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Camilla Gallin April 15, 2018

Effects of Social Loss and Oxytocin Signaling on Depression and Suicidal Ideation in Returning War Veterans

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2019

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Sciences with Honors

Department of Neurobehavioral Biology

2019

Abstract

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There has recently been a disproportionately high rate of suicide among war veterans relative to the civilian population, with a lack of consensus as to the specific reason for this epidemic. Returning war veterans may suffer a lack of social connectedness and emotional support, which can negatively impact mental health. Research has implicated oxytocin (OT) in social bonding, and specific single nucleotide polymorphisms (SNPs) in the oxytocin receptor gene (*OXTR*), rs53576 and rs2254298, have been suggested to influence prosocial and empathetic traits in humans. In this study, we examine the effects of social loss and oxytocin signaling on depression and suicidal ideation in returning male war veterans. Subjects (n=73) completed the Mini-International Neuropsychiatric Interview, Sixth edition (M.I.N.I. 6.0), PTSD Checklist for DSM-5 (PCL-5), Beck Depression Inventory (BDI), Columbia-Suicide Severity Risk Scale (C-SSRS) Military Version, Social Connectedness Scale (SCS), Postdeployment Social Support Scale (PDSS), and the Pittsburgh Sleep Quality Index (PQSI). Subjects (n=54) also provided biological samples (blood, saliva, and urine) for plasma OT assessments and SNP genotyping. Results indicate that subjects with low social connectedness and low post-deployment social support report higher levels of depression, after controlling for PTSD symptomology and sleep quality. Subjects reporting low post-deployment social support also reported higher levels of suicidal ideation. There was no significant effect of rs53576 or rs2254298 genotype on social connectedness, depression, or suicidal ideation. However, the

genotype frequencies of rs53576 in our study population differed significantly from those in a population genomic database, suggesting that this study may have attracted participants with a genotype linked with increased social sensitivity. These results identify factors that lead to depression and suicidal ideation in war veterans, which can be useful for refining preventative treatments following service.

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Figures and Tables

Introduction

Suicide among War Veterans

According to the Office of Suicide Prevention of the U.S. Department of Veterans Affairs (VA), on average, 16 veterans die by suicide every day (Department of Veterans Affairs, 2016). As of 2016, the age- and sex-adjusted risk of suicide among veterans was 21% higher than civilians, and although veterans only make up 8.5% of the U.S. adult population, they account for 18% of deaths by suicide in adults in the US (Department of Veterans Affairs, 2016). As of 2016, the suicide rate for 18-to-34-year-old veterans has increased to 45 deaths per 100,000 population, up from 40.4 in 2015 and from 35 in 2014, and suicide rates are highest among this age cohort (Department of Veterans Affairs, 2016).

While there are many hypotheses for high veteran suicide rates, combat experience itself has not been found to have a direct effect on suicide risk (Bryan et al., 2013). According to the 2016 VA National Suicide Data Report, nearly four out of 20 veteran suicides per day were among National Guard and Reserve veterans who never deployed to a combat zone. These findings suggest that this epidemic is not driven by the nature of deployment, but by the nature of separation from the military. In a survey of 3.9 million US military personnel who served during Operation Enduring Freedom or Operation Iraqi Freedom between 2001 and 2007, separation from the military was associated with a 63% increase in suicide rate, regardless of whether service members had deployed or not (Reger et al., 2015).

When soldiers separate from the military, they are separating from comrades with whom they have formed strong social bonds. Castro and Kintzle (2014) attempt to explain the high rates of suicide among veterans by combining the interpersonal-psychological theory of suicide and military transition theory (2014). The interpersonal-psychology theory of suicide hypothesizes

that a feeling of burdensomeness, social isolation, and the ability to complete an act of suicide must all be present for death by suicide to occur (Joiner 2005). According to Castro and Kintzle, since all military veterans have acquired military training to enact lethal harm, this component of the interpersonal-psychological theory of suicide is always present in all service members. Therefore, shifting the focus onto feelings of social isolation and burdensomness among veterans is more useful for understanding suicidal ideation.

Military transition theory accounts for social isolation by describing the progression of soldiers leaving military culture and entering a civilian culture that lacks a shared military cultural identity. The first phase of this transition involves the personal, cultural, and transitional factors that determine how a service member leaves the military. These include personal characteristics and preparedness (e.g., physical and mental health, expectations) and the nature of discharge (e.g., predictable/unpredictable, positive/negative). The second phase of leaving the military describes the transition into civilian culture, accounting for the individual's coping mechanisms, attitudes, beliefs, surrounding community, and military resources (i.e. VA benefits, education benefits, career planning). The final phase of leaving the military describes the transitional outcomes, measured by secured employment, physical and psychological health, re-adjustment to family roles, engaging in the community, and finding new social networks.

It is this final phase that is the focus in the current study. The transitional outcomes can influence and exacerbate each other. For example, an inability to secure employment can affect emotional wellbeing and prevent community engagement. An inability to start a family due to unemployment, or a physical disconnection from comrades, can result in feelings of social isolation, which may worsen physical and psychological health (Holt-Lunstad et al. 2015). Altogether, the final phase of the military transition can result in a loss of shared military identity

and a sense of community belongingness (Castro & Kintzle, 2014). In a qualitative study by Brenner et al. (2008), veterans overwhelmingly expressed the sense of connection with their comrades resulting from "shared experiences" and "common values, miseries, and joys" during deployment. Veterans shared their feelings of disconnection with non-veterans following discharge, with one veteran sharing that his connection was with his "Army buddies, the Army, but everyone else, nothing," while another said, "I separate myself from society, that part of society … I just keep myself away," (Brenner et al. 2008). It follows that a failure to develop support networks after military discharge can exacerbate the feelings of social isolation, increasing the probability of suicide in the context of the interpersonal-psychological theory of suicide (Monteith et al., 2013; Blow et al., 2018).

In general, social isolation has been associated with suicidal ideation and suicide in both veterans and non-veteran civilians (Fassberg et al., 2012). The importance of social relationships is evident when holistically examining human health. House et al. conducted a meta-analysis describing several studies linking conditions of tuberculosis, schizophrenia, heart disease, etc. to social isolation (1988). The detrimental effects of social isolation have even been shown to rival the effects of cigarette smoking, obesity, blood pressure, blood lipids, and lack of physical activity (House et al., 1988; Holt-Lunstad et al. 2015). A survey of 272 veterans conducted by Pietrzak et al. tested the buffering effects of postdeployment social support on health (2009). Results replicated previous findings in demonstrating the moderating effect of postdeployment social support on depressive symptoms and psychosocial difficulties. The buffering effects of social support may be attributed to reduced feelings of loneliness, increased feelings of self-efficacy and reduced feelings of burdensomeness, reduced involvement in high-risk behaviors and avoidance coping, and even reducing stress-related arousal from the hypothalamic-pituitary-

adrenal (HPA) axis (Pietrzak et al., 2009). However, veterans were less likely to seek mental health treatment if they reported high levels of perceived stigma from their surrounding community, which could possibly account for low rates of postdeployment social support in the form of psychotherapy (Pietrzak et al., 2009; Southwick et al., 2015).

In addition to social isolation, perceived burdensomness contributes to the interpersonal-psychological theory of suicide. The aforementioned social isolation, in combination with unresolved physical or psychological problems (Castro and Kintzle, 2014) and loss of both sense of self and purpose (Brenner et al., 2008) may result in the development of a belief among service members that they are a burden to their family, friends, and community. Only 62% of veterans have utilized VA health care services between 2001 and 2015 (U.S. Department of Veterans Affairs, 2017). Thus, physical and mental ailments may go undiagnosed in many veterans. There has been an increasing association of self-perceived burden with suicidal ideation in veterans and non-veterans with chronic medical conditions, particularly chronic pain (Kanzler et al., 2012; Kowal et al., 2012; Wilson et al., 2017). A chronic medical condition like pain can have long-term physical, psychological, and economic consequences on an individual, contributing to the belief that his or her caretaker, significant other, general community, etc. would be better off if the individual were dead or gone (Wilson et al., 2017). In addition to unresolved medical issues, perceived burdensomness may result from a loss of sense of self and purpose. In a qualitative study assessing potential suicide risk from perceived burdensomness, veterans assessed their civilian duties to be less valuable, impactful, and important than their combat duties (Brenner et al., 2008). They also report difficulties in integrating back into society, linking feelings of burdensomness and belongingness (Brenner 2008). Together, these perceptions can lead veterans to believe that they are a burden to both society and friends. One

veteran expresses: “I feel like I am a burden, 100%, I don’t feel like I belong anywhere … if I’m out with some friends, I don’t feel like I belong … I’m the outsider,” (Brenner 2008). Veterans also reported perceived burdensomness to family and friends due to their inability to provide financial support (Brenner et al., 2008). Vocational rehabilitation services have been deemed necessary for veterans in order to ease their transition back into civilian life and reduce feelings of burdensomeness and suicidal ideation (Brenner et al., 2008). In a study examining the interpersonal-psychological theory of suicide in an inpatient veteran sample, an interaction between burdensomness and belongingness significantly predicted suicidal ideation (Monteith et al., 2013).

Oxytocin, Social Bonding, and Depression/Suicide

Research on the biological basis of social bonding has contributed to our understanding of the damaging effects of social loss. Animal studies have shown that the interaction between dopamine (DA) and oxytocin (OT) in the nucleus accumbens (NAcc) promotes both mother-infant and adult pair-bond attachments. Central OT, and its receptor, facilitate partner preference formations in female prairie voles during prolonged cohabitation and mating, and monogamous species like the prairie vole demonstrate higher densities of OT receptors in the NAcc compared with polygynous species (Insel and Shapiro, 1992). Prairie voles also showed an increase in DA turnover in the NAcc after mating in both females and males, supporting the reinforcing effects of bond formation (Gingrich et al., 2000; Aragona et al., 2003). In addition, Bosch et al. found that separating male prairie voles from a female partner resulted in suppression of striatal oxytocin signaling and chronic activation of corticotropin-releasing factor receptor 2 (CRFR2) in the NAcc (2016). The interaction between CRFR2 and OT withdrawal may contribute to passive stress-coping in the bereaved male voles, resulting in depressive-like behavior (Bosch et al.,

2009; Bosch et al., 2016). Altogether, these findings indicate that OT plays an important role in both social bonding reinforcement and the pain of social separation.

Beyond the role of OT in reproductive pair-bonds and maternal attachments (Bosch and Neumann, 2012), there is evidence that OT promotes social behavior among humans in both sexes. OT has been shown to promote in-group cooperation and out-group aggression in order to protect oneself and/or vulnerable in-group members (DeDrue et al., 2012). Intranasal OT also improves human memory of faces and the ability to infer the emotions of others based on facial expressions (Rimmele et al., 2009; Domes et al., 2007), potentially by increasing human gaze to eye regions of human faces (Guastella et al., 2007). These social cues and affiliative behaviors could explain the maintenance of social selectivity, friendships, organization of broad social structures, and maintenance of social relationships within individuals and groups (Anacker and Beery, 2013). Intranasal administration of OT has been found to increase interpersonal trust during economic games (Kosfeld et al., 2005), even after experiencing betrayal (Baumgartner et al., 2008). Intranasal OT can also enhance the buffering effects of social support in times of stress, decreasing salivary cortisol levels and reported anxiety (Henrichs et al., 2003). These effects of OT can be attributed to OT modulation of brain function. OT has been shown to strengthen the control of regulatory prefrontal areas over the amygdala, a primary component of fear processing (Adolphs et al., 2005). OT administration can result in reduced amygdala activation and reduced coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear (Kirsch et al., 2005). Amygdala activation has been associated with social fear in social phobia (Stein et al., 2002), anxiety and depression (Pezawas et al., 2005), and social fear during face-processing in autistic patients (Dalton et al., 2005).

Therefore, the effect of OT on amygdala activation and regions mediating the fear response suggests OT as a therapeutic approach to socially relevant fear (Kirsch et al., 2005).

This anxiolytic property of OT may also be moderated by gender. In the largest current sample of plasma OT, males with high levels of OT demonstrated lower trait and attachment anxiety, whereas females demonstrated a positive correlation between plasma OT and anxiety (Weisman et al., 2013). Intranasal OT administration in males enhances trust and cooperation and increases dorsal and ventral striatum activation in response to positive social interactions, suggesting that OT also enhances the reward or saliency of positive social interactions (Baumgartner et al., 2008; Feng et al., 2015).

Considering the buffering effects of social support on mental health and the role of OT in social bonding, current research is exploring the relationship between OT, depression, and suicidality. Mohiyeddini and Opacka-Juffry (2015) found that depression was negatively associated with plasma OT concentrations when patients reported maladaptive rumination, a cognitive avoidance strategy common among patients with post-traumatic stress disorder (PTSD) that can accelerate depressive symptoms through re-activation of distress and social withdrawal (2015). In terms of suicidal ideation, Jokinen et al. found significantly lower levels of cerebrospinal fluid (CSF) and plasma OT in male suicide attempters (2012). Another study reported lower plasma OT levels in patients with major depression (Scantamburlo et al. 2007). Deisenhammer et al. noted a trend of lower basal OT plasma levels in psychiatric patients with a recent suicide attempt relative to patients with no history of suicide attempts (2012). These findings suggest that low levels of OT may mediate depression and/or suicidality and raise the possibility of oxytocin administration as a treatment for depression and suicidal ideation.

