of children and adolescents, anxiety and depression were significant predictors of PCS symptoms three months following a motor vehicle accident, without significant differences in PCS between those with and without mTBI (Segev et al., 2016). Additionally, factors such as female gender (e.g., Bazarian et al., 2010; Miller et al., 2016; Ponsford et al., 2012), older age (e.g., Ponsford et al., 2012; Thornhill et al., 2000), and involvement in litigation or receiving financial compensation (e.g., see Binder and Rohling, 1996 and Carroll et al., 2004) have all been shown to be associated with greater and more prolonged symptoms of PCS. Research with combat Veterans has replicated many of these findings. For example, a cross-sectional study of combat infantry soldiers showed that PTSD and depression nearly completely explained the association of mTBI with post-concussive and other generalized health symptoms (Hoge et al., 2008). A study of UK military personnel found that self-reported mTBI was no more likely to be associated with subsequent PCS than was self-reported exposure to non-TBI combat events, such as helping the wounded (Fear et al., 2009). Similarly, a US military study involving poly-trauma patients concluded that emotional distress, but not injury or event characteristics, was predictive of persistent PCS (e.g., Lippa et al., 2010; Waldron-Perrine et al., 2014). Finally, in a more recent study of OEF/OIF Veterans, a significant relationship between mTBI and PCS during a 3 month follow-up, but also showed that posttraumatic stress, pain, and combat exposure were also predictors of PCS (Schwab et al., 2017).

Several studies have specifically highlighted the relationship between PTSD symptoms and PCS. For instance, in a sample of Veterans and service members, it was shown that participants with a history of mTBI reported a significantly higher number of PCS compared with those participants with moderate to severe TBIs (Belanger et al., 2010). However, this difference was no longer present after controlling for PTSD symptoms. Similarly, several other studies have shown that after accounting for the effects of PTSD symptoms, the relationship between mTBI and PCS is no longer significant (e.g., Hoge et al., 2008; Levin et al., 2010; Polusny et al., 2011). It has also been demonstrated that experiencing a TBI during a deployment was a better predictor of PTSD, than combat severity, predeployment PTSD symptoms, and previous TBIs, further highlighting the relationship between these conditions (Hoge and Castro, 2014).

Taken together, these findings provide uncertainty about causality of these symptoms of PCS following mTBI, and raise questions about the extent to which psychological conditions contributes to generalized health symptoms labeled as PCS. Additionally, given that PCS shares several symptoms with mental health conditions common in Veterans, the exact nature of the association between PCS and psychological distress requires further clarification.

In this study, we evaluated assessments of psychological distress (focused on posttraumatic stress and depressive symptoms, both of which are commonly experienced post-mTBI, Howlett and Stein, 2016) and PCS in combat Veterans participating in a multisite treatment study of posttraumatic stress disorder (PTSD). Utilizing several analytical methods on baseline data, we tested the hypothesis that PCS would be more robustly associated with psychological distress than with a history of mTBI. Further, we hypothesized that this relationship would persist even after controlling for symptom overlap between PCS and symptoms of PTSD and depression.

2. Method

2.1. Participants

Two hundred eighteen combat Veterans from Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND) were included in this study. All data were obtained during an eligibility evaluation for participation in the PROGrESS (PROlonGed ExpoSure Sertraline: Randomized Controlled Trial of Sertraline, Prolonged Exposure Therapy and Their Combination in OEF/OIF Veterans with PTSD) study. The PROGrESS study is a multisite treatment outcome study for PTSD that took place from 2011 to 2017. Details of the methodology of the larger clinical trial, including a full list of inclusion and exclusion criteria are published elsewhere (Rauch et al., 2018). The current project includes participants who were approached to be part of the larger study, and completed the initial baseline self-report data specific to the aims of this study regardless of their inclusion into the larger treatment study. The vast majority of participants met criteria for current PTSD (84.3%), and were eligible for the larger treatment study (80.3%). However, a portion of participants in the current sample, did not qualify for inclusion for the treatment study (4.6%), most often because of subthreshold PTSD symptoms. Additionally, a portion (15.2%) had been approached and screened as part of a combat control sample. For the purposes of this study, all participants were included to provide a greater range of PTSD symptoms and a sample that is more analogous to general treatment seeking populations.

Participants in this study were predominately male (90.4%), had been deployed to Iraq (79.4%), and had a mean of 2.27 (SD = 1.55) deployments. The average age of the sample was 34.66 years (SD = 9.78). Please see Table 1 for additional demographic information.

2.2. Measures

The Brief Traumatic Brain Injury Screen (BTBIS; Schwab et al., 2006) was utilized to determine if a participant reported experiencing a TBI during their deployment. This 3-item screening questionnaire has been routinely used with military samples to assess for potential mild TBIs (mTBI). The BTBIS assesses for a history of events during deployment that could potentially cause a TBI, alterations in consciousness and symptoms of concussion at the time of the event, as well as ongoing symptoms that the participant currently attributes to a potential head injury. A participant is considered to have a positive screen if the endorse items on the first two questions, which assesses for a potential TBI exposure during their deployment (e.g., blast from an IED, shrapnel to the head, vehicle accidents) and corresponding alterations and symptoms at the time. Although a positive screen is not considered a definitive TBI diagnosis, this measure has been widely used in DoD and VA screening programs to identify those who need further evaluation for TBI. Data on the psychometric properties of the BTBIS are limited, however, initial data regarding concurrent validity were mixed. Results showed that the BTBIS had high levels of agreement

Table 1
Sample characteristics (N = 218).

	Mean (SD) or N (%)
Age	34.66 (9.76)
Gender	
Male	197 (90.4%)
Marital Status	
Married	104 (47.9%)
Never Married	60 (27.7%)
Divorced or Separated	53 (24.4%)
Race	
White	143 (65.6%)
Black	48 (22.0%)
Other	27 (12.3%)
Served in Iraq	173 (79.4%)
Served in Afghanistan	98 (45.0%)
Number of Deployments	2.27 (1.55)
Positive for Current PTSD	183 (84.3%)
Positive TBI Screen	105 (48.2%)
PCL Total	54.56 (16.87)
BDI-II Total	22.20 (13.28)
NSI Total	32.48 (18.10)

Notes: NSI= Neurobehavioral Symptom Inventory. BDI-II= Beck Depression Inventory-II. PCL= PTSD Checklist.

with other self-report measure in cases where the criterion measures identified the case as positive for TBI, but had a higher tendency to identify cases as positive for probably TBI than the other measure (Schwab et al., 2007). However, 83% of cases identified as positive by the BTBIS were confirmed by interview. In the current study, the BTBIS was administered in an interview format, rather than as a self-report questionnaire as used in most screening processes. Questions and responses were read directly from the screener, minimizing the potential impact of this change in administration. However, it is possible this may influence responses.

In addition to the BTBIS, all participants completed the Neurobehavioral Symptom Inventory (NSI; Cicerone & Kalmar, 1995), a 22-item self-report measure of PCS over the preceding two weeks. All items are measured on a Likert scale with ratings between 0 and 4, where 0 represents "none," and 4, indicating "very severe." The NSI one of the most commonly used scales to measure PCS, and has a high degree of internal consistency ($\alpha = 0.95$ for total scale; King et al., 2012), though few studies have been conducted to determine the degree to which NSI symptoms occur in conditions other than mTBI. In a study of OEF/OIF Veterans receiving care within the VA, a 4-factor structure was found, consisting of vestibular, somatosensory, affective, and cognitive subscales (Meterko et al., 2012). This finding has been replicated in other military samples and has received support for use in DOD and VA samples (Department of the Army, 2014). Of note, the BTBIS and the NSI were not administered next to each other during the intake evaluation. The BTBIS was completed during the interview portion of the evaluation, and the NSI was completed along with other self-report questionnaires.

Finally, the PTSD Checklist-Stressor Version (PCL-S, Weathers et al., 1993), and the Beck Depression Inventory-II (BDI-II, Beck et al., 1996) were used to measure PTSD and depression symptoms. The PCL-S used corresponds to the DSM-IV-TR (American Psychiatric Association, 1994) symptoms of PTSD (which were in use at the start of this study). The measure is a 17-item self-report questionnaire that assesses symptoms on a 1–5 scale, with higher scores indicating increased symptoms. The PCL is commonly used in VA and DOD settings, and previous research indicates that is has strong psychometric properties (e.g., Weathers et al., 1993; Blanchard et al., 1996). Similarly, the BDI-II is a self-report measure that is frequently used and has been shown to be reliable measure (e.g., Beck et al., 1996; Dozois et al., 1998). It includes 21-items that are measured on a 0–3 scale, where higher scores indicated greater levels of depression.

2.3. Statistical analyses

T-tests were initially conducted to determine if there were group differences on the total score of the NSI based on if a participant reported a history of TBI according to the BTBIS. The decision was made that if the NSI failed to differentiate between those with a history of TBI and those without such a history, then the entire dataset would be evaluated for associations between TBI history, PTSD symptoms, and depression symptoms with PCS. We also analyzed the association of symptoms reported at the time of the TBI, and PCS controlling for PTSD and depression symptoms in the subset of participants who also met criteria for TBI. The four subscales of the NSI identified by Meterko et al. (2012) were also examined. This subscale structure was chosen because it has been recommended for use in military samples (Department of the Army, 2014) and confirmatory factor analysis demonstrated that it was a good fit for this data.

In order to examine the contribution of psychological distress to symptoms on the NSI, separate sets of regressions were conducted in which the PCL-S, BDI-II, and TBI screen were used as predictor variables. In the first regression, the standard scoring of the total NSI score was applied. Given the conflicting research findings on the relationship between the NSI and measures of psychological distress, additional regressions were run in which these overlapping symptoms were removed.

Overlapping symptoms were addressed in two ways. First, five independent raters compared items on NSI, PCL-S, and BDI-II. Items on the NSI were identified as "overlapping" if raters viewed them as measuring the same symptom as an item on either the PCL-S or BDI-II. For an item to be determined an "overlapping" item, 100% blind agreement was required from all five raters. All told, there were 8 NSI items (12- "increased or decreased appetite," 13- "poor concentration, cannot pay attention, easily distracted," 15- "difficulty making decisions," 17- "Fatigue, loss of energy, getting tired easily," 18- "difficulty falling or staying asleep," 20- "feeling depressed or sad," & 21- "easily annoyed/irritability") that were deemed overlapping with items on the PCL-S or BDI-II. Correlations between these overlapping items and the corresponding items on the PCL-S and BDI-II were examined to ensure that intercorrelations were high (average $r = 0.745$, range of 0.651–0.828). A total NSI score with these items removed was then developed (NSI- overlap removed, NSI-OR).

In the third set of regressions, we conceptualized overlap in regard to NSI subscales, and removed the items found on the affective scale of the NSI (items 17, 18, 19, 20, 21, & 22). A total NSI score with this subscale was calculated for this series of regressions (NSI-affective removed, NSI-AR).

In addition to these regressions, additional analyses were conducted using PTSD symptom clusters identified in the DSM-IV-TR, and the BDI-II as covariates to determine if specific PTSD symptoms clusters independently predicted NSI scores beyond depression.

3. Results

Since results from independent samples t-tests demonstrated no significant differences between individuals who did and did not screen positive for a history of TBI on the BTBIS for any of the versions of the NSI scoring (NSI Total, $t(216) = -1.31$, $p = .191$, $M = 34.14$, SD = 17.39 for TBI positive screen, $M = 30.93$, SD = 18.68 for negative screen; NSI-OR, $t(216) = -1.57$, $p = .118$ M = 21.60, SD = 12.16 positive, $M = 18.96$, SD = 12.60 negative; NSI-AR, $t(216) = -1.65$, $p = .101$ M = 17.36, SD = 10.61 positive, $M = 14.94$, SD = 11.00 negative). Subsequent analyses therefore included all participants. Differences were also examined in regard to the NSI subscales. A significant difference was noted only on the vestibular subscale of the NSI ($t(216) = -2.96$, $p < .01$), with participants screening positive on the BTBIS scoring higher (M = 2.39 SD = 2.47 for BTBIS positive and M = 1.50 SD = 1.94 for negative) than participants who did not screen

Table 2
Intercorrelations among predictor and criterion variables.

	1	2	3	4	5	6	7	8
1. NSI Total	–	.98**	.96**	.78**	.77**	.67**	.73**	.76**
2. NSI-OR	–	–	.98**	.72**	.72**	.63**	.68**	.70**
3. NSI-AR	–	–	–	.71**	.68**	.59**	.65**	.65**
4. BDI-II	–	–	–	–	.76**	.64**	.76**	.69**
5. PCL Total	–	–	–	–	–	.91**	.94**	.94**
6. PCL-RE	–	–	–	–	–	–	.75**	.81**
7. PCL-AV	–	–	–	–	–	–	–	.82**
8. PCL-HY	–	–	–	–	–	–	–	–

Notes: NSI = Neurobehavioral Symptom Inventory. NSI-OR = NSI- overlap removed. NSI-AR = NSI with affective subscale removed. BDI-II = Beck Depression Inventory-II. PCL = PTSD Checklist. PCL-RE = Re-experiencing symptoms on the PCL. PCL-AV = Avoidance symptoms on the PCL. PCL-HY = Hyperarousal symptoms on the PCL. * = $p < .05$, ** = $p < .01$.

positive.

Significant positive correlations were found between all predictor and criterion variables. See Table 2 for associations among predictor and criterion variables. Separate regression analyses with BDI-II total score, PCL-S total score, and BTBIS screen using the different NSI scoring versions were conducted. Results for these regressions are presented in Table 3. For the NSI total score, the model accounted for 68.3% of the variance. Depression symptoms (BDI-II total; $\beta = 0.45$, $t = 7.74$, $p < .01$, $sr = 0.30$) and PTSD total symptoms (PCL-S total; $\beta = 0.43$, $t = 7.24$, $p < .01$, $sr = 0.28$) were both significant independent predictors of greater postconcussive symptoms. The TBI screen was not a significant independent predictor in this model (BTBIS screen; $\beta = 0.07$, $t = 1.87$, $p = .06$, $sr = 0.07$). With regard to the NSI with overlapping items removed (NSI-OR), the overall model predicted 59.1% of the variance. Symptoms of depression ($\beta = 0.42$, $t = 6.22$, $p < .01$, $sr = 0.27$), PTSD total symptoms ($\beta = 0.40$, $t = 6.01$, $p < .01$, $sr = 0.26$), and TBI screen ($\beta = 0.09$, $t = 2.06$, $p = .04$, $sr = 0.09$) all significantly predicted greater postconcussive symptoms. For the NSI with the affective scale removed (NSI-AR), the overall model accounted for 55.1% of unique variance. Again, depression symptoms ($\beta = 0.46$, $t = 6.53$, $p < .01$, $sr = 0.30$) PTSD total symptoms ($\beta = 0.33$, $t = 4.69$, $p < .01$, $sr = 0.21$), and TBI screen ($\beta = 0.10$, $t = 2.17$, $p = .03$, $sr = 0.10$) were all significant predictors of postconcussive symptoms.

Table 3
Depression, PTSD total score, and TBI Screen, Predicting Postconcussive Symptoms.

Predictor	B	SE	β	adjR^2	*F*	*p*
Criterion Variable: NSI Total						
				.683	157.150	< .001
BDI-II	.619	.080	.454			< .001
PCL	.456	.063	.425			< .001
BTBIS	1.299	.694	.072			.063
Criterion Variable: NSI-OR						
				.591	105.679	< .001
BDI-II	.389	.062	.415			< .001
PCL	.296	.049	.401			< .001
BTBIS	1.117	.542	.090			.040
Criterion Variable: NSI-AR						
				.551	89.626	< .001
BDI-II	.374	.057	.457			< .001
PCL	.211	.045	.329			< .001
BTBIS	1.076	.496	.099			.031

Notes: NSI = Neurobehavioral Symptom Inventory. NSI-OR = NSI- overlap removed. NSI-AR = NSI with affective subscale removed. BDI-II = Beck Depression Inventory-II. PCL = PTSD Checklist. BTBIS = Brief Traumatic Brain Injury Screen.

Table 4
Depression and PTSD subscale scores and TBI Screen, Predicting Postconcussive Symptoms.

Predictor	B	SE	β	adjR^2	*F*	*p*
Criterion Variable: NSI Total						
				.696	100.326	< .001
BDI-II	.643	.080	.472			< .001
PCL-RE	.091	.219	.028			.677
PCL-AV	.083	.188	.033			.658
PCL-HY	1.272	.257	.380			< .001
BTBIS	1.282	.680	.071			.061
Criterion Variable: NSI-OR						
				.595	64.709	< .001
BDI-II	.405	.064	.423			< .001
PCL-RE	.183	.174	.081			.292
PCL-AV	.081	.149	.047			.543
PCL-HY	.664	.204	.289			.001
BTBIS	1.109	.539	.089			.041
Criterion Variable: NSI-AR						
				.552	54.491	< .001
BDI-II	.383	.059	.469			< .001
PCL-RE	.090	.159	.046			.573
PCL-AV	.067	.137	.045			.623
PCL-HY	.506	.187	.252			.007
BTBIS	1.070	.495	.099			.032

Notes: NSI = Neurobehavioral Symptom Inventory. NSI-OR = NSI- overlap removed. NSI-AR = NSI with affective subscale removed. BDI-II = Beck Depression Inventory-II. PCL = PTSD Checklist. PCL-RE = Re-experiencing subscale. PCL-AV = Avoidance subscale. PCL-HY = Hyperarousal subscale. BTBIS = Brief Traumatic Brain Injury Screen.

Additional analyses were run using the PCL-S subscales to see if specific PTSD clusters were associated with NSI scores. These results are presented in Table 4. For the NSI total score, the model accounted for 69.6% of the variance. Depression symptoms (BDI-II total; $\beta = 0.47$, $t = 7.99$, $p < .01$, $sr = 0.30$) and PTSD hyperarousal symptoms (PTSD-HY; $\beta = 0.38$, $t = 4.95$, $p < .01$, $sr = 0.19$) were significant predictors. PTSD re-experiencing symptoms (PCL-RE), PTSD avoidance symptoms (PCL-AV), and TBI screen were not significant predictors in the model. With regard to the NSI-OR, the overall model predicted 59.5% of the variance. Symptoms of depression ($\beta = 0.43$, $t = 6.34$, $p < .01$, $sr = 0.27$) significantly predicted greater postconcussive symptoms, as did PTSD-HY, ($\beta = 0.29$, $t = 3.26$, $p < .01$, $sr = 0.14$), and TBI screen ($\beta = 0.09$, $t = 2.06$, $p = .04$, $sr = 0.09$). PCL-RE and PCL-AV were not shown to be significant predictors. Finally, for the NSI-AR, the overall model accounted for 55.2% of unique variance. Similar to other findings, depression ($\beta = 0.46$, $t = 6.54$, $p < .01$, $sr = 0.30$) and PCL-HY ($\beta = 0.25$, $t = 2.70$, $p < .01$, $sr = 0.12$), and TBI screen ($\beta = 0.10$, $t = 2.16$, $p = .03$, $sr = 0.10$) were significant, but the other clusters were not.

4. Discussion

Given the high rates of exposure to physically and emotionally traumatic events faced by Veterans who served in OIF/OEF/OND and the potential healthcare implications, it is important to develop a better understanding of the various presentations and sequelae observed in this population. The current study was designed to examine the relationship between psychological distress (specifically level of severity of PTSD and depressive symptoms), and PCS in a sample of Veterans seeking care for PTSD with and without a reported lifetime history of head injury. Consistent with some previous research (e.g., Meares et al., 2011; Ponsford et al., 2012; Segev et al., 2016) we did not find significant differences in levels of PCS measured by the NSI between people with and without a reported history of TBI or concussion, further

suggesting that these symptoms are not specific to TBI. Although in most analyses, TBI remained a significant predictor of NSI PCS symptoms, its relative contribution was much smaller than that of depression and PTSD.

Our results support previous findings that PTSD and depression symptom severity account for the largest proportion of variance in PCS and extend this literature by establishing that this relationship is not simply an artifact of symptom similarity or overlap. The findings that the relationship between PTSD, depression, and reported PCS symptoms remained consistent even after affective subscales and overlapping items were removed, demonstrates that there is a robust relationship between psychological distress and PCS independent of similarities in constructs. These findings suggest that for some combat Veterans with PTSD, symptoms measured on the NSI might be better understood as non-specific generalized or somatic health symptoms, rather than a measure of symptoms directly attributable to head injury or concussion.

Further, the finding that hyperarousal symptoms account for a significant amount of variance in NSI scores may offer some insights into the relationship between PTSD and reported PCS. Previous research has demonstrated that hyperarousal symptoms in PTSD are predictive of generalized somatic symptoms (e.g., Kimerling et al., 2000; Zhang et al., 2015). There are several reasons this could be the case, including neuroendocrine and autonomic nervous system dysregulation leading to increased physical symptoms, as well as changes in increased attention or awareness of somatic symptoms. Additionally, hyperarousal symptoms (e.g., problems with sleep, trouble with concentration) may contribute directly to cognitive symptoms reported in PCS. These hypotheses are consistent with recent research in a military sample with PTSD that found that perceived cognitive symptom severity from the NSI was very high and linked to impaired quality of life regardless of TBI history, and was instead associated with comorbid depression (Silverberg et al., 2017).

These findings have potentially important clinical ramifications. Results raise concerns regarding the validity of the NSI as a measure of PCS in a population with high rates of PTSD. The NSI effectively appeared to be primarily measuring non-specific health symptoms, rather than symptoms specific to mTBI. In addition, since the NSI lacks certain common symptoms that occur in chronic multi-symptom illnesses (e.g., gastrointestinal or musculoskeletal pain), this scale is also inadequate as a measure of generalized symptoms. Instruments such as the PHQ-15 somatic symptom scale would be much better suited to this purpose. At minimum, extreme caution should be exercised when discussing results of the NSI measure with patients, as inaccurately labeling symptoms as TBI- or concussion-related may result in negative expectations that could hinder recovery or lead to non-evidence-based treatment approaches. Previous literature has demonstrated that the information people receive regarding mTBI, as well as attributions regarding their symptoms can have an impact on symptom presentation and expectations regarding recovery (e.g., Suhr and Gunstad, 2005; Waldron-Perrine et al., 2015).

