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Journal Title: PSYCHONEUROENDOCRINOLOGY
Volume: Volume 126
Publisher: PERGAMON-ELSEVIER SCIENCE LTD | 2021-02-11, Pages 105085-105085
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.psyneuen.2020.105085
Permanent URL: https://pid.emory.edu/ark:/25593/vvqb4

Final published version: http://dx.doi.org/10.1016/j.psyneuen.2020.105085

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Accessed October 28, 2023 7:01 AM EDT
The role of oxytocin signaling in depression and suicidality in returning war veterans


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Abstract

Many war veterans struggle with depression and suicidality, and separation from the military is a time of particularly high risk. Based on research in non-human animals, we hypothesized that reduced oxytocin signaling would mediate symptoms of depression and suicidality in war veterans recently separated from their close comrades. We also hypothesized that veterans with more frequent contact with comrades would have fewer symptoms of depression and suicidality. In this cross-sectional study, male veterans from the Iraq and Afghanistan wars (n = 86) provided blood and urine samples for measurement of peripheral oxytocin (OT) levels, as well as saliva samples for DNA extraction followed by genotyping of oxytocin receptor gene (OXTR) Single Nucleotide Polymorphisms, and CpG-methylation assessment. Participants also completed a series of mental health questionnaires and interviews. Veterans reported feeling very close to their comrades during war, and missing them greatly upon returning home. Neither peripheral OT levels nor OXTR genotypes were related to symptoms of depression or suicidality. On the other hand, methylation...
at OXTR CpG −924 was negatively correlated with depressive symptomology, after controlling for possible confounds. Veterans who socialized with comrades more frequently had higher levels of urinary, but not plasma OT, as well as less depressive symptomology. Social connectedness was a strong negative predictor of symptoms of both depression and suicidality, eclipsing the predictive power of other variables such as post-deployment social support, the degree to which participants reported missing their comrades, and the frequency with which they socialized with comrades. Our results suggest that veteran mental health is more impacted by lack of social connectedness than by separation from close comrades per se. While there is some evidence that OXTR methylation relates to depressive symptomology, decreased OT signaling does not appear to mediate the relationship between social disconnectedness and depression or suicidality. Sleep quality and anxiety disorders were also significantly associated with mental health symptoms, independent of social connectedness. Our findings suggest that efforts aimed at alleviating the burden of depression and suicidality in returning war veterans should focus on re-integrating veterans into society and establishing a feeling of social connectedness, as well as on treating anxiety disorders and sleep problems.

Keywords
Oxytocin; Veterans; Depression; Suicide; Social connectedness

1. Introduction

Suicide is a growing problem among U.S. military veterans. In 2017, the suicide rate for veterans was 1.5 times the rate for non-veteran adults, after adjusting for population differences in age and sex. Veteran suicide rates have increased from an alarming 15.9 per day in 2005–16.8 per day in 2017 (Affairs, 2019). Separation from the military is a time of particularly high risk, being associated with a 63% increase in suicide rate (Reger et al., 2015). When soldiers separate from the military, they also often separate from comrades with whom they have forged strong social bonds. Suicidal acts are predicted by poor perceived social support (Isometsa, 2014), so this separation from comrades may result in low levels of perceived social support and place soldiers at increased risk for suicide (Brenner et al., 2008). On the other hand, unit cohesion can buffer against the deleterious effects of stress, the development of PTSD and other psychiatric symptoms, and potentially against the occurrence of suicidal behavior (Nock et al., 2013). Another explanation for high suicide rates in returning war veterans is offered by Military Transition Theory which posits that the loss of a shared military identity can result in returning soldiers experiencing limited social connectedness (Castro and Kintzle, 2014), which has been associated with suicidal ideation, non-fatal suicidal behavior and suicide (Fassberg et al., 2012).

Animal studies suggest a potential physiological mechanism for the psychological distress that accompanies separation from close comrades. Both mother-infant attachments and adult pair-bond attachments are mediated by the interaction of oxytocin (OT) and dopamine (DA) in the ventral striatum (Numan and Young, 2016). Emerging evidence suggests that the same mechanism is operational in humans (Rilling and Young, 2014; Ross and Young, 2009; Skuse and Gallagher, 2009). Although oxytocin has traditionally been considered a maternal
hormone, it can also modulate both behavior and brain activity in men (Baumgartner et al., 2008; De Dreu, 2012; Declerck et al., 2014; Kosfeld et al., 2005; Naber et al., 2010; Weisman et al., 2012). One fMRI study showed that intranasal oxytocin administration increased the striatal response to cooperative social interactions among men (Feng et al., 2014), suggesting that OT may be enhancing the reward or salience of these positive social interactions. Given this role of OT in attachment and bonding, it is not surprising that animal studies implicate reduced OT signaling in the distress that follows separation from a social partner. When adult male prairie voles are separated from their female partners, they exhibit passive stress coping, indicative of depressive-like behavior. This depressive-like behavior is mediated by chronic activation of R2 Corticotrophin Releasing factor (CRF) receptors which suppress oxytocin signaling in the nucleus accumbens, part of the ventral striatum. Infusion of OT into the shell of nucleus accumbens eliminates depressive-like behavior in response to separation. Moreover, blockade of OTR in the NAc shell increases passive stress coping in paired males, mimicking the effect of partner loss (Bosch et al., 2016). Here, we present the first study to attempt to translate these findings to humans by asking if oxytocin signalling is related to symptoms of depression and suicidality in veterans of the Iraq and Afghanistan wars who have been separated from their close comrades.