OXTR SNPs

Since the OT neuropeptide has been preserved across mammalian species, differences in sociality among species have been attributed to variations in genes encoding OT (Li et al., 2015). More specifically, animal research has suggested that variation in the oxytocin receptor gene (OXTR), located on chromosome 3p25, influences OT functionality by affecting the distribution and expression of OT receptors throughout the brain and body (King et al., 2016).

Emerging research on the social behavioral correlates of polymorphisms of the OXTR gene has implicated a particular single nucleotide polymorphism (SNP) of a guanine (G) to adenine (A) substitution within the third intron (rs53576) in human prosocial behavior. Neurologically, GG homozygotes tend to have larger hypothalamic volumes and greater amygdala activation when viewing emotionally salient social cues, compared to AA homozygotes (Tost et al., 2010). Feng et al. found that intranasal OT administration increased activity in the left ventral caudate nucleus during reciprocated cooperation in the Prisoner's Dilemma Game among men, but decreased activity in women, and this difference was only present in GG individuals (2015). The ventral caudate nucleus receives axonal projections from the mesolimbic DA pathway, which may account for the salience and rewarding effect of cooperative social interactions in male GG homozygotes. A study by Kogan et al. found that individuals homozygous for the GG genotype of rs53576 were judged to be more prosocial (i.e., displaying affiliative, nonverbal cues, such as nodding, gaze duration, smiling, openness of arm posture) than carriers of the A allele (2011). The observers also judged a more pronounced difference in prosociality among GG and AA males relative to females. Another study found that GG and AG individuals exhibited lower cortisol responses to stress in the presence of social support compared to GG and AG individuals who did not receive social support, whereas AA

individuals did not show any significant differences in cortisol and subjective stress responses with or without support (Chen et al., 2011).

Interestingly, while the GG genotype is associated with traits like elevated trust, empathy, and self-esteem (Smith et al., 2014), GG individuals may exhibit greater social sensitivity and vulnerability to adverse effects of negative social stressors relative to AA individuals. A study by McQuaid et al. found that GG individuals undergoing social ostracism in an online game experienced prominent increases in blood pressure and salivary cortisol and decreases in feelings of belonging, control, meaningful existence, and self-esteem relative to AA individuals (2015). These results could be attributed to low baseline levels of optimism, self-esteem, and sense of meaningful existence associated with the AA genotype (McQuaid et al., 2015; Saphire-Bernstein et al., 2011). Carriers of the A allele have previously reported lower feelings of optimism, personal mastery, and self-esteem, and higher levels of depressive symptomatology (Saphire-Bernstein et al., 2011). However, the empathetic and prosocial nature of the GG genotype may result in higher levels of anxiety about social rejection and a need for approval. In a study of patients with depression, Costa et al. found a positive association between patients with the GG genotype and depression, as well as elevated levels of adult separation anxiety and self-reported "need for approval" within their relationships (2009). Among male veterans, however, Sippel et al. found that individuals with insecure attachment styles were at significantly higher risk of PTSD if they had at least one A allele, and that individuals with one or more A alleles would benefit more from post-traumatic interventions through social connectedness and OT-related treatment (2017).

Few other variants in the OXTR had been studies in relation to human behavioral phenotypes and/or psychiatric diseases (Seeley et al., 2018). Among these, another SNP of

interest within OXTR is rs2254298 (9073G>A), with the G allele being associated with high levels of adult separation anxiety, attachment insecurities, and unipolar depression (Chen et al., 2011; Costa et al., 2009). Examining these two SNPs could potentially elucidate the underlying biological mechanisms of prosociality and depression, and even suicidality.

Based on the evidence that depression and suicidality may be related to social isolation and variation in the OXTR gene, this study aims to test the effect of social loss and OT signaling on depression and suicidal ideation in returning war veterans.

Hypotheses

1. Subjects who report feeling closer to their comrades during war will experience higher levels of depression and suicidal ideation post-deployment.
2. Subjects who report missing their comrades more will experience higher levels of depression and suicidal ideation post-deployment.
3. Subjects who spend more time socializing with comrades post-deployment will have lower levels of depression and suicidal ideation post-deployment.
4. Subjects who have been back from deployment longer will have lower levels of depression and suicidal ideation.
5. Subjects scoring lower on the Social Connectedness Scale will have higher levels of depression and suicidal ideation.
6. Subjects scoring lower on the Postdeployment Social Support Scale will have higher levels of depression and suicidal ideation.
7. Subjects with the GG genotype at rs53576 and rs2254298 will report stronger bonds with comrades during war.

8. Subjects with the GG genotype at rs53576 and rs2254298 will report missing their comrades more.
9. Subjects with the GG genotype at rs53576 and rs2254298 will report higher levels of depression.
10. Subjects with the GG genotype at rs53576 and rs2254298 will report higher levels of suicidal ideation.

Methods

Subjects

Male veterans from the Iraq and Afghanistan wars who had returned from war less than 10 years ago were eligible for a screening over the phone (n=73). They were also assessed with the Mini-International Neuropsychiatric Interview, Sixth edition (M.I.N.I. 6.0) administered by a licensed clinical social worker. Veterans with major unstable medical illnesses or major Axis I disorders that might contribute to depression, such as Schizophrenia and Bipolar Disorder, were excluded. Veterans with DSM-5 positive alcohol or substance dependence within the past 6 months were excluded, due to their association with suicidality. The PCL-5, a 20-item self-report scale that assesses the 20 DSM-4 symptoms of PTSD, was used to include veterans with mild to moderate PTSD, while excluding veterans with severe PTSD. Veterans reporting no or low current suicidality were included, while veterans reporting high current suicidality were excluded to avoid exacerbating their condition. Veterans with current and/or past history of Major Depression were also included. Veterans with moderate to severe traumatic brain injury (TBI; loss of consciousness for greater than 1 hour) were excluded, meanwhile veterans with mild TBI (<1 hour loss of consciousness) were included.

Eligible individuals provided questionnaire data for the psychosocial component, as well as biological samples (blood, urine and saliva) for the genetic and hormonal component of the study. Data were collected in a single session in the morning to control for diurnal fluctuation in oxytocin levels. Subjects were instructed to abstain from drug and alcohol use for 24 hours prior to testing.

Psychosocial Questionnaires: Questionnaires were administered at the Laboratory for Darwinian Neuroscience at Emory University. All participants completed the M.I.N.I. 6.0, PCL-5, Beck Depression Inventory (BDI), Columbia-Suicide Severity Risk Scale (C-SSRS) Military Version, Social Connectedness Scale, Postdeployment Social Support Scale (PSSS), and the Pittsburgh Sleep Quality Index (PQSI).

Biological Samples: Biological samples were collected at the Atlanta Clinical and Translational Science Institute Clinical Research Network in Emory University Hospital. Each participant provided blood and urine samples for measurement of OT levels.

Saliva samples for genotyping: Saliva was also collected for genotyping. Each subject provided a saliva sample using Oragene kits (DNA Genotek). DNA was extracted using automated DNA extraction by Omega-Biotek (Omegabiotek.com).

OXTR SNP genotyping: We genotyped using TaqMan assays on the Applied Biosystems 7900 system in 384-well format. This included sequence-specific forward and reverse primers to amplify the polymorphic sequence of interest, and two TaqMan minor groove binder (NGB) probes with nonfluorescent quenchers (NFQ): one VIC^{TM}-labeled probe to detect Allele 1 sequence, and one FAM^{TM}-labeled probe to detect Allele 2 sequence.

Statistical Analysis: All statistical tests were conducted with the statistical package for the social sciences (SPSS). $p<0.05$ was considered statistically significant.

For the first six hypotheses, single-item bivariate correlations were run to determine if there was a correlational relationship between the psychosocial variables and depression. Furthermore, independent samples t-tests were conducted to compare subjects with and without suicidal ideation. Multiple linear regression models were then used to determine the effect of any confounding variables on depression or suicidality.

For the genetics hypothesis (hypotheses 7-10), independent samples t-tests were used to compare psychosocial variables between OXTR genotypes. A Chi-square test was used to determine if the observed genotype frequency in our population of veterans was statistically different from expected values based on frequencies in the general population (National Center for Biotechnology, 2018).

Results

Psychosocial Data

All 73 participants abstained from drug and alcohol use for 24 hours prior to testing as revealed by alcohol test strips. Recruitment and data collection continued following this analysis, and participants will be re-contacted regarding any missing values in the psychosocial questionnaires (Table 1). Sum values for the Social Connectedness score and the Postdeployment support mean score were re-formatted and summed at checkpoints during data collection, with only one checkpoint occurring prior to my analysis (n=59), but all 73 subjects completed the two scales.

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Beck Depression Inventory	73	0	38	13.80	9.43
How close were you with your comrades?	70	2	7	5.91	1.38
How much do you miss your comrades?	70	1	7	5.41	1.51
How often do you socialize with comrades?	68	1	6	3.37	1.37
Years back from deployment	72	.00	13.00	5.64	2.83
Social Connectedness sum score	59	36.00	115.00	73.20	16.53
Post deployment support mean score	59	1.60	4.90	3.60	.90

Table 1. Descriptive statistics of subjects (n=73).

There was not a statistically significant correlation between closeness to comrades during war and depression (r=.14, p=.26) or suicidal ideation post-deployment (t(67)=1.24, p=.22; Supplemental Figures 1 and 2). There was a statistically significant correlation between missing comrades and depression post-deployment (r=.28, p=.02), but not between missing comrades and suicidal ideation (t(67)=-.93, p=.36; Supplemental Figures 3 and 4). There was a trend toward statistical significance between spending more time socializing with comrades post-deployment and depression (r=-.21, p=.09), but not a significant correlation between time spent socializing and suicidal ideation (t(65)=.89, p=.38; Supplemental Figures 5 and 6). There was not a statistically significant correlation between the number of years back from war and depression (r=.03, p=.80) or suicidal ideation (t(69)=.26, p=.80; Supplementary Figures 7 and 8). There was a statistically significant correlation between Social Connectedness Scale scores and depression (r=-0.60, p<0.001) and suicidal ideation (t(57)=3.07, p=0.00; Figures 1 and 2). There was also a statistically

significant correlation between Postdeployment Social Support Scale scores and depression (r=-0.49, p<0.001) and suicidal ideation (t(57)=3.71, p<0.001; Figures 3 and 4).

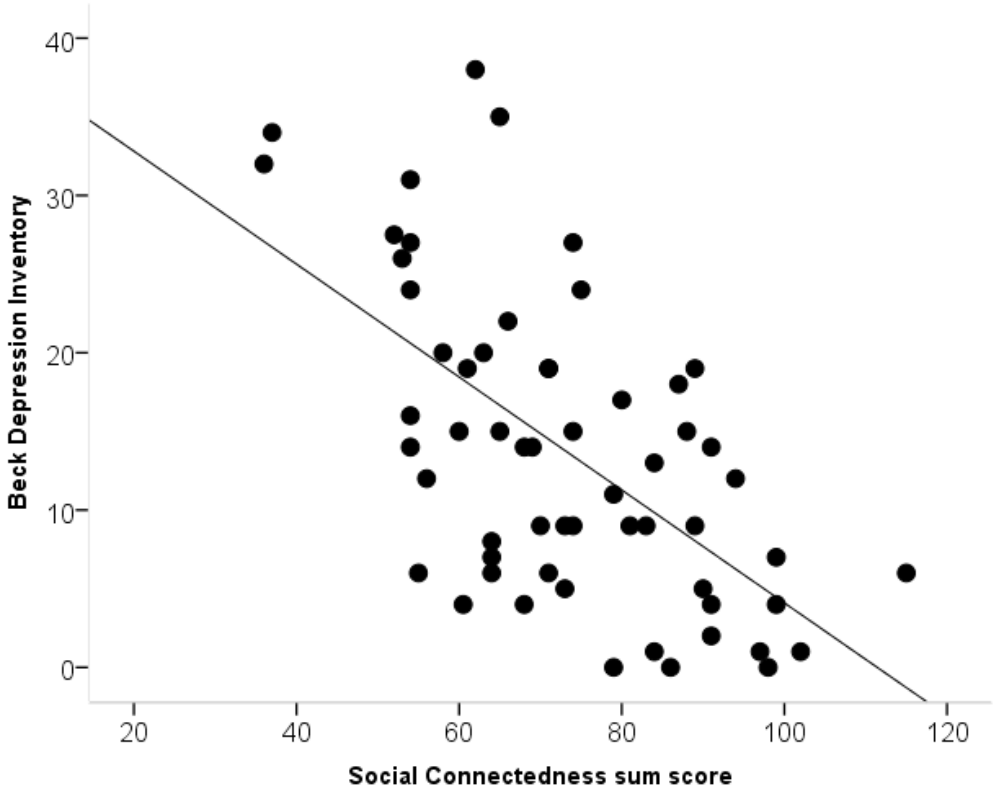

Figure 1. Negative correlation between Social Connectedness sum score and the Beck Depression Inventory.