Given that psychiatric symptoms appear to contribute to higher scores on the NSI, it should not be assumed or communicated to patients that these symptoms are necessarily indicative of a residual brain injury. Rather, the results of this study suggest that in addition to thoroughly evaluating a history of TBI, elevated scores on the NSI should prompt further assessment and screening for broader psychological distress, including depression and PTSD as well as implementation of holistic step-care approaches to appropriate evaluate and treat unexplained medical symptoms. Some Veterans may be more likely to present for care of a perceived physical injury, such as a TBI, as opposed to emotional distress. Treatment facilities focused on TBI would be well advised to consider and, if appropriate, provide broader evidence-based care aligned with best practices for addressing chronic multi-symptom, multi-etiological concerns being labeled as PCS.

Limitations of this study include the use of self-report screeners to determine a history of potential TBI, PCS, and psychological conditions. However, all scales are widely used for medical screening and follow-up in clinical settings in DoD and VA. It is possible that results may differ in populations in which a history of TBI has been confirmed diagnostically. Additionally, this study only looked at head injuries that occurred during deployment, and these injuries may have occurred years before enrollment in this study. Similarly, the assessment of PCS was limited to current symptoms (past two weeks). It is possible that the relationship between the symptoms on the NSI and TBI may vary with time, and that contributions from TBIs occurring outside of deployment were missed. It is also unclear if the results of this study will extend to subpopulations not well represented in this sample, such as older Veterans or primarily female samples. Finally, this sample involved combat Veterans participating in a treatment outcomes study of PTSD. Although results of this study cannot generalize beyond treatment-seeking PTSD populations, the results are highly consistent with many other studies in the literature, supporting the study conclusions.

In conclusion, results from this study demonstrate that within a population of combat Veterans seeking treatment for PTSD, scores on the NSI are more substantially explained by co-occurring PTSD and depressive symptoms, rather than by a history of TBI. This relationship is robust in nature and is not the result of overlapping symptoms between psychiatric constructs and PCS.

Disclosures

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2018.03.004.

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Trauma related guilt cognitions partially mediate the relationship between PTSD symptom severity and functioning among returning combat veterans

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ABSTRACT

Trauma related guilt, a distressing emotion associated with negative cognitions regarding one's actions or inaction during a traumatic event, is common among individuals with posttraumatic stress disorder (PTSD). We hypothesized that trauma related guilt cognitions would partially explain the relationship between PTSD symptom severity and functioning. The sample consisted of 254 combat veterans or active duty military personnel who served in Operation Enduring Freedom, Operation Iraqi Freedom or Operation New Dawn (OEF/OIF/OND) who consented to participate in a larger PTSD treatment study. Results revealed a significant relationship between PTSD severity and guilt cognitions (standardized $\beta = 0.40$), as well as PTSD and overall functioning ($\beta = 0.49$). Guilt cognitions (β's = 0.13 to 0.32) were significantly associated with nearly all domains of functioning, including overall functioning ($\beta = 0.27$), and partially explained the relationship between PTSD and functioning. This study lends support to the addition of guilt as a symptom of PTSD in the DSM-5 as it contributes significantly to functional impairment even when accounting for other symptoms of PTSD, although co-occurring mental health problems may also contribute to functional impairments associated with PTSD. Future studies are needed to investigate whether reductions in traumatic guilt are related to improved functional outcomes in PTSD treatments.

1. Introduction

Difficulties with functioning are highly prevalent among individuals with posttraumatic stress disorder (PTSD, see Schnurr et al., 2009 for review) and can have profound impact on a person's life. Functional impairments tend to increase with PTSD severity; however, even subthreshold PTSD is associated with functional deficits (e.g., Norman et al., 2007; Shelby et al., 2008; Stein et al., 1997). In a sample of marines who served in Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND), the strongest predictor of functional impairment within the first year of separation from the military was PTSD symptom severity at the time of separation and at the time impairment was measured (Larson and Norman, 2014). Functional difficulties associated with PTSD cut across many domains including interpersonal difficulties, difficulties in achieving professional or academic goals, and ability to take care of ones' daily and medical needs (Amaya-Jackson et al., 1999; Bovin et al., 2018; Erbes et al., 2007; Marx et al., 2009; Zatzick et al., 1997).

PTSD is associated with interpersonal problems within romantic relationships (Taft et al., 2011), family relationships (Sayers et al., 2009), parenting (Wilson et al., 2017), and social networks and friendships (Fang et al., 2015; McCaslin et al., 2016; Ozer et al., 2003).

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Military and veteran populations with PTSD may be at heightened risk. A meta-analysis revealed a stronger association between PTSD symptoms and relationship discord for military samples than civilian samples (Taft et al., 2011). In one study, severity of PTSD symptoms in male veterans was positively associated with greater likelihood that their female partners would report dissatisfaction with intimacy, shared activities, and responsibilities within the relationship (LaMotte et al., 2015), suggesting that problems impact both the veterans with PTSD and their romantic partners. PTSD also has a negative effect on several aspects of parenting and family functioning, including quality of parent-child relationship (Ruscio et al., 2002), parenting satisfaction (Samper et al., 2004), parenting behaviors (Gewirtz et al., 2010), and family conflicts (Sayers et al., 2009).

PTSD is related to impairments in occupational and academic functioning in both veteran and civilian populations (e.g., Erbes et al., 2011; Momartin et al., 2004; Shelby et al., 2008). Studies with veteran samples have found PTSD to be associated with higher rates of unemployment, underemployment, and lower hourly wages (Savoca and Rosenheck, 2000; Smith et al., 2005). Among OEF/OIF/OND veterans, PTSD was associated with poorer time management, reduced output, difficulties with psychological and interpersonal aspects of a job, greater absenteeism (Hoge et al., 2007), poorer workplace functioning over time (Erbes et al., 2011), and worse academic functioning including lower grade point average (Barry et al., 2012; see Bryan et al., 2014, for an exception).

PTSD may also contribute to difficulties with self-care, which can range from having trouble with daily activities such as keeping up with household chores and personal hygiene to taking care of ones' physical and psychological health (Bovin et al., 2018; Marx et al., 2009). In one study of recently separated OEF/OIF/OND veterans (Sayer et al., 2010), over 35% of 754 veterans reported “some” to “extreme” problems completing tasks needed for work, home, or school, and 45% reported problems taking care of their health. The odds of reporting “some” to “extreme” difficulties in these domains were five to eight times higher among veterans with probable PTSD than those without. Engaging in medical care is another aspect of self-care. Among veterans with PTSD, even among those who present to veterans Affairs (VA) for PTSD treatment, rates of engagement in and completion of PTSD treatments are low (Garcia et al., 2011). While there may be many reasons veterans do not engage in or complete PTSD treatment, not engaging in available recovery oriented care may be a component of difficulties in the functional domain of self-care.

Understanding the relationship between PTSD and functioning difficulties is important for understanding the impact of PTSD and ensuring that treatments not only reduce symptoms but also help people function to their highest potential. In some cases, the connection between certain symptoms of PTSD and functioning difficulties may be straightforward. For example, emotional numbing or feelings of detachment and estrangement contribute to impaired interpersonal functioning (Beck et al., 2009; Kuhn et al., 2003; LaMotte et al., 2015; Nunnink et al., 2010; Riggs et al., 1998; Ruscio et al., 2002). Symptoms such as hypervigilance and problems with concentration may detract from the ability to study for school or succeed in certain jobs (American College on Education, 2014).

PTSD and functioning difficulties may also be connected through more nuanced mechanisms. One possible mechanism is trauma related guilt, a distressing emotion associated with maladaptive cognitions regarding one's behavior and oneself during the trauma in comparison to valued standards (Kubany and Watson, 2003). Kubany and Watson (2003), identified four types of maladaptive cognitions common in individuals who experience posttraumatic guilt: hindsight-bias (i.e., believing that the outcome was known at the time of the trauma), lack of justification (i.e., believing there was no justification for the course of action one chose to take), responsibility (i.e., believing one was solely or mostly responsible for the traumatic event), and wrongdoing (i.e., believing one purposely did something that was wrong or violated important values). Guilt following trauma is common; 83% of trauma-exposed individuals with probable PTSD report experiencing trauma related guilt in their lifetime, and 34% report experiencing trauma related guilt in the past month (Miller et al., 2013). In fact, guilt is so commonly reported by individuals with PTSD that it is now recognized as a symptom in DSM-5 (American Psychiatric Association, 2013; i.e., criterion D3: distorted cognitions about the cause or consequences of the traumatic event that lead the individual to blame himself/herself or others).

Although some research has found that guilt can be prosocial and associated with adaptive outcomes such as making reparations for one's actions (see Tangney et al., 2007), guilt specifically related to trauma (e.g., guilt about failing to prevent a trauma, guilt about witnessing a traumatic act that violates one's values) is associated with a host of negative outcomes and psychopathology. These negative outcomes include more severe PTSD symptoms (Beck et al., 2011; Browne et al., 2015; Held et al., 2011; Kubany and Watson, 2003; Marx et al., 2010), poorer response to PTSD treatment (Owens et al., 2008), more severe depressive symptoms (Browne et al., 2015; Kim et al., 2011; Marx et al., 2010), substance use problems (Wilkins et al., 2013), and suicidal ideation (Bryan et al., 2013; Hendin and Haas, 1991; Tripp and McDevitt-Murphy, 2017). Although trauma-related guilt is linked to worse mental health, there is a dearth of literature examining how trauma related guilt relates to functional impairments among individuals with PTSD.

There are several reasons to suspect that trauma related guilt cognitions may be associated with poorer functioning in PTSD. Trauma related guilt cognitions are associated with emotional distress, even when controlling for PTSD symptoms (Browne et al., 2015), and distress can interfere with how individuals engage with others, work, self-care, and other important activities. Also, guilt can cause individuals to believe they do not deserve to feel happy or that they deserve to suffer (e.g., Norman et al., 2014) which may keep them from pursuing career or educational goals or taking part in self-care activities like treatment. Finally, frequent guilt cognitions may keep individuals focused on the past which could interfere with maximally engaging in and functioning the in the present.

The aim of this study was to evaluate whether the relationship between PTSD symptoms and functioning is mediated by trauma related guilt cognitions in a sample of OEF/OIF/OND veterans. We hypothesized that guilt related cognitions would partially explain the relationship between PTSD symptom severity and functioning. We examined specific domains of functioning, including interpersonal (romantic, family, friendship, and parenting domains), professional (educational and work domains), and self-care, as well as overall functioning. We also examined whether specific guilt cognitions (hindsight bias/responsibility, lack of justification, and wrongdoing) partially mediated the relationship between PTSD symptom severity and overall functioning.

2. Method

2.1. Participants

The study included 254 veterans or active duty military personnel (mean age 35.7 years, 89.4% male) who served in combat during OEF/OIF/OND and consented to participate in a multisite PTSD treatment randomized controlled trial funded by the Department of Defense between 2011 and 2016 (PROlonGed ExpoSure Sertraline [PROGrESS]: Randomized Controlled Trial of Sertraline, Prolonged Exposure Therapy and Their Combination of OEF/OIF with PTSD). Data for the current study were obtained during evaluation for inclusion into either the primary treatment study or a linked study of combat controls for an fMRI portion of the study (see Rauch et al., 2018, for more information regarding the larger research study). Participant characteristics are presented in Table 1.

Table 1
Cohort characteristics (N = 254).

Characteristics	
Age in years, mean (*SD*)	35.7 (12.2)
Women, *n* (%)	27 (10.6)
Race	
White, *n (%)*	160 (63.0)
Black, *n (%)*	63 (24.8)
Other or unknown, *n (%)*	31 (12.2)
Hispanic ethnicity, *n (%*[a]*)*	31 (12.6)
Marital Status	
Married or remarried, *n (%*[a]*)*	124 (49.0)
Separated or divorced, *n (%*[a]*)*	64 (25.3)
Never married, *n (%*[a]*)*	65 (25.7)
Education	
Completed high school or less, *n (%)*	83 (32.7)
Employment Status	
Fulltime employed, *n (%)*	129 (50.8)
Unable to find work, of those not employed, *n/N (%)*	32/95 (33.7)
Military history	
Regular armed services, *n (%*[a]*)*	214 (84.9)
National Guard, *n (%*[a]*)*	30 (11.9)
Reserve, *n (%*[a]*)*	8 (3.2)
Deployed more than once, *n (%*[a]*)*	161 (64.9)
Enrolled in Randomized Clinical Trial, *n (%)*	207 (81.5)

[a] For ethnicity, 8 persons with unknown ethnicity are excluded, for marital status, 1 person with unknown status is excluded, and for military history, 2 persons without military status and 6 persons without the number of deployment were excluded.

2.2. Procedure

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, the study design was reviewed by ethics committees at each institution where data collection took place, and informed consent of the participants was obtained after the nature of the procedures had been fully explained. Following informed consent, participants took part in initial screening procedures for PROGrESS, which included self-report measures and structured diagnostic interviews, at one of the following four sites: VA Ann Arbor Healthcare System/University of Michigan, Massachusetts General Hospital, Ralph H. Johnson VA Medical Center/Medical University of South Carolina, and VA San Diego Healthcare System/University of California San Diego. Only those participants who completed the Clinician-Administered PTSD Scale (CAPS) for DSM-IV (Blake et al., 1995) the Inventory of Psychosocial Functioning (IPF; Bovin et al., 2018; Marx et al., 2009), and the Trauma Related Guilt Inventory (TRGI; Kubany et al., 1996) were included in the analyses of this study.

2.3. Measures

2.3.1. Clinician Administered PTSD Scale (CAPS)

The CAPS (Blake et al., 1995) is a semi-structured diagnostic interview for PTSD that assesses the intensity and frequency of PTSD symptoms. It has strong test-retest reliability and internal consistency of .94 for total score (Blake et al., 1995). Based on the timeline of the study, the original CAPS utilizing criteria from DSM-IV-TR was used. Total scores were computed for this study. Interrater reliability was conducted on 20% of randomly selected CAPS and was over 0.98.

2.3.2. Trauma Related Guilt Inventory (TRGI)

The TRGI is a self-report of 32-items that measure cognitive and emotional attributes of guilt associated with the experience of a traumatic event (Kubany et al., 1996). The TRGI has excellent test-retest reliability and internal consistency (see Myers et al., 2012). The TRGI has three scales (4-item global guilt; 6-item distress; 22-item guilt cognitions), and three subscales within the guilt cognitions scale (7-item hindsight-bias/responsibility, 5-item wrongdoing, and 4-item lack of justification). The guilt cognitions scale (e.g., "I could have prevented what happened," "I should have known better") and its subscales were utilized for the present study.

2.3.3. Inventory of Psychosocial Functioning (IPF)

The IPF (Bovin et al., 2018; Marx et al., 2009) is an 80-item self-report questionnaire of functional impairment across several domains including relationships, work, parenting, education, and general daily functioning over the past 30 days. Domain scores can range from 0 to 100 with higher values corresponding to higher functioning. Overall functioning score was calculated as the mean of all completed IPF domain scores. As participants may skip certain domains that do not apply to them (thus leading to different sample sizes for analyses predicting different domains of functioning), overall score was calculated as total sum of all completed IPF domain scores divided by the actual number of domains completed by the participant. In one study (Marx et al., 2009), the domain scores demonstrated internal consistency (subscale Cronbach's alphas between .76 and .91) and correlated highly with other established measures of functional impairment.

2.4. Analytic plan

All analyses were conducted using Stata 15.0. We used a series of multiple regression models to evaluate whether the relationship between PTSD symptoms (CAPS total score) and functioning (overall functioning, as well as seven functioning subscales) is partially mediated by trauma related guilt cognitions (e.g., Baron and Kenny, 1986). We first assessed for the total effect of PTSD symptoms on functioning. We then assessed if PTSD symptoms were associated with guilt cognitions (potential mediator). Lastly, we assessed if the relationship between PTSD symptoms and functioning was partially explained by guilt cognitions by including both PTSD symptoms and guilt cognition as predictors, adjusting for other covariates. We expected that guilt cognitions would partially mediate the effect of PTSD on functioning, such that PTSD symptoms would predict increased guilt cognitions, which would predict poorer functioning. We also expected that the direct effect of PTSD symptoms on functioning would remain significant when accounting for guilt cognitions. Separate analyses also tested three specific guilt cognitions (hindsight bias/responsibility, lack of justification, and wrongdoing) as mediators of the effect of PTSD symptoms on overall functioning. The indirect/mediated effects of PTSD symptoms on functioning via guilt cognitions were computed based on the product of the coefficients method (MacKinnon et al., 2004). Standard errors and p-values were obtained by bootstrapping. All coefficients reported below are standardized (βs). All models adjusted for the following covariates: age, sex, race, marital status, and employment status. Because marital status and employment status may be related to functioning, PTSD symptoms, and trauma-related guilt, we also conducted analyses excluding marital and employment status as covariates. Findings were unchanged (trauma related guilt mediated the influence of PTSD symptoms on overall functioning as well as interpersonal, professional, and self-care functioning).

3. Results

3.1. Zero-order correlations

Correlations among study variables are presented in Table 2. More severe PTSD symptoms and overall scores on guilt cognitions were associated with worse functioning across all domains (see Table 3).

3.2. Mediation analyses

As expected, PTSD symptoms were significantly associated with all domains of functioning, while adjusting for covariates (standardized β's ranged from .60 for overall functioning to .34 for parenting; p's < .001). Results from mediation analyses indicated that PTSD symptom

Table 2
Zero-order correlations.

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.
1. PTSD symptoms	–													
2. Overall functioning	.62***	–												
3. Romantic functioning	.51***	.77***	–											
4. Family functioning	.48***	.80***	.51***	–										
5. Friendship	.58***	.85***	.55***	.65***	–									
6. Self-care	.54***	.79***	.57***	.53***	.61***	–								
7. Parenting	.36***	.78***	.48***	.48***	.54***	.50***	–							
8. Educational functioning	.44***	.81***	.58***	.56***	.63***	.48***	.67***	–						
9. Work functioning	.45***	.79***	.56***	.52***	.61***	.58***	.60***	.66***	–					
10. Global guilt	.46***	.46***	.32***	.34***	.46***	.37***	.39***	.23*	.35***	–				
11. Guilt cognitions	.40***	.47***	.30***	.36***	.44***	.40***	.39***	.32*	.32***	.69***	–			
12. Hindsight bias	.34***	.37***	.23*	.29***	.35***	.32***	.34***	.16	.24*	.66***	.89***	–		
13. Wrongdoing	.40***	.43***	.21*	.33***	.39***	.40***	.38***	.41***	.27***	.56***	.72***	.56***	–	
14. Lack of justification	.28***	.35***	.24*	.27***	.35***	.25***	.16	.24*	.30***	.38***	.65***	.40***	.25***	–

Note. *$p < .05$, ***$p < .001$.

Table 3
Results of regression analyses examining guilt cognitions as potential mediator of the relationship between PTSD symptom severity and overall functioning and other function domains.

Predictor	*Outcome*	Beta	*SE*	p-value	Indirect Effect (*SE*; p-value)
PTSD symptoms	Guilt Cognition (n = 245)	.40	.05	< .001	
PTSD symptoms	Overall functioning (n = 245)	.49	.05	< .001	.11 (.03; < .001)
Guilt cognitions		.27	.05	< .001	
PTSD symptoms	Romantic functioning (n = 192)	.39	.06	< .001	.05 (.02; .04)
Guilt cognitions		.13	.06	.033	
PTSD symptoms	Family functioning (n = 229)	.42	.06	< .001	.08 (.03; .005)
Guilt cognitions		.20	.06	.001	
PTSD symptoms	Friendship (n = 200)	.47	.05	< .001	.09 (.03; .001)
Guilt cognitions		.23	.06	< .001	
PTSD symptoms	Parenting (n = 139)	.24	.08	.001	.09 (.03; .002)
Guilt cognitions		.32	.08	< .001	
PTSD symptoms	Educational functioning (n = 96)	.37	.10	< .001	.07 (.05; .17)
Guilt cognitions		.16	.11	.116	
PTSD symptoms	Work functioning (n = 165)	.35	.07	< .001	.08 (.04; .029)
Guilt cognitions		.18	.08	.024	
PTSD symptoms	Self-care functioning (n = 245)	.45	.05	< .001	.09 (.03; .001)
Guilt cognitions		.22	.06	< .001	

Note. All analyses are also adjusted for demographic covariates (results not shown). Betas are standardized. Betas are from models including both PTSD symptoms and guilt cognitions. Indirect effects computed with product of coefficients method.

severity was significantly associated with guilt cognitions (standardized $\beta = .40$, $p < .001$), which in turn was significantly associated with overall functioning ($\beta = .27$, $p < .001$) as well as all functioning outcomes (i.e., romantic, family, friendship, work, and self-care) except for education (see Table 3). The direct effects of PTSD symptoms (accounting for the indirect effect via guilt cognitions) on all measures of functioning were significant, but were reduced from the effects of PTSD symptom severity on each measure of functioning when guilt cognitions were not in the model. The indirect effect of PTSD symptom severity on overall functioning via guilt cognitions was significant ($\beta = 0.11$, $p < 0.001$). The indirect effects of PTSD symptoms on each domains of functioning via guilt cognitions were positive in direction with the standardized β's ranging from 0.05 to 0.09 (see Table 3), but the statistical significance of the indirect effect depended largely on the sample size available for each functioning domain.

Fig. 1 presents results from simultaneously examining three specific

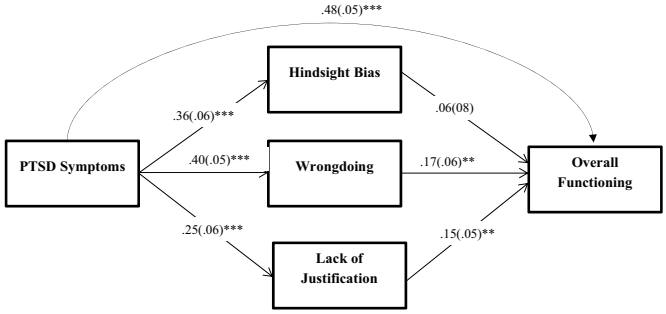

Fig. 1. Results of Analyses Examining Domains of Guilt Cognitions as Mediators of PTSD Symptoms on Overall Functioning. Standardized betas and standard errors (in parentheses) are presented.
***p < .001; **p < .01; *p < .05.

guilt cognitions (hindsight bias/responsibility, lack of justification, and wrongdoing) as potential mediators of the relationship between PTSD symptom severity and overall functioning. PTSD symptoms were significantly associated with all three measures of guilt cognitions. Lack of justification ($\beta = .15$, $p = .002$) and wrongdoing ($\beta = .17$, $p = .003$) in turn were significantly associated with overall functioning, but hindsight bias/responsibility was not ($\beta = .06$, $p = .46$). The indirect effects of PTSD symptoms on overall functioning through the combined three specific guilt cognitions were significant ($\beta = .13$, $p < .001$, 95% CI = 0.07, 0.19). In case of suppression effects, we ran three separate models entering only one type of cognition in each mediation model. All three types of guilt cognitions were significantly associated with overall functioning ($\beta = .19$, $p = .002$ for hindsight bias/responsibility; $\beta = .22$, $p < .001$ for wrongdoing; $\beta = .19$, $p = .001$ for lack of justification), and each partially mediated the effect of PTSD symptoms on overall functioning. When the specific guilt cognition measures were examined separately, all indirect effects of PTSD symptoms on overall functioning via specific guilt cognitions were significant.