Recent studies have examined OT correlates of both suicidality and depression. One study found no difference in plasma OT between suicide attempters and non-suicide attempters (Deisenhammer et al., 2012). Another study found that plasma OT decreased following social exclusion in young adults with a history of suicide attempt but not among depressed or healthy controls (Chu et al., 2020). A third study reported lower CSF OT levels in suicide attempters compared with healthy controls, as well as a negative correlation between plasma OT and the planning subscale of the Beck Suicide Intent Scale (SIS) among male suicide attempters (Jokinen et al., 2012). Several studies have reported negative associations between plasma OT and depressive symptomology (Gordon et al., 2008; Scantamburlo et al., 2007; Zetzsche et al., 1996). However, positive associations have also been reported (Holt-Lunstad et al., 2011; Parker et al., 2010). It has been suggested that elevated OT levels in depression may be a compensatory response to motivate affiliative behaviors that could mitigate depressive symptoms (McQuaid et al., 2014). Based on the animal research described above, we predicted that current peripheral OT levels would be negatively related to self-reported degree of bonding with comrades during war, as well as sense of social loss, depression and suicidal ideation upon returning home from war and experiencing separation from close comrades.

OT signaling in the brain depends on both the concentration of OT and the density and distribution of the OT receptor (OXTR). The human OXTR gene is located on chromosome 3p25, spans about 17 kb and consists of 3 introns and 4 exons (Inoue et al., 1994). A single-nucleotide polymorphism (SNP) of an adenine (A) or guanine (G) substitution within the third intron (rs53576) has been suggested as a particularly promising candidate to modulate oxytocinergic function (Tost et al., 2010; Wu et al., 2005). In fact, the G allele is associated with a number of traits that might be adaptive during war, including increased empathy for ingroup members (Luo et al., 2015), higher likelihood of aggression on behalf of a close other in distress (Buffone and Poulin, 2014), and a lower cortisol response to stress in the presence of social support (Chen et al., 2011b). Neuroimaging research has established

*Psychoneuroendocrinology. Author manuscript; available in PMC 2022 April 01.*
that intranasal OT augments the caudate nucleus response to cooperative interactions with other men, but only among men homozygous for the G allele (GG) at rs53576 (Feng et al., 2015b). This implies that OT may augment the reward of cooperative interactions in men who carry the GG allele. Another OXTR SNP, rs2254298, is also of interest since the G allele has been associated with unipolar depression, decreased attachment security and high levels of separation anxiety (Chen et al., 2011a; Costa et al., 2009). We therefore predicted that GG homozygotes of both rs53576 and rs2254298 would report stronger bonding with comrades during war, as well as greater sense of social loss, depression and suicidal ideation upon returning home from war and experiencing separation from close comrades.

Methylation of OXTR apparently affects its expression in both mice and humans. In mice, a reporter gene assay showed that methylation of specific CpG sites in the Oxtr promoter region inhibited transcription (Mamrut et al., 2013). In humans, Kusui et al. (2001) used a reporter gene assay to show that methylation of the OXTR 5-prime CpG island (spanning exons 1–3) suppresses transcription in a hepatoblastoma cell line. A 405 base-pair fragment known as MT2 appears to be most involved in suppressing transcription. Evidence is accumulating that OXTR methylation can have functional consequences in humans (Kader et al., 2018; Maud et al., 2018). Within MT2, CpG sites −901, −924 and −934 are among those most commonly implicated in these effects (Kumsta et al., 2013). Based on the above studies, we predicted that methylation of OXTR at sites −901, −924 and −934 would be negatively related to self-reported degree of bonding with comrades during war, as well as sense of social loss, depression and suicidal ideation upon returning home from war and experiencing separation from close comrades. We also expected endogenous OT to have more impact in participants with greater OXTR expression, so we predicted there would be interactions between peripheral OT and OXTR SNPs, and between peripheral OT and OXTR methylation, on symptoms of depression and suicidal ideation.

Finally, we surmised that separation-induced feelings of social loss and resulting depressive symptomology would be ameliorated by frequent contact with comrades after returning home from war, and that this would be mediated by increased OT levels and/or increased social connectedness. We therefore predicted that veterans who had more frequent contact with comrades would have higher OT, greater social connectedness and fewer symptoms of depression and suicidality.

2. Materials and methods

2.1. Subjects

Participants were male veterans from the Iraq and Afghanistan war (N = 86). Although female soldiers are becoming more common in the U.S. armed forces, participation was limited to male war veterans for four reasons: (1) substantial evidence for sex differences in OT effects suggests that pooling men and women would be inappropriate (Borland et al., 2019; Chen et al., 2016; Feng et al., 2015a), (2) women constitute approximately 15% of the active duty force (https://www.pewresearch.org/wp-content/uploads/sites/3/2011/12/women-in-the-military.pdf), suggesting that it would be challenging to amass an adequate sample of female soldiers, (3) one study found a relationship between low CSF OT and suicidal symptoms among male but not female participants (Jokinen et al., 2012), and (4)
suicide rates are three times higher in male compared with female veterans of the Iraq and Afghanistan wars (Kang et al., 2015). The study was approved by the Emory Institutional Review Board, and all participants gave written informed consent.

**2.2. Recruitment and inclusion/exclusion criteria**

Veterans were recruited by posting physical flyers at the Atlanta VA Medical Center, electronic flyers on list-serves of several major veterans’ organizations, and through an on-line social media marketing campaign using Splash Clinical (https://splashclinical.com/). The overwhelming majority of veterans were recruited via Splash Clinical. A medical history was collected from each participant. Veterans with severe, acute suicidal symptoms were to be excluded and referred for medical attention; however, no participants were determined to be at this level. We excluded veterans with major unstable medical illnesses that themselves may lead to depression. In addition, veterans with a current or past diagnosis of schizophrenia or bipolar disorder were excluded. On the other hand, veterans with current and/or past history of Major Depression were included. We also excluded veterans with DSM-5 positive alcohol or substance abuse within the past 6 months, given their association with suicidality. The PCL-5 (Weathers et al., 2013) was used to exclude veterans with severe PTSD, defined as a score of 50 or higher, since severe PTSD was likely to cause depression. On the other hand, we included those with mild to moderate PTSD. Veterans with moderate to severe traumatic brain injury (TBI; loss of consciousness greater than 1 h) were excluded. Veterans with mild TBI (<1 h loss of consciousness, <1 h post traumatic amnesia and normal brain imaging results) were included.