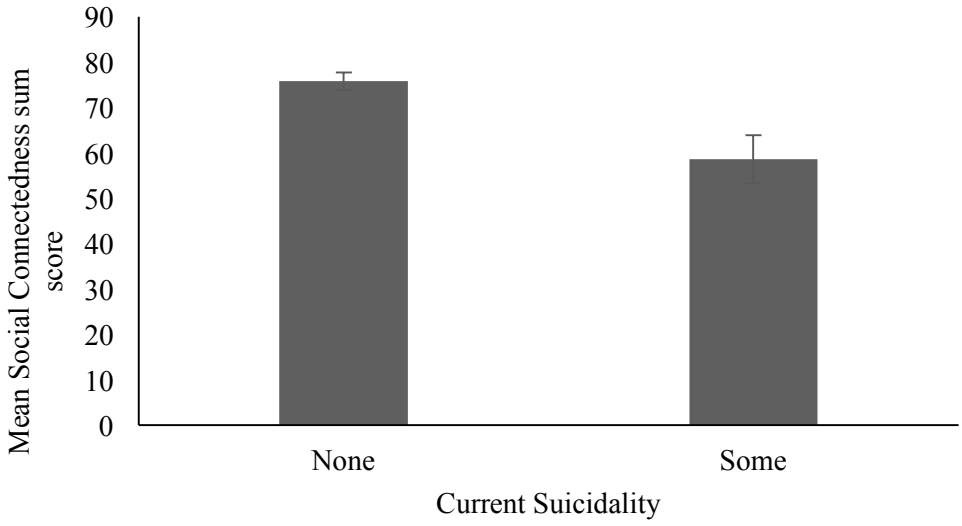

Figure 2. Social Connectedness as a function of current suicidality.

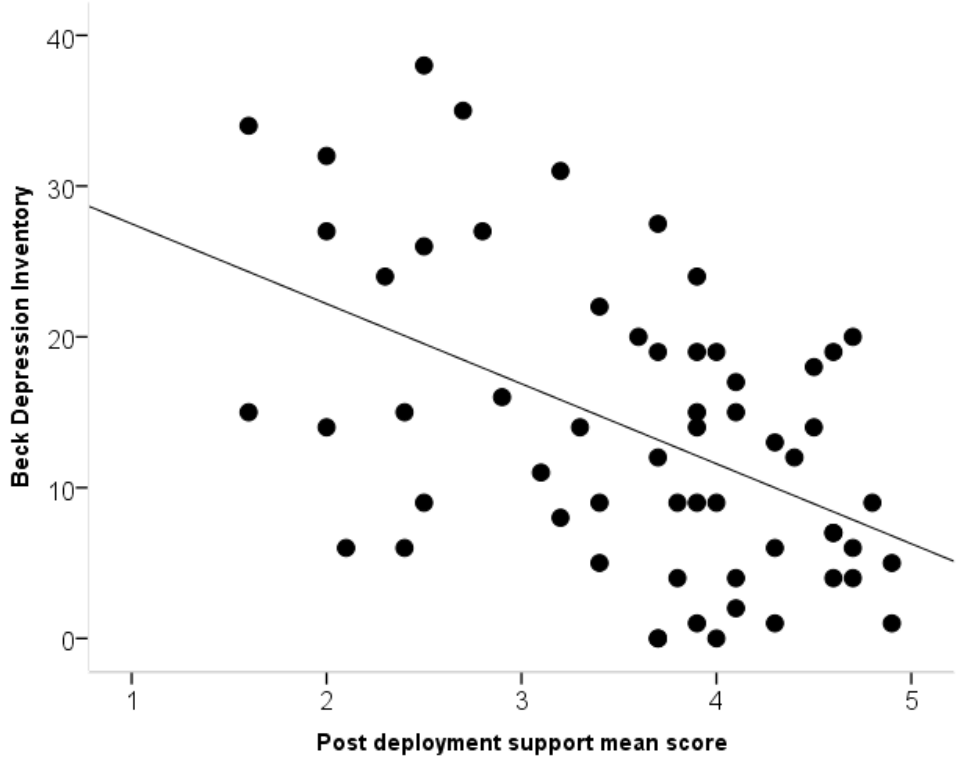

Figure 3. Negative correlation between the Post-deployment support score and the Beck Depression Inventory score.

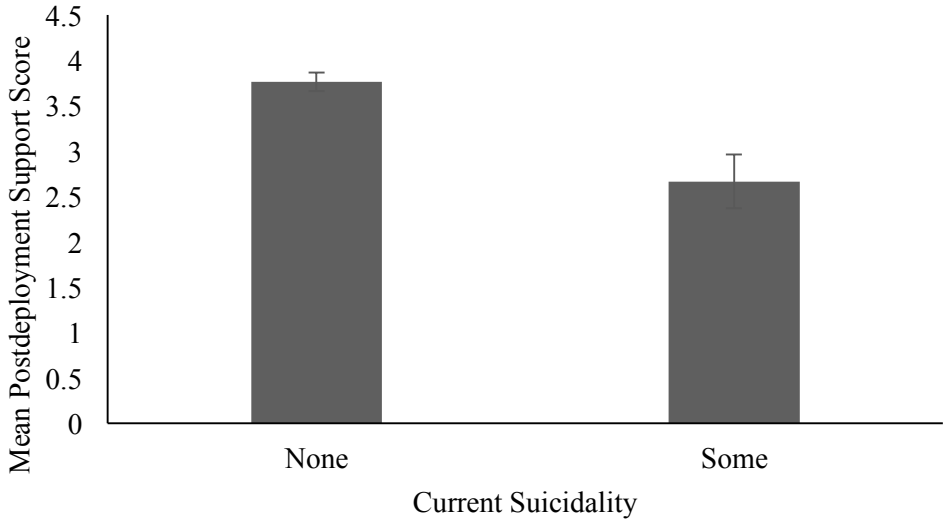

Figure 4. Post-deployment Social Support as a function of current suicidality.

We identified a number of variables that might also be related to depression and suicidality and could therefore confound our observed relationships. These included: PCL-5 score, alcohol use disorder, substance abuse disorder, current generalized anxiety disorder (GAD), sleep quality,

and bipolar disorder. However, in a regression model, current GAD only trends towards significance (p=.059), while the PCL-5 score (p<.01) and sleep quality (p<.01) were significantly correlated with the Beck depression. These variables were then included in multiple linear regression models that evaluated hypotheses 1-4 while controlling for PCL-5 score and sleep quality. The independent variables of hypotheses 1-4 were all non-significant predictors of depression, so how much subjects missed their comrades no longer had a significant association with depression (Supplemental Tables 1-4). However, the Social Connectedness Scale maintained a significant negative correlation with depression, independent of the PCL-5 score and sleep quality rating (p=.002). The Postdeployment Social Support Scale also maintained a significant negative correlation with depression, independent of the PCL-5 score and sleep quality rating (p=.003). In a regression model including the PCL-5 score, sleep quality rating, level of social connectedness, and level of post-deployment social support, the relationship between the Postdeployment Social Support Scale and depression becomes non-significant (p=.52). To create a model that best accounts for Depression, we included a subject's PCL-5 score, sleep quality, and level of social connectedness, accounting for 75% of the variance in the Beck Depression scores (R^2=0.75). With the addition of anti-depressant use (yes, no), this model accounts for 80% of the variance in the Beck Depression scores (R^2=.795; Table 2).

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	11.726	5.133		2.284	.027
	PCL-5 Score (PTSD screening)	.282	.063	.389	4.478	.000
	How would you rate your sleep overall?	4.565	.919	.342	4.965	.000
	Social Connectedness sum score	-.179	.050	-.298	-3.576	.001
	medication	8.660	2.636	.229	3.285	.002
a. Dependent Variable: Beck Depression Inventory						

Table 2. Linear regression model predicting Beck Depression Scores.

The PCL-5 score, current GAD, and bipolar disorder were significantly correlated with suicidal ideation. However, in a regression model, current GAD becomes insignificant (p=.093). When accounting for PCL-5 score and bipolar disorder, the independent variables of hypothesis 1-4 demonstrated a non-significant relationship with suicidal ideation (Supplemental Tables 7-10). The Social Connectedness Scale became a non-significant predictor of suicidal ideation (p=.195, Supplemental Table 11), but Postdeployment Social Support maintained a significant relationship with suicidal ideation (p=.019, Supplemental Table 12). The model best accounting for suicidal ideation included bipolar disorder and level of postdeployment social support, accounting for 37% of variance in the reports of suicidal ideation (R^2=.371; Table 3).

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.648	.162		3.997	.000
	Bipolar d/o	.505	.127	.425	3.963	.000
	Post deployment support mean score	-.152	.043	-.378	-3.525	.001

Table 3. Linear regression model predicting current suicidal ideation.

Genetic Data

Out of 73 subjects, 54 have been genotyped thus far. For the rs53576 gene, 57.7% of the sample was GG, 36.5% was AG, and 5.8% was AA. This distribution was significantly different from a genomic database of 18,468 individuals of European descent that reported 41.5% GG, 45.8% AG and 12.7% AA, X^2 (2, N=52)=6.21, p=0.045 (Figure 5). For the rs2254298 gene, 78.8% of the sample was GG, 19.2% was AG, and 1.9% was AA. This distribution did not significantly differ from a genomic database of 18,484 individuals of European descent that reported 81.7% GG, 18.2% AG, and 0.92% AA, X^2 (2, N=52)=.652, p=.722 (Figure 6).

None of the independent variables of interest in hypotheses 7-10 (how close they were with their comrades during war, how much subjects report missing their comrades, the levels of depression, and the levels of suicidal ideation) differed between GG and AG/AA genotypes for both rs53576 and rs2254298 (Supplementary Figures 9-16). After adding race to the model as covariate, race shows not to be a significant confounding factor in the depression (p=.55) or suicidal ideation (p=.34) model.

Supplementary Figures 17-28 demonstrate the varying distributions of the Beck depression scores in the GG versus AG/AA genotypes for both rs53576 and rs2254298 as a function of the psychosocial independent variables in hypotheses 1-4.

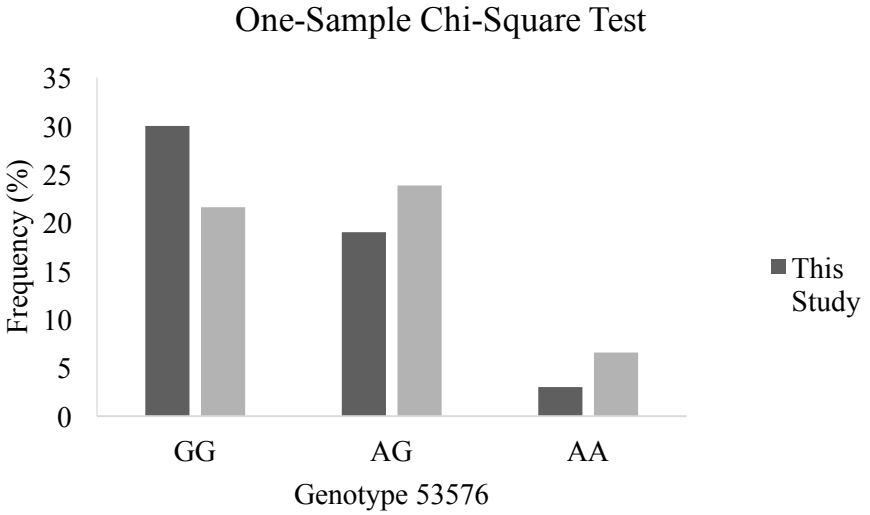

Figure 5. Differences in genotypic frequencies of the rs53576 gene in study population versus European database (p=0.045).

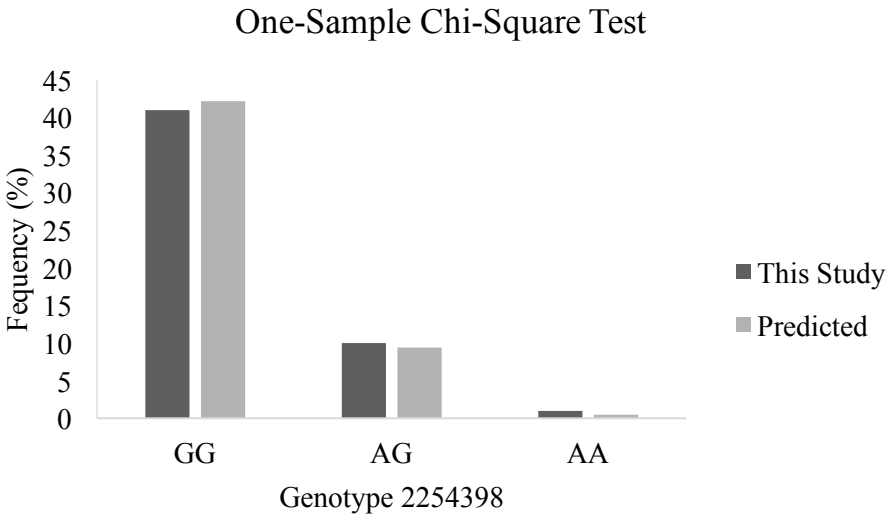

Figure 6. Differences in genotypic frequencies of the rs2254298 gene in study population versus European database (p=0.72).

Discussion

There is and has been a disproportionately high rate of suicide among veterans relative to the civilian population, with a lack of consensus on a specific reason for this epidemic (Department of Veterans Affairs, 2016). Considering the fact that research has suggested that lack of social connectedness and emotional support negatively impacts mental health, in this

study we examine the effects of social loss and oxytocin signaling on depression and suicidal ideation in returning war veterans.