4. Discussion

Impairment in functioning is common in individuals with PTSD. The goal of this study was to assess whether maladaptive trauma related guilt cognitions contribute to functional impairment associated with PTSD. Consistent with our hypotheses, we found that trauma related guilt cognitions partially mediated the relationship between PTSD symptom severity and overall functioning as well as interpersonal, professional, and self-care functioning. Furthermore, we found that specific types of guilt cognitions—hindsight bias, responsibility, and wrongdoing—each contributed to functional impairment. In addition, greater severity of all three types of guilt cognitions evaluated

(hindsight bias/responsibility, lack of justification, and wrongdoing) were associated with poorer overall functioning, suggesting that any type of guilt cognition can have detrimental correlates.

Our hypothesis that maladaptive guilt cognitions would be associated with worse academic functioning was not supported. This may be because guilt does not affect academic functioning or it may be that we were not powered to find the difference in regard to academics. Only 96 participants endorsed that they were attending school so analyses on academic functioning were completed with only these participants. Given the overall findings of this study, it is warranted to examine whether trauma related guilt plays a role in this functioning domain in future well powered studies.

Maladaptive cognitions have been associated with poorer functioning across a variety of mental health conditions including depression (e.g., Zauszniewski and Rong, 1999) and chronic pain (e.g., Stroud et al., 2000). Ours is among the first studies that has examined guilt related maladaptive cognitions and functioning in PTSD. One reason why maladaptive cognitions regarding the trauma are related to functional impairment in PTSD may be because of additional maladaptive beliefs regarding the self, stemming from beliefs regarding one's role in the trauma. Examples of such beliefs may be "I don't deserve to be loved because of what I did" or "I don't deserve to feel better because of what I did." Such beliefs about the self are often labeled as shame beliefs (Norman et al., 2014), often accompany trauma related guilt (Mills, 2005; Norman et al., 2014) and may further contribute to negative posttraumatic outcomes (Beck et al., 2011; Crocker et al., 2016). Furthermore, such beliefs may translate into withdrawing from relationships or not engaging in PTSD treatment, thus further contributing to functional impairment. Future research is needed to better understanding the role of shame in tandem with trauma related guilt.

This study lends support to the recent addition of guilt as a symptom of PTSD in the DSM-5 (American Psychiatric Association, 2013; Friedman et al., 2011) as it contributes significantly to functional impairment even when accounting for other symptoms of PTSD. However, it is noted that co-occurring mental health problems (e.g., depression) may also contribute to functional impairments associated with PTSD and trauma related guilt. Nonetheless, this study raises the question of whether resolving maladaptive guilt cognitions will result in improved functioning for patients with PTSD. Only one study of which we are aware has examined the role of guilt in functioning following PTSD treatment. Promisingly, Allard et al. (2016) found that improvements in trauma related guilt at mid-treatment translated to improvements in functioning (a composite measure of work, social, and family functioning), as well as improvements in PTSD by the end of treatment, among survivors of intimate partner violence engaging in cognitive trauma therapy. The PTSD treatment in the Allard et al. study was Cognitive Trauma Therapy for Battered Women (Kubany et al., 2004), a model that explicitly addresses trauma related guilt cognitions. It is important to note that the direct effect of PTSD symptom severity on functioning was larger than the effect of guilt-related cognitions. Thus, while the findings suggest that research to assess whether addressing guilt cognitions in treatment improves functioning is needed, they similarly underscore the importance of research on addressing PTSD to improve functioning.

How explicitly guilt cognitions need to be addressed in PTSD treatment also remains an empirical question. Existing evidence-based treatments for PTSD such as prolonged exposure therapy (PE) and cognitive processing therapy (CPT) are effective at reducing trauma related guilt (Clifton et al., 2017; Resick et al., 2002; Smith et al., 2013). However, greater guilt severity may result in less PTSD symptom reduction over the course of treatment (Oktedalen et al., 2015) and some studies have not shown changes in trauma related guilt severity over the course of PTSD treatment (e.g., Owens et al., 2008). It is possible that in these studies there was variability in how much clinicians focused on traumas that caused guilt or on guilt cognitions with their patients. In fact, studies of clinicians who are treating traumatized veterans have found that clinicians would like more information on how to address guilt (Becker et al., 2004; Drescher et al., 2011). These mixed findings suggest that, as recommended in previous studies (Nishith et al., 2005; Resick et al., 2002), addressing guilt explicitly in evidence-based PTSD treatment may be important to resolving trauma related guilt. One suggestion would be for more training for clinicians on how to assess and address trauma related guilt within these treatment models; for example, during processing in PE or through challenging belief worksheets in CPT. Given our findings, we would suggest that such training include attention to specific beliefs regarding hindsight bias, wrong doing, and lack of justification. There are also emerging transdiagnostic therapies that target guilt cognitions as a primary focus of the intervention (e.g., Maguen et al., 2017; Norman et al., 2014). The role of these in helping to resolve guilt among individuals with PTSD also remains an empirical question.

Limitations of this study include that the sample was exclusively OEF/OIF/OND veterans and mostly male. It is not clear how well these observations generalize to women, veterans of other eras, and non-veterans. All measures were self-report. The study would have been strengthened by the addition of collateral or objective measures of functioning, such as partner report or employment records. In addition, this data was cross-sectional and thus does not allow for definitive conclusions about causality. Replication of this study's results using longitudinal data would increase confidence in the findings.

In summary, this study indicates that impairments in functioning experienced by individuals with PTSD are partially explained by trauma related guilt cognitions. Future studies are needed to investigate whether reductions in trauma related guilt cognitions during PTSD treatment facilitate improvements in functional outcomes, and whether explicitly focusing on guilt cognitions in PTSD treatment may help to resolve guilt cognitions.

Conflicts of interest

The authors have no conflicts of interest to report.

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ClinicalTrials.gov

NCT01524133.

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Integrating biological treatment mechanisms into randomized clinical trials: Design of PROGrESS (PROlonGed ExpoSure and Sertraline Trial)

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ABSTRACT

Increased emphasis on mechanisms of treatment effectiveness, biomarker predictors, and objective indicators of treatment response has sparked interest in integrated, translational treatment outcomes trials. The PROlonGed ExpoSure and Sertraline Trial (PROGrESS) is one such randomized controlled trial (RCT) focused on a key question in clinical management of posttraumatic stress disorder (PTSD) - the comparative and combined effectiveness of medication and psychotherapy. PROGrESS employs a state of the art trial design to examine psychotherapy and medication effects across three conditions: 1) Prolonged Exposure (PE) plus pill placebo, 2) Sertraline (SERT) plus Enhanced Medication Management (EMM), and 3) Combined treatment (PE/SERT). Innovative measures will capture potential biomarker predictors and indicators of treatment response within and across these three treatment conditions in Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) service members and veterans with PTSD. Assessments include clinician-rated measures, self-report outcome measures, saliva for salivary cortisol and cortisol response to awakening at six assessment points, blood at baseline and week 24 for genetic and genomic analysis, as well as resting state connectivity and emotion processing and regulation using functional Magnetic Resonance Imaging (fMRI) paradigms in a subsample of veterans. Accordingly, the current study is designed to provide pragmatic clinical direction for the delivery of PTSD treatment through its primary outcomes in an effectiveness design, and will also provide informative results to elucidate underlying mechanisms and biomarkers involved in PTSD treatment response.

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1. Introduction

Posttraumatic Stress Disorder (PTSD) is a major public health concern and a growing problem for the Department of Veterans Affairs (VA) and the Department of Defense (DoD) [18,22]. The prevalence of PTSD in service members returning from deployment in Afghanistan and Iraq averages 6–16%, with variability depending primarily on the level of combat exposure [21,35,47]. PTSD is associated with significant psychological, physical, and economic burdens for sufferers and society [25,40].

Based on treatment guidelines [3,55] and recent meta-analyses [38], trauma focused psychotherapy such as Prolonged Exposure (PE), is recommended as a first-line treatment followed by specific selective serotonin reuptake inhibitors (SSRIs) such as sertraline and paroxetine. Current guidelines do not speak to combination medication and psychotherapy as sufficient evidence is not available. The recommendation of psychotherapy over medication in the latest clinical practice guideline is based on effect sizes and meta-analyses drawn from separate medication and psychotherapy studies with varying methodologies, making it difficult to draw conclusions regarding relative efficacy. Double-blind placebo-control groups used in medication trials are not equivalent to waitlist or supportive psychotherapy conditions. Further, medication trials often have more restrictive inclusion and exclusion criteria than many psychotherapy trials, including differences in levels of key comorbidities (i.e., depression and alcohol abuse). These methodological differences likely influence effect size. Additionally, in practice, many veterans receive psychotherapy and medication concurrently, but little is known regarding the efficacy of receiving both relative to one or the other. The evidence has been insufficient, and current guidelines do not speak to the question of whether combination medication and psychotherapy may be more effective than either treatment alone. Thus, direct comparison of these treatments as well as their combination delivered in the same protocol is required to address this key clinical effectiveness question.

While both PE and SSRIs are recommended treatments for PTSD, relevant data are not available to inform clinicians as to when to provide which intervention individually and when to combine treatments. Thus, treatment is most often guided by convenience (e.g. patient choice, treatment availability/feasibility) and clinical practice patterns. To date, there have been no randomized, direct comparisons of medication, psychotherapy, and combined treatment for PTSD. Also lacking are adequate studies of PTSD-relevant biomarkers and treatment mechanisms within these primary treatments. Delineation of these factors and their specificity to psychotherapy or medication is a critical step toward treatment refinements, improved effectiveness and efficiency of PTSD treatment, and individualized treatment. Finally, examination of PTSD-relevant biomarkers and treatment mechanisms within effective treatments can help inform what treatment is most likely to work for whom and why. Finally, examination of PTSD-relevant biomarkers and treatment mechanisms within effective treatments might help inform which treatments work for whom and why.

The current manuscript presents the design and methods of the PROlonGed ExpoSure and Sertraline Trial (PROGrESS), a four-site randomized-controlled trial (RCT) designed to address these critical gaps (N = 223). The study will examine comprehensive longitudinal outcome data in response to randomized treatment with Prolonged Exposure plus placebo (PE/PLB), Sertraline plus Enhanced Medication Management (SERT/EMM), or combined treatment (PE/SERT). PROGrESS is designed to also examine neurobiological predictors and proximal correlates of effective treatment response and mechanisms including hypothalamic-pituitary-adrenal axis (HPA), brain, and genetic/genomic biomarkers.

2. Aims and hypotheses

Aim 1. Examine the relative effectiveness of PE/PLB, SERT/EMM, and PE/SERT in OEF/OIF/OND returnees with PTSD (N = 223). The primary outcome is PTSD symptoms as rated on CAPS [5]. Secondary outcomes include related psychopathology (e.g., depression, alcohol/substance abuse, general anxiety) as well as general functioning (e.g., violence, employment, pain, etc.) and self-report of PTSD symptoms. Detailed information on acceptability, adherence, and compliance for all treatment will also be evaluated. Based on previous studies of the interventions [48], we hypothesize that all three treatments will demonstrate significant reductions in PTSD, general anxiety, and depression, with PE/SERT resulting in larger PTSD symptom reductions and greater response than either PE/PLB or SERT/EMM. We also hypothesize that PE/PLB will result in larger PTSD symptom reductions than SERT/EMM. Finally, based on the idea that increased side effects of medication may interfere with early learning and symptom reduction in PE leading patients to discontinue treatment, we hypothesize that the treatment drop out in PE/SERT will be larger than in either SERT/EMM or PE/PLB.

Aim 2. Identify genetic variants associated with treatment response to SERT and PE. While our sample size is small for pharmacogenetic analyses, we will conduct exploratory analyses of association with treatment responses with variants in genes previously implicated in SSRI antidepressant responses (e.g. *HPRTP4*, *NRG1, VSTM5*, *ZNF626*) and with PTSD pathophysiology (e.g. *ANKRD55*, *FKBP5, KLHL1, ADRB2*). We are not aware of any genes previously implicated in psychotherapy response. Genome-wide genotyping (Illumina “PsychArray”) also allows for polygenic analyses of contribution of common genetic variants on treatment responses.

Aim 3. Identify gene expression predictors of treatment response. We will examine gene expression patterns in peripheral whole blood leukocytes collected at intake and following treatment (Wk 24) to identify effects of SERT and PE/PLB on gene expression patterns and potential predictors of treatment response. Treatment-related gene expression changes in leukocytes likely reflect both medication and symptom-related changes in immune cell functioning, and moreover may also reflect changes in brain gene expression related to pathophysiology and treatment responses. We hypothesize that both SERT and PE/PLB will be associated with changes in leukocyte gene expression (mRNA) profiles from pre- to post-treatment that will predict treatment responses.

Aim 4. Characterize the effects of SERT/EMM, PE/PLB, and PE/SERT on amygdala, insula, and ventromedial prefrontal cortex (vmPFC) function in OIF/OEF/OND PTSD veterans and identify brain-based predictors of treatment response to PE/PLB, SERT/EMM and PE/SERT. Based on research from our lab and others, PTSD is associated with amygdala and insula hyperactivity, and hypoactvity in regulatory areas of PFC (e.g., vm, dm and dl) when processing signals of threat and/or during negative emotional experience. We will use responses to emotion perception (viewing negative emotional faces) and emotion regulation (cognitive reappraisal) paradigms at pretreatment to predict general and specific treatment response. Specifically, baseline and pre- to post-treatment changes in these areas and the resting state connectivity between these regions using threat detection/emotional processing and emotion regulation paradigms will be examined and related to these response patterns to treatment in SERT/EMM, PE/PLB and PE/SERT.

We hypothesize that changes in amygdala-vmPFC function will be associated with treatment response such that pre-to-post treatment change in amygdala-insula reactivity to threat perception [as probed by the Emotional Faces Assessment Task (EFAT)] and areas of PFC (e.g., dl, vl, dm and vm) engagement during emotion regulation (as probed by the Emotional Reappraisal Task (ERT)) will differentiate treatment responders from non-responders. Specifically, significant change will be observed in treatment responders to SERT/EMM (i.e., reduction in amygdala reactivity) and to PE/PLB (i.e., enhancement of dlPFC, vlPFC, dmPFC and vmPFC response) but not in non-responders (see below for how response is defined). In addition, pre-

treatment amygdala reactivity to social signals of threat (angry/fearful faces) will predict the extent of SERT/EMM response (pre-to-post change), such that higher amygdala reactivity will be associated with a greater reduction in PTSD symptoms. Finally, pre-treatment prefrontal cortex (dlPFC, vlPFC, dmPFC and vmPFC) response during emotion regulation will predict the extent of PE response (pre-to-post change), such that lower vmPFC response will be associated with a greater reduction in PTSD symptoms.

Aim 5. Examine alterations in hypothalamic- pituitary-adrenal (HPA) axis function over treatment and their relationship to treatment response both as predictors and mechanisms of change. Cortisol Awakening Response (CAR) will be used to examine HPA axis function. This measure has been related to PTSD symptom severity and preliminary data have demonstrated it is related to change with treatment in PE [45]. We hypothesize that positive treatment response will be associated with increased cortisol awakening response (CAR) across treatment.

3. Study design

3.1. Overview

The primary study design includes assessment of OEF/OIF/OND combat veterans and randomization of those with significant PTSD symptoms who meet minimal inclusion and exclusion criteria (see below) to PE/PLB, SERT/EMM, or PE/SERT. All veterans receive either sertraline or a placebo pill in a double-blind manner. Enhanced medication management (EMM) is provided for the sertraline only group to control for some of the time, psychoeducation, and clinician support in the two conditions that include PE. Psychological and symptom assessment (e.g., PTSD, depression, generalized anxiety) occur at 6 major assessment time points: Intake/Week 0, Weeks 6, 12, 24, 36 and 52 (See Table 1 and Fig. 1). Neurobiological assessments include salivary cortisol awakening response (CAR) at each major follow-up assessment time and Week 0. Blood draws occur for genetic and genomic analysis at Week 0 (or 7 days prior to) and Week 24. Self-report assessments of PTSD, depression, and anxiety symptoms are collected bi-weekly. Treatment adherence related data are also collected. fMRI is an optional portion of the study at Intake and Week 24 (N = 66; described below). Imaging includes response to emotion processing and regulation tasks [EFAT, Shifted-Attention Emotion Appraisal Task (SEAT), and Emotional Reappraisal Task (ERT)] as well as resting state scans.

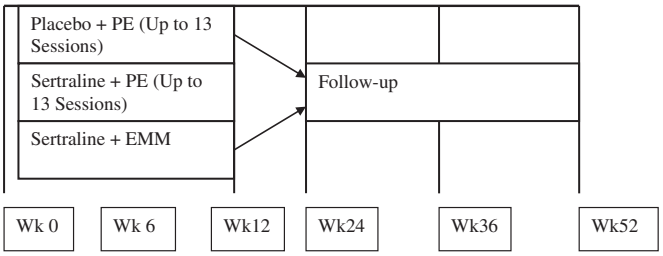

Fig. 1. Design overview.

3.2. Design considerations

While PTSD is one primary mental health condition in OEF/OIF/OND returnees, high rates of depression [23], and substance abuse [41] often co-occur [53]. In order to ensure a systematic and multifaceted examination of outcomes in the context of complex presentations, the study design includes assessments of primary comorbid conditions as well as general health and functioning to provide comprehensive data to inform real world clinical practice.

PROGrESS is designed as a comparative effectiveness trial with examination of neurobiological predictors and proximal correlates of effective treatment and candidate treatment mechanisms. The key question of who responds to which treatment or treatment combination provides specific direction to the field. In addition, delineation of biomarkers and their specificity to medication or PE is a critical step toward treatment refinements, improved effectiveness and efficiency of PTSD treatment, enhanced dissemination, and individualized treatment. All design choices were made with regard to their potential contribution to the field balanced by patient burden to minimize the impact on subject recruitment and retention.

Placebo medication is used because there is a need to establish the relative effect of PE without SERT pharmacotherapy compared to combination treatment. However, this does leave the study without a PE alone condition- an important design note because taking a pill along with therapy increases patient burden and may also impact attribution of change. As a comparative effectiveness trial, there is no placebo alone control condition, and all veterans receive at least one intervention with previous demonstrated efficacy for PTSD (PE and/or SERT).

Table 1
Assessment schedule, source, and domain.

Measure	Domain	Source	Intake	Wk 0	@ Med. Manage	Wk 6	Wk 12	Wk 24	Wk 36	Wk 52
MINI	Diagnoses	IE	X	[a]				X	X	X
Primary outcome										
CAPS	PTSD	IE	X	[a]		X	X	X	X	X
Secondary outcomes										
PCL-S	PTS Severity	Patient		X	X[b]	X	X	X	X	X
DASS-21	Depression, Anxiety and Stress Severity	Patient		X	X	X	X	X	X	X
PTCI	PTSD Cognitions	Patient		X	X	X	X			
NSI	PCS Symptoms	Patient		X		X	X	X	X	X
Alcohol/SUD	Alcohol/Substance Use	Patient		X		X	X	X	X	X
Related comorbidities										
BTBIS	Screen TBI Status	IE	X				X			X
C-SSRS	Suicidality	IE	X		X		X	X	X	X
CES	Combat Exposure	Patient		X						
PHQ-15	General Distress	Patient		X		X	X	X	X	X

MINI- Mini International Neuropsychiatric Interview; CAPS- Clinician Administered PTSD Scale; PCL-S- PTSD Checklist- Symptom version; DASS-21- Depression, Anxiety, and Stress Scale 21 item version; PTCI- Posttraumatic Cognitions Inventory; NSI- Neurobehavioral Symptom Inventory; SUD- Substance Use Disorder; BTBIS- Brief Traumatic Brain Injury Screen; C-SSRS- Columbia-Suicide Severity Rating Scale; CES- Combat Exposure Scale; PHQ-15- Patient Health Questionnaire- 15 items.

[a] Measures repeated for Week 0 only if delay from intake of 4 weeks or more.

[b] Completed at each therapy appointment.

3.3. Randomization

The study randomizes veterans (with masked allocation) using a secure centralized interactive web-based randomization application, TATUM (Treatment Assignment Tool – University of Michigan). Randomization is stratified by site with treatment assignments randomly permuted in varying block sizes within site. The study biostatistician generates a randomization list and provides it to TATUM for central distribution. For each eligible participant to be randomized, the site study coordinator requests randomization using TATUM, which generates an email indicating therapy status that is sent to the site coordinator and another email indicating pill status that is sent to the study site pharmacist to ensure that blind is maintained. Further, all evaluators are blind to both medication and therapy assignments.

4. Recruitment

4.1. Inclusion/exclusion

Inclusion criteria are OEF/OIF/OND Veterans and/or active duty with combat-related PTSD with significant impairment (CAPS ≥ 50) of at least three months duration. Exclusion criteria include only those factors that contraindicate primary treatment for PTSD, that prevent the veteran from benefiting from treatments being tested, or that may interfere with the mechanisms under study. Exclusion criteria are: 1) current, imminent risk of suicide (as indicated on the Columbia-Suicide Severity Rating Scale: C-SSRS) 2) active psychosis, 3) alcohol or substance dependence in the past 8 weeks per DSM-IV criteria, 4) inability to attend regular appointments, 5) prior failure of an adequate trial of PE (defined as a previous trial of PE that included at least 3 imaginal sessions focused on the same target trauma identified for this study) or SERT (defined as at least 3 months of SERT at least 100 mg/day), 6) medical illness likely to result in hospitalization or for which treatments are contraindicated (based on lab results, medical history and physical exam), 7) serious cognitive impairment (see below), and 8) concurrent antidepressants or antipsychotics. Benzodiazepines, prazosin, and sleep agents (e.g., Zolpidem) are allowed as long as the dose was stable for at least 2 weeks. Any deviation is recorded.