**2.3. Data collection procedures**

Participants provided biological samples and completed questionnaires in a single session. Each participant provided blood and urine samples for measurement of peripheral oxytocin levels. In contrast to plasma, urinary OT provides an integrated value reflecting the secretion of the hormone over time (Amico et al., 1987). We therefore consider urinary OT to be complementary to plasma OT. Saliva samples were also provided for genotyping and methylation analyses. Finally, we collected questionnaire data to measure symptoms of suicidality and depression, as well as perception of social loss and potential confounding or moderating variables.

**2.3.1. Blood samples for OT levels**—3 ml of blood were collected by venipuncture in an EDTA tube. Tubes were mixed briefly and kept on ice until centrifuging at 4 °C for 10 min at 1300 RPM. 0.5 ml plasma was pipetted into 2 ml Eppendorf vials.

**2.3.2. Urine samples for OT levels**—0.5 ml urine was pipetted into 1.5 ml Eppendorf vials. Vials were kept at −20 °C until extraction and analysis.

**2.3.3. Saliva samples for genotyping and methylation**—Subjects provide a saliva sample for genotyping analyses using Oragene kits (DNA Genotek). DNA was extracted in house using the prep-IT-L2P extraction kit following manufacture instructions (DNA Genotek). DNA integrity was assessed by agarose gel electrophoresis.
2.3.4. Questionnaires—All participants completed the following self-report measures:
the Beck Depression Inventory (BDI) (Beck et al., 1961), the Social Connectedness Scale
(Lee et al., 2001), the Postdeployment Support Scale and the Postdeployment Life Event
Scale (Vogt et al., 2008), the Buss Perry Aggression Questionnaire (Buss and Perry, 1992),
and the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). All participants also
completed two interview measures: the M.I.N.I. International Neuropsychiatric Interview
(M.I.N.I. 6.0) (Sheehan et al., 1998) and the Columbia- Suicide Severity Risk Scale
(C-SSRS) Military Version (Posner et al., 2011). Both interviews were administered by
licensed social workers and under the supervision of a clinical social worker to establish
current reported mental health symptoms. The Beck Depression Inventory (BDI) is a self-
reporting 21 item rating inventory that measures symptoms and characteristics to assist in
the diagnosis and treatment of depression. The Social Connectedness Scale is a 20 item
Likert questionnaire designed to assess the degree of feeling connected in their social
environment. The Post-deployment Support Scale is a 10-item self-report measure that
assesses post-deployment emotional support and instrumental assistance provided by family,
friends, and broader society. It was included to control for current levels of social support
that could also influence symptoms of suicidality and depression. The Post-deployment
Life Events Scale is a 14-item instrument that measures stressful life events since returning
home from war. It was included to control for social loss (e.g., divorce, bereavement) and
other stressful life events that may have occurred since returning home from war. The Buss
Perry Aggression Questionnaire (AGQ) is a 29-item scale that measures physical aggression,
verbal aggression, anger and hostility. It was included to account for the strong association
between aggression and suicidal ideation and behavior (Conner et al., 2003). The Pittsburgh
Sleep Quality Index is a 9 item instrument that measures quality and patterns of sleep. The
C-SSRS Military Version is an 11 item interview questionnaire designed to quantify the
severity of suicidal ideation and behavior. This was used to exclude veterans with severe
and acute suicidal symptoms, and refer them for emergency medical attention. Likert scale
questions were also included to measure perceived camaraderie during war (How close were
you to your fellow soldiers during the war? 1 = not close at all, 4 = moderately close, 7 =
extremely close), social loss upon returning home (How much do you miss your comrades?
1 = not at all, 4 = somewhat, 7 = extremely), and level of contact with comrades after
returning home (How often do you socialize with the soldiers you served with during war?
1 = not at all, 2 = at least once per year but less than once per month, 3 = at least once per
month but less than once per week, 4 = at least once per week, but less than once per day, 5
= once per day or more). Finally, all participants were asked how long they have been back
from war, and whether they have received mental health treatment during this time, what
type (group, individual, pharmacotherapy) and for how long. Collectively, the interview and
questionnaires required approximately one hour for completion.

2.4. Assays

2.4.1. OT assay—Plasma and urinary OT was estimated using a highly sensitive and
specific radioimmunoassay (RIAgnosis, Munich). The assay was standardized and validated
in animal and human studies using a variety of stimuli (hypertonicity, parturition, lactation,
stress, etc.) to reliably detect bioavailable OT. This validation included centrally released
(as measured in microdialysates, and in CSF) and peripherally secreted (as measured in

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plasma) neuropeptide (Landgraf and Neumann, 2004). All samples were treated identically and assayed in the same batch at the same time to avoid inter-assay variability; intra-assay variability is <8%.

2.4.2. OXTR SNP genotyping—Genotyping was performed using Sequenom Mass Array Technology, a medium-throughput method that relies on matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) analysis (Ehrich et al., 2005). PCR primers and extension primers were automatically designed using MassARRAY Assay Designer Suite (V2.0) software (https://agenacx.com/online-tools/) and ordered from Integrated DNA Technologies (Coralville, Iowa; primer sequences are available on request). Four panels were created to assess all variants; each panel was added to a quarter of one 384-plate. For quality control, the 384 well genotyping plate contains multiple duplicate samples, as well as positive and negative controls. Genotype calls were made using Spectrotyper software (Sequenom), and standard quality control analyses, including evaluation of Hardy Weinberg Equilibrium, call rates and minor allele frequencies then performed.

2.4.3. OXTR methylation assay—OXTR methylation assay by Pyrosequencing was performed by EpigenDex (https://www.epigendx.com). The relative proportion of methylated and unmethylated alleles at each of three CpG sites was assessed by direct Pyrosequencing after genomic bisulfite conversion, and PCR amplification. The three sites were at −934, −924 and −901, within the MT2 region of the 5-prime CpG island of OXTR.

2.5. Statistical analysis

A summary of hypotheses and analyses that were conducted to evaluate hypotheses is depicted in Fig. 1.