Psychosocial Analysis

We found that veterans reporting lower scores on the Social Connectedness Scale and lower scores on the Postdeployment Social Support Scale scored higher on the Beck Depression Inventory. These findings suggest that veterans who feel less socially connected with and socially supported post-deployment are more likely to experience depression. In a study assessing social connectedness among 301 veterans with major depression, loneliness was found to have the strongest association with depression severity and suicidality (Teo et al., 2018). This is consistent with another study that found that social support was a protective factor against loneliness, stress, and high-risk behaviors and avoidance-coping, which has shown to exacerbate depression (Pietrzak et al., 2009). The causality between loneliness and depression is unclear, but it is hypothesized that loneliness contributes to the development of depression and depression also increases loneliness in a mutually reinforcing relationship (Cacioppo et al., 2006). In a survey of 2,025 veterans aged 60 years and older, 44% of veterans reported feeling lonely at least some of the time, which can affect several health and psychosocial variables (Kuwert et al., 2014). For example, loneliness may be positively associated with depression, cognitive dysfunction, and greater medical burden, and negatively associated with greater social support, optimism, resilience, and religiosity (Kuwert et al., 2014). Kuwert et al. (2014) found that loneliness has a positive association with greater age, disability in daily activities, and current depressive and PTSD symptoms. Kuwert et al. (2014) also found that loneliness was negatively associated with social support, greater subjective cognitive functioning, secure attachments, cohabitation, and marriage. Among non-veterans, loneliness is associated with functional decline

and increased risk of death in individuals older than 60 years (Perissinotto et al., 2012). While geriatricians are attentive to loneliness, the condition is not well recognized in young adults. It would be beneficial to spread awareness of loneliness among primary care physicians and the Veterans Health Administration, as chronic loneliness can be present among individuals of any age and affects 10-30% of the population (Teo et al., 2018). This is of great importance considering that the greatest increase in the military suicide rate has been among 18-to-34-year-old veterans (Department of Veterans Affairs, 2016).

A possible explanation for self-reported deficits in social connectedness and support in the veterans of the wars in Afghanistan and Iraq may be due to their return to a civilian community that lacks direct experience with the military. According to Castro and Kintzle, veterans under the age of 35 compose only 12% of the U.S. male population; the majority of the American population has not served in the Afghanistan or Iraq wars (2014). In comparison, about 50% of the U.S. male population under the age of 35 were World War II veterans (Castro and Kintzle, 2014). Therefore, the modern veteran may enter a community lacking a shared military cultural identity in contrast to older generations of veterans. In addition, serving the military during wartime may warrant feelings of accomplishment and entitlement among veterans that may not be understood or reciprocated by civilians (Castro and Kintzle, 2014). According to the aforementioned military transition theory, the lack of a shared military cultural identity, along with a sense of unacknowledged entitlement, might interfere with forming meaningful social connections and networks with civilians.

In addition to feelings of low social connectedness and low post-deployment social support, poor sleep quality and PTSD symptoms were significant predictors of depression in our study. Interestingly, poor sleep quality was significantly correlated with PTSD ($r=.36$, $p=.003$),

but PTSD maintained an effect on depression independent of poor sleep quality and vice versa. While our study demonstrates a relationship between PTSD and sleep disturbances, the causal relationships between depression, PTSD, and sleep is unclear. Sleep abnormalities are commonly linked with depression. In a meta-analysis of 48,934 participants, both short and long sleep duration was significantly associated with increased risk of depression in adults (Zhai et al., 2015). Increased rapid-eye movement sleep (REM) has also been implicated in depressed patients (Riemann et al., 2001). Sleep disturbances seem to be a core feature of PTSD, and manifest through intrusive flashbacks and nightmares, avoidance symptoms, and hyperarousal symptoms (i.e. insomnia) (Spoormaker and Montgomery, 2008). In general, PTSD patients also experience more REM sleep (Kobayashi et al., 2007), and during REM sleep the prefrontal cortex exerts less control over the amygdala and its fear-related information processing, resulting in nightmares (Hobson et al., 1998). Insomnia has been shown to precede and contribute to the development of psychological problems like depression and PTSD among veterans (Wright et al., 2011). However, while PTSD patients commonly seek treatment for their night-time complaints, a common cognitive therapy model for PTSD does not include more efficient sleep strategies (Ehlers et al., 2005), and insomnia tends to remain a residual symptom following PTSD treatment (Spoormaker and Montgomery, 2008; Zayfert and DeViva, 2005). According to Spoormaker and Montgomery, 40% to 50% of PTSD patients experience insomnia and over 90% of patients seeking help for post-traumatic sleep disturbances experienced sleep-disordered breathing (2011). Yet, in a meta-analysis of 38 randomized controlled trials of varying psychological treatments for PTSD, only six acknowledged the effects of PTSD treatment on sleep, and only one accounted for the subjective measures of nightmares and insomnia (Bisson et

al., 2007). Perhaps by initially screening patients for sleep-disorders, clinicians can identify a front-line treatment more efficiently.

Veterans who reported lower levels of social-connectedness and lower levels of post-deployment social support also exhibited higher levels of suicidal ideation. These results are expected based on previous research examining greater social connectedness as a protective factor against suicidal ideation (Pietrzak et al., 2010; Smith et al., 2016). The military transition theory further predicts that a loss of shared military identity and difficulty developing a new civilian social support system can contribute to feelings of alienation and increased risk of suicide (Reger et al., 2015; Castro and Kintzle, 2014). In fact, veterans who are married and veterans who report greater satisfaction with social networks tend to report less suicidal ideation and behaviors suggestive of elevated suicide risk (Jakupcak et al., 2010; Lemaire and Graham, 2010). The association between occupational stress and suicidal ideation was also mitigated by social support in a survey of professional firefighters (Carpenter et al., 2015).

Our results show an inverse relationship between depression and social connectedness, and between PTSD and social connectedness ($r=-.581$, $p<.001$). These results are concerning because the co-occurrence of both PTSD and depression, along with feelings of low post-deployment social support, has been positively associated with suicidal ideation (DeBeer et al., 2014). However, the causal relationships between PTSD, social networks, and mental health is still unclear. It has been shown that PTSD moderates the relationship between social support and suicide risk in Iraq and Afghanistan war veterans seeking mental health treatment, diminishing the protective effect of social connectedness (Jakupcak et al., 2010). However, in a more recent study, social connectedness was found to directly protect against the severity of PTSD symptoms, serving as a better predictor for PTSD than combat experiences and non-honorable

discharge status (Kintzle et al., 2018). While a linear regression model did not reveal a significant interaction between social connectedness and PTSD on suicidal ideation in our study, it is still important to note the significant relationships between social connectedness, PTSD, and depression and their role in suicidal ideation.

In addition to a lower levels of post-deployment social support, a diagnosis of bipolar disorder (BD) on the MINI was shown to contribute to suicidal ideation. BD is commonly associated with suicidal ideation or attempt, with a rate of suicide of untreated bipolar patients 20-30 times higher than the general population, and over 30% of bipolar patients having attempted suicide (Berkol et al., 2016; Novick et al., 2015). This could be attributed to impulsivity and aggression in patients with BD resulting from abnormalities in the anterior white matter tracts that project to the frontal lobes to mediate emotional regulation (Reich et al., 2019). While depression and preceding suicidal behavior have been shown to predict suicidal risk, a diagnosis of bipolar disorder can further increase the probability of suicide in veterans and is a significant factor to consider (Valtonen et al., 2005).

From 2001 to 2015, only 62% of veterans have used VA health care services (U.S. Department of Veterans Affairs, 2017). Thus, mental illness may go undiagnosed in many veterans. Yet, veterans continue to operate in the military or transition into civilian society. The Occupational Mental Health Model in a military context describes this phenomenon as "functioning while suffering" (Adler and Castro, 2013). Besides the Department of Veterans Affairs, the GI bill, and other state, federal, and local organizations aiming to assist veterans in meeting basic needs, there are currently minimal efforts that seek to assist veterans in feeling a sense of belonging and recognition in their community (Castro and Kintzle, 2014). While our study did not demonstrate a significant relationship between chronic pain and depression or

suicidal ideation, chronic pain has been shown to contribute to feelings of perceived burdensomness and suicidal ideation (Wilson et al., 2017). These deficits in mental and physical well-being may altogether contribute to feelings of perceived burdensomness and hinder development of meaningful relationships and social connectedness. Ultimately, these variables may further exacerbate psychological and physiological distress. Buddy-to-Buddy, a soldier peer support program that aims to counteract stigma, PTSD, depression, and suicide has been found to recognize unmet clinical needs, increase referrals for assistance with veteran benefits, job-placement services, financial assistance, and legal help through regular interaction and advising with a Buddy (Greden et al., 2010). Programs like this need increased dissemination in order to alleviate loneliness and perceived burdensomness among veterans and enhance feelings of self-efficacy when reintegrating into civilian society.

It is worth examining generalized anxiety disorder (GAD) as a contributor to both depression and suicidal ideation as it demonstrated a trend towards significance in both correlational analyses. GAD is one of the most common mental disorders, and while GAD and depression symptoms frequently co-occur, they have distinct and independent effects on functional impairment and disability (Spitzer et al., 2006). Both GAD and subthreshold GAD, which can be characterized by meeting some, but not all, of the diagnostic criteria required for GAD, affect similar percentages of a study of 24,785 people (2.6% for GAD and 2.3% for subthreshold GAD) (Gilmour, 2016). Both GAD and subthreshold GAD also demonstrate a significant association with suicidal ideation (Gilmour, 2016). While GAD affects approximately 3% of the U.S. population (Anxiety and Depression Association of America, 2018), up to 12% of a population of 884 veterans met diagnostic criteria for GAD, reporting significantly worse emotional and physical wellbeing and pain (Milanak et al., 2013). In a study of 486 treatment-

seeking veterans, the second most common comorbidity was GAD (52.3%), following PTSD and major depressive disorder (MDD) (61.5%) (Richardson et al., 2017). Many current antidepressants are effective in treating both MDD and GAD in order to reduce suicidal ideation and behavior in adults (Thase et al., 2017).

Genetic Analysis

Based on the literature on the OXTR SNPs rs53576 and rs2254298, we hypothesized a significant relationship between the GG genotypes and prosociality through reports of stronger bonds with comrades during war and missing their comrades more. We also predicted that the GG genotype would be associated with higher levels of depression and suicidal ideation in veterans who have returned home from war and have been separated from their comrades. However, our genetic analysis did not reveal a significant relationship between genotype and prosociality, or between genotype and depression or suicidal ideation. Similarly, a meta-analysis of 2,177 people by Li et al. found no evidence of an association between the rs53576 polymorphism and depression (2015). However, the meta-analysis found a variety of evidence linking polymorphisms in both rs53576 and rs2254298 to general sociality (Li et al., 2015), so our results might reveal more significant relationships if the sample size were larger.

Since the majority of individuals self-identified their race as “White,” we compared our study population’s genotype frequencies to a genetic database of individuals of European descent. Interestingly, our study population demonstrated significantly different proportions of the rs53576 genotypes, with 57.7% of individuals with the GG genotype compared to the expected value of 41.5% (National Center for Biotechnology, 2018). Our results also indicate 36.5% of individuals express the AG genotype relative to the expected value of 45.8% (National Center for Biotechnology, 2018). Finally, 5.8% of individuals possess the AA genotype relative

to the expected value of 12.7% (National Center for Biotechnology, 2018). It is important to note that when we compared only the population of our "White" military subjects to a European population, the proportions were not significantly different, X^2 (2, N=38) =1.466, p=.481, Supplemental Figure 29). The other demographics genotyped in this study included nine subjects who identified as "Black," two subjects who identified as "Hispanic," and one subject who identified as "Asian." There were not enough subjects in these demographics to conduct chi-square analyses with their respective genomic databases. However, it is interesting to note that all nine subjects who identified as "Black" had the rs53576 GG genotype, which reflects the higher proportion of GG individuals (60.0%) in an African American population (National Center for Biotechnology, 2018). This could explain the higher proportion of GG individuals overall in our study's population (Figure 5), and why the genomic proportions are not significantly different when comparing only "White" subjects to a European population (Supplemental Figure 29). Genotyping the remainder of our population when recruitment concludes will further reveal the role of race in genotypic frequency, as well as the contribution of race to depression and suicidal ideation.

The higher number of GG participants in our sample population is not surprising in the context of our study's aims. The GG genotype is associated with both increased self-reported empathic concern and parochial altruism (Huetter et al., 2016; Dreu et al., 2010). It is possible that individuals with the GG genotype were more likely to find and enroll into this study, even if certain participants did not report any behavioral deficits, in order to help other veterans who struggle with depression or suicidal thoughts. It is also possible that enrolling into the military is a self-selection process and recruits a higher rate of GG individuals. And while the GG genotype is associated with traits like elevated trust, empathy, and self-esteem, they may also be more

aversive to social stressors like low levels of social connectedness or post-deployment social support (Smith et al., 2014). This may contribute to the intrinsic motivation to enroll into this study and take personal time off from their jobs to travel to our lab from out-of-state locations that may exceed the time it takes to actually complete the study. Some subjects were also not aware of the compensation for the study, and would spread awareness about the study even if they were not eligible themselves.

Limitations

While a feeling of low levels of social connectedness seems to predict depression among subjects, a feeling of low post-deployment social support seems to predict the presence of suicidal ideation. This could partially be explained by the nature of the scales. The Social Connectedness Scale (SCS) assesses the degree of social connectedness an individual feels in their social environment. The SCS reflects feelings ranging from comfortableness around strangers, to being in tune with the world, to seeing people as friendly and approachable, and fitting in well in new situations. The SCS seems to span a larger breadth in its measurements (i.e., a broad scale covering "people," "strangers," and "society"), and could account for general feelings of social isolation, consequently contributing to feelings of depression. Meanwhile, the PDSS assesses emotional and instrumental support veterans feel from three distinct constructs: support from friends, support from family, and support from society. The PDSS accounts for a sense of belonging in American society, positive self-regard following service, the extent to which an individual receives material or financial aid from friends and family, etc. This scale demonstrates strong internal consistency reliability and face validity (Vogt et al., 2013). Our results may suggest factors that contribute to more extreme feelings of suicidal ideation in veterans.