Of note, veterans with mild traumatic brain injury (mTBI) are not excluded from the study. Only those with significant cognitive impairment at intake (as evidenced by confusion, inability to track discussion or answer questions, or other indicators of significant cognitive impairment) are excluded. A history of mTBI is examined using the Brief Traumatic Brain Injury Screen (BTBIS; Schwab, Baker, Ivins, Sluss-Tiller, Lux, & Warden, 2006) to determine its impact on outcomes. fMRI sub study specific exclusion criteria include: 1) left-handedness (as determined by a standard questionnaire), 2) ferromagnetic material within the body (e.g., aneurysm clips, shrapnel/retained particles), and 3) inability to tolerate small, enclosed spaces (e.g. claustrophobia) 4) patient's girth exceeds allowable fMRI machine dimensions.

4.2. Recruitment and screening

The study includes 4 sites: VA Ann Arbor Healthcare System, Ralph H Johnson VA Medical Center, VA San Diego Healthcare System, and Massachusetts General Hospital with active enrollment between November 2011 and May 2016. Recruitment is centered on established VA primary care and PTSD Specialty care services, except for Massachusetts General Hospital where the established Home Base Program that provides mental health treatment to veterans and service members is located. Veterans are assessed for eligibility during intake evaluation at each site.

5. Assessment

All intakes and interview measures are completed by independent evaluators (IE) blind to treatment assignment and trained in both the CAPS (primary outcome) and the Mini International Neuropsychiatric Interview (MINI) [51] which are used for intake assessment of eligibility. Prior to conducting study related assessments, IEs complete trainings on all of the primary interview measures. IEs are required to rate a sample evaluation and reach agreement with trainers (90% agreement with all items on the CAPS, with no item being > 1 point off on frequency or intensity; 100% agreement on diagnoses and 90% agreement on all symptoms for the MINI). Throughout the study, interviews are audio-recorded for recalibration and inter-rater reliability assessment. Regular recalibration meetings are completed bimonthly. Table 1 provides the timetable for assessments. Standard demographic variables were collected, including but not limited to gender, race, ethnicity, trauma history, service connection, employment, age, etc.

5.1. Primary outcome

Clinician Administered PTSD Scale (CAPS) [5] is an interview measure of PTSD severity with excellent reliability and validity. Because this study started recruitment prior to DSM5, the DSM-IV version of CAPS is used. However, additional yes/no items are included to assess for the DSM5 criteria that were in draft form at the time. Current PTSD severity is assessed in relation to the OEF/OIF/OND war-zone trauma that is currently most upsetting and served as primary outcome. Current PTSD diagnosis and CAPS severity are both used as outcome measures. CAPS will remain the primary outcome but DSM5 diagnostic status will be available as well based on our preliminary items (Table 2).

5.2. Secondary measures

PTSD Checklist – Symptom (PCL-S) is a 17-item self-report assessment of PTSD severity using a 5-point scale, from 1 (not at all) to 5 (very often) with good reliability and validity [1]. The PCL-S anchors the assessment to a specific traumatic experience and for this study it is the target trauma at intake.

Table 2
Demographic characteristics of enrolled participants (N = 223).

	Mean (SD) or N (%)
Age	34.31 (8.28)
Sex	
Male	194 (87.0%)
Race	
White	129 (57.8%)
Black	65 (29.1%)
Other	29 (13.0%)
Hispanic or Latino Ethnicity	32 (14.3%)
Marital status[a]	
Married	114 (51.1%)
Never married	50 (22.4%)
Divorced	43 (19.3%)
Separated	15 (6.7%)
Education	
High school (or equivalent)	84 (37.7%)
Some college (13–15 years)	97 (43.5%)
Bachelor's or above (16 +)	42 (18.8%)
Work status	
Full time	114 (51.1%)
Part time	25 (11.2%)
Not working	84 (37.7%)
Served in Iraq	175 (78.5%)
Served in Afghanistan	108 (48.4%)
CAPS	77.27 (14.30)
BDI-II	24.68 (10.89)

Notes: CAPS- Clinician Administered PTSD Scale, total score for the past month; BDI-II- Beck Depression Inventory-II.
[a] One unknown marital status. Percentages are calculated out of N = 223.

Depression Anxiety Stress Scale (DASS-21) [2] assesses depression, general anxiety, and stress symptomatology. The DASS short version is a 21-item scale with 3 subscales (depression, anxiety, and stress). The subscales show low intercorrelations between factors and high item loading within factors [2]. Internal consistency of subscales (0.87 to 0.94) and concurrent validity is excellent [2].

Substance Abuse Outcomes Module (SAOM) [52] measures alcohol and drug use in the past month. Alcohol use items include the number of days of alcohol use, the average consumption per drinking day, the maximum consumption, and the number of binge days (days that more than five drinks were consumed). The SAOM also examines use for various recreational drugs (e.g., marijuana, cocaine or crack, prescribed stimulants, heroin, anabolic steroids, and tobacco).

Posttraumatic Cognitions Inventory (PTCI) ([15]) is a 36-item assessment of negative thoughts about the self, negative thoughts about the world, and self-blame. It has good psychometrics and is related to change in PTSD symptoms with treatment ([16]).

Neurobehavioral Symptom Inventory (NSI) [4] is a 22-item self-report of common symptoms of postconcussive syndrome and is used to assess severity of symptoms over the course of the study.

5.2.1. Measures of additional related comorbidities

Brief Traumatic Brain Injury Screen (BTBIS) [50] is used to assess for possible history of TBI. As per measure protocol, all positive items are queried at interview to ensure accuracy and validity. The BTBIS is completed at pre-treatment only.

Columbia-Suicide Severity Rating Scale (C-SSRS) [44] is a standardized 8 point clinician-administered suicidal rating system designed to track suicidal adverse events across a treatment trial and covering the wide spectrum of suicidality.

Combat Experiences Scale (CES) [30] is a seven-item measure of combat exposure severity and enquires about the frequency of various combat experiences including receipt of or witnessing someone hit by enemy fire, conducting combat patrols etc. Total scores range from 0 to 41. The CES has demonstrated good reliability.

Revised Patient Health Questionnaire (PHQ-15) [36] is used to assess physical health status with five additional post-concussive symptoms added as reported by Hoge and colleagues [24]. The original scale has a range of 0 to 30 with high severity indicated by a score of 15 or higher. The five additional questions, which are not part of the PHQ-15, covered memory, balance, concentration, ringing in the ears, and irritability.

6. Interventions

Veterans complete 13 weeks of the randomly assigned treatment followed by 12 additional weeks of pill continuation (i.e., Sertraline or Placebo) and completion of any missed sessions (total 13 sessions) for PE (as described in detail below). As part of randomized treatment, the design includes an early remission criterion. Veterans who obtain a PCL score below 28 for two consecutive weekly assessments are considered early completers for PE or enhanced medication management visits. For those in enhanced medication management who meet the early remission criterion, pharmacotherapy visits continue on the manualized schedule without the additional EMM supportive contact. For those in PE who meet the remission criterion, PE sessions end and pharmacotherapy visits continue on the manualized schedule without the additional EMM supportive contact. After all week 24 assessments are completed, the blind is broken and all symptomatic and interested veterans receive medication management and are offered or referred for additional treatment as warranted (PE or alternate medication). Data collection on any treatment changes and follow up continues until the end of the study period (week 52). Response is defined as 50% or more reduction in CAPS from baseline to week 24.

6.1. Prolonged exposure therapy (PE)

PE is used because of the strong support for its efficacy and its dissemination across Veterans Affairs facilities. PE ([14]) is a manualized treatment protocol typically administered over 8 to 15 weekly 90-minute sessions. Our study protocol includes up to 13 PE sessions. PE primary elements include: a) psychoeducation, b) repeated and prolonged imaginal exposure to traumatic memories in session, c) discussion/processing of the traumatic memories and imaginal exposures, and d) repeated in-vivo exposure to objectively safe though avoided trauma-related situations assigned as between-session homework. All study therapists are trained using the standard VA PE four-day workshop and therapists complete at least two supervised test cases with audio-recording session review to demonstrate and practice PE skills and fidelity prior to receiving randomized cases. The training regimen and pre-randomization case review is repeated for new therapists who join the multiyear study. During the active treatment phase, fidelity to both PE and PE-related study protocol guidelines is protected via weekly therapist supervision calls, where therapist problems, successes, and questions are addressed systematically via a structured template and therapist attendance and participation is tracked. The structured template also queries PE process-oriented information, such as weekly therapist-rated patient homework compliance and imaginal exposure completion as a real-time check on adherence and fidelity balance among the sites. As described below, independent fidelity monitoring to criterion of a randomly selected 20% of sessions is completed throughout the course of the study. The final study therapy staff consists of a total of 15 certified therapists across the 4 study sites.

6.2. Medication management

Medication management (either sertraline or placebo) is manualized to standardize delivery of pharmacotherapy when administered alongside PE as brief (approximately 15 min) adjunctive medication management visits (MM) or enhanced medication management (EMM: approximately 30 min) for those randomized to SERT to help balance time, psychoeducation, and support from providers between the PE and medication alone conditions. All pharmacotherapists are trained and certified in MM and EMM with a 3 h training, and participate in monthly cross-site group supervision calls to enhance fidelity. Both forms of medication management include manualized brief PTSD psychoeducation with rationale for medication use in PTSD and a positive expectation for potential treatment response. Each visit includes review of symptoms, side effects monitoring, and decisions regarding medication dosing. EMM includes additional psychoeducation about PTSD and present centered supportive content modified with permission from the Present Centered Therapy manual [49].

All MM and EMM visits during the active treatment phase occur weekly for the first 3 weeks, and then decrease to every other week for weeks 4, 6, 8, 10, and 12. Active treatment ends at Week 12. Medication dose remains stable after week 10 unless changes are indicated for safety until week 24. Continuation phase visits occur at weeks 16, 20, and 24.

6.2.1. Acute treatment with blinded SERT (weeks 0 to 12)

The study medication, sertraline (SERT), is used as it is one of only two SSRIs that are FDA approved for the treatment of PTSD, with strong evidence for efficacy [38]. Consistent with the recommended dosing of SERT, the study medication is flexibly dosed with a target of providing a recommended minimum effective dose of 50 mg/day up to a maximum of 200 mg/day. During the 12 weeks of acute treatment, all veterans receive blinded SERT or PLB titrated flexibly based on tolerability and symptomatic response. Guidelines for determination of dose increases are established to enhance consistency across prescribers. Specifically, the general rule is to increase dosing if tolerated and still symptomatic [defined as a CGI-S score of >2 (borderline ill)]. The

Frequency, Intensity, and Burden of Side Effects Rating (FIBSER: [56] is a self-report scale that rates frequency, intensity, and overall burden or degree of interference in day-to-day activities and function due to the side effects attributable specifically to the antidepressant treatment each on a Likert-type scale rated 0–6. The FIBSER is used to measure side effect burden with a score of 5 or greater triggering extra attention and review and a score of 7 or more signaling no increase in dose without specific clear justification.

Double-blind medication is initiated at baseline (week 0) with 25 mg/day followed by a dose increase to 50 mg/day at week one if tolerated. If veterans are unable to initially tolerate 50 mg/day they are permitted to remain at 25 mg/day during week 1, but the dose must titrate to 50 mg/day by week 8. If unable to tolerate SERT 50 mg/day at week 8, veterans are discontinued from the protocol and transferred to clinical care. If no slowing of dose titration is required, at week 2 the blinded SERT dose is raised to 100 mg/day. Upward dose titration is slowed and the dose decreased if necessary due to side effects but the clinician attempts to titrate all symptomatic veterans to at least 100 mg/day and up to 200 mg/day if tolerated by week 8.

6.2.2. Continuation pharmacotherapy (weeks 12 to 24)

All study veterans who do not meet study discontinuation criteria based on lack of effectiveness or tolerability are continued on blinded medication during the 12-week follow-up phase. No dose changes occur during the follow up phase. Follow up pharmacotherapy visits at weeks 16, 20 and 24 monitor compliance, safety and symptomatic status, with pharmacotherapists available for consultation as needed if side effects or symptomatic worsening develop between visits.

6.2.3. Capsule adherence monitoring

At each session, the physician or study coordinator collect, count, and record unused capsules. In addition, the physician reviews the Adherence Questionnaire, a 2-item questionnaire used to determine what proportion of the time between visits the participant took their study medication as recommended, and to establish the reason(s) for any deviation from the recommended dose (e.g., forgot, side effects, thought not needed, etc.). The study physician records the use of both study medications and concomitant medications on a study tracking form, and attempts to address any issues related to compliance when indicated.

6.2.4. Concomitant medications

Concomitant antidepressants and antipsychotics are prohibited in the study. The use of benzodiazepines, prazosin, and hypnotics (such as zolpidem) is allowed as long as the participant is stable on the medication and dose for at least 2 weeks. Veterans assigned to PE are instructed not to take their medication before, during, or for 1 h after any exposure exercises. Veterans (and their prescribing providers) are asked to not begin any additional psychotropic medication during the course of the study or make changes to any other medication unless specifically approved. All deviations are recorded.

6.3. Fidelity monitoring

6.3.1. PE

Distinct from the ongoing therapist supervision described above, 20% of cases are also reviewed and rated for treatment fidelity by fidelity raters at each study site. The fidelity measure, used in a number of previous PE trials, varies in content by each session but includes an average of 14 items related to core PE components and 9 items related to general CBT therapist factors. Deviations in PE procedures are addressed in supervision throughout the study to enhance fidelity.

6.3.2. EMM and MM

As noted above, all pharmacotherapists are trained and certified in MM and EMM with a 3 h training, and participate in monthly cross-site group supervision calls to enhance fidelity. Key EMM behaviors include active listening, encouragement of expression of feelings, and provision of accurate information about PTSD. Specifically prohibited for all pharmacotherapy visits are behavioral activation, instructions to decrease avoidance, or passive or active exposure interventions. Sessions are videotaped. Twenty percent of session tapes are rated for fidelity to ensure that prescribed and proscribed interventions coincide with the assigned groups (i.e., no directions for exposure in EMM). Any deviation concerns in MM or EM procedures are addressed in supervision throughout the study to enhance fidelity.

7. Neurobiological measures

7.1. Genetic variables

Genomic DNA is obtained from blood specimens collected at intake and post-treatment (Wk 24), centrifuged to separate plasma from cellular components, frozen, and shipped to VAAAHS. Genomic DNA is purified using a semi-automated membrane method (QuickGene610, Autogen, Inc.), quantified (Nanodrop, Thermoscientific, Inc.) and stored at − 80C. Genotyping is performed at the University of Michigan DNA Sequencing Core using the Infinium "PsychArray-24" beadassay (Illumina, Inc., includes 265,000 tag SNPs, 245,000 genomic markers, and 50,000 additional markers associated with common psychiatric disorders). Beadchips are hybridized with ~400 ng of genomic DNA and scanned using standard Illumina protocols. Illumina GenomeStudio is used for standard clustering QC and to generate genotype calls.

7.2. Gene expression variables

Whole blood leukocyte samples are obtained at week 0 and week 24. Blood is drawn in the morning (8 am–11 am, following overnight fast), collected into RNA stabilization blood collection tubes ("Tempus", Ambion Inc.), and stored at − 80C until shipped to VAAAHS. Total RNA is purified (MagMax kit, Thermo Fischer Scientific Inc.), and yield and RNA integrity (RIN) assessed (Bioanalyzer 2100, Agilent, Inc). Transcriptome mRNA libraries are prepared (TruSeq Stranded kit, Illumina, Inc.) at University of Michigan Sequencing Core in pools of 96 samples, and single-end 50 nt mRNA sequencing (~30million reads/sample) perform using HiSeq 4000 (Illumina, Inc.). mRNA sequence data cleaning, filtering, alignment, transcript quantification, and normalizing transcript counts between samples and runs are performed by the University of Michigan Bioinformatics Core using their standard methods.

7.3. fMRI paradigm and tasks

fMRI scans occur at week 0 and week 24. Each scanning session includes four tasks – 1) an emotional faces task (matching emotional faces to target) EFAT; 2) an emotion regulation task (effortful reappraisal of aversive pictures) ERT; 3) an attentional control with emotional faces task (SEAT); and 4) a resting state scan [all described in detail below]. All scanning is done at the VAAAHS fMRI Center, on a 3.0 Tesla Phillips scanner (Excite release, Neuro-optimized gradients). Although only a subset of clinical trial participants are expected to undergo scanning, all study participants from other sites are offered housing and travel to undergo fMRI at VAAAHS. We measure heart rate and respiration as general markers of physiological arousal. With structural data acquisition, veterans spend about 1 h in the bore of the magnet, for a 30 to 50 min of data collection.

7.3.1. Emotional face assessment task

The EFAT is a variant of the Emotional Face Processing Task [20]. It has been previously shown to reliably and robustly engage the amygdala and insula and has been used in other pharmacological fMRI studies [42,54]. Moreover, our group has used to it to track neural changes

to psychosocial intervention in PTSD and anxiety disorders [31,32]. Veterans view a trio of faces and are instructed to match one of the two faces (bottom) that expressed the same emotion as the target face (top). The identity of all three faces is always different, and an equal number of male and female faces are presented. This task allows isolation of amygdala and insula reactivity specifically to threat (Angry and Fearful faces) relative to non-threat (Happy and Neutral faces). Angry, fearful, happy and neutral target faces are presented in separate blocks. Three blocks of each target expression are presented, and no target stimuli are repeated. Face matching tasks are interspersed with a 'baseline' task, of matching simple geometric shapes (circles, rectangles or triangles). The paradigm consists of 24 experimental 20 s blocks: twelve blocks of matching emotional faces, interleaved with twelve blocks of matching shapes, counterbalanced across 2 runs. Each task block contains four sequential matching trials/faces, 5 s each. Veterans respond to tasks by pressing the left or right response buttons with their dominant hand. These responses also provide a measure of veterans' response accuracy and reaction time.

7.3.2. Emotional regulation task

The ERT task employs three conditions: Maintain (looking at negative images), Reappraise (reframing negative images), and Look (looking at neutral images). Cognitive reappraisal to down-regulate negative affect has been previously shown to reliably and robustly engage the prefrontal cortex (dlPFC, vlPFC, dmPFC and vmPFC), whereas negative affective experience (Maintain) has been shown to engage amygdala and insula [8,11]. Moreover, it tracks neural changes to pharmacological and psychosocial intervention in PTSD and anxiety disorders [10,33,34,39]. On look blocks, veterans are instructed to passively view pictures and simply experience the emotional state elicited by the neutrally valenced pictures. On Maintain blocks, veterans are instructed to passively view pictures and simply experience the emotional state elicited by the negatively valenced pictures. On the Reappraisal blocks, veterans are instructed to decrease the intensity of their negative emotional responses by engaging in the cognitive strategy of reappraisal. For each picture viewed, veterans are asked to reinterpret the content of the picture so that it elicits a less negative emotional response. After each block, subjects are asked to rate their subjective emotional responses to each picture on a scale of 1–5 by button press. The stimulus set consists of 60 highly aversive and arousing pictures and 30 neutral pictures from the IAPS [37] and 15 blank gray-scale images (fixation cross). The aversive pictures elicit negative affect and generally depict complex scenes of dead animals, people crying, burns etc. Pictures are chosen as 'aversive' and arousing based upon normative ratings from the IAPS. They have been extensively validated (e.g. [43]) to evoke negative emotions and activations in the amygdala and limbic regions. Prior to pre-treatment scanning, veterans receive instruction and practice the reappraisal task using pictures not shown in scans.

7.3.3. SEAT

Picture stimuli are presented in the scanner using E-Prime (Psychological Software Tools, Inc., Pittsburgh, PA). Pictures are composite face/scene images comprised of 20 angry, 20 fearful, and 20 neutral expressions [13,19] superimposed on 20 building scenes (10 indoor, 10 outdoor) (Klumpp, et al. [57]; Sripada et al. [58]: Ma et al. [59]). To localize the face and place processing brain areas, an additional 10 neutral faces and 10 indoor or outdoor scenes are used as non-composite pictures. There are 80 unique gray scale pictures in total. This builds on prior work that uses simple face pictures to study emotion labeling as an emotion regulation procedure (Chen, Welsh, Liberzon, & Taylor, [60]), allowing study of both attention shifting and appraisal in a single paradigm. Veterans are shown the composite images and asked to respond to three different questions regarding each image: 1) pay attention to the face on the composite picture and determine if it is male or female; (Male/Female condition); 2) pay attention to the scene on the composite picture, and determine if it is indoor or outdoor (Indoor/Outdoor condition); 3) pay attention to the face on the composite picture, and determine if you like or dislike the face (Like/Dislike condition). In all conditions the composite pictures display fearful, angry or neutral faces. The Male/Female condition maintains attention on the emotional stimuli without engaging appraisal and is a standard fMRI approach to studying implicit emotional processing [17]. The other two conditions involve the same type of implicit emotional processing (emotional facial expressions are present and are processed), but additionally involve two types of non-intentional emotional regulation, namely: 1) attention redirection (Indoor/Outdoor condition); and 2) appraisal (Like/Dislike condition). Each composite picture is presented three times, once in each condition, with condition type in random order (180 trials total). Correct responses in the Male/Female and Indoor/Outdoor conditions involve accurately identifying the sex of the face (Male/Female) or the location of the scene (Indoor/Outdoor). Non-composite pictures (face or place only) are presented in 40 trials in which veterans are simply asked to determine whether it was a face or place. A total of 220 trials are randomly ordered across 4 runs with 55 trials per run. Trials comprise a centered fixation crosshair for 3–8 s, judgment cue for 750 ms + 250 ms blank screen, and then composite pictures for 1500 ms. Prior to experimental trials, subjects complete a practice session with images not used in the experiment.

7.3.4. Resting state scan

During the resting state task, a white fixation cross on a black background is displayed at the center of the screen for 8 min. Veterans are instructed to relax and to keep their eyes open and fixed on the cross.

7.4. Cortisol awakening response (CAR)

CAR is a measure of HPA axis homeostasis and is assessed with collection of salivary cortisol. Subjects receive instructions and 3 Salivettes for collection of saliva samples at awakening, 30 min and 45 min after awakening. Saliva is collected by cotton swabs ("Salivettes") placed in the patient's mouth for 30 s for each collection. Veterans are instructed to refrain from eating, drinking, brushing their teeth, or smoking for at least 1 h before sampling. They are instructed to collect and bring the samples to their study assessment the same day. Cortisol is assayed using IMMULITE™ (Siemens, Inc.), a rapid and highly sensitive and precise semi-automated chemiluminescent assay, and has an intra- assay and inter-variability of $< 5\%$. CAR is calculated as AUC produced by the three samples with reference to the awakening sample.