2.5.1 Hypothesis 1: Veterans with lower peripheral OT levels will report stronger bonding with comrades during war, as well as greater sense of social loss, depression and suicidal ideation. The Pearson Product-Moment Correlation Coefficient was used to test for a bivariate associations between peripheral OT levels and likert scale response to the question, “How close were you to your fellow soldiers during the war?”, likert scale response to the question, “How much do you miss your comrades”, and Beck Depression Score as well as Current Suicidality as assessed by the MINI (0 = none, 1 = low, 2 = moderate). Multiple linear regression was also used to test for an association between peripheral OT and both Beck Depression Score and Current Suicidality, after controlling for multiple possible confounding variables.

2.5.2 Hypothesis 2: Veterans with the GG genotype at rs53576 and rs2254298 will report stronger bonding with comrades during war, as well as greater sense of social loss, depression and suicidal ideation. Independent, two-sample t-tests were used to compare GG participants and A carriers (A-) on likert scale response to the question, “How close were you to your fellow soldiers during the war?”, likert scale response to the question, “How much do you miss your comrades”, Beck Depression Score and Current Suicidality. Multiple linear regression was also used to test for an association between SNP genotype
and both Beck Depression Score and Current Suicidality, after controlling for multiple possible confounding variables.

We also used the Genotype-Tissue Expression Portal (https://gtexportal.org/home/) to identify a group of 27 SNPs in and around OXTR that significantly influence human OXTR gene expression within the caudate nucleus (Supplementary Table 1). We then identified the high expressing allele for each SNP and calculated the total number of high expressing alleles across all 27 SNPs to generate a multi-locus profile score (MPS) for each subject. This score is expected to be positively associated with overall caudate nucleus OXTR expression levels. Pearson’s correlation coefficient was used to test for an association between our MPS and likert scale response to the question, “How close were you to your fellow soldiers during the war?”, likert scale response to the question, “How much do you miss your comrades”, Beck Depression Score and Current Suicidality score. Multiple linear regression was also used to test for an association between MPS and both Beck Depression Score and Current Suicidality, after controlling for multiple possible confounding variables.

2.5.3 Hypothesis 3: Methylation at three sites within the MT2 region of the 5-prime CpG island of OXTR (−934, −924 and −901 from transcription start site) will be negatively correlated with degree of bonding with comrades during war, sense of social loss, depression and suicidal ideation. Pearson’s correlation coefficient was used to test for an association between methylation at each site and likert scale response to the question, “How close were you to your fellow soldiers during the war?”, likert scale response to the question, “How much do you miss your comrades”, Beck Depression Score and Current Suicidality score. Multiple linear regression was also used to test for an association between methylation at each site and both Beck Depression Score and Current Suicidality, after controlling for multiple possible confounding variables. In addition, a mediation analysis was preformed utilizing the PROCESS macro in SPSS (Hayes, 2013). The mediation assessed whether PCL-5 score mediate the relationship between methylation at CpG – 901 and Beck depression scores.

2.5.4 Hypothesis 4: Peripheral oxytocin levels will interact with OXTR SNP genotype and/or OXTR methylation to predict levels of depression and suicidality. Multiple linear regression models from hypotheses 1–3 above were expanded to include interaction terms between peripheral OT and OXTR SNP genotypes and between peripheral OT and OXTR methylation.

2.5.5 Hypothesis 5: Veterans who maintain more contact with former comrades will have higher peripheral OT levels, as well as less depression and suicidal ideation. Pearson’s correlation coefficient was used to test for an association between frequency of contact with comrades and both Beck Depression Score and Current Suicidality score. Multiple linear regression was also used to test for an association between frequency of contact with comrades and both Beck Depression Score and Current Suicidality, after controlling for multiple possible confounding variables. A mediation analysis was performed as described above to assess whether peripheral OT mediates the relationship between socialization with comrades and Beck depression scores. An additional mediation model assessed whether
social connectedness mediates the relationship between socialization with comrades and Beck depression scores.

Finally, automatic linear modeling with forward stepwise regression, as implemented in SPSS Version 25, was used to determine the overall best models to predict both depression and suicidality.

3. Results

3.1. Demographics and descriptive statistics (see Table 1)

Sample demographics are provided in Table 1. Veterans averaged 36.1 years of age (SD = 9.0, range = 25–69) and had been back from war an average of 6.0 years (SD = 3.0).

As assessed with the MINI, 16% of participants had current depression, 23% had past depression, 21% had recurrent depression, and 40% had no depression. 20% suffered a depressive episode prior to deployment. 17% of veterans were currently using antidepressant medications. 85% had no current suicidality, 14% had low current suicidality, which included vague thoughts of suicide such as wishing to be dead or wishing to go to sleep and not wake up, and 1% (n = 1) had moderate suicidality, defined as more specific thoughts of self-harm but without any intention of acting and without an actual plan. 25% had generalized anxiety disorder, 17% had current social anxiety disorder, 44% had current panic disorder, 35% had agoraphobia, and 2% had obsessive compulsive disorder. Despite excluding veterans with diagnosed bipolar disorder, 11% reported symptoms consistent with bipolar disorder on the MINI. 18% had current PTSD, 5% had mild alcohol use disorder, and 1% had mild substance abuse disorder. 1

In response to the question, “What was the most challenging experience to cope with since returning from war”, 45% indicated, “loss of brotherhood”, 15% indicated “combat stress”, 5% indicated “none”, and 35% indicated “other” (Fig. 2).

Two likert scale questions were asked using a 7 point scale. In response to the question, “How close were you with your comrades?”, the average response was 6.0 (SD = 1.4; 1 = not close at all, 4 = moderately close, 7 = extremely close). In response to, “How much do you miss your comrades”, the average response was 5.4 (SD = 1.6; 1 = not at all, 4 = somewhat, 7 = extremely). In response to the question, “How often do you socialize with comrades”, 12% indicated “not at all”, 16% indicated less than once per year, 27% indicated at least once per year but less than once per month, 21% indicated at least once per month but less than once per week, 13% indicated at least once per week but less than once per day, 11% indicated at least once per day or more.