Another factor to consider in the future is which branch of military participants identified with, the nature of their discharge, and mental health conditions prior to military enrollment. This would provide more information in the context of military transition theory and suicidal ideation (Castro and Kintzle, 2014; Reger et al., 2015) and the severity of PTSD symptoms and other mental health disorders (Kintzle et al., 2018; Kessler et al. 2014), serving as better predictors for depression and suicidal ideation.

The 11% of our population of veterans were informally diagnosed with bipolar disorder using the M.I.N.I. 6.0. It would be beneficial to refine our methods of diagnosing bipolar disorder in participants, and to compare the incidence of formally diagnosed bipolar disorder in our sample with that of the general population.

Previous research that has found significant differences between genotypes examined sample sizes ranging from 116 to over 2,100 subjects (Kogan et al., 2011; Sippel et al., 2017). For our study, recruiting a greater number of participants is needed to more fairly evaluate the genetic hypotheses.

Conclusion

A variety of factors can contribute to feelings of depression and suicidal ideation in returning war veterans, and this study identifies certain risk factors that caretakers, physicians, family, and friends can recognize and prevent. Enabling veterans to both form meaningful connections within their social networks and providing them with post-deployment social support from their non-veteran peers are two critical ways to mitigate feelings of isolation and loneliness. In addition, this study identifies that PTSD and poor sleep quality contribute to feelings of depression, and a diagnosis of bipolar disease contributes to suicidal ideation. However, further research is necessary to determine the contribution of each risk factor to

depression and suicidal ideation in order to prioritize varying treatments. It is also necessary to standardize the diagnoses of bipolar disorder among participants, and to further clarify the branch of military each participant served during service. Altogether, these findings may enable researchers to identify and implement preventative measures that are both clinical and non-clinical to treat feelings of social isolation. Such measures may include increased development of supportive social networks for veterans, prioritization of behavioral deficits and mental illnesses during primary-care visits, and oxytocin administration.

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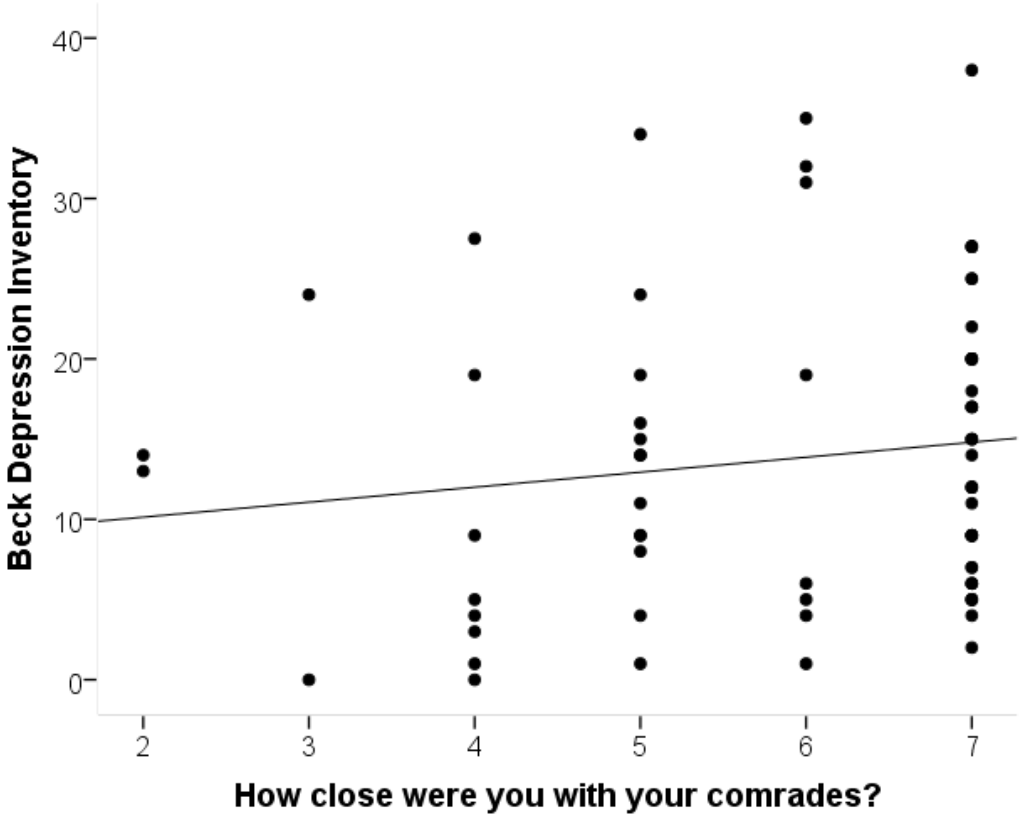
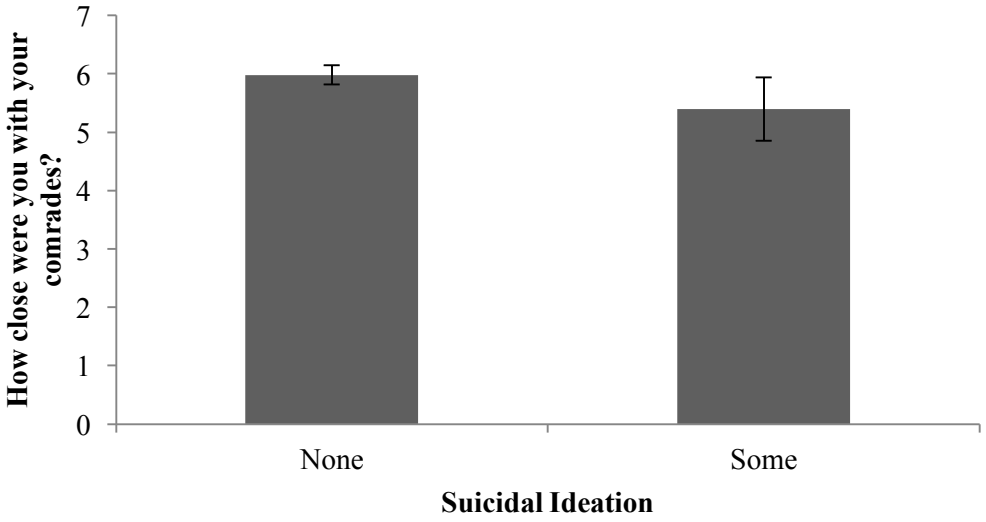
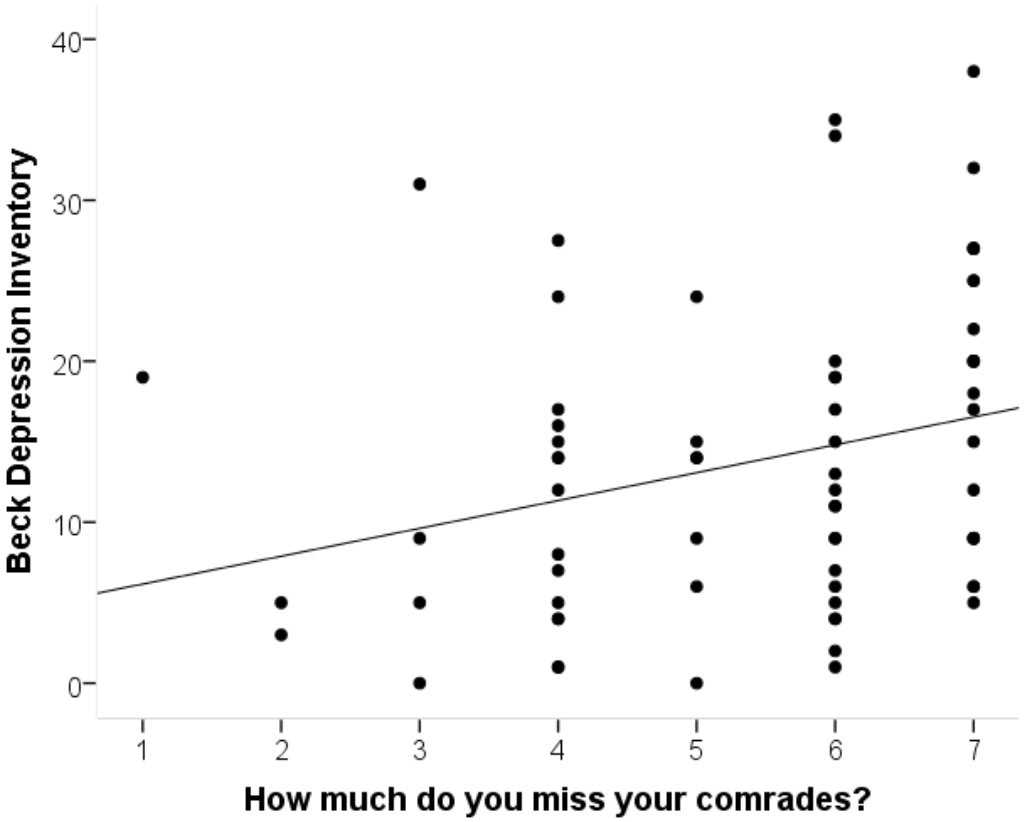
Supplemental Materials



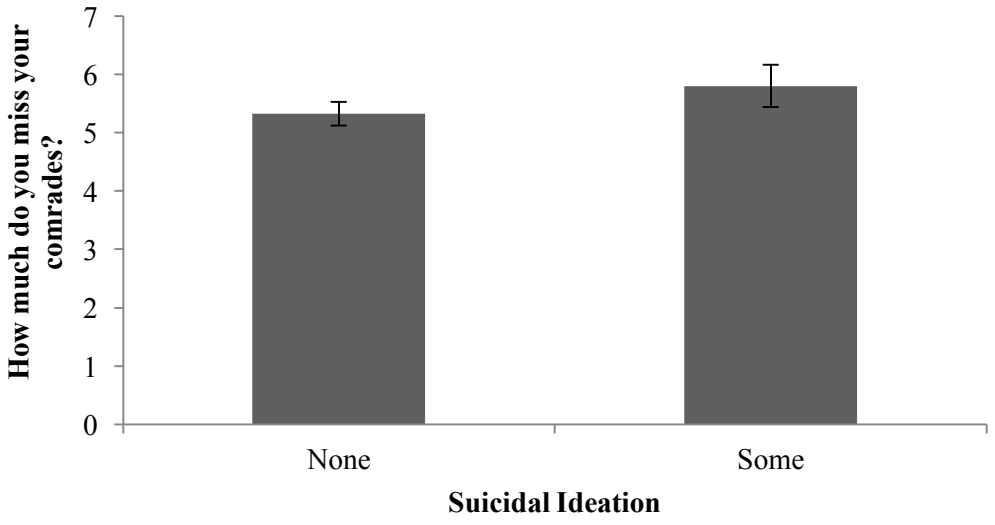
Supplemental Figure 1. Relationship between how close subjects were with their comrades and the Beck Depression Inventory score (r=.14, p=.26).



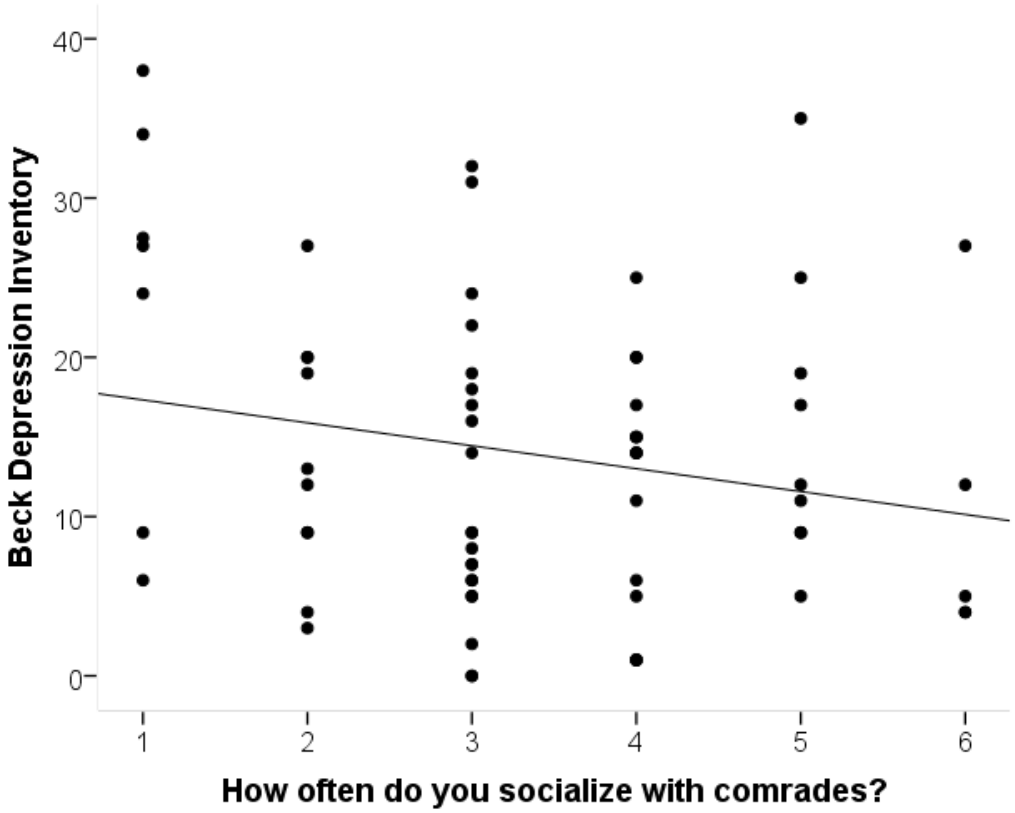
Supplemental Figure 2. How close subjects were with comrades as a function of current suicidality (t(67)=1.24, p=.22).