8. Data analytic approach

8.1. Primary outcomes

Our hypotheses are that all three interventions will be effective in reducing PTSD related symptoms, with PE/SERT being most effective, followed by PE/PLB, and then by SERT/EMM. The study is powered to detect outcome differences between the PE/PLB compared with SERT/EMM to assess the effect of PE/PLB relative to sertraline, and PE/SERT compared with PE/PLB to assess the augmentation effect of SERT to PE. We hypothesize that the effect sizes between the two comparisons will be similar; i.e., PE/PLB effect relative to sertraline will be similar to the augmentation effect of sertraline to PE. CAPS scores serve as the primary outcome for the study. Treatment response is defined as 50% or more reduction in CAPS from baseline to week 24 (or the last observed CAPS score prior to week 24). Accepted standards for estimating clinically significant and reliable difference/change are based on the reliability of the measure [28]. Given estimates for test-retest reliability for the CAPS, a conservative estimate of clinically reliable PE effect is

11.4 points [29]. With a standard deviation of 24 for the CAPS from an OEF/OIF/OND PTSD treatment trial of N = 24, the clinically meaningful and detectable standardized effect size (Cohen's d) is 0.48 [46]. We calculated sample size to have adequate power to detect this effect size using a 0.025 level test (adjusted for the pairs of comparison) based on a mixed-effects model using three repeated assessments at weeks 6, 12 and 24 after initiation of treatment. The study has 82% power with 70 veterans enrolled per group. Power calculations assume a within-person correlation of 0.6 for repeatedly assessed follow-up data, a correlation of 0.5 between baseline and follow-up data, an average of 10 veterans per therapist with 0.03 within-therapist correlation, and an estimated 30% drop by 24 weeks follow-up (3 months after the end of 12-week acute treatment period) [45]. Because we expect even the least effective group (SERT/EMM) to show an effect size as large as the assumed clinically meaningful effect size of 11.4 points, the proposed sample size is expected to provide adequate power to detect pre- to post treatment effects across all three intervention groups.

The primary analytic cohort is designed as intent-to-treat, excluding veterans who consented but are not dispensed any medication (veterans are unaware of their randomized group until medication is dispensed). All veterans who are dispensed any study medication (SERT or PLB) are analyzed within their respective randomized groups, regardless of their treatment adherence status. While the primary outcome focus is symptom change, differential drop out, early response, and treatment adherence are included outcomes of interest. As-treated ("per protocol") analyses are also planned. This is especially relevant to the mechanistic biological variables assessed across treatment. For the as-treated analysis, groups are defined by the actual intervention each participant is randomized to, but the outcomes are censored at the time when veterans switch or stop the treatment to which they are assigned. For veterans in the PE/PLB or PE/SERT group, data is censored at the time when both therapy and medication (SERT or placebo) stop. Because side effects or medication intolerance can result in early medication discontinuation, the as-treated analysis may give a better outcome estimate for the SERT group compared to the intent-to-treat analysis.

8.2. Longitudinal outcome comparison

Outcomes over the 12-month follow-up period enable examination of the pace of recovery and comparison of retention trends after intervention. Planned analyses include plotting cross-sectional means of various outcome measures at each measurement time as well as outcomes over time for each individual to assess individual trends. Additional exploratory analyses can consider a range of predictors of 12 month outcomes including group assignment, week 24 outcome, study treatment completion and intercurrent treatment.

8.3. Genetic association with treatment response

Exploratory pharmacogenetic analyses are planned to identify genetic predictors of treatment responses to SERT and PE/PLB, including testing replication of SNPs in genes previously associated with SSRI response and PTSD pathophysiology (e.g. *ANKRD55*, *FKBP5, KLHL1, ZNF626*), and exploratory genome-wide analyses, using continuous measures of symptom improvement (e.g., % improvement or residualized change scores), controlling for sex, age, and ancestry. Standard data cleaning of PsychArray genotype calls, imputation, and principal components analyses (PCA) for ancestry and population stratification controls are performed. Statistical models are designed to compare veterans treated with SERT (SERT/EMM and PE/SERT) and PE (PE/PLB and PE/SERT), controlling for presence of the other treatment. The study sample allows for detection of large genetic effects (e.g. OR > 2.0) in dominant models (80% power at Bonferonni adjusted $p < 0.002$ (25 SNPs) and MAF 0.05–0.25). Genome-wide studies of SSRI effects in depression have been inconclusive; while there have been several recent case-control GWAS studies of PTSD diagnosis (e.g. [12]) to our knowledge there have been no genome-wide studies of SSRI effects in PTSD. While our sample is clearly underpowered for GWAS (requiring genome-wide significance ca. $p < 5 \times 10^{-8}$), again strong gene effects (e.g. OR > 2) in dominant models may be detected in this sample [26], and moreover these genome-wide genotype and longitudinal symptom response data are a valuable resource for future collaborative studies (e.g. Psychiatric Genomics Consortium PTSD Committee, PGC-PTSD) of genetic predictors of treatment responses in PTSD. In addition, polygenic approaches utilizing polygenic risk scores from previous PTSD GWAS data [12] can be used to explore association with treatment responses.

8.4. Gene expression analyses

We hypothesize treatment with SERT will be associated with changes in leukocyte gene expression related to primary pharmacological effects, whereas treatment response in both PE/PLB and SERT will also be associated with changes in leukocyte gene expression related to therapeutic change, which may partially overlap the main effects of SERT. Because we are studying a heterogeneous cell population (whole blood leukocytes), a latent variable computational approach is designed to control for cell-type proportions across samples (e.g. CellCODE [9]). Testing for differential expression of genes from pre- to post-treatment within each treatment arms (SERT/EMM, PE/SERT, and PE/PLB) and comparison of the three arms is planned. Other planned analyses include identifying expression profiles at intake that predict treatment responses to SERT/EMM and PE/PLB, identifying pre- to post-treatment gene expression profiles that correlate with treatment responses, and exploring enrichment of differentially expressed genes in functional and pathway gene sets using gene ontology (GO) biological processes. Finally, this study design enables examination of the effects of treatments (SERT/EMM and PE/PLB on changes in gene expression networks using network analytic tools, such as recently reported in another longitudinal study of gene expression in combat PTSD of similar size [6].

8.5. Neuroimaging data analysis

The fMRI analysis procedures are described in detail elsewhere [31,39]. Briefly, fMRI data are processed using conventional preprocessing steps (e.g., realignment, normalization, smoothing) (SPM12; Wellcome Trust Center for Neuroimaging, London). Analyses include modified Generalized Linear Model (GLM) in combination with a temporal convolution for block- and even-related analyses in a random effects model. To characterize the effects of SERT/EMM, PE/SERT and PE/PLB on amygdala, insula, and prefrontal function (e.g., vmPFC, dmPFC and dlPFC), complementary approaches to test regional activations and connectivity patterns are implemented: 1) hypothesis-driven region-of-interest (ROI) analysis (ROIs: amygdala, insula, dlPFC, vlPFC, dmPFC and vmPFC), using small-volume correction ($p < 0.05$, FWE) and resting state connectivity analysis using connectivity estimates for pre- and post-treatment scans extracted for seeds in DMN and Salience networks 2) whole-brain activation search at a threshold of $p < 0.05$ (FDR, False Discovery Rate).

To test our hypotheses, we extract patterns of brain activation using specific contrasts for EFAT, ERT, and SEAT, and extract parameter estimates of activation (β) in anatomically-derived ROIs, and connectivity estimates for ICN nodes for resting state scans. Logistic regression analysis [27], including age, gender, age of onset, duration of illness, and pre-treatment CAPS scores as additional potential predictor variables, test if amygdala, insula and PFC region (mPFC, dlPFC and vlPFC) activations as well as connectivity estimates at baseline (pre-treatment) can be used as a predictor of treatment response. For exploratory whole-brain voxel-by-voxel analysis, we employ a voxel-wise analysis of BOLD signal change across the entire brain correcting for multiple comparisons. Finally, we examine correlations between treatment

response and functional MRI and connectivity changes.

Power analysis for pharmaco-fMRI studies is still an area under active development. Based on preliminary data from naturalistic study using SEAT task, 35 subjects per group, provide > 85% power, with $\alpha = 0.05$ (www.fmripower.org), to detect group differences in activation on SEAT appraisal task (effect size = 0.64 SD) in the left medial superior FC [as defined on Automated Anatomical Labeling (AAL)]. Similar size groups is sufficient, to detect over-time changes in resting state connectivity (seed in PCC), in right middle orbital frontal cortex [88% power, effect size = 0.68 SD], and 42 subjects per group, offers > 85% power to detect group differences in the progressive changes between two time points, for example, in the resting PCC connectivity in the left amygdala and hippocampus.

9. Conclusions

The primary goal of the comparative effectiveness PROGrESS study is to compare the two best-supported treatments for PTSD and their typically used combination to guide clinical practice. This study is the only comparison of psychotherapy, medication, and their combination for the treatment of PTSD in veterans and one of only a few studies of comparative effectiveness in PTSD (e.g., [48]. While meta-analyses have found that effect sizes for trauma-focused psychotherapy are larger than for medication, these were not based on direct comparisons. This unique three arm RCT design allows for assessment of the effectiveness of each treatment individually as well as their combination. While the two PE conditions provide a greater total amount of treatment time than the SERT/EMM condition, the enhanced medication management incorporating present-centered therapy techniques is included to help offset this difference. The embedded double-blind placebo-control of sertraline, combined with blinded independent measures for all three treatment arms provides the most objective assessment of outcomes possible in a trial of this nature.

PROGrESS is among the most comprehensive PTSD treatment studies to date of prognostically-relevant biomarkers or treatment mechanisms. By integrating measurement of biomarkers into this comparative treatment study, PROGrESS has the potential to move the field toward important treatment refinements, improved effectiveness and efficiency of PTSD treatment, and individualized treatment. If valid biomarkers (HPA, brain, genetics) can differentially predict treatment response to PE and/or SSRI, these biomarkers can be used to guide patients to a particular treatment pathway. Using specific neurobiological predictors, treatment techniques (psychotherapeutic and medication) can be more efficiently delivered and monitored. Increased efficiency may increase treatment acceptability, reduce dropout, and aid in expanding access to specialty PTSD care, as a greater proportion of early responders translates into more patients treated per provider. Thus identifying patient-level predictors of response to specific treatment has important implications related to treatment effectiveness and efficiency.

Understanding the neurobiological mechanisms behind effective treatment for PTSD can guide further treatment development, the development of rational and effective combined treatments, and the modification of existing protocols. Knowledge of predictors and mechanisms can improve the match of the individual patient to specific therapy, and as a result improve efficiency, effectiveness and dissemination. With regard to existing pharmacotherapy, predictors and mechanisms can inform whether medication is used alone, started first, started simultaneous with therapy, or started after partial response to therapy. Thus, understanding treatment mechanisms will improve development of new treatments and help to optimize existing therapies and lead to improved treatment efficiency.

In designing the study, the team chose potential biomarkers that showed promise as predictors or mechanisms that may show change associated with treatment response. Beginning with specific emotional response and regulation approaches that previous research suggested may be related to patients responding better to medications or psychotherapy [7]. Given the previous work in our research group, we drew upon these findings to create a thorough assessment of emotion regulation and response in fMRI while minimizing scanner time and patient burden. Examination of HPA axis function as a potential predictor and mechanism is also included in the study design; while including script driven imagery was considered, in order to reduce patient burden we instead included CAR. This measure has shown both stable associations with PTSD severity and associated changes with treatment response [46]. In addition, our procedures for collection have produced high levels of compliance and we expect them to provide informative results. Finally, we included genetics and genomic analysis. Despite the small sample size, our targeted examination of mRNA across treatment and genetic predictors of specific treatment conditions can provide a basis for combination with other datasets or signal for larger dataset targets.

Despite significant innovation, all study designs have limitations. PROGrESS focuses on veterans and active duty service members with PTSD. As such, the sample may not generalize to other populations of trauma survivors. This may be especially relevant given the gender distribution of combat veterans weighting toward males. Second, because we did not include a PE only condition, we will not be able to speak to relative effects of PE treatment alone; all patients in PE have the additional burden of medication-related appointments added to their PE psychotherapy, and may attribute benefits to one or the other part of their treatment. These issues may negatively impact the effect size of PE. Lack of a placebo-only control comparison makes it impossible to determine the relative contribution of the placebo pill. Comparison of the PE response in PROGrESS to other PE studies in VA or DOD is warranted to determine whether the study's PE plus a pill placebo treatment response approximates PE alone.

PROGrESS represents a groundbreaking and innovative study that will directly inform clinical practice and PTSD treatment research for years to come in both military and civilian populations. The integration of biomarkers of response and mechanism will provide results to direct treatment decisions, treatment research development, and research into PTSD development and treatment more generally. This large study of veterans and service members during PTSD treatment promises to provide long awaited answers to who may best respond to SSRI or psychotherapy.

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RESEARCH ARTICLE

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The loss of a fellow service member: Complicated grief in post-9/11 service members and veterans with combat-related posttraumatic stress disorder

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Abstract

Bereavement is a potent and highly prevalent stressor among service members and veterans. However, the psychological consequences of bereavement, including complicated grief (CG), have been minimally examined. Loss was assessed in 204 post-9/11, when service members and veterans with combat-related posttraumatic stress disorder (PTSD) took part in a multicenter treatment study. Those who reported the loss of an important person completed the inventory of complicated grief (ICG; $n = 160$). Over three quarters (79.41%) of the sample reported an important lifetime loss, with close to half (47.06%) reporting the loss of a fellow service member (FSM). The prevalence of CG was 24.75% overall, and nearly one third (31.25%) among the bereaved. CG was more prevalent among veterans who lost a fellow service member (FSM) (41.05%, $n = 39$) compared to those bereaved who did not (16.92%, $n = 11$; OR = 3.41, 95% CI: 1.59, 7.36). CG was associated with significantly greater PTSD severity, functional impairment, trauma-related guilt, and lifetime suicide attempts. Complicated grief was prevalent and associated with adverse psychosocial outcomes in veterans and service members with combat-related PTSD. Clinicians working with this population should inquire about bereavement, including loss of a FSM, and screen for CG. Additional research examining CG in this population is needed.

KEYWORDS
combat-related PTSD, bereavement, military, death, war buddy suicide, complicated grief

1 | INTRODUCTION

Bereavement is a highly distressing and disruptive experience. It is associated with the onset of a range of mental health conditions, including major depressive disorder (MDD) and posttraumatic stress disorder (PTSD; Keyes et al., 2014). In addition, approximately 7% of bereaved individuals will experience complicated grief (CG), a syndrome associated with adverse psychosocial outcomes, including increased risk for suicide (Kersting, Brahler, Glaesmer, & Wagner, 2011; Marques et al., 2013; Simon et al., 2011; Tal et al., 2016).

Significance

This study found that exposure to the loss of a fellow service member occurs commonly and is associated with complicated grief (CG) amongst service members and veterans with combat-related posttraumatic stress disorder (PTSD). Further, the presence of CG was associated with more severe PTSD, guilt, and lifetime suicide attempts, as well as poorer function. This study supports that clinicians should ask veterans and service members with PTSD about military losses and associated CG symptoms and future research should examine the optimal way to address CG in this military population.

Complicated grief (also referred to as prolonged grief disorder or traumatic grief) was recently proposed as a disorder needing further study within the newly formed trauma and stressor related conditions category of DSM-5 under the name persistent complex bereavement disorder (PCBD). (American Psychiatric Association, 2013). Unlike acute grief, a variable but time-limited response to loss, CG is a persistent, intense and impairing condition diagnosed when distressing and disabling grief has persisted at least 6 months following the loss.

Core symptoms of CG include intense yearning or longing for the deceased, sorrow or emotional pain, and preoccupation with thoughts about the death or the deceased (Simon et al., 2011). Additional symptoms include difficulty accepting the death, avoidance of reminders of the deceased or of the permanence of the loss, difficulty planning for the future, role and identity confusion, feeling that life is unbearable without the deceased, and a wish to die to join the deceased (Mauro et al., 2016; Simon et al., 2011). Although CG shares many similar symptoms with other stress-related disorders, such as PTSD and MDD, it also includes symptoms that are not observed in PTSD or MDD, and CG can occur independently of these conditions (Bonanno et al., 2007; Simon, 2012). For instance, fear is a central component of PTSD, but is not characteristic of CG, whereas yearning and attachment-related concerns are characteristic of CG but not PTSD (Simon, 2012). Nonetheless, due to the partial overlap of symptoms and etiological factors, CG frequently co-occurs with psychiatric disorders such as PTSD, MDD, and a range of other anxiety disorders. Additionally, comorbidity between CG and these disorders is associated with significantly greater grief severity as well as greater work and social impairment (Marques et al., 2013; Simon et al., 2007).

Service members and veterans are at especially high risk for exposure to potentially traumatic events, including sudden and violent combat losses, suggesting bereavement-related distress may be prevalent (Wisco et al., 2014). In a representative sample of 3,157 United States veterans of all eras, 87% reported exposure to at least one potentially traumatic event, and sudden death of a loved one was the most frequently endorsed of those events (Wisco et al., 2014). One study of Vietnam veterans seeking treatment for PTSD reported that the loss of fellow service members (FSM) in combat was associated with increased grief, but not with PTSD or depression (Pivar & Field, 2004). Notably, the authors concluded that grief following the loss of a FSM was similar in severity to the level of grief following spousal losses (Pivar & Field, 2004). In another study of Vietnam veterans, combat-related losses were uniquely associated with impairment, yet not related to the severity of PTSD, suggesting more attention to grief after combat losses is needed in all veterans (Currier & Holland, 2012). To date, a small number of studies have examined grief in post-9/11 service members and veterans. In one study of active duty service members, 75% reported having lost a FSM and 21% reported having difficulty coping with the death of someone close (Toblin et al., 2012). Further, bereavement has been associated with physical and functional impairment in this population, even when accounting for PTSD and depression (Fink, Gallaway, & Millikan, 2013; Toblin et al., 2012).

Veterans of all eras are also at risk for psychiatric sequelae of bereavement from suicide as a result of the high rate of suicide in this population (Hom, Stanley, Gutierrez, & Joiner, 2017). A recent study of 931 veterans found that nearly half (47%) reported lifetime exposure to suicide, which in turn was associated with increased rates of depression, anxiety, PTSD, and prolonged grief (Cerel et al., 2015). Similarly, a large study in veterans found that 51% reported loss of a friend to suicide, and such exposure was in turn associated with suicidal thoughts and behaviors (Hom et al., 2017). Despite the high level of exposure to sudden and violent losses such as suicides among veterans and the negative outcomes associated with these exposures, grief remains understudied in this population. Indeed, while there is a vast literature on PTSD prevalence and its impact on veterans and service members, very little is known about CG in the military, especially among our most recent service members. Further, while veterans with combat-related PTSD may be particularly at risk for exposure to loss and the development of co-occurring psychiatric conditions, there is limited knowledge about the prevalence of co-occurring CG or the severity of CG symptoms in this population.

The present study aims were to examine the prevalence of loss, and the prevalence, severity, and impact of CG in a well-characterized, post-9/11 veteran population seeking care for combat-related PTSD. We hypothesized that the presence of CG would be associated with greater clinical severity, including PTSD severity, functional impairment, trauma-related guilt, and suicidal ideation and behaviors. We also hypothesized that the loss of a fellow service member in veterans with combat-related PTSD would be associated with a higher prevalence of CG compared to other types of losses.

2 | MATERIALS AND METHODS

2.1 | Participants

Participants were post-9/11 active-duty service members or veterans who served during Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and/or Operation New Dawn (OND) with combat-related PTSD who were enrolled in and met entry criteria for a Department of Defense-funded multicenter randomized controlled treatment trial between November 2011–May 2016. The parent treatment study, PROGrESS: PROlonGed ExpoSure Sertraline: Randomized Controlled

Trial of Sertraline, ProlongedExposure Therapy and Their Combination of OEF/OIF with PTSD examined clinical and biological predictors and outcomes for prolonged exposure (PE) therapy compared to sertraline plus enhanced medication management, or the combination of sertraline and PE. Eligible participants had a primary diagnosis of combat-related chronic PTSD with at least three months duration defined by the clinician administered PTSD scale for DSM-IV (CAPS) score of 50 or higher, as assessed by certified raters. Combat-related trauma was defined as any directly witnessed or directly participated in event that involved violence, the threat of violence, or the aftermath of violence (e.g., firefights, IED attacks, bombings, recovering bodies, suicide attacks). Exclusion criteria were designed to include a generalizable treatment-seeking population. Excluded participants were those with active psychosis, alcohol or substance dependence within the previous 8 weeks, current antidepressants or antipsychotic use, prior intolerance to sertraline or PE, medical illness likely to result in hospitalization, and serious cognitive impairment that would preclude meaningful participation. Participants with bipolar disorder who were currently euthymic and on a mood stabilizer (e.g., lithium, valproate) at stable doses for at least 2 weeks prior to entry were included. Women of childbearing age were required to use contraception, and not be pregnant or lactating.

2.2 | Procedure

All participants signed informed consent prior to clinical screening procedures at one of four sites: the VA Ann Arbor Healthcare System, University of Michigan; Massachusetts General Hospital; Ralph H. Johnson VA Medical Center, Medical University of South Carolina; and VA San Diego Healthcare System, University of California San Diego. The intake assessment consisted of a structured clinical interview with the MINI international neuropsychiatric interview (MINI) for DSM-IV version 5.0 (Sheehan et al., 1998) as well as the clinician-administered PTSD scale (CAPS) for DSM-IV (Blake et al., 1995) with a trained rater, followed by baseline self-report forms, which included the 19-item inventory of complicated grief (ICG) (Prigerson et al., 1995). This study reports on baseline assessments only, which were completed prior to randomization to one of the three treatment conditions.

2.3 | Measures

In addition to a standard assessment of demographics and type of military service, DSM-IV psychiatric diagnoses were assessed using the MINI interview by trained and certified raters (Sheehan et al., 1998). The total number of comorbid psychiatric disorders was calculated as the sum of all current Axis-I disorders assessed by the MINI, combining substance and alcohol use disorders, which yielded a maximum possible total of 9 independent diagnoses (Table 3).