Finally, all but one of our participants tested negative for alcohol in urine at the time of testing.

1While we refer to specific diagnoses (e.g. agoraphobia, social anxiety disorder), these references indicate a strong symptomology of the disorder and not an official diagnosis, which would require further interviews and time spent with the participant.
3.1.1 **Hypothesis 1:** Veterans with lower peripheral OT levels will report stronger bonding with comrades during war, as well as greater sense of social loss, depression and suicidal ideation. Neither plasma nor urinary OT levels were significantly correlated with responses to the questions, “How close were you to your fellow soldiers during the war?” (plasma OT r = -0.04, urinary OT r = 0.08) or “How much do you miss your comrades” (plasma OT r = 0.09, urinary OT r = 0.14). Furthermore, neither plasma nor urinary OT levels were significantly correlated with Beck Depression score (plasma OT r = -0.02, urinary OT r = -0.01) or current suicidality (plasma OT r = -0.04, urinary OT r = -0.04).

To identify variables that might obscure a relationship between peripheral OT levels and Beck Depression Score, we tested for associations between Beck Depression score and other variables besides separation from comrades that could plausibly cause depression. Beck Depression score was related to head trauma (r = 0.31, p = 0.004), PCL-5 score (r = 0.68, p < 0.001), current panic disorder (r = 0.28, p = 0.009), agoraphobia (r = 0.38, p < 0.001), social anxiety disorder (r = 0.35, p = 0.001), generalized anxiety disorder (r = 0.45, p < 0.001), sleep quality (r = 0.52, p < 0.001), post-deployment life events (r = 0.39, p < 0.001), social connectedness (r = -0.63, p < 0.001), and post-deployment social support (r = -0.48, p < 0.001). We then entered these variables in a multiple linear regression model along with peripheral OT levels to predict Beck Depression score. In the resulting model, PCL-5 score, and social connectedness were significant, but neither plasma nor urinary OT were significant (Supplementary Table 2).

A parallel analysis for peripheral OT and suicidal ideation revealed that suicidal ideation was related to plasma testosterone level (r = 0.22, p = 0.05), PCL-5 score (r = 0.30, p = 0.006), bipolar disorder (r = 0.34, p = 0.002), agoraphobia (r = 0.25, p = 0.02), social anxiety (r = 0.37, p < 0.001), generalized anxiety (r = 0.38, p < 0.001), social connectedness (r = -0.42, p < 0.001), post-deployment social support (r = -0.36, p = 0.001), and Buss-Perry Aggression Score (r = 0.30, p < 0.005). In a multiple linear regression model to predict suicidal ideation that included these variables plus peripheral OT, only bipolar disorder was significant in the model (Standardized Beta = 0.22, p = 0.04). Neither plasma nor urinary OT were significant (Supplementary Table 3).

3.1.2 **Hypothesis 2:** Veterans with the GG genotype at rs53576 and rs2254298 will report stronger bonding with comrades during war, as well as greater sense of social loss, depression and suicidal ideation. Responses to the questions, “How close were you to your fellow soldiers during the war?” and “How much do you miss your comrades” did not differ between rs53576 GG individuals and rs53576 A carriers (t(77) = 0.99 and t(77) = 0.26, respectively). In addition, Beck Depression score and current suicidality did not differ between rs53576 GG individuals and rs53576 A carriers (t(77) = 1.22 and t(77) = 0.38 for depression and suicidality, respectively).

Similarly, rs2254298 GG individuals and rs2254298 A carriers did not differ on responses to the questions, “How close were you to your fellow soldiers during the war?” (t(77) = 0.54) and “How much do you miss your comrades” (t(77) = 0.26). In addition, neither Beck Depression score nor current suicidality differed between rs2254298 GG individuals and rs2254298 A carriers.
and rs2254298 A carriers (t(77) = −0.22 and t(77) = 0.56 for depression and suicidality, respectively).

Both SNPs remained non-significant in multiple linear regression models that included race and other potential confounders that were associated with Beck Depression Score or Current Suicidality (Supplementary Tables 4 and 5).

The multi-locus profile score (MPS) is the total number of high expressing alleles across 27 SNPs in OXTR that are significantly associated with OXTR expression in the human caudate nucleus. MPS was not significantly correlated with responses to the question, “How close were you to your fellow soldiers during the war?” (r = −0.09), Beck Depression score (r = 0.01, p > 0.05) or current suicidality (r = −0.05, p > 0.05). However, the correlation between MPS score and “How much do you miss your comrades” was marginally significant (r = −0.22, p = 0.05).

In a multiple regression model that included race and other variables associated with Beck Depression Score, MPS did not explain Beck Depression score (Supplementary Table 6). Similarly, MPS did not explain suicidality in a multiple linear regression model that included race and other variables associated with suicidality (Supplementary Table 7).

3.1.3 Hypothesis 3: Methylation at three sites within the MT2 region of the 5-prime CpG island of OXTR (−934, −924 and −901 from transcription start site) will be negatively correlated with strength of bonding with comrades during war, sense of social loss, depression and suicidal ideation. There was no association between methylation at any of the three sites and responses to either “How close were you to your fellow soldiers during the war?” (−901 r = 0.16, −924 r = −0.02, −934 r = 0.11) or “How much do you miss your comrades” (−901 r = 0.14, −924 r = −0.20, −934 r = −0.01). Methylation at the −901 site was positively correlated with Beck depression score (r = 0.25, p = 0.03). Methylation at sites −934 and −924 were not significantly correlated with Beck Depression score (r = 0.080 and r = −0.13, respectively). Suicidality was not correlated with methylation at any of the three sites (−901 r = 0.11, −924 r = 0.05, −934 r = −0.06).