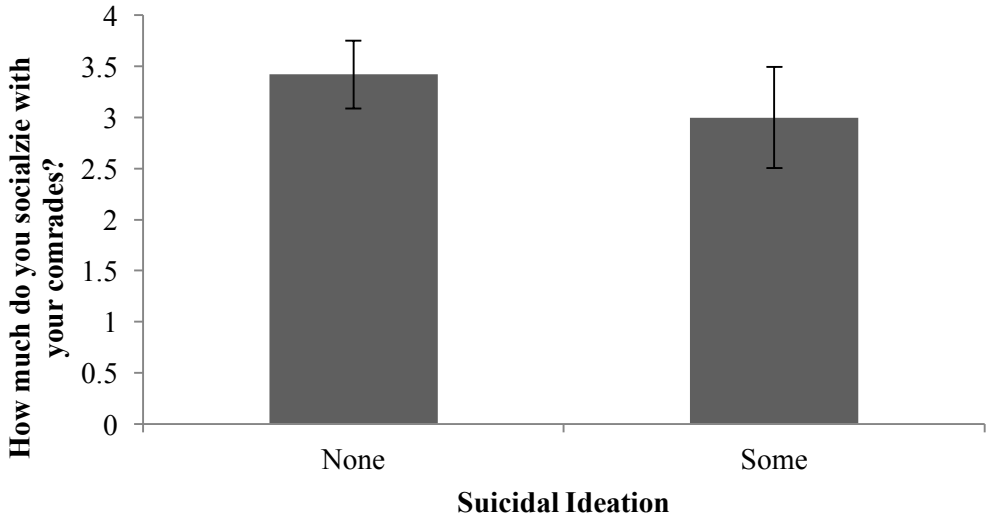
Supplemental Figure 3. Positive correlation between how much subjects reported missing their comrades and Beck Depression scores (r=.28, p=.02).



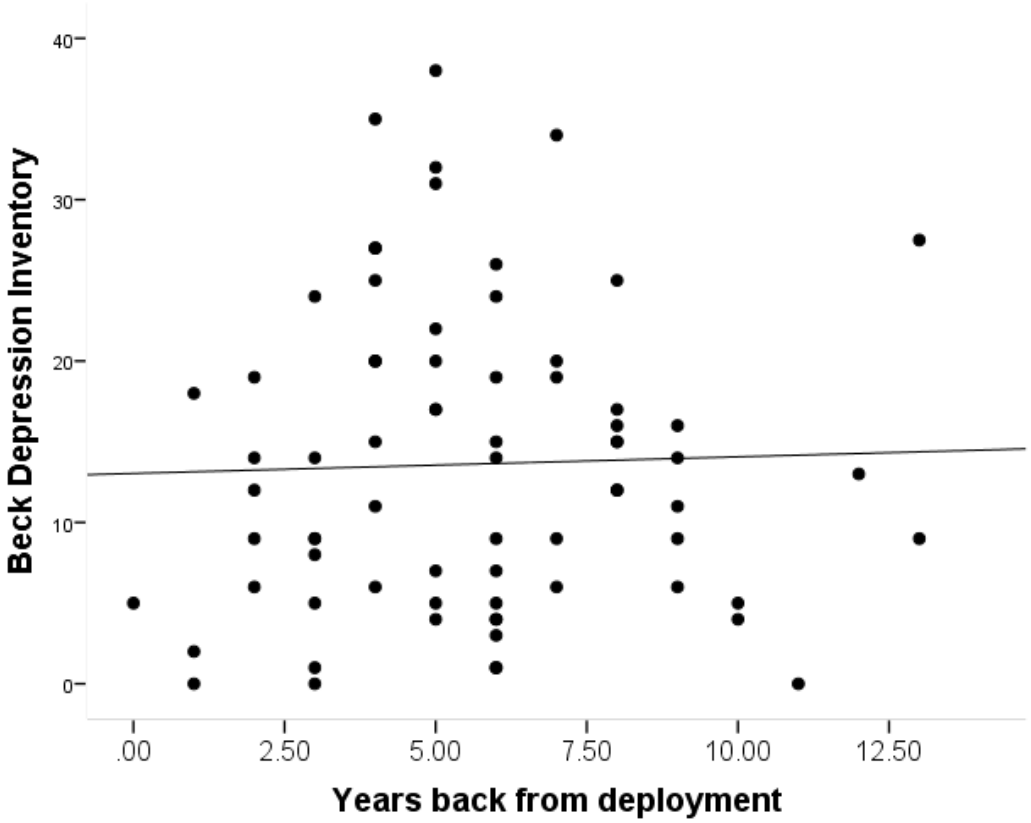
Supplemental Figure 4. How much subjects miss their comrades as a function of current suicidality (t(67)=-.93, p=.36).



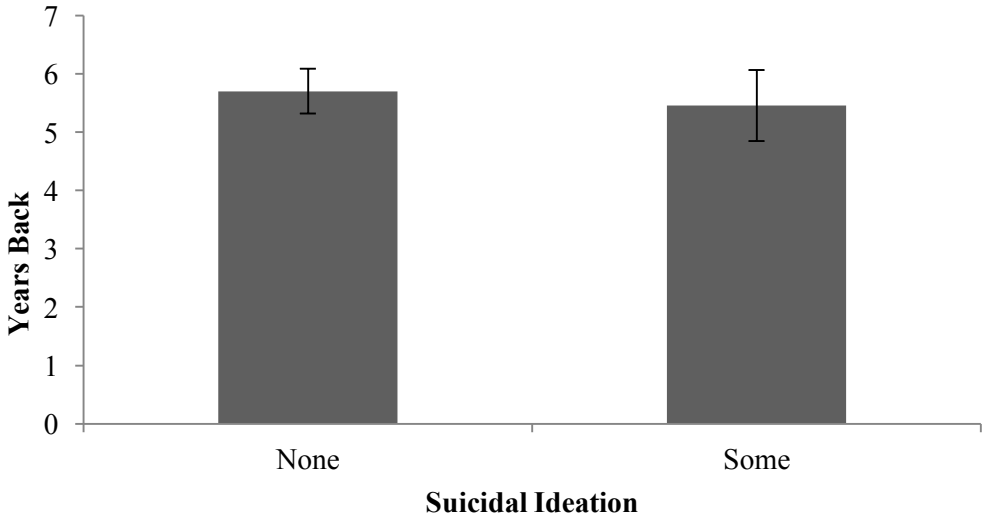
Supplemental Figure 5. Relationship between how often subjects socialize with their comrades post-deployment and Beck depression scores (r=-.21, p=.09).



Supplemental Figure 6. How often subjects socialize with comrades as a function of current suicidality (t(65)=.89, p=.38).



Supplementary Figure 7. Relationship between number of years back from deployment and Beck depression scores (r=.03, p=.80).



Supplemental Figure 8. How long veterans have been back from war as a function of current suicidality (t(69)=.26, p=.80).

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-2.829	3.611		-.784	.436
	PCL-5 Score (PTSD screening)	.398	.059	.594	6.784	.000
	How would you rate your sleep overall?	3.678	.997	.326	3.690	.000
	How close were you with your comrades?	.208	.573	.030	.363	.718

Supplemental Table 1. Linear regression model predicting Beck depression scores.

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-2.316	2.928		-.791	.432
	PCL-5 Score (PTSD screening)	.394	.061	.589	6.471	.000
	How would you rate your sleep overall?	3.682	1.002	.326	3.673	.001
	How much do you miss your comrades?	.149	.553	.024	.269	.789

Supplemental Table 2. Linear regression model predicting Beck depression scores.

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.125	2.928		.043	.966
	PCL-5 Score (PTSD screening)	.389	.060	.580	6.464	.000
	How would you rate your sleep overall?	3.797	.990	.336	3.835	.000
	How often do you socialize with comrades?	-.489	.593	-.069	-.824	.413

Supplemental Table 3. Linear regression model predicting Beck depression scores.

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-3.088	2.486		-1.242	.219
	PCL-5 Score (PTSD screening)	.390	.060	.566	6.506	.000
	How would you rate your sleep overall?	4.095	.977	.367	4.192	.000
	Years back from deployment	.172	.278	.051	.617	.539

Supplemental Table 4. Linear regression model predicting Beck depression scores.

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	10.611	5.610		1.891	.064
	PCL-5 Score (PTSD screening)	.340	.066	.470	5.145	.000
	How would you rate your sleep overall?	4.647	1.007	.348	4.616	.000
	Social Connectedness sum score	-.177	.055	-.295	-3.234	.002

Supplemental Table 5. Linear regression model predicting Beck depression scores.

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	2.625	4.520		.581	.564
	PCL-5 Score (PTSD screening)	.396	.064	.548	6.177	.000
	How would you rate your sleep overall?	5.209	1.046	.390	4.979	.000
	Post deployment support mean score	-2.102	.939	-.191	-2.239	.030

Supplemental Table 6. Linear regression model predicting Beck depression scores.

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-.023	.206		-.114	.909
	PCL-5 Score (PTSD screening)	.010	.003	.329	3.059	.003
	Bipolar d/o	.461	.141	.355	3.279	.002
	How close were you with your comrades?	-.018	.033	-.060	-.547	.586

Supplemental Table 7. Linear regression model predicting suicidal ideation.

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-.154	.166		-.927	.357
	PCL-5 Score (PTSD screening)	.009	.003	.311	2.748	.008
	Bipolar d/o	.474	.138	.365	3.422	.001
	How much do you miss your comrades?	.007	.031	.025	.217	.829

Supplemental Table 8. Linear regression model predicting suicidal ideation.

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-.132	.159		-.829	.410
	PCL-5 Score (PTSD screening)	.009	.003	.302	2.752	.008
	Bipolar d/o	.542	.148	.394	3.667	.001
	How often do you socialize with comrades?	.007	.033	.022	.201	.842

Supplemental Table 9. Linear regression model predicting suicidal ideation.

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-.084	.123		-.680	.499
	PCL-5 Score (PTSD screening)	.011	.003	.347	3.288	.002
	Bipolar d/o	.445	.141	.333	3.158	.002
	Years back from deployment	-.009	.016	-.063	-.597	.553

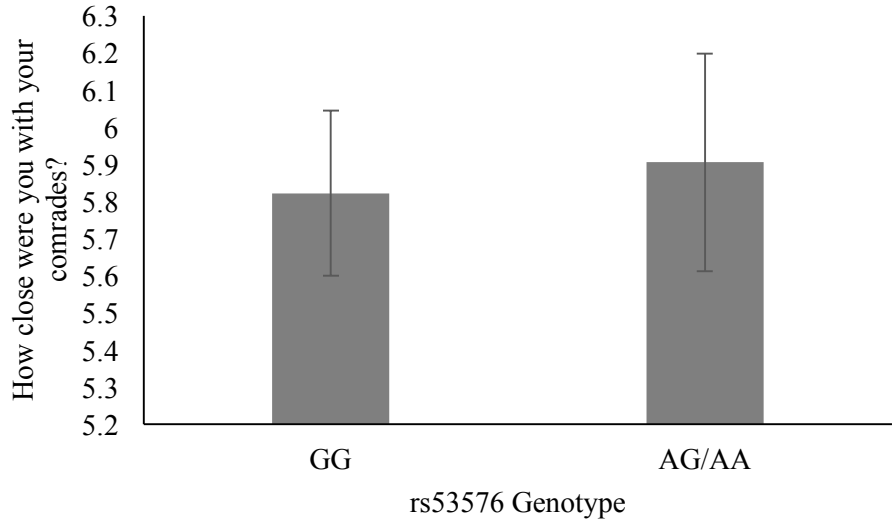
Supplemental Table 10. Linear regression model predicting suicidal ideation.

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.215	.278		.773	.443
	PCL-5 Score (PTSD screening)	.006	.004	.242	1.833	.072
	Bipolar d/o	.504	.129	.423	3.893	.000
	Social Connectedness sum score	-.004	.003	-.174	-1.312	.195

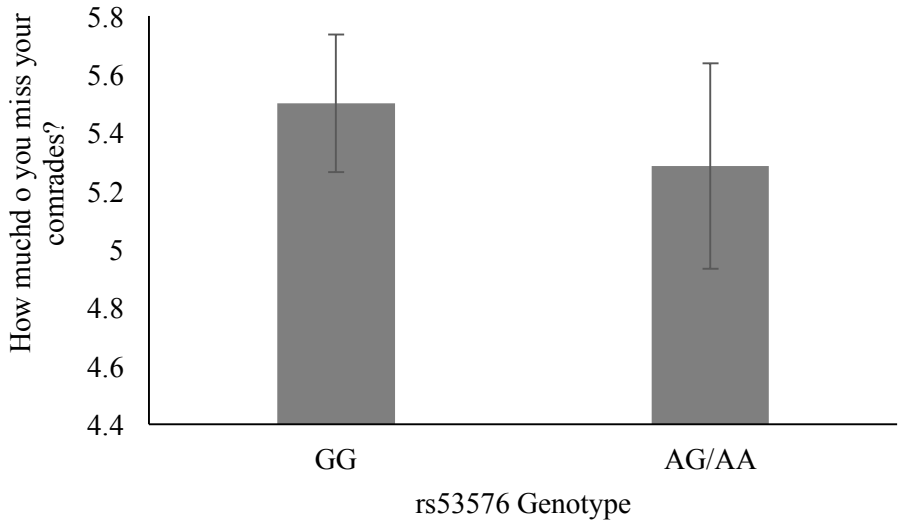
Supplemental Table 11. Linear regression model predicting suicidal ideation.