2.3.1 | Inventory of complicated grief

Inventory of complicated grief (ICG) is a validated, 19-item self-report measure used to assess the impact of loss and to identify individuals with threshold CG, which is defined as an ICG score of 30 or higher (Prigerson et al., 1995). Each item is rated on a scale from 0 (not at all) to 4 (always) and summed. The scale was completed only if the participant selected yes to the cover sheet question "Have you had an important person in your life pass away?" The cover sheet also included questions about the relation of the important loss or losses they had experienced in their lifetime on a checklist, including spouse, parent, child, sibling, grandparent, grandchild, other relative, significant other, partner, fiancé, friend, fellow service member, or other. More than one important loss could be reported. Participants were then asked to indicate which death was the most distressing, and to complete the ICG symptom questionnaire in relation to this loss.

2.3.2 | Clinician-administered PTSD scale

Clinician-administered PTSD scale (CAPS) is a structured clinician interview commonly used to assess the intensity, frequency, and severity of PTSD symptoms (Blake et al., 1995; Weathers, F.W., Keane, T.M., & Davidson, 2001. The CAPS is a 30-item clinician administered scale that assesses the frequency (scale 0 [none of the time] to 4 = [most or all of the time]) and intensity (scale 0 = [none] to 4 = [extreme]) of PTSD symptoms based on the DSM-IV criteria. Clinicians assess re-experiencing, avoidance and numbing, and hyperarousal symptoms as they relate to the primary reported traumatic event. All study raters underwent certification procedures including completion of standardized training developed by the National Center for PTSD.

2.3.3 | PTSD checklist

PTSD checklist-specific stressor version (PCL-S) is a 17-item, self-report assessment of DSM-IV PTSD symptoms using a 5-point scale, from 1 (not at all) to 5 (very often) such that higher scores represent greater PTSD severity. (Weathers, Litz, Herman, Huska, & Keane, 1993) It has been well-validated to assess PTSD symptoms in civilian and military populations (Wilkins, Lang, & Norman, 2011).

2.3.4 | Trauma-related guilt inventory

Trauma-related guilt inventory (TRGI) is a 32-item, self-report questionnaire designed to measure cognitive and emotional aspects of guilt associated with the experience of a traumatic event (Kubany et al., 1996). The TRGI has three factors (guilt, distress, and guilt cognitions). The guilt cognitions factor is split into three sub-scales (hindsight-bias/responsibility, wrongdoing, and lack of justification). All factor and subscale scores are reported on a scale from 0 to 4, where high scores represent the strongest endorsement of cognitions or most extreme or frequent symptoms.

2.3.5 | Inventory of psychosocial functioning

Inventory of psychosocial functioning (IPF) is an 80-item self-report measure to evaluate functional impairment related to PTSD and other stress-related disorders in seven life domains (romantic relationships, family relationships, work, friendships and socializing, parenting, education, and self-care). The scale is rated on a 0–100% scale, where higher values indicate greater functional impairment (Rodriguez, Holowka, & Marx, 2012).

2.3.6 | Columbia suicide severity rating scale

Columbia suicide severity rating scale (C-SSRS) is a standardized 8-point clinician-administered rating assessing a wide spectrum of suicidal ideation and behaviors (Posner et al., 2008; Posner et al., 2011). We utilized the measure in the present study to determine the presence of past month and lifetime suicidal ideation as well as lifetime history of suicide attempts.

2.4 | Statistical methods

The prevalence of different types of losses as well as the overall prevalence of CG (defined as ICG scores ≥ 30) was examined in participants at the study baseline visit, excluding individuals with missing loss data. We then limited our analyses about the impact of CG to those veterans who had experienced the loss of at least one important person and who had completed the ICG ($n = 160$), and divided the sample into those with CG and those without CG, consistent with many prior studies (Marques et al., 2013; Shear et al., 2016; Shear et al., 2014; Simon et al., 2007; Simon et al., 2011). The types of losses were determined by the ICG coversheet checklist of the relation(s) of the deceased as well as additional losses mentioned as the most distressing losses on the ICG or in the CAPS and TRGI form event descriptions. Types of losses experienced overall were then recoded into fellow service member (FSM), parent (mother or father), sibling (brother or sister), partner (spouse or significant other/partner/fiancée), child (son or daughter), grandparent (grandfather or grandmother), other relative (grandson, granddaughter, or 'other relatives'), friends, and 'other'. In cases where participants indicated both "fellow service member" and "friend" as the most important loss, which occurred for 29.31% of individuals that reported a FSM loss, the losses were counted in both categories (i.e., FSM and friend).

T-tests (for continuous variables) and Barnard's Exact Tests (for categorical variables) were used to assess for differences between bereaved veterans with and without CG for demographics, the presence of co-occurring mood, anxiety, and substance use disorders, the presence of any suicidal ideation lifetime or past month, lifetime suicide attempts, PTSD symptom severity (CAPS and PCL-S), trauma-related guilt (TRGI), and psychosocial functioning (IPF; Lydersen, Fagerland, & Laake, 2009). We conducted multiple regression analyses to assess the association of grief symptoms (ICG total scores) with psychosocial functioning (IPF score) after adjusting also for comorbid depression (current MDE diagnosis vs. not) and PTSD symptom severity (CAPS totals scores) as covariates. In order to examine the overall impact of the loss of a FSM, we first evaluated whether the prevalence of CG and grief symptom severity (ICG total scores) differed for those who had reported the loss of a FSM as an important loss (regardless of whether it was listed as the most distressing of the losses selected) compared to those bereaved who had not reported having lost a FSM, using logistic regression and a one-way ANOVA, respectively. Given the ICG loss summary allowed the inclusion of multiple losses and instructed participants to complete the ICG in relation to the most distressing loss the participants listed, we then repeated the same analyses among those who specifically identified their most distressing loss as a FSM compared to those with any other type of loss listed as the most distressing loss to confirm the prevalence of CG and grief symptom severity was specifically tied to the loss of a FSM. All tests were done using two-sided .05 level tests, and analyses were performed using SAS 9.4 of the SAS System for Windows (https://www.sas.com/en_us/home.html; RRID: SCR_008567).

3 | RESULTS

Among the 223 post-9/11 veterans with a primary diagnosis of PTSD who entered the trial, 19 had missing data about loss and were excluded. Thus, the overall prevalence of loss was examined in the 204 participants who responded with data about whether they had lost "an important person" in their life, of whom 79.41% ($n = 162$) reported at least one death and 47.06% ($n = 96$) reported the loss of at least one FSM. Two individuals reported a loss but did not complete the ICG and were excluded from all subsequent analyses. Among the remaining 202 veterans, 50 had ICG scores ≥ 30; thus, the CG prevalence in the combined bereaved and non-bereaved PTSD sample was 24.75%. For all remaining analyses, we included only the 160 participants who reported the loss of at least one important person and completed the ICG.

Demographics of our bereaved sample ($n = 160$) are described in Table 1. The bereaved veterans were predominantly male (88.75%) and White (55.97%) or Black (32.08%), with a mean age of 35.03 years (SD = 8.54, range: 20–61). Most of the bereaved veterans (68.79%) had been deployed more than once. The mean number of types of losses reported was 2.07 (see loss categories above; SD = 1.06, range: 1–5), with 63.75% ($n = 102$) reporting more than one loss type. Participants' relationships to the deceased are described in Table 2. No veterans reported the loss of a daughter, grandson, or spouse. Fully, 59.4% ($n = 95$) reported the loss of a FSM, and nearly two-thirds of these (61.1%, $n = 58$) identified this loss in the description of their most distressing loss.

3.1 | Presence and correlates of co-occurring complicated grief in bereaved veterans

For the bereaved sample, the mean ICG score was 23.79 (SD = 13.46: Figure 1 for distribution). The prevalence of CG in the bereaved sample was 31.25% ($n = 50$), with a mean ICG score of 39.70 (SD = 7.98) in this CG subgroup. There were no significant differences in any demographic variables between bereaved veterans with or without CG (Table 1). The prevalence of comorbid mental health conditions in addition to the primary combat-related PTSD diagnosis or the presence of CG were high overall, with only 5.00% ($n = 8$) with no comorbid conditions and 71.88% ($n = 115$) with more than one comorbidity. The mean number of comorbid conditions did not vary by presence of CG (mean [SD] by group: 2.25[1.26] without CG vs. 2.48[1.20] with CG; $t_{158} = -1.06$, $p = .29$). Many (62.50%, $n = 100$) met criteria for a major depressive episode (MDE), with an even higher prevalence among those with CG (74.00%) than those without (57.27%; Barnard's $Z = 2.03$, $p = .0452$; Table 3). The prevalence of anxiety and substance use disorders did not vary by the presence of CG.

TABLE 1 Sociodemographic variables for bereaved post-9/11 veterans overall with and without CG

	Loss without CG *N* (%)	Loss with CG *N* (%)
	N = 110	*N* = 50
Age, years, *M*(SD)	35.56 (8.98)	33.9 (7.44)
Women	14 (12.73)	4 (8.00)
Race		
White	61 (55.96)	28 (56.00)
Black	35 (32.11)	16 (32.00)
Other	13 (11.93)	6 (12.00)
Hispanic ethnicity	12 (11.11)	2 (4.08)
Marital Status		
Married or remarried	57 (51.82)	26 (52.00)
Separated/divorced	27 (24.55)	12 (24.00)
Never married	26 (23.64)	12 (24.00)
Education		
Completed high school or less	40 (36.36)	21 (42.00)
Employment Status		
Fulltime employed	52 (47.27)	28 (56.00)
Unable to find work, of those not employed	17/44 (38.64)	6/15 (40.00)
Military history		
Regular armed services	94 (85.45)	44 (88.00)
National Guard	13 (11.82)	4 (8.00)
Reserve	3 (2.73)	2 (4.00)
Deployed more than once	75 (69.44)	33 (67.35)

Note: All between-group differences were non-significant ($p > 0.05$). The following demographic variables had missing observations: race-1 without CG; ethnicity-2 without CG, 1 with CG; number of deployments-2 without CG, 1 with CG.

Participants with CG reported higher PTSD severity compared to those without CG as measured by both the clinician-rated CAPS past month score and the self-rated PCL-S total scores, as well as all PCL-S subscales (Table 4). In addition, those with CG had greater levels of trauma-related guilt and distress as measured by the three factors of the TRGI (global guilt, distress, and guilt cognitions) and all guilt cognition subscales, with the exception of the lack of justification subscale (Table 4). CG was also associated with greater functional impairment, as measured by the IPF.

In order to examine the independent association of CG with psychosocial function, we examined the association of CG symptoms (ICG score) with functional impairment (IPF score) in a multiple regression model including covariates for PTSD severity (CAPS total score) and current depression. This analysis indicated that both grief symptoms

TABLE 2 Prevalence of various loss types and self-report of most distressing losses reported by bereaved veterans ($n = 160$)

Types of Losses	Prevalence *N* (%)	Loss characterized as most distressing *N* (%)
Fellow service member	95 (59.38)	58 (36.25)
Parent	38 (23.75)	22 (13.75)
Sibling	15 (9.38)	5 (3.13)
Partner	3 (1.88)	0 (.00)
Child	2 (1.25)	2 (1.25)
Grandparent	88 (55.00)	40 (25.00)
Other relative	40 (25.00)	16 (10.00)
Friend	48 (30.00)	28 (17.50)
Other	2 (1.25)	1 (.63)

Note: More than one loss category could be reported for both important and most distressing losses.

TABLE 3 Prevalence of current psychiatric comorbidities for bereaved post-9/11 veterans with and without CG

	Loss without CG *N* (%) *N* = 110	Loss with CG *N* (%) *N* = 50
Any mood disorder	84 (76.36)	44 (88.00)
Major Depressive Episode (MDE), past 2 weeks[a]	63 (57.27)	37 (74.00)
Dysthymia, past 2 years	11 (10.19)	4 (8.00)
Bipolar, current	10 (9.09)	3 (6.00)
Any anxiety disorder	45 (40.91)	23 (46.00)
Social Anxiety Disorder (SAD), past month	14 (12.73)	10 (20.00)
Generalized Anxiety Disorder (GAD), past 6 months	27 (24.55)	15 (30.00)
Panic disorder with agoraphobia, past month	10 (9.09)	5 (10.00)
Panic disorder without agoraphobia, past month	2 (1.83)	1 (2.00)
Obsessive-compulsive Disorder (OCD), past month	10 (9.09)	4 (8.00)
Any substance-related disorder[b]	24 (21.82)	10 (20.00)
Alcohol abuse, past 12 months	9 (8.33)	7 (14.00)
Alcohol dependence, past 12 months	13 (11.82)	2 (4.00)
Substance abuse, past 12 months	2 (1.82)	1 (2.00)
Substance dependence, past 12 months	1 (.91)	0 (.00)
Total comorbid axis-I disorders		
No comorbid psychiatric disorders	8 (7.27)	0 (0.00)
One psychiatric disorder	23 (20.91)	14 (28.00)
Two psychiatric disorders	36 (32.73)	12 (24.00)
Three psychiatric disorders	24 (21.82)	11 (22.00)
> 3 psychiatric disorders	19 (17.27)	13 (26.00)

Note: All group differences were non-significant ($p > .05$) except for the group difference in current MDE. The following diagnoses had missing observations: dysthymia ($n = 2$), panic disorder without agoraphobia ($n = 1$), alcohol abuse ($n = 2$).

[a]MDE group difference: Barnard's $Z = 2.03$, $p = .045$.

[b]Alcohol- and substance-related dependence disorder determined based on occurrence in the past 12 months, but not the past 2 months, which was exclusionary in the present study.

(ICG total, $\beta \pm$ SE: .20 ± .08, standardized $\beta = .19$, $t = 2.59$, $p = .0106$) and PTSD symptom severity (CAPS total, $\beta \pm$ SE: .43 ± .07, standardized $\beta = .42$, $t = 5.80$, $p < .0001$) were independently associated with impairment in psychosocial functioning, while a current major depressive episode was not ($\beta \pm$ SE: .97 ± 2.18, standardized $\beta = .03$, $t = .44$, $p = .66$). There was no evidence of multicollinearity (all VIFs < 1.09).

Although rates of any current or lifetime suicidal ideation, as measured by the C-SSRS, were high among those with CG (16.67% current, 52.08% lifetime), they did not significantly differ from those without CG (12.38% current, 40.95% lifetime; Table 4). Bereaved veterans with CG, however, were significantly more likely to report the occurrence of one or more lifetime suicide attempts (14.58%, $n = 7$) compared to those without CG (4.81%, $n = 5$; Table 4). The overall prevalence of veterans reporting lifetime suicide attempts was 7.89% ($n = 12$ out of 152 participants with suicide data); it is worth noting, however, that 11 of the 12 veterans with a lifetime suicide attempt also had a diagnosis of a current MDE.

3.2 | Impact of loss of a fellow service member

In order to better understand the impact of the loss of a FSM on the prevalence of CG among a military population with combat-related PTSD, we compared those who reported the loss of a FSM ($n = 95$) to those who had not ($n = 65$). The prevalence of CG was significantly higher among those who lost a FSM (41.05%; $n = 39$) compared to those who did not (16.92%, $n = 11$; odds ratio = 3.41, 95% confidence interval: 1.59, 7.36), and ICG symptom scores were on average 6.99 points higher in the bereaved veterans who reported a FSM as an important loss compared to those who did not (mean [SD] by group: 26.63[12.95] vs. 19.65[13.20]; $F_{1,158} = 11.05$, $p = .0011$). In confirmatory analyses, those who specifically identified a FSM as their most distressing loss ($n = 58$) were more likely to meet threshold criteria for CG (48.28%, $n = 28$) compared to those who reported another, non-FSM loss as the most distressing (21.57%, $n = 22$; OR: 3.39, 95% CI: 1.69, 6.82). Similarly, the ICG scores of bereaved veterans who had lost a FSM and identified that loss as their most distressing loss were on average 7.90 points higher than those of veterans who identified another loss as most distressing (mean [SD] by group: 28.83[11.93] vs. 20.93[13.49]; $F_{1,158} = 13.75$, $p = .0003$).

4 | DISCUSSION

These data, derived from a well-characterized treatment-seeking sample of post-9/11 veterans with a primary diagnosis of combat-related PTSD, demonstrate the high prevalence and significant impact of exposure to loss and associated grief among treatment-seeking veterans. More than three quarters (79.41%) of the overall sample reported an important lifetime loss, with close to half (47.06%) reporting exposure to the loss of a FSM. Regardless of loss exposure, the prevalence of

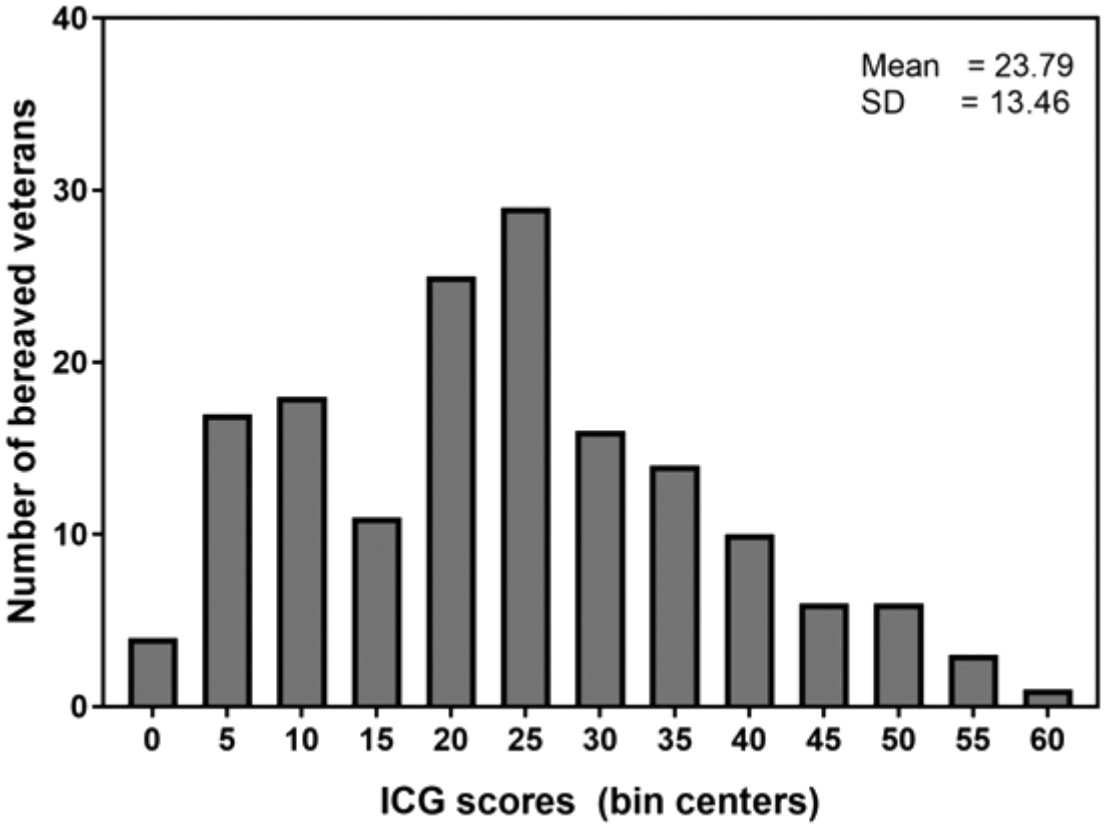

FIGURE 1 Distribution of Inventory of Complicated Grief (ICG) scores for 160 veterans with Posttraumatic Stress Disorders (PTSD) and an important loss. The prevalence of complicated grief (CG) in the combined bereaved and non-bereaved PTSD sample was 24.75%, with 50 bereaved veterans meeting the clinical threshold score for CG (ICG $\geq$ 30).

complicated grief was one in four; among those who reported a loss, the prevalence of CG was nearly one third (31.25%), despite the relative youth of the sample (mean age = 35.03) and the use of a relatively high ICG symptom threshold of 30. Among individuals who lost a FSM, the rate of CG was 41.05%; further, for individuals who reported the loss of a FSM as their most distressing loss, the rate was remarkably high at nearly half (48.23%). Though previously reported CG prevalence rates in general have varied and more epidemiological research is needed, one study of 2,520 individuals aged 14–95 estimated a prevalence of 6.7% in the general population, further highlighting the substantially higher prevalence of CG in this treatment-seeking veteran population with combat-related PTSD (Kersting et al., 2011).

These findings are also consistent with prior reports that suggest elevated prevalence of CG among individuals with mood and anxiety disorders (Marques et al., 2013). For example, among non-military, clinical samples of bereaved adults with major depressive disorder or bipolar disorder, the prevalence of CG was 25% and 24%, respectively (Simon et al., 2005; Sung et al., 2011). Of note, these reports utilized a lower ICG threshold of 25, and we would expect somewhat lower rates of CG had the cut-score of 30 from the present study been used. The high rates of CG in this population of bereaved veterans with PTSD appear especially elevated compared to previously reported rates in other bereaved clinical populations, suggesting they may be particularly at risk. One study using an identical ICG threshold of 30 similarly reported a rate of CG of 27.6% among a non-military bereaved sample with a primary PTSD diagnosis, further supporting the conclusion that individuals with PTSD may be at unique risk for CG (Marques et al., 2013). The present study found a similar overall prevalence of co-occurring CG with PTSD, but much higher prevalence of CG for those with the loss of a FSM. This suggests that bereaved veterans with PTSD who lost a FSM may be a particularly high-risk group for CG even when compared to other clinical populations including non-military populations with PTSD. It is also worth highlighting that in contrast to data suggesting female gender maybe a risk factor for CG and that treatment seeking samples have tended to have higher rates of women, this sample was largely men. More research with larger samples of women veterans and service members with and without combat PTSD is needed to examine whether rates of CG or the impact of the loss of a FSM varies by gender (Kersting et al., 2011; Shear et al., 2016; Shear et al., 2014; Simon et al., 2005).