In multiple linear regression models that controlled for race and for variables related to Beck Depression, methylation in −924 became significant (Standardized Beta = −0.20, p = 0.02; Fig. 3), whereas methylation in −901 methylation became non-significant (Standardized Beta = 0.06) and methylation in −934 remained insignificant (Standardized Beta = 0.14) and (Supplementary Table 8).

The fact that −901 methylation became non-significant in the multiple regression model raised the possibility that one of the other covariates in the model could be mediating its association with Beck Depression score. Given that −901 methylation was positively correlated with PCL-5 score (r = 0.37, p = 0.001) and PCL-5 score had a strong positive correlation with Beck depression score (r = 0.68, p < 0.001), we conducted a post-hoc test to determine if PCL5 score mediated the relationship between −901 methylation and Beck depression score. Indeed, a mediation analysis revealed that the effect of −901 score on Beck
depression is completely mediated through PCL5 scores (unstandardized indirect effect = 0.32, 95% CI [0.12, 0.53]). PCL5 accounted for approximately 95% of the total effect.

In multiple linear regression models that controlled for race and for variables related to suicidality, methylation at all three sites remained non-significant in predicting suicidality.

3.1.4 **Hypothesis 4:** Peripheral oxytocin levels will interact with OXTR SNP genotype and/or OXTR methylation to predict levels of depression and suicidality. In multiple linear regression models that controlled for race and for variables related to Beck Depression, there was a significant interaction between plasma OT and OXTR rs2254298 (Standardized Beta = 0.75, p = 0.02).

Specifically, the relationship between plasma OT and depression was positive in A allele carriers and negative in GG individuals, however neither relationship reached significance in bivariate correlation analyses (A carriers: r = 0.26, p > 0.05, n = 15; GG: r = −0.12, p > 0.05, n = 64). In a parallel analysis examining plasma OT and OXTR rs 53576, no significant interaction was present. In addition, there was no significant interaction between urinary OT and either OXTR rs53576 or OXTR rs2254298 genotype on Beck Depression scores (Supplementary Table 9).

Similarly, there was no significant interaction between either plasma or urinary OT and either OXTR rs53576 or OXTR rs2254298 genotype on current suicidality (Supplementary Table 10). Finally, MPS score did not interact with either plasma or urinary OT in explaining either Beck Depression score or suicidality (Supplementary Table 11).

There was no significant interaction between either plasma or urinary OT and OXTR methylation at any of the three sites in explaining either Beck Depression score or suicidality (Supplementary Table 12 and 13).

3.1.5 **Hypothesis 5:** Veterans who maintain more contact with former comrades will have higher peripheral OT levels, as well as less depression and suicidal ideation. Veterans who socialized with comrades more frequently had higher levels of urinary (r = 0.24, p = 0.03), but not plasma OT (r = 0.07, p > 0.05). They also had marginally lower Beck Depression scores (r = −0.21, p = 0.05) (Fig. 4). However, urinary OT did not mediate the relationship between socialization with comrades and depression (unstandardized indirect effect = 0.05, 95% CI [−0.28, 0.41]).

Although significant in bivariate analyses, socialization with comrades was not a significant predictor of Beck Depression in a regression model that included other variables associated with depression (Supplementary Table 14). Post-hoc analysis showed that social connectedness completely mediates the negative association between socialization with comrades and Beck Depression score (unstandardized indirect effect = −1.71, 95% CI [−2.68, −0.81]). Social connectedness accounted for approximately 79% of the total effect. Socialization with comrades is positively correlated with social connectedness (r = 0.40, p < 0.001) and social connectedness is negatively correlated with Beck Depression Score (r = −0.63, p < 0.001).
There was also no significant association between frequency of socialization with comrades and suicidality in either bivariate correlation \((r = -0.13, p > 0.05)\) or regression analyses that controlled for other variables associated with suicidality (Supplementary Table 15).

### 3.2. Best overall model to explain beck depression score and Suicidality in returning war veterans

Forward step-wise multiple linear regression was used to identify significant predictors of both Beck Depression and suicidality. For Beck Depression score, all variables that were associated with Beck Depression score in bivariate analyses were considered for inclusion in the model. However, due to high collinearity between social connectedness and post-deployment social support \((r = 0.64, p < 0.001)\), only social connectedness was considered for inclusion in the model because it was more strongly associated with Beck Depression in bivariate analyses. Modeling identified three significant predictors that explained 63% variance (Table 2). In decreasing order of explained variance, the model included the following variables: PCL5, social connectedness, and sleep quality (Fig. 5a, b).

A parallel analysis was conducted for suicidality, again excluding post-deployment social support due to high collinearity with social connectedness. Modeling identified three significant predictors that explained 31% variance in suicidality. In decreasing order of explained variance, the model included the following variables: social connectedness, bipolar disorder, and generalized anxiety disorder symptoms (GAD) (Table 3) (Fig. 5c, d).

### 4. Discussion

Veterans reported both feeling very close to their comrades during war, and missing them to a great extent upon returning home. 48 veterans (56%) said they were “extremely close” with their comrades, and 26 (30%) said they missed their comrades “extremely”. Consistent with these data, veterans most often listed “loss of brotherhood” as their most challenging experience to cope with since returning home from war. This “loss of brotherhood” may contribute to feelings of limited social connectedness, and our data show that social disconnectedness is a strong predictor of symptoms of both depression and suicidality, as predicted by Military Transition Theory.