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.362	.221		1.638	.107
	PCL-5 Score (PTSD screening)	.006	.003	.217	1.860	.068
	Bipolar d/o	.488	.125	.410	3.898	.000
	Post deployment support mean score	-.113	.047	-.282	-2.406	.019

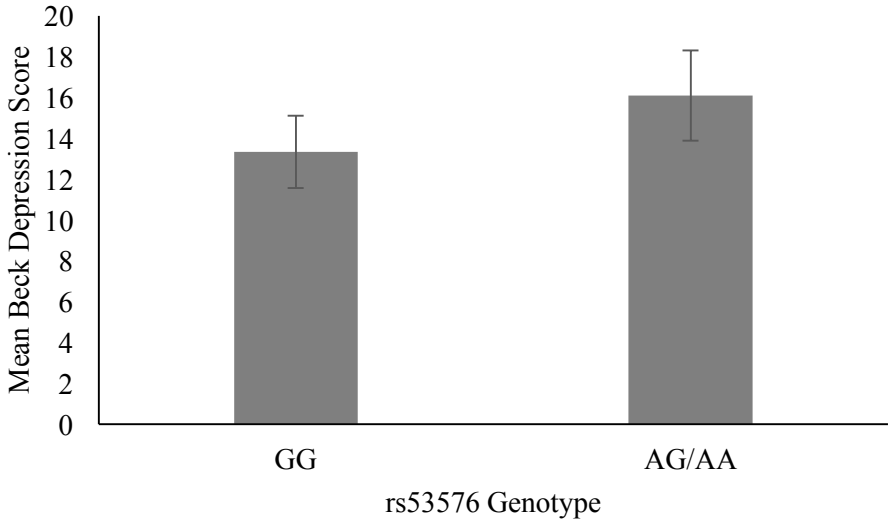
Supplemental Table 12. Linear regression model predicting suicidal ideation.



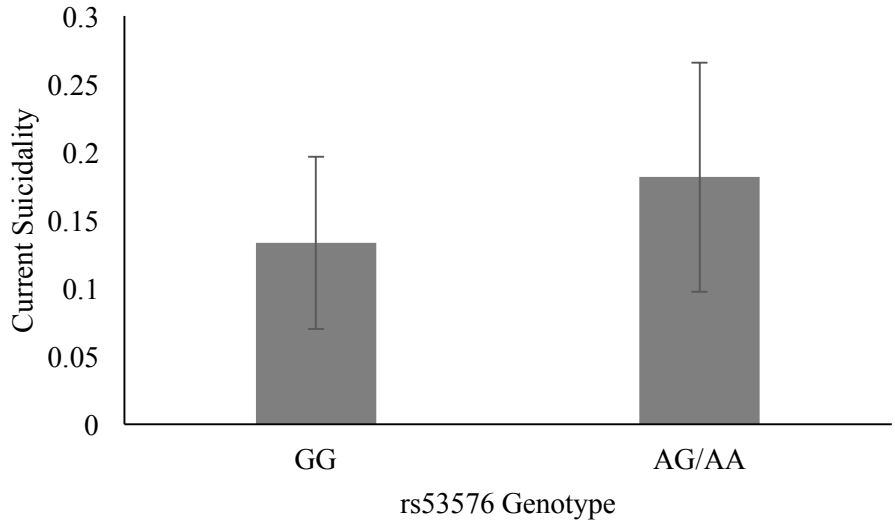
Supplemental Figure 9. How close subjects were with comrades as a function of genotype rs53576 (t(47)=-.224, p=.824).



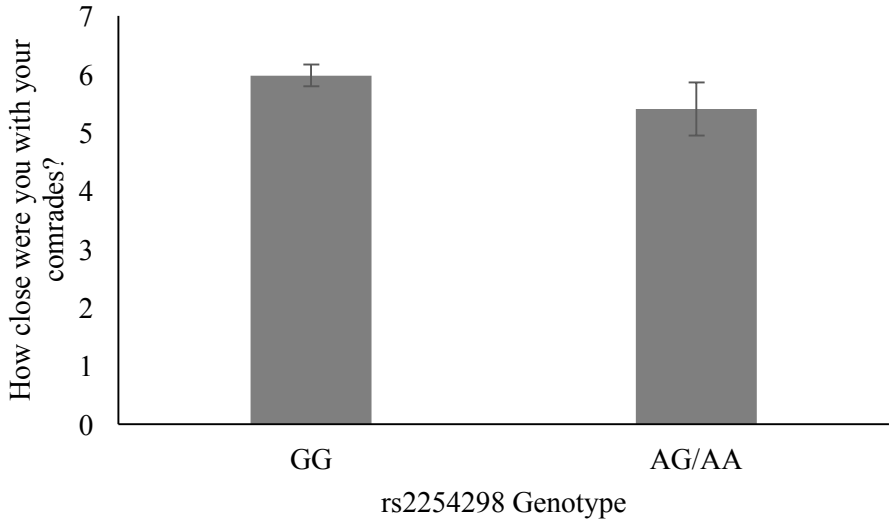
Supplemental Figure 10. How much subjects miss their comrades as a function of genotype rs53576 (t(47)=.511, p=.612).



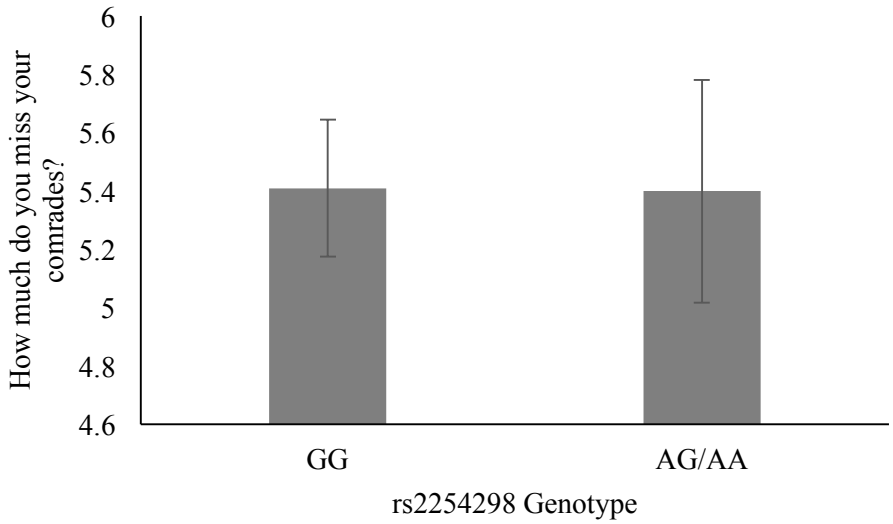
Supplemental Figure 11. Beck depression scores as a function of genotype rs53576 (t(50)=-.974, p=.335).



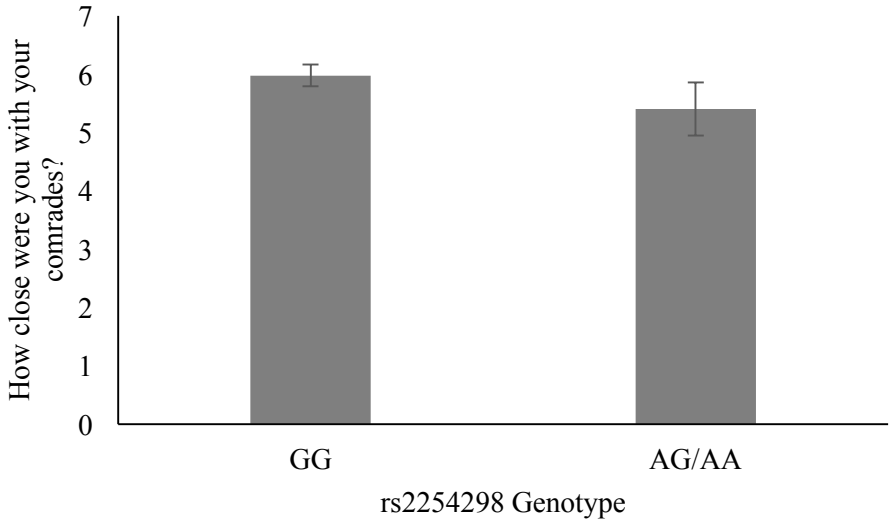
Supplemental Figure 12. Suicidal ideation as a function of genotype rs53576 (t(50)=-.470, p=.640).



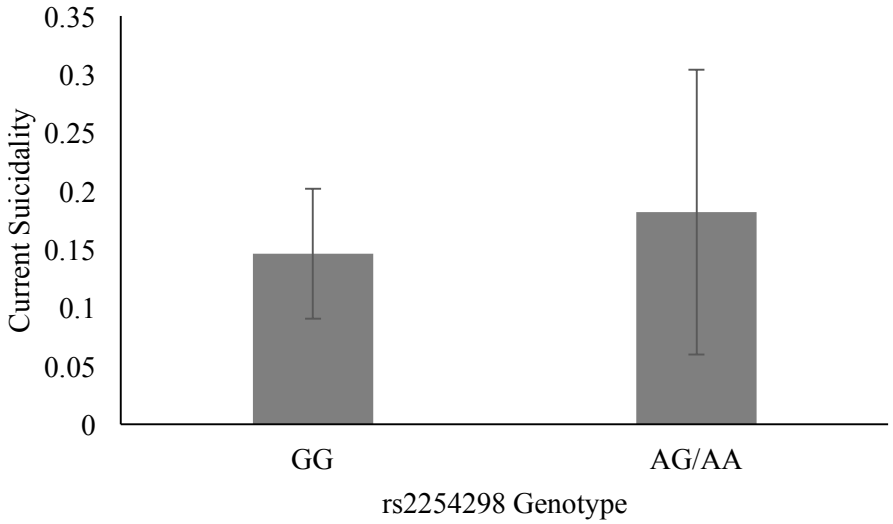
Supplemental Figure 13. How close subjects were with comrades as a function of genotype rs2254298 ($t(47)=1.28$, $p=.21$).



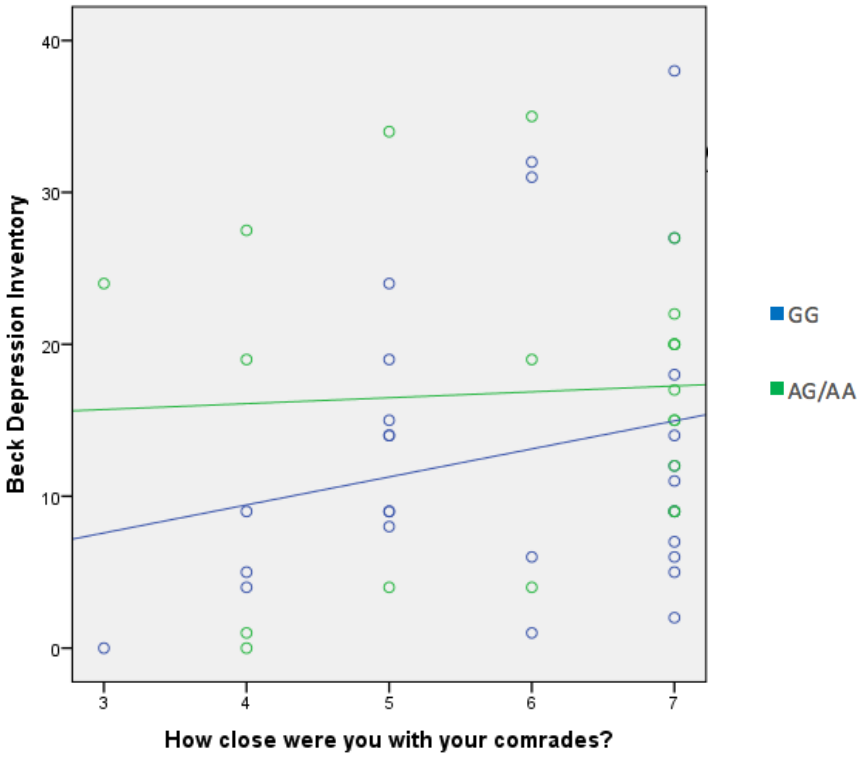
Supplemental Figure 14. How much subjects miss their comrades as a function of genotype rs2254298 ($t(47)=.02$, $p=.98$).



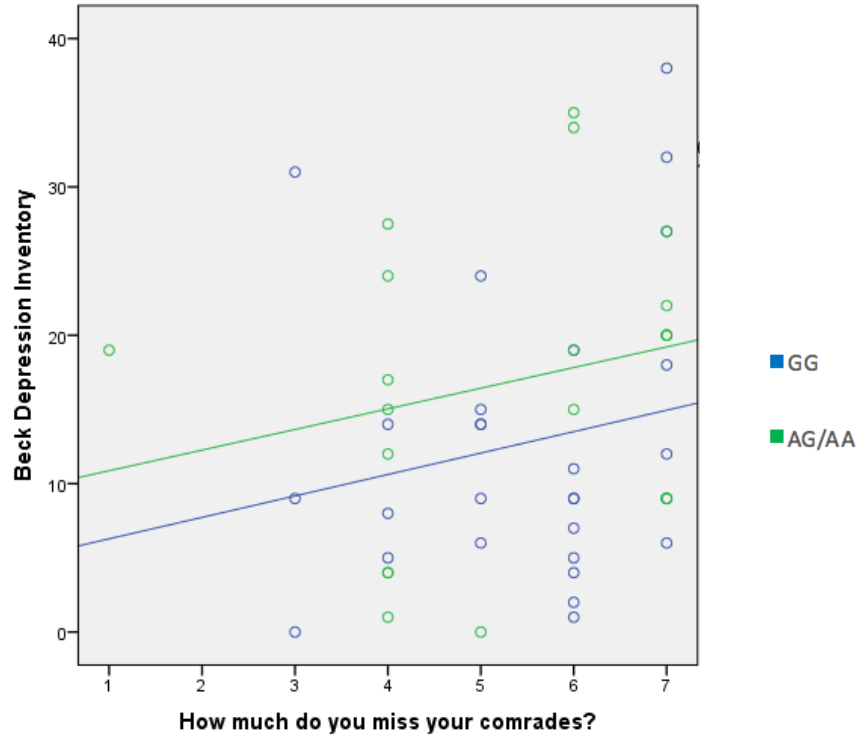
Supplemental Figure 15. Beck depression scores as a function of genotype rs2254298 (t(50)=.72, p=.47).