The overall prevalence of co-occurring conditions was high in this population of veterans with PTSD. CG comorbidity was also linked to greater severity of PTSD as well as higher rates of depression. This is not surprising, given that depression, PTSD, and CG are all disorders that can develop in response to a traumatic life stressor, such as a death, and they fall on a continuum of stress-related syndromes with partially overlapping symptoms and clinical presentations (Bonanno et al., 2007; Simon, 2012; Sung et al., 2011). CG, like depression, may

TABLE 4 Symptoms and functioning of bereaved post-9/11 veterans with and without CG

	Loss without CG M (SD) N = 110	Loss with CG M (SD) N = 50	Group differences t(df), p
CAPS			
Total Score, past month	75.88 (14.10)	81.56 (14.37)	$t(158) = -2.35$, $p = .02$
PCL-S			
Total Score	57.90 (1.43)	64.67 (11.44)	$t(156) = -3.68$, $p < .01$
Re-experiencing subscale	16.34 (4.01)	18.90 (4.11)	$t(156) = -3.70$, $p < .01$
Avoidance subscale	22.70 (5.15)	25.52 (5.61)	$t(156) = -3.11$, $p < .01$
Hyperarousal subscale	18.87 (3.41)	2.23 (3.35)	$t(156) = -2.34$, $p = .02$
TRGI			
Global Guilt	1.57 (1.19)	2.61 (1.16)	$t(154) = -5.15$, $p < .01$
Distress	2.32 (.73)	2.99 (.71)	$t(155) = -5.42$, $p < .01$
Guilt cognitions[a]	.85 (.65)	1.39 (.83)	$t(76) = -4.03$, $p < .01$
Hindsight bias/responsibility subscale[a]	.67 (.84)	1.38 (1.08)	$t(76) = -4.06$, $p < .01$
Wrongdoing subscale	1.04 (.81)	1.44 (.86)	$t(151) = -2.81$, $p < .01$
Lack of justification subscale	1.57 (1.13)	1.89 (1.21)	$t(150) = -1.62$, $p = .11$
IPF			
Functional Impairment	41.25 (14.03)	47.72 (15.24)	$t(158) = -2.63$, $p < .01$
	N (%)	**N (%)**	**Z, p**
C-SSRS			
Any suicidal ideation, lifetime	43 (41.95)	25 (52.08)	$Z = 1.29$, $p = .24$
Any suicidal ideation, past month	13 (12.38)	8 (16.67)	$Z = .71$, $p = .50$
Any suicide attempts, lifetime	5 (4.81)	7 (14.58)	$Z = 2.08$, $p = .0386$

Measures: Clinician-Administered PTSD Scale (CAPS); PTSD Checklist-Specific Stressor Version (PCL-S); Trauma-Related Guilt Inventory (TRGI); Inventory of Psychosocial Functioning (IPF); Columbia Suicide Severity Rating Scale (C-SSRS).
[a]Two-sample t-tests with unequal variance.

serve as an additional clinical severity marker for individuals with PTSD exposed to a death.

Trauma-related guilt was also greater in those with CG comorbidity; future studies should, in more detail, inquire about guilt-related cognitions and distress and what the individual specifically attributes them to before definitive conclusions about the relative role of specific types of loss and other traumatic events to guilt can be drawn. Nonetheless, this initial finding is consistent with previous studies of veterans that have highlighted the role of guilt and responsibility, including guilt specifically associated with the loss of a combat buddy, highlighting the special bonds formed within units as well as the relationship of those in decision-making roles to those who may die in service (Fontana et al., 1992; Lee, Scragg, & Turner, 2001; Litz et al., 2009; Milgram, 1986; Nazarov et al., 2015). These considerations have become more widely recognized in PTSD treatments as well as highlighted as an aspect of moral injury, which was not assessed in this study (Litz et al., 2009; Nazarov et al., 2015; Norman, Wilkins, Myers, & Allard, 2014; Øktedalen, Hoffart, & Langkaas, 2015; Steenkamp et al., 2011). Further, guilt has also been linked to increased suicidal ideation, particularly among those with direct combat exposure (Bryan, Ray-Sannerud, Morrow, & Etienne, 2013). Contrary to our initial hypotheses, the presence of CG did not influence the rate of lifetime or current suicidal ideation in bereaved veterans. CG was, however, associated with an increased rate of one or more lifetime suicide attempts, although the timing of the suicide attempt in relation to the loss could not be determined. Further, all but one participant with reported lifetime suicide attempts were also diagnosed with depression. It is therefore possible that this finding may be unique to this specific veteran study population and may not generalize to other populations with co-occurring PTSD and CG. A larger sample with more detail about the timing of CG and depression onset as well as suicide attempts may be needed to determine if CG has a unique contribution to increased suicide attempt risk in this population. Prior data have supported increased rates of suicidal ideation and behavior in individuals with CG, and these rates may be even greater among suicide survivors, indicating the need to continue investigations of the relationship between suicide and CG across other populations (Baker et al., 2016; Mitchell, Kim, Prigerson, & Mortimer-Stephens, 2004; Young et al., 2012).

Consistent with prior reports and clinical experience, our data support that the loss of a FSM poses a particular challenge for veterans, and that this type of loss is often reported as the most distressing in post-9/11 veterans. Exposure to loss of a FSM was associated with twice the rate of CG compared to those with other types of losses (41.05% vs. 16.92%). When the loss of a FSM was reported as the most distressing loss, the rate of CG was even higher (48.23%). While it is worth noting that the rates of child and spousal loss were very low

in this relatively young cohort with PTSD and may have contributed to the significantly greater impact of loss of a FSM compared to other types of losses, this does not alter the significance of our finding that high levels of CG symptoms are present following the loss of a FSM among post-9/11 veterans. These data clearly support that veterans seeking care for PTSD should be asked about the loss of a FSM and screened for associated grief symptoms as part of standard evaluations in clinical settings. The identified PTSD-related trauma might not always be the same event as the primary loss. Further, CG after loss can also occur without PTSD, whether the losses occur in war, after terrorist attacks, or in non-violent settings (Morina, Rudari, Bleichhardt, & Prigerson, 2010; Neria et al., 2007; Simon et al., 2007). Many veterans may not raise loss and grief-related concerns about the death of a FSM during their interactions with medical professionals. Further, well-meaning professionals may use terms such as the "loss of a loved one," which may lead to false negatives in screening. Clinicians are encouraged to ask specifically about the loss of a FSM when screening veterans with PTSD. As this population faces many barriers to seeking treatment for mental health concerns in general, efforts to incorporate evaluations of grief-related symptoms into standard clinical care settings should be implemented (Hoge et al., 2004; Pietrzak, Johnson, Goldstein, Malley, & Southwick, 2009; Sayer et al., 2009; Stecker, Shiner, Watts, Jones, & Conner, 2013).

Findings from this study should be interpreted in light of a number of limitations. First, although the ICG has been used commonly to examine threshold CG symptoms, it carries with it the limitations of any self-report measure. We selected a previously studied threshold score of 30 instead of 25 to assure we were more likely to be detecting a sample with current CG; to date, cut scores for threshold levels of CG using the ICG have varied, with some other studies reporting both somewhat lower or higher cut-off scores (Kersting et al., 2011; Kersting et al., 2009; Ott 2003; Prigerson et al., 2009). Although a structured clinician-rated interview is now available and is recommended for future studies, CG was not confirmed using a structured clinical interview in this study (Bui et al., 2015). While CG has been included as a provisional diagnosis (PCBD) in DSM-5 and substantial evidence supports its inclusion as a diagnosis, final components are still being finalized and more than one proposal exists. Once the diagnosis is finalized in the DSM, a structured interview module should be integrated into diagnostic assessment tools, such as the MINI and Structured Clinical Interview for DSM, to standardize diagnosis (American Psychiatric Association, 2013; Prigerson et al., 2009; Shear et al., 2011). The ICG, however, offers a simple reliable screening tool for clinicians to detect grief symptoms and to monitor change with treatment. Additionally, it is likely that this sample of veterans underreported rather than over-reported their grief symptoms, since they were not seeking care related to grief or asked about grief specifically. We did not collect specific date of loss (only year) and thus, were unable to determine the precise time since the loss. Although a subset of the sample ($n = 40$) had experienced a loss in the past year, it is possible that this loss occurred less than 6 months prior to assessment of grief symptoms for some.

Unfortunately, this analysis also did not include more detail on the relationship of the veteran to the FSM who died such as proximity (e.g., whether the FSM was in the same unit or under the veteran's command) or about the precise nature of the death to examine factors such as whether the loss was due to combat, suicide, or natural causes, or occurred while the veteran was deployed. It would also be important for future studies to have larger samples that could enable study of potential differences by service branch, specific aspects of command culture (e.g., within a unit or battalion), and the handling of deaths during or after deployment, (e.g., differences in opportunities to honor or memorialize the deceased for combat-related versus suicide-related deaths).

Given our sample all met a combat-related PTSD diagnosis and were participating in a treatment study, these data do not address the prevalence of CG related to loss in veterans in general but instead in a higher risk treatment-seeking sample with combat PTSD.

While additional research is needed to fully understand how CG may alter clinical presentation, outcomes, or response to PTSD interventions, these data are among the first to find that the loss of a FSM is very highly associated with CG in a veteran population with PTSD, and demonstrate the additive impact of CG symptoms on psychosocial functioning above and beyond PTSD severity. We encourage clinical providers to screen for loss of a FSM and address associated grief symptoms when working with veterans with combat exposure. Future studies should examine the contribution of concurrent and separately occurring losses on the development of CG symptoms among veterans and service members with PTSD, as well as examine how to optimize treatment outcomes.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors had full access to the data in the study manuscript and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: S.A.M.R., N.S.

Acquisition of data: E.O., M.C., E.B., E.G., A.B., A.R., M.N.V., M.V., N. S., S.A.M.R. Analysis and interpretation of data: S.S.H., S.A.M.R., N. S., H.M.K. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: S.S.H., H.M.K. Obtained funding: S.A.M.R., N.S. Administrative, technical, and material support: M.V., E.O., S.N.H., H.M.K. Study supervision: S.A.M.R., N.S.

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Randomized Controlled Trial of Prolonged Exposure, Sertraline and Their Combination in Combat Veterans with PTSD

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Abstract

Importance: Meta-analyses of posttraumatic stress disorder (PTSD) treatments suggest that trauma-focused psychotherapies produce greater bene□ts than antidepressant medications. Head-to-head clinical trials are urgently needed to inform treatment guidelines.

Objective: The current study aimed to determine the relative efficacy of: 1) prolonged exposure plus placebo (PE + PLB); 2) PE + sertraline (PE + SERT); and 3) SERT + enhanced medication management (SERT + EMM). We hypothesized larger symptom reductions with PE+SERT than PE+PLB, and larger symptom reductions with PE+PLB than SERT+EMM. We hypothesized treatment dropout in PE+SERT would be larger than in either SERT+EMM or PE+PLB.

Design: The PROlonGed ExpoSure and Sertraline Trial (PROGrESS) was a randomized multisite 24-week clinical trial conducted between 2011 and 2016. Participants and providers were blind to pill condition, and outcome evaluators were blind to assignment. Participants completed assessments at weeks 0 (intake), 6, 12, 24, and 52 (Follow-up).

Participants: Participants (N = 223) were service members or veterans of Iraq/Afghanistan wars with combat-related PTSD and significant impairment (Clinician Administered PTSD Scale (CAPS) ≥50) of at least three months duration.

Setting: The study had 4 sites: VA Ann Arbor Healthcare System (VAAAHS), VA San Diego Healthcare System (VASDHS), Ralph H. Johnson VA Medical Center (RHJVAMC), and Massachusetts General Hospital Home Base Veterans Program (MGH).

Intervention: Participants completed up to thirteen 90-minute sessions of PE by week 24. SERT was titrated over 10 weeks and continued until week 24; medication management was manualized. Main Outcome and Measures: Primary outcome was past month PTSD symptom severity on Clinician-Administered PTSD Scale (CAPS) at week 24.

Results: Of 223 randomized participants, 149 completed the study at 24 weeks. Participants were 87% male, mean age 34.5. Modi□ed intent-to-treat analysis (n=207) using Mixed Models Repeated Measurement showed that PTSD symptoms decreased significantly during the 24 weeks (p<.001); however, slopes did not differ by treatment arms (p=0.81), and at 24 weeks, the difference between PE+PLB vs. SERT+EMM was 9.1 (p=0.05) and PE+PLB vs. PE+SERT was 6.7 (p=0.16).

Conclusion and Relevance: No difference in PTSD symptom change or symptom severity at 24 weeks were found across the three groups (SERT+EMM, PE+PLB, and PE+SERT). Trial Registration: ClinicalTrials.gov: NCT01524133.

Changes in Whole-blood Leukocyte Gene Expression in Epigenetic Pathways Associated with Treatment Response in Combat PTSD Patients

Authors: King, Anthony, PhD; Sheynin, Jony, PhD; Tagett, Rebecca, MS; Rajaram, Nirmala, PhD; Duval, Elizabeth, PhD; Phan, K. Luan, MD; Simon, Naomi, MD; Martis, Brian, MD; Porter, Katherine, PhD; Norman, Sonya, PhD; Stein, Murray, MD; MPH; Liberzon, Israel, MD; Rauch, Sheila, PhD

Abstract

Posttraumatic stress disorder (PTSD) is associated with a number of aberrations in neuroendocrine and Neuroimmune processes, including increased circulating catecholamines, increased inflammatory cytokines, and altered HPA axis, including hypocortisolemia and hyper-responsive glucocorticoid feedback. Recent studies have also seen evidence of transcriptional dysregulation in PTSD, including leukocyte gene expression related to cytokine, innate immunity, and type I interferon pathways. Such transcriptional dysregulations in leukocytes could play dynamic roles in the expression and maintenance of pathophysiological processes in the syndrome of PTSD. Successful treatment of PTSD might also involve normalization of transcriptional dysregulation and might point to treatment targets. We collected whole blood from OEF/OIF combat-exposed veterans without history of PTSD, and in PTSD patients seeking treatment the week before evidence-based treatment (T1), and 24 weeks later (T2). Leukocyte RNA was purified, and transcriptome-wide gene expression analyzed using RNA sequencing (RNASeq). Transcriptome libraries were prepared from RNA with RIN values >7.0 using Illumina poly(A) capture and HiSeq4000 single-end 50nt sequencing. RNASeq data were processed using our standard RNASeq processing pipeline and QC, and reads were aligned to transcriptome. Reads per transcript were quantified and normalized for differential expression analyses. In preliminary analyses we compared N=23 Combat Controls to N=39 PTSD patients, and a comparison of before (T1) and after (T2) treatment in PTSD patents randomly assigned to Prolonged exposure plus pill placebo (PE+PLB; N=8), sertraline plus enhanced medication management (SERT+EMM; N=9), and PE plus sertraline (PE+SERT; N=12). Standard differential expression (DE) analyses did not find DE between PTSD and healthy combat veterans that met transcriptome-wide threshold for significance; weighted gene co-expression network analysis (WGCNA) are being performed. To identify DE of genes from pre- to post-treatment in PTSD patients associated with treatment response, we examined correlation of fold-change in gene expression in paired RNA samples (using EdgeR with TMM normalization) with changes in PTSD (deltaCAPS) at T1 vs T2. Differential expression was found in 261 genes in the N=14 treatment responders (>20 pt reduction in CAPS), which contained patients from all treatment groups. No DE genes were identified in the N=11 Treatment Non Responders. Analysis of these 261 genes in String (String-db.org) found these genes were highly connected (PPI enrichment p-value=0.009) and enriched with genes for epigenetic influences. Hub genes include KDMA (histone demethylase), HDAC9, (histone deacetylase), and Ash1 (Histone methyltransferase). While highly preliminary, these data suggest PTSD treatment response may be associated with increased transcription of genes involved in epigenetic pathways.

Neural Activation during Reappraisal of Emotion and Assessment of Negative Faces Associated with PTSD Symptoms

Authors: Joshi, Sonalee, MA; Sheynin, Jony, PhD; Duval, Elizabeth, PhD; King, Anthony, PhD; Angstadt, Mike, MS; Phan, K. Luan, MD; Simon, Naomi, MD; Liberzon, Israel, MD; Rauch, Sheila, PhD

Abstract

Post-Traumatic Stress Disorder (PTSD) is a debilitating condition often associated with deficits in regulating emotion and assessment of emotional, and particularly negative, faces. These deficits have been associated with differences in neural activation in emotion processing regions such as the amygdala and regulatory medial and dorsolateral prefrontal cortices. This study assessed neural mechanisms underlying emotion regulation and appraisal in veterans following treatment for PTSD symptoms. Thirty-six veterans with PTSD were assigned to evidence-based treatment groups: Prolonged exposure plus pill placebo (PE + PLB; N = 6), sertraline plus enhanced medication management (SERT + EMM; N = 16), and PE plus sertraline (PE + SERT; N = 14). Participants completed assessments of symptoms in addition to emotion regulation, modulation, and appraisal tasks in an fMRI scanner prior to and following treatment.

The Emotional Faces Assessment Task (EFAT) examined neural activation during implicit processing of Emotional faces. The Emotion Regulation Task (ERT) assessed neural activation during passive viewing, Maintenance of emotional response, and reappraisal of emotional response to distressing images. Greater pre-treatment symptom severity was associated greater activation of the Left Amygdala ($\beta = .45$, $p = .02$) and less activation in the Right Amygdala ($\beta = -.55$, $p = .01$) for Negative Face trials on the EFAT Task. ERT results for reappraisal of emotion compared to maintenance of emotion yielded less dmPFC activation with greater treatment response with PTSD participants ($M = .24$, $SD = .43$) demonstrating greater dmPFC activation compared to controls ($M = .04$, $SD = .38$) pre-treatment; $t(51.89) = 2.01$, $p = 0.049$. Within the PTSD group, less pre-treatment dmPFC activation was associated with trend level improvement of symptoms from pre to post treatment ($\beta = -.33$, $p = .09$). Decreased amygdala activation ($\beta = -.48$, $p = .04$) and increased dlPFC activation ($\beta = .79$, $p = .05$) from pre to post treatment for reappraisal compared to maintenance of emotion were also associated with symptom reduction following treatment.

This is one of the first studies to examine neural activation across different treatments for PTSD and provides greater insight into emotion regulation and processing in PTSD.

Predicting Treatment Outcome in PTSD: Neural Function during Attention Shifting and Emotional Appraisal

Authors: Duval, Elizabeth, PhD; Sheynin, Jony, PhD; King, Anthony, PhD; Phan, K. Luan, MD; Simon, Naomi, MD; Martis, Brian, MD; Porter, Katherine, PhD; Norman, Sonya, PhD; Liberzon, Israel, MD; Rauch, Sheila, PhD

Abstract

Posttraumatic stress disorder (PTSD) has been associated with exaggerated threat reactivity and difficulties modulating emotion. These deficits have been linked to aberrant neural function, including increased activation in regions associated with emotion processing, decreased activation in emotion modulation regions, and differences in connectivity between emotion processing and modulation regions. The purpose of this study was to examine neural mechanisms underlying emotion processing and modulation, associated with treatment outcome in PTSD. Thirty-six military veterans with PTSD were assigned to evidence-based treatment groups: Prolonged exposure plus pill placebo (PE + PLB; N = 7), sertraline plus enhanced medication management (SERT + EMM; N = 14), and PE plus sertraline (PE+ SERT; N = 15). Symptom assessment and MRI scanning occurred before and after treatment. During MRI scanning, the Shifted Attention Emotion Appraisal Task (SEAT) probed brain activation during implicit emotional processing, attention modulation of emotion, and emotion modulation by appraisal. During appraisal, brain activation at pretreatment predicted change in PTSD symptoms across treatments ($R2 = .28$, $F(7, 42) = 2.33$, $p = .040$). Specifically, activation in insula ($\beta = 2.03$, $p = .049$), dlPFC ($\beta = -.414$, $p = .012$), and vmPFC ($\beta = 2.33$, $p = .025$) before treatment was associated with symptom reductions over the course of treatment. Greater connectivity between left amygdala and superior parietal cortex at pre-treatment predicted greater reductions in symptoms over time ($p < .05$, FEW corrected). Increased connectivity between left amygdala and dlPFC over the course of treatment was associated with greater reductions in symptoms over time ($p < .05$, FWE). During attention modulation at pre-treatment, greater connectivity between right dorsolateral prefrontal cortex and superior parietal cortex predicted (at a trend level) reductions in PTSD symptoms over time ($p = .052$ FWE). Increased connectivity between these regions over the course of treatment was also associated with greater reductions in symptoms over time ($p < .05$, FWE). This study is one of the first to examine task-based activation and connectivity in a PTSD treatment trial, with evidence to suggest that the function of regions involved in emotion processing and modulation are important predictors of treatment response.

Resting-State functional connectivity predicts treatment outcome in patients with PTSD

Authors: Sheynin, Jony, PhD; Duval, Elizabeth, PhD; King, Anthony, PhD; Angstadt, Mike, MS; Phan, K. Luan, MD; Simon, Naomi, MD; Rauch, Sheila, PhD; Liberzon, Israel, MD

Abstract

Background: Resting-state functional connectivity (rsFC) magnetic resonance imaging (MRI) represents a powerful method for illuminating brain network function. Moreover, abnormalities in rsFC have been recently demonstrated in posttraumatic stress disorder (PTSD), suggesting they may have particular relevance for this condition. The current study examined pre to post treatment changes in rsFC in PTSD during the randomized treatment trial (PROGrESS; Rauch et al., 2018).

Methods: Sixty-four combat veterans with PTSD were randomly assigned to three treatment groups: Prolonged Exposure plus placebo (PE + PLB), sertraline plus enhanced medication management (SERT + EMM), or the combination (PE + SERT). Twenty-nine combat veterans without PTSD were recruited as a control group. Symptom assessment and resting-state MRI scanning occurred before and after treatment. Seed-based and connectome-based approaches were used to analyze rsFC.

Results: Before treatment, PTSD was associated with lower connectivity between PCC, vmPFC and other default-mode network (DMN) regions (both $p < .050$; FWE corrected), replicating prior findings of lower within-DMN connectivity in PTSD. PCC and vmPFC, as well as the insula (salience-network (SN) seed), had greater connectivity with regions within the dorsal-attention network (DAN) in patients, suggesting cross-network desegregation in PTSD (all $p < .050$; FWE corrected). Patients who had more than a 50% decrease in PTSD symptoms with treatment (i.e., “high responders”) had lower pre-treatment amygdala-PCC connectivity ($p = .011$), suggesting the pivotal role of SN-DMN segregation in PTSD treatment. In addition, these patients had lower global centrality ($p = .042$), suggesting that topological features of the brain may also be related to PTSD treatment response.

Conclusions: These findings replicate and extend our knowledge of network-level abnormalities in PTSD, and importantly, suggest potential neural biomarkers of PTSD treatment response.

Examination of Cognitive Change in SSRI, Prolonged Exposure plus Placebo, and SSRI+PE: Do Thoughts Drive Change When Pills Are Involved?