Our hypothesis that separation-induced symptoms of depression and suicidality would be mediated by withdrawal of oxytocin signaling received limited support. Peripheral OT levels were not related to either depression or suicidality. Nor was \(OXTR\) genotype. However, methylation of \(OXTR\) was related to depression at two of the three sites we examined. At site \(-901\), methylation was significantly positively correlated with symptoms of depression, but this correlation became non-significant after controlling for other variables related to depression. On the other hand, methylation at site \(-924\) became a significant negative predictor of depressive symptomology only after controlling for other variables related to depression. Finally, consistent with our hypothesis, socialization with comrades was associated with less depressive symptomology, and this was mediated by increased feelings of social connectedness.
Our initial hypothesis was that low levels of *OXTR* methylation would involve increased *OXTR* expression and increased OT signaling, thereby facilitating stronger bonding with comrades during war and more distress upon separation. This hypothesis predicts a negative relationship between *OXTR* methylation and depression. This is the pattern we observed for site −924. On the other hand, we observed a positive association at −901. Stress can increase *OXTR* methylation (Unternaehrer et al., 2012) so it is possible that combat stress led to both increased methylation at −901 and increased depressive symptomology, resulting in a non-causal association between −901 methylation and depression. Alternatively, there could be a causal relationship between −901 methylation and depression. Many studies have tested for a relationship between *OXTR* methylation and depression, but results have been mixed (Li et al., 2019). In our study, the relationship between-901 methylation and depression was eliminated once PTSD symptomology was included in the model, and PTSD symptomology was found to mediate this relationship. One speculative possibility is that war trauma induces *OXTR* methylation which increases vulnerability to PTSD, and this in turn increases symptoms of depression. Although increased *OXTR* methylation has been reported for women with PTSD, this relationship was not previously found in men (Nawijn et al., 2019).

The lack of a relationship between either peripheral OT levels or *OXTR* genotype and symptoms of depression and suicidality challenge our hypothesis that OT signaling is an important determinant of Veteran mental health. However, there are other possible explanations for our findings. Oxytocin is largely impermeable to the blood-brain barrier (Meisenberg and Simmons, 1983), so central and peripheral levels are not necessarily related (Landgraf and Neumann, 2004). Thus, it is conceivable that a relationship exists between brain OT levels and mental health symptoms, but that this is not reflected in peripheral OT levels measured here. Similarly, it is possible that *OXTR* methylation in saliva does not accurately reflect *OXTR* methylation in relevant brain areas, although similar methylation profiles have been observed across *OXTR* in blood, brain and saliva (Smith et al., 2015), and evidence is accumulating that peripheral *OXTR* methylation has functional correlates in humans (Andari et al., 2020; Dadds et al., 2014; Gregory et al., 2009; Jack et al., 2012; Puglia et al., 2015). Future studies could further investigate the hypothesis that separation-induced depression is mediated by decreased OT signaling by measuring oxytocin levels in CSF, and by looking at these levels during the more acute post-deployment period. It would also be informative to conduct within-subject longitudinal studies to track changes in veteran OT signaling from deployment to the post-deployment period in order to better characterize separation-induced effects on OT levels.

There are a multitude of studies showing that post-deployment social support protects against depression and suicide in war veterans (Boscarino et al., 2018; Ciarellegio et al., 2018; Debeer et al., 2014; Lemaire and Graham, 2011; Pietrzak et al., 2010a; Pietrzak et al., 2010b; Pietrzak et al., 2009; Pietrzak et al., 2011a). Our data also reveal robust associations between post-deployment social support and depression (r = −0.48, p < 0.001), and between post-deployment social support and suicidality (r = −0.36, p = 0.001). However, associations between these mental health outcomes and social connectedness were even stronger (r = −0.63 for depression and r = −0.42 for suicidality, p < 0.001 for each) than associations between mental health and social support. In contrast, the degree to which veterans reported
missing their comrades was not significantly associated with either depression ($r = 0.19, p > 0.05$) or suicidality ($r = 0.14, p > 0.05$). Collectively, these results suggest that veteran mental health is more impacted by feeling disconnected from society than by separation from close comrades per se. This finding echoes Emile Durkheim’s conclusion more than one hundred years ago that lack of social integration is a principal cause of suicide (Durkheim, 1951). Our data further suggest that one means by which veterans can increase social connectedness and decrease depression is by maintaining frequent contact with comrades. There was no evidence that decreased OT signaling is involved in depression and suicidality resulting from low social connectedness since social connectedness was not significantly correlated with any of our measures of OT signaling, including peripheral OT levels, *OXTR* SNPs or *OXTR* methylation (all $p > 0.05$).

PCL-5 score, a measure of PTSD symptomology, was the strongest predictor of Beck Depression score. This is not surprising given that approximately half of veterans suffering from PTSD also meet criteria for major depressive disorder (MDD) (Rytwinski et al., 2013). The co-occurrence of PTSD and MDD has been found to impose an even greater burden on mental and physical health than PTSD alone (Nichter et al., 2019). In one recent study, higher levels of community integration were associated with decreased co-occurrence of PTSD and MDD, consistent with the beneficial effects of social connectedness implied by the results discussed above (Nichter et al., 2020).

In addition to PCL-5 score and social connectedness, sleep quality was also a significant predictor of depressive symptomology in our multiple linear regression model. Poor sleep quality was associated with higher Beck Depression scores. Previous studies have demonstrated a bidirectional relationship between poor sleep quality and depression (Dinis and Braganca, 2018). Sleep problems affect up to 41% of Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) veterans. One recent study of OIF/OEF veterans found that sleep problems statistically mediated the association between greater rumination and more depressive symptoms (Borders et al., 2015).

Social connectedness was the strongest predictor of suicidality in our multiple linear regression model. Bipolar disorder was also a significant predictor in this model. This is a well-known relationship (Latalova et al., 2014). In fact, between one-third and one-half of patients with bipolar disorder attempt suicide at least once in their lifetime (Grande et al., 2016). Finally, GAD symptoms were also a significant predictor of suicidality in our multiple linear regression model. This result is consistent with evidence that patients with GAD are at particularly high risk for suicide attempts (DeMartini et al., 2019).