Authors: Rauch, Sheila, PhD; Kim, Myra, ScD Venners, Margaret, MPH, MSW; Porter, Katherine, PhD; Norman, Sonya, PhD; Simon, Naomi, MD; Rothbaum, Barbara, PhD; Tuerk, Peter, PhD; Bui, Eric, MD, PhD; Powell, Corey, PhD; Smith, Erin, PhD; Goetter, Elizabeth, PhD; McSweeney, Lauren, PhD

Abstract

A relationship between posttraumatic negative thoughts about the self and the world and PTSD severity has been consistently reported (Foa & Rauch, 2004). In addition, changes in these cognitions are highly related to change in psychotherapy interventions for PTSD (Kumpula et al., 2017; Rauch et al., 2015; Zalta et al., 2014). Finally, several studies examining change in cognitions and PTSD symptoms over Prolonged Exposure (PE) have demonstrated that change in cognitions occurs prior to change in PTSD symptoms (Kumpula et al., 2017; Zalta et al., 2014). The current study aims to examine the planned mechanistic comparisons of cognitive change over PE+ pill placebo, Sertraline (SERT)+Enhanced Medication Management, and PE+SERT (N = 176 veterans) as part of a larger treatment outcomes study comparing treatment response to sertraline, PE and their combination. Time lagged regression modeling was conducted. Analyses revealed that change in cognitions are related to change in PTSD symptoms, in the conditions where participants were receiving SERT. However, contrary to previous research both models starting with cognitive change and symptom change showed significance indicating that cognitions are not driving PTSD or vice versa in these conditions. Additionally, when PE was combined with pill placebo, the relationship between posttraumatic cognitions and PTSD symptoms were not significant in either direction. These results suggest that mechanisms of change in psychotherapy combined with pill administration (either active or placebo) might be different than what has been found in psychotherapy alone. Specifically, the previous robust and replicated findings that cognitions changes drive PTSD change do not occur. Models examining patterns of change within and across conditions will be presented.

Resting-state functional connectivity is associated with treatment outcome in PTSD patients

Authors: Sheynin, Jony, PhD; King, Anthony, PhD; Angstadt, Mike, MS; Phan, K. Luan, MD; Stein, Murray, MD, MPH; Simon, N, MD; Rauch, Sheila, PhD; Liberzon, Israel, MD

Abstract

Resting-state functional connectivity (rsFC) magnetic resonance imaging (MRI) represents a powerful method for illuminating brain network function. Moreover, it has a particular relevance for posttraumatic stress disorder (PTSD), where abnormalities in rsFC have recently been demonstrated. The current study is part of the PROlonGed ExpoSure and Sertraline Trial (PROGrESS; Rauch et al. Contemporary Clinical Trials, 2018), and examined the role that rsFC abnormalities might play in therapeutic interventions in PTSD. Methods: Sixty-one military veterans with PTSD were assigned to evidence-based treatment groups: Prolonged Exposure (PE) plus placebo, Sertraline (SERT) plus enhanced medication management, or PE/SERT. Twenty-nine veterans without PTSD were recruited as a control group. Symptom assessment and MRI scanning occurred before and after treatment. Seed-based results were thresholded at p=.001 uncorrected and then subsequently, at p<.050 (FWE) at the cluster level. Results: At baseline, seed-based analyses revealed that PTSD was associated with lower connectivity between PCC, vmPFC and other default-mode network (DMN) regions, replicating prior findings of decreased within-DMN connectivity in PTSD. In contrast, PCC and vmPFC, as well as the insula (salience-network (SN) seed), had greater connectivity with regions within dorsal-attention network (DAN) in patients, which is in line with the cross-network desegregation in PTSD. Graph-theoretic analysis showed that DMN and DAN were also characterized by decreased small-worldness in patients, further suggesting these networks' decreased integration in PTSD. When testing treatment effect, we found that patients who responded to treatment had lower baseline amygdala-PCC connectivity, supporting the importance of DMN-SN segregation in PTSD. In sum, these findings confirm and extend our knowledge of network-level abnormalities in PTSD, and importantly, propose a neural biomarker to predict successful response to treatment.

Understanding the Impact of Complicated Grief on Posttraumatic Stress Disorder Outcomes in Post-9/11 Service Members and Veterans

Authors: Goetter, Elizabeth, PhD; Hoeppner, Susanne, PhD; Hellberg, Samantha, BA; Acierno, Ron, PhD; Rauch, Sheila, PhD; Simon, Naomi, MD

Abstract

Background: Bereavement and complicated grief (CG) are more common than previously recognized amongst service members and veterans. Complicated grief (CG), a persistent and impairing form of grief, is distinct from but also co-occurs with posttraumatic stress disorder (PTSD) and major depressive disorder (MDD). Little is known about the impact of comorbid CG on PTSD outcomes or how best to address it in practice.

Method: The impact of comorbid CG on PTSD treatment outcomes in a multi-site, randomized controlled trial for veterans with combat PTSD was examined. Participants were 194 veterans (M age = 34, SD = 8; 87% male, 59% White) with PTSD who started treatment, completed a structured PTSD assessment (CAPS), and assessments of grief (Inventory of Complicated Grief).

Results: Veterans with CG at baseline presented with greater PTSD severity ($p < .01$). CG was associated with reduced likelihood of PTSD treatment response (without CG: 42%, with CG 17%; OR: 0.25, 95%CI: 0.10-0.59, $p < .01$) and remission (without CG: 40%, with CG: 15%; OR: 0.23, 95%CI: 0.09-0.57, $p < .01$). The effect did not vary adjusting for baseline CAPS.

Conclusions: Comorbid CG is associated with reduced response to PTSD treatment. Additional detailed outcomes analyses and clinical implications will be presented.

Understanding the Relationship between PTSD and Comorbid Major Depression: The Role of Pre-, Peri-, and Post-Deployment Adversity and Social Support

Authors: Goetter, Elizabeth, PhD; Charney, Meredith, PhD; Hoeppner, Susanne, PhD; Khan, Amanda, MA; Wieman, Sarah, BA; Venners, Margaret, MPH, MSW; Avallone, Kimberly, PhD; Rauch, Sheila, PhD, Simon, N, MD

Abstract

Background: Nearly 75% of combat veterans with posttraumatic stress disorder (PTSD) have comorbid major depressive disorder (MDD), which is associated with greater mental health burden and higher social and economic costs.

Method: This secondary analysis of a multi-site, randomized controlled trial for veterans with combat PTSD examined the relationship of baseline childhood adversity, unit cohesion, and post-deployment social support (PDSS) with co-occurring depression. Participants received structured diagnostic assessments and completed the Deployment Risk and Resilience Inventory and the Beck Depression Inventory.

Results: Among 223 veterans (87% male, 58% white, M age = 34.20, SD = 8.26), with PTSD, 30.5% had current comorbid MDD. A series of univariate logistic regressions controlling for sex revealed that only PDSS predicted baseline comorbid MDD ($\chi 2(2) = 6.45$, $p = .04$). Self-reported depression severity regardless of diagnosis was correlated ($p < .05$) with postdeployment stressor exposure ($r = .20$), PDSS ($r = -.37$), concerns about family disruptions while deployed ($r = .26$), and general harassment within the unit ($r = .16$).

Conclusion: Among veterans with PTSD, PDSS is associated with comorbid MDD. Interventions that enhance social support alongside societal efforts to foster successful reintegration following deployment are critical for reducing mental health burden.

Activation in Pre-Treatment Emotion Modulation Circuitry is Associated with Treatment Response in PTSD

Authors: Duval, Elizabeth, PhD; Sheynin, Jony, PhD; King, Anthony, PhD; Phan, K. Luan, MD; Simon, Naomi, MD; Martis, Brian, MD; Porter, Katherine, PhD; Norman, Sonya, PhD; Stein, Murray, MD, MPH; Rauch, Sheila, PhD; Liberzon, Israel, MD

Abstract

Posttraumatic stress disorder (PTSD) has been associated with exaggerated threat reactivity and difficulties modulating emotion. These deficits have been linked to aberrant neural function, including increased activation in regions associated with emotion processing, decreased activation in emotion modulation regions, and differences in connectivity between emotion processing and modulation regions. The purpose of this study was to examine neural mechanisms underlying emotion processing and modulation, associated with treatment outcome in PTSD. Thirty-six military veterans with PTSD were assigned to evidence-based treatment groups: Prolonged exposure plus pill placebo (PE + PLB; N = 7), sertraline plus enhanced medication management (SERT + EMM; N = 14), and PE plus sertraline (PE+ SERT; N = 15). Symptom assessment and MRI scanning occurred before and after treatment. During MRI scanning, the Shifted Attention Emotion Appraisal Task (SEAT) probed brain activation during implicit emotional processing, attention modulation of emotion, and emotion modulation by appraisal. During appraisal, brain activation at pretreatment predicted change in PTSD symptoms across treatments ($R^2 = .28$, $F(7, 42) = 2.33$, $p = .040$). Specifically, activation in insula ($\beta = 2.03$, $p = .049$), dlPFC ($\beta = -.414$, $p = .012$), and vmPFC ($\beta = 2.33$, $p = .025$) before treatment was associated with symptom reductions over the course of treatment. Greater connectivity between left amygdala and superior parietal cortex at pre-treatment predicted greater reductions in symptoms over time ($p < .05$, FEW corrected). Increased connectivity between left amygdala and dlPFC over the course of treatment was associated with greater reductions in symptoms over time ($p < .05$, FWE). During attention modulation at pre-treatment, greater connectivity between right dorsolateral prefrontal cortex and superior parietal cortex predicted (at a trend level) reductions in PTSD symptoms over time ($p = .052$ FWE). Increased connectivity between these regions over the course of treatment was also associated with greater reductions in symptoms over time ($p < .05$, FWE). This study is one of the first to examine task-based activation and connectivity in a PTSD treatment trial, with evidence to suggest that the function of regions involved in emotion processing and modulation are important predictors of treatment response.

An Examination of the Relationship between PTSD, Depression, and Postconcussive Symptoms Measured by the NSI

Authors: Porter, Katherine, PhD; Stein, Murray, MD, MPH; Brian Martis, MD; Avallone, Kimberly, PhD; Smith, Erin, PhD; Simon, Naomi, MD; Gargan, Sean, MS; Liberzon, Israel, MD; Rauch, Sheila, PhD

Abstract

Mild traumatic brain injury (m-TBI), Posttraumatic Stress Disorder (PTSD), and depression often co-occur and a strong relationship exists between these symptoms. However, several symptoms attributed to m-TBI, described as postconcussive syndrome (PCS), overlap with symptoms of PTSD and depression, complicating our understanding of this connection. The current study attempts to help clarify this relationship by examining if PTSD and depressive symptoms continue to be related to PCS after overlapping symptoms are removed.

Method: 242 OEF/OIF/OND Veterans completed several self-report questionnaires including the Beck Depression Inventory- II (BDI-II), the Brief Traumatic Brain Injury Screen (BTBIS), the Neurobehavioral Symptom Inventory (NSI), and the PTSD Checklist-Stressor Version (PCL-S) as part of an evaluation for a larger treatment study. Multiple regressions with PCL-S total, BDI-II total, and two interaction terms (PTSD and TBI, depression and TBI; based on the BTBIS screener) predicting NSI total with overlapping items removed were conducted.

Results: Results demonstrated that PTSD and depression, but not the interaction terms, significantly predicted NSI scores.

Discussion: Results from this study demonstrate that there is a relationship between PTSD, depression, and PCS, and suggest that this relationship is not simply an artifact of symptom overlap. Clinical implications will be discussed.

PTSD as a Mediator in the Relationship between TBI Symptoms and Pain among OIF/OEF Veterans

Authors: Avallone, Kimberly, PhD; Smith, Erin, PhD; Ma, Sean, PhD; Gargan, Sean, MS; Porter, Katherine, PhD; Authier, Caitlin, BA; Martis, Brian Martis, MD; Liberzon, Israel, MD; Rauch, Sheila, PhD

Abstract

Objective: Traumatic brain injury (TBI), pain, and posttraumatic stress disorder (PTSD) commonly co-occur in Veteran populations, particularly among Veterans returning from the recent conflicts in Iraq and Afghanistan. Both TBI and PTSD can negatively impact pain broadly; however, less is known about how these variables impact one another. The current study evaluates the potential mediating role of PTSD in the relationship between TBI symptoms and both pain severity and pain interference among Veterans with PTSD.

Methods: Participants were 126 OEF/OIF/OND Veterans that who were being evaluated for participation in a multisite treatment outcomes study. Participants completed several self-report measures and interviews, including the Neurobehavioral Symptom Inventory, Brief Pain Inventory and the Clinician Administered PTSD Scale.

Results: Greater symptoms of TBI significantly predicted increased pain severity and that there was a significant indirect effect of TBI symptoms on pain severity through PTSD. Similar results were found for pain interference.

Conclusions: These findings replicate and extend previous findings regarding the relationship between TBI, pain, and PTSD. Results from the present study indicate that TBI symptoms negatively impact both pain severity and pain interference among Veterans, and that PTSD serves as a mediator in these relationships.

Examining the Relationship between TBI Symptoms and Pain among OIF/OEF Veterans with PTSD

Authors: Avallone, Kimberly, PhD; Smith, Erin, PhD; Ma, Sean, PhD; Gargan, Sean, MS; Porter, Katherine, PhD; Authier, Caitlin, BA; Martis, Brian Martis, MD; Liberzon, Israel, MD; Rauch, Sheila, PhD

Abstract

Background: Traumatic brain injury (TBI), pain, and posttraumatic stress disorder (PTSD) commonly co-occur in Veteran populations, particularly among Veterans returning from the recent conflicts in Iraq and Afghanistan. Extant research has identified that both TBI and PTSD can negatively impact pain broadly; however, less is known about the impact of TBI on pain severity and interference, above and beyond the effects of PTSD. The current study attempts to add to this literature by examining the impact of TBI symptoms on both pain severity and pain interference among Veterans with PTSD.

Methods: Participants were comprised of combat Veterans that served in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) who were being evaluated for participation in a multisite treatment outcomes study. Data presented in this abstract is from an initial 103 participants (analyses will be conducted using a larger data set prior to conference). As part of an initial evaluation for inclusion in the study, participants completed several self-report measures and interviews, including the Neurobehavioral Symptom Inventory (NSI), Brief Pain Inventory (BPI) and the Clinician Administered PTSD Scale (CAPS), which were utilized in these analyses.

Results: Results from hierarchical regression indicated that, after controlling for PTSD symptoms, symptoms of TBI significantly predicted increased pain severity ($R2 = .17$, $\beta = .35$, $t = 3.57$, $p < .01$) and pain interference ($R2 = .22$, $\beta = .44$, $t = 4.55$, $p < .001$).

Conclusion: These findings replicate and extend previous findings regarding the relationship between TBI, pain, and PTSD. Indeed, results from the present study indicate that TBI symptoms negatively impact both pain severity and pain interference among Veterans, even after accounting for the effects of PTSD symptom severity. These findings have important treatment implications.

Complicated Grief and the Impact of Loss of a Fellow Service member in Post 9/11 Service Members and Veterans with Combat Related PTSD

Authors: Simon, Naomi, MD; Rogers, Andrew, BA; Kim, Hyungjin Myra, ScD; Charney, Meredith, PhD; Bui, Eric, MD, PhD; Goetter, Elizabeth, PhD; Nadal-Vicens, Mireya, MD, PhD; Robinaugh, Donald, PhD; Venners, Margaret, MPH, MSW; Rauch, Sheila, PhD; and the PROGrESS Team

Abstract

Background: While service members serving post 9/11 have been reported to have significant exposure to loss (e.g., 75% having lost a fellow service member: Hoge et al 2004) and approximately 21% report difficulty coping with the death of someone close (Toblin et al 2011), relatively little is known about the presence and impact of complicated grief in service members and veterans with PTSD. Further, loss in the military may occur concurrent with or independent of the A1 trauma in PTSD.

Methods: We examined the presence of different types of losses and complicated grief symptoms in the first 180 participants of a multicenter treatment study of PTSD pharmacotherapy and psychotherapy (PROGrESS). All participants served post 9/11 (OEF/OIF/OND) and had combat-related PTSD (CAPS>50) confirmed by a certified clinician rater. CG symptoms were assessed with the 19-item Inventory of Complicated Grief (ICG; Prigerson et al., 1995) at baseline; syndromal level complicated grief was defined as an ICG score of 30 or higher, consistent with prior research.

Results: Full 79% of participants reported having lost an important person in their lives, with 40% indicating the loss of a fellow service member. Overall, one in four service members (n=44, 24.4%) met ICG severity levels for complicated grief (CG), while 31.4% of those exposed to a loss did. Fully 40% reported the loss of a fellow service member, which was the most common loss. Rates of CG were substantially higher for a service member loss (43.7%, 31/71) than when the loss was a different relationship (18.8%, 13/69: Chi Square p=0.002). Similarly, ICG severity was higher for loss of a fellow SM (mean (SD): 27.5(12.9) vs 20.4(13.2: p=0.001). Additional data examining the impact of grief symptoms for SM with PTSD including whether the loss was the primary trauma will be presented.

Conclusions: Complicated grief symptoms are common in service members and veterans presenting for the treatment of PTSD and should be assessed and treated. Additional research examining the optimal approach to addressing CG symptoms in the setting PTSD and in particular loss of a service member is needed.

Increased Within-Network and Cross-Network Functional Connectivity in Returning Veterans with Posttraumatic Stress Disorder

Authors: Sripada, Rebecca, PhD; Heffernan, Joseph, MS; Ma, Sean, PhD; Rauch, Sheila, PhD; and the PROGrESS Study Team

Abstract

Background: Posttraumatic stress disorder (PTSD) is characterized by disruptions in arousal/interoception, executive function, and sense of self. These functions are subserved by intrinsic brain connectivity networks, which are distributed, functionally coherent regions that interact to coordinate complex behavior and cognitive functions. The three key networks that coordinate the functions disrupted by PTSD are the salience network, the central executive network, and the default mode network. The salience network (anchored in dorsal anterior cingulate cortex, amygdala, and anterior insula) is responsible for detecting and orienting to salient stimuli. The central executive network (anchored in dorsolateral prefrontal cortex and lateral parietal cortex) is associated with goal-directed behavior and high level cognitive function, including planning, decision-making, and working memory. The default mode network (anchored in medial prefrontal cortex, posterior cingulate cortex and hippocampus) is associated with stimulus-independent, internally-focused thought and autobiographical memory. The salience network mediates between the central executive network and default mode network to maintain an adaptive balance between internal mentation and externally-oriented focus and task execution. PTSD symptoms have been linked to alterations in each of these networks. However, the interplay between these three critical networks has not yet been examined in patients with PTSD. Thus, the current study was designed to investigate patterns of connectivity within and between these three central intrinsic connectivity networks.

Methods: 19 OEF/OIF/OND combat veterans with chronic PTSD (Clinician-Administered PTSD Scale Score ≥ 50) and 14 combat-exposed healthy control veterans underwent 3T fMRI prior to initiating PTSD treatment as part of a comparative outcomes study for PTSD. A standard series of processing steps was performed using statistical parametric mapping. Based on previous research with the triple-network model, seed regions for salience network were anatomical anterior insula and amygdala. The seed region for the central executive network was a 10-mm-radius sphere placed in dorsolateral prefrontal cortex (MNI: 46, 6, 34). The seed regions for the default mode network were 10-mm-radius spheres placed in medial prefrontal cortex (-2, 48, -4) and posterior cingulate cortex (0, -56, 20). Functional connectivity analysis was performed using the ConnTool package. We extracted the spatially averaged time series from seed regions for each participant. Next, linear detrending was performed, followed by nuisance regression with motion regressors and five principal components of the BOLD time series extracted from white matter and cerebrospinal fluid masks. The residuals from this regression were then retained for further analysis. Since resting-state functional connectivity measures low-frequency spontaneous BOLD oscillations (.01–.10 Hz band), the time-course for each voxel was band-pass filtered in this range. Next, motion scrubbing was performed. Participants with more than 60% of their frames removed by scrubbing were excluded from further analysis. Pearson product-moment correlation coefficients were calculated between average time courses in the seed regions of interest (ROIs) and all other voxels of the brain, resulting in a 3-dimensional correlation coefficient image (r-image). These r-images were then transformed to z-scores using the Fisher r-to-z transformation. Z-score images from the individual activation maps were entered into second-level random-effects analyses implemented in SPM8.

Results: Veterans with PTSD demonstrated greater within-network salience network connectivity, as well as greater cross-network connectivity between central executive network seeds and salience network regions and between default mode network seeds and salience network regions. Specifically, the PTSD group demonstrated stronger connectivity than the control group between anterior insula (salience network) and anterior cingulate cortex (-3, 15, 28; Z = 3.69)(salience network), between dorsolateral prefrontal cortex (central executive network) and right amygdala (30, 5, -20; Z = 4.44)(salience network), between medial prefrontal cortex (default mode network) and anterior cingulate cortex (-9, 26, 25; Z = 3.55)(salience network), and between posterior cingulate cortex (default mode network) and anterior cingulate cortex (-15, 23, 25; Z = 4.51)(salience network).

Conclusions: Here we replicate previous findings in PTSD of increased within-network salience network connectivity and increased cross-network connectivity between salience network and default mode network. We extend these findings by demonstrating additional cross-network connectivity or desegregation between salience network and central executive network. Desegregation between these intrinsic connectivity networks may reflect sustained and likely inappropriate activation of salience network, which may negatively impact the adaptive balance between networks that is needed for appropriate cognitive resource allocation. This finding may reflect or help to explain sustained hypervigilance and hyperarousal in PTSD patients. These aberrant neural circuits may serve as targets for examination of change with treatment and future development of therapeutic interventions for PTSD.

Designing a Combined Effectiveness and Mechanisms Randomized Trial in PTSD: Finding a Balance

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Abstract

This talk covers a large, multi-site PTSD treatment study that examines effectiveness of proven PTSD treatments (Prolonged Exposure (PE)), sertraline, and their combination) and biomarkers related to predictors of response and mechanisms of change. Through submission to a DOD Broad Agency Announcement, funding was secured at a level to examine effectiveness and biomarkers not possible through standard randomized trial funding mechanisms. A direct head to head comparison of these proven treatments in military service members will provide outcomes that are directly relevant to their care. Specifically, the strengths of the study team incorporating sites with expertise in PTSD psychotherapy and medication study conduct will provide the highest quality data on how these treatments work in this population. Further, clinical follow-up for 52 weeks from randomization will provide additional information on maintenance of gains and function that are of key importance. Biological assessment of emotional processing and regulation in fMRI, HPA axis, genetics, and genomics are conducted with all participants across the study to examine factors predictive of response and factors related to change over all treatments and for specific intervention conditions. Discussion will focus on design selection factors involved in design choices (i.e., cost and reliability of data).

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