Our study revealed some additional noteworthy findings not directly related to our hypotheses. The majority of veterans in our study (61%) reported struggling with chronic pain. Other studies have similarly reported high rates of chronic pain in OEF/OIF veterans. For example, 47% of veterans entering the VA system reported having pain during their initial visit (Gironda et al., 2006). Although chronic pain did not emerge as a significant predictor of suicidality in our study, another study of OEF/OIF veterans found that suicide contemplators were more likely to report a deployment-related pain condition or complaint (Pietrzak et al., 2011b). One potential explanation for the lack of a relationship...
between chronic pain and suicidality in the present study is that we excluded veterans with severe, acute suicidal symptoms. Another noteworthy finding was that the prevalence of panic disorder in this sample of Veterans (44%) was much higher than the lifetime prevalence in the general population (~5%) (https://www.nimh.nih.gov/health/statistics/panic-disorder.shtml). Additionally, the prevalence of GAD in our sample (25%) was markedly higher than the lifetime prevalence of GAD (~6%) in the general population (Stein and Sareen, 2015) (https://www.nimh.nih.gov/health/statistics/agoraphobia.shtml). Although our sample is not nationally representative, it is possible that war trauma contributes to the high prevalence of these anxiety disorders in our sample. Lastly, consistent with high rates of Traumatic Brain Injury (TBI) in those deployed to Iraq and Afghanistan (Hoge et al., 2008), 41.7% of veterans in our study reported having experienced head trauma at some point in their lives.

While this study identified a number of factors that may contribute to depression and suicidality in war veterans, limitations are also apparent. First, our sample was restricted to male veterans only. As a result, it is unclear whether these findings generalize to the growing female veteran population. Replication and extension to women is warranted. Second, OT levels and OT methylation were measured in the periphery. Levels in the brain, which may differ from peripheral levels, are likely more relevant to mental health. Third, although we excluded veterans with diagnosed bipolar disorder because of its overlap with depression and known strong association with suicidality, several participants nonetheless reported symptoms consistent with that diagnosis using the MINI. Fourth, we initially powered the study for n = 100, but our recruitment efforts fell short of that goal and we were only able to recruit n = 86. Thus, particularly for our genetic hypothesis, we may be underpowered. Nevertheless, if limited power were the explanation for the lack of genetic effects, we would expect to see trends emerging in the predicted direction but this was not the case. For suicidality, our ability to detect effects was likely further limited by the small proportion of veterans (15%) presenting with suicidal symptoms. Finally, we conducted a large number of tests overall and we did not correct for multiple comparisons in order to guard against false negative results in light of our limited statistical power. However, this raises the possibility that some of our findings could be false positives. This is less likely to be the case for our more robust findings, including the effects of social connectedness, PTSD symptomology and sleep quality on depression.

5. Conclusion

In conclusion, although veterans of the Iraq and Afghanistan wars report forming very strong bonds with their comrades during war, separation-induced distress upon returning home does not seem to be the most important contributor to their mental health. Rather, their mental health appears to be more dependent upon broader connection to peers and society. While peripheral OT levels and OXTR genotype did not predict mental health symptoms, methylation of particular CpG sites within OXTR did predict depressive symptomology. Other important factors related to veteran depression and suicidality are the degree to which they are struggling with PTSD and other anxiety disorders, as well as poor sleep quality. Efforts aimed at re-establishing a feeling of social connectedness and at treating anxiety...
and sleep problems are potentially productive interventions for alleviating their burden of depression and suicidality.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgements**

This project was supported by Grant SRG-1–116-16 awarded to Emory University from the American Foundation for Suicide Prevention. The content is solely the responsibility of the authors and does not necessarily represent the official views of the American Foundation for Suicide Prevention. This project was also supported by a pilot grant from the Emory Silvio O. Conte Center for Oxytocin and Social Cognition funded by NIH grant P50MH100023.

**Data availability statement**

The data that support the findings of this study are available in Open Science Framework at https://osf.io/nw3kz/?view_only=a9f39cd41ac54731a270c11734411666.

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Psychoneuroendocrinology. Author manuscript; available in PMC 2022 April 01.


Psychoneuroendocrinology. Author manuscript; available in PMC 2022 April 01.


Fig. 1.
Schematic summary of study hypotheses. Numbers refer to each of the hypotheses. Hypothesis 4 is a test for interaction and is not included in the schematic. Hypotheses that were partially supported are highlighted. Where multiple measures were tested, significance is indicated by bold font.
Fig. 2.
Greatest challenge since returning home from war. Percentage of veterans choosing each of four different response options to the question, “What was the most challenging experience to cope with since returning from war?”
Fig. 3.
OXTR methylation and depression in war veterans. Plot of residuals from a regression on Beck Depression score (Y axis) against methylation at OXTR CpG −924 (X-axis) (Standardized Beta = −0.20, p = 0.02). Residuals were obtained from a regression that included independent variables that were correlated with Beck Depression in bivariate correlation analyses, along with race.
Fig. 4.
Depression and socialization with comrades. Plot of Beck Depression score against frequency with which participants socialized with comrades. 1 = not at all, 2 = less than once a year, 3 = once per year or more, less than once per month, 4 = once per month or more but less than once per week, 5 = once per week or more but less than once per day, 6 = once per day or more.
Fig. 5.
Correlates of Beck Depression and Suicidality Scores. (a) plot of Beck Depression score against PCL5 score, a measure of PTSD symptomology, (b) plot of Beck Depression Score against Social Connectedness Score, (c) plot of Social Connectedness Score by level of suicidal symptomology, (d) plot of suicidal symptomology for those with and without Bipolar Disorder.
### Table 1

Descriptive statistics.

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<td>Mean</td>
<td>Std. deviation</td>
<td>Minimum</td>
<td>Maximum</td>
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Table 2
Automatic linear regression model showing significant predictors of Beck Depression score.

<table>
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<tr>
<th>Variable</th>
<th>Sum of squares</th>
<th>df</th>
<th>Mean square</th>
<th>F</th>
<th>p</th>
<th>Stand β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected Model</td>
<td>4838.10</td>
<td>6</td>
<td>806.35</td>
<td>23.87</td>
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<td>PCL5 Score</td>
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<td>5.92</td>
<td>0.017</td>
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Table 3
Automatic linear regression model showing significant predictors of Suicidality.

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<th>df</th>
<th>Mean square</th>
<th>F</th>
<th>p</th>
<th>Stand β</th>
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<td>1.51</td>
<td>13.14</td>
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<td>Corrected Total</td>
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