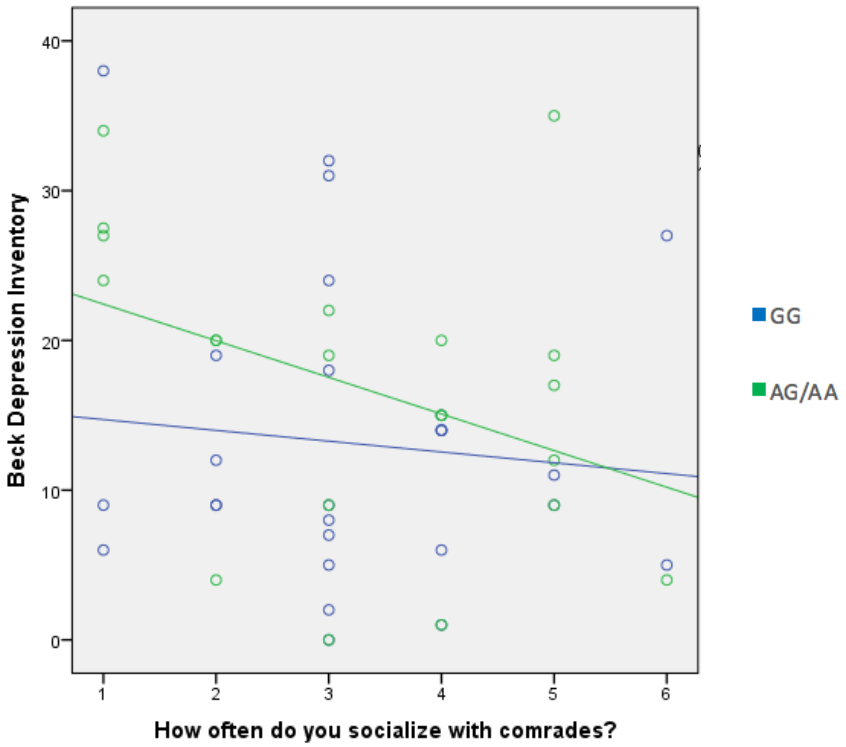
Supplemental Figure 16. Suicidal ideation as a function of genotype rs2254298 (t(50)=-.28, p=.78).



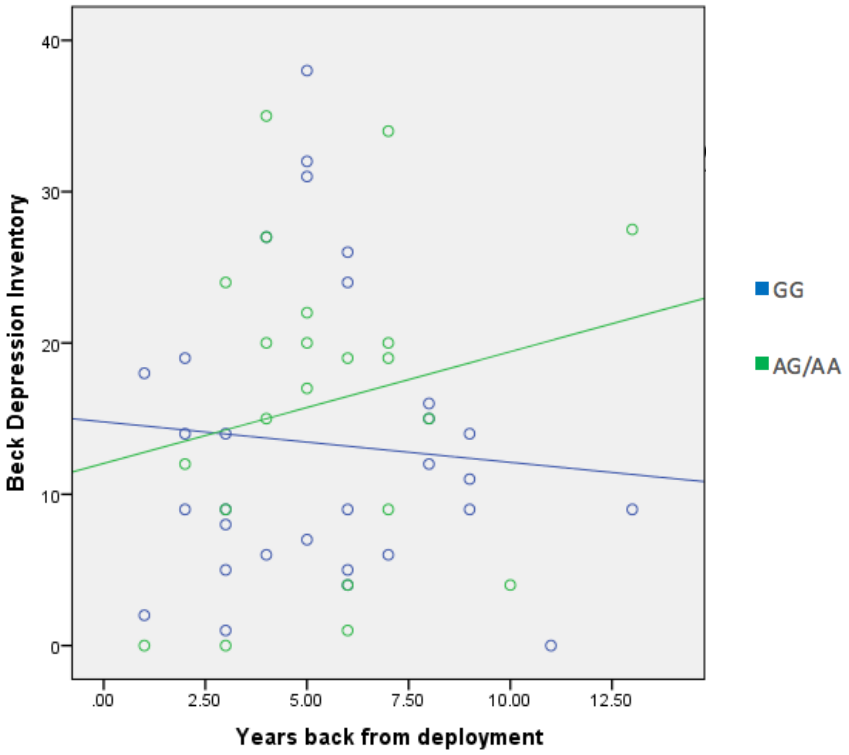
Supplemental Figure 17. Relationship between how close subjects were with their comrades and Beck depression scores in rs53576 GG genotype versus AG/AA genotype.



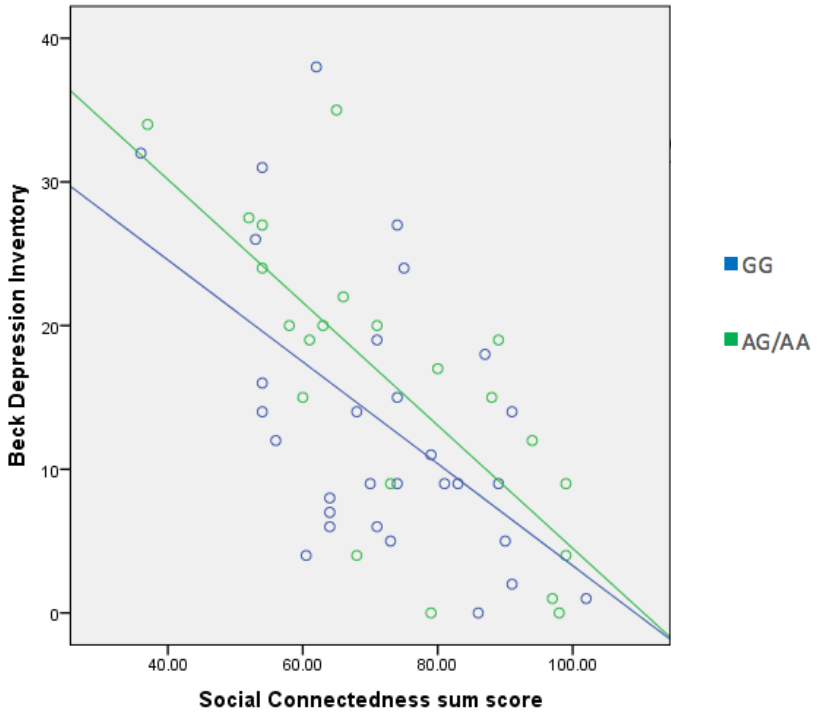
Supplemental Figure 18. Relationship between how much subjects miss their comrades and Beck depression scores in rs53576 GG genotype versus AG/AA genotype.



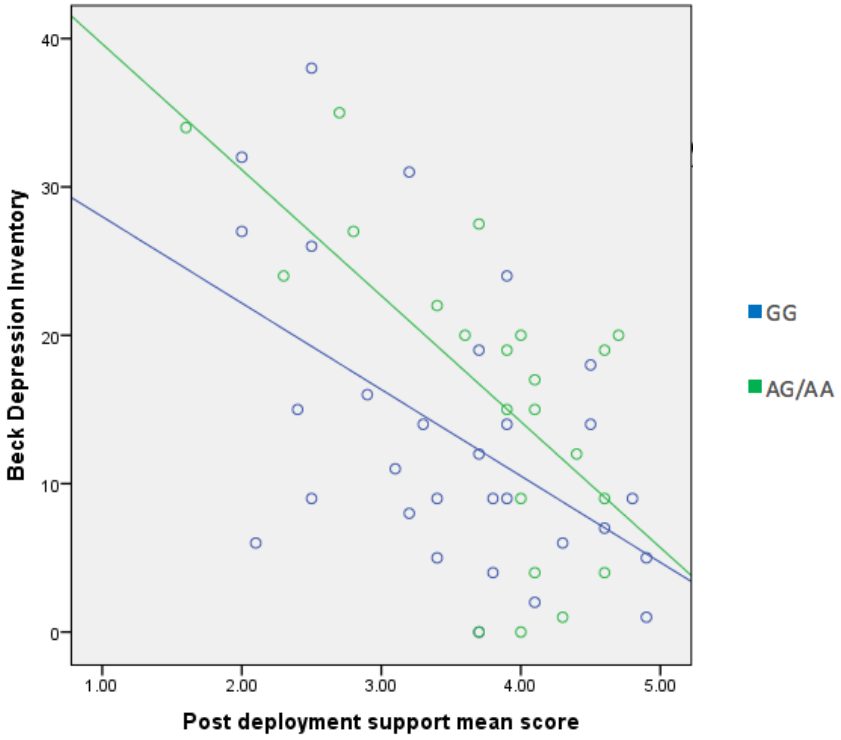
Supplemental Figure 19. Relationship between how often subjects socialize with their comrades and Beck depression scores in rs53576 GG genotype versus AG/AA genotype.



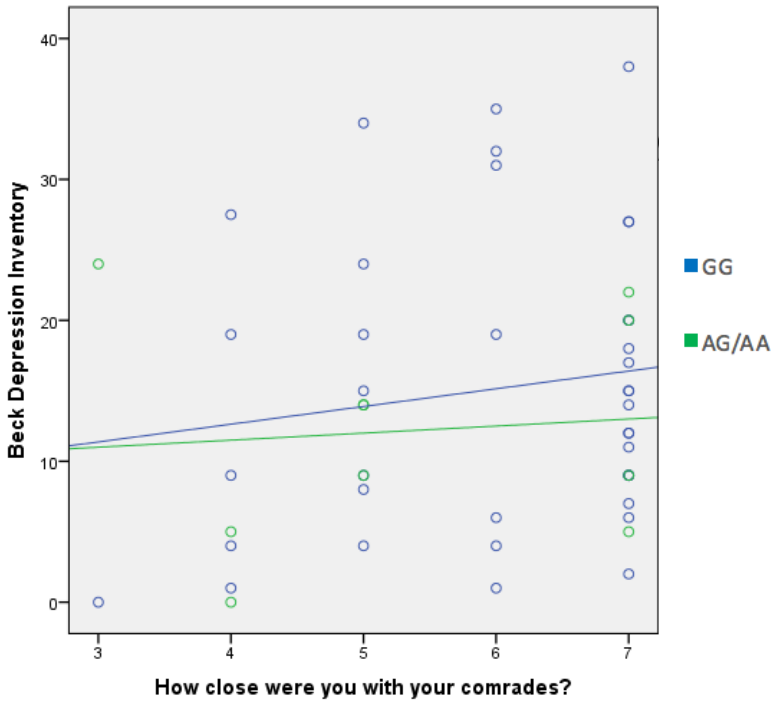
Supplemental Figure 20. Relationship between how long subjects have been back from war and Beck depression scores in rs53576 GG genotype versus AG/AA genotype.



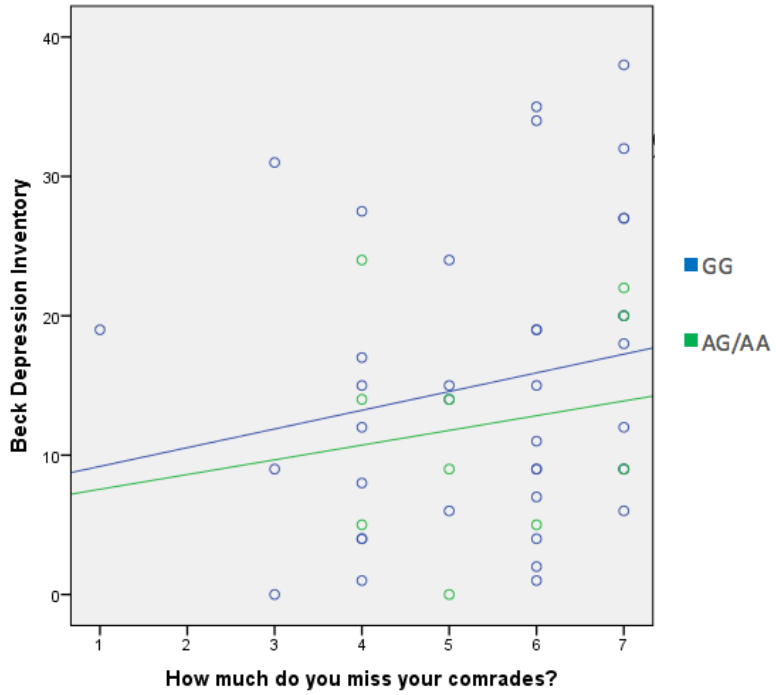
Supplemental Figure 21. Relationship between Social Connectedness sum score and Beck depression scores in rs53576 GG genotype versus AG/AA genotype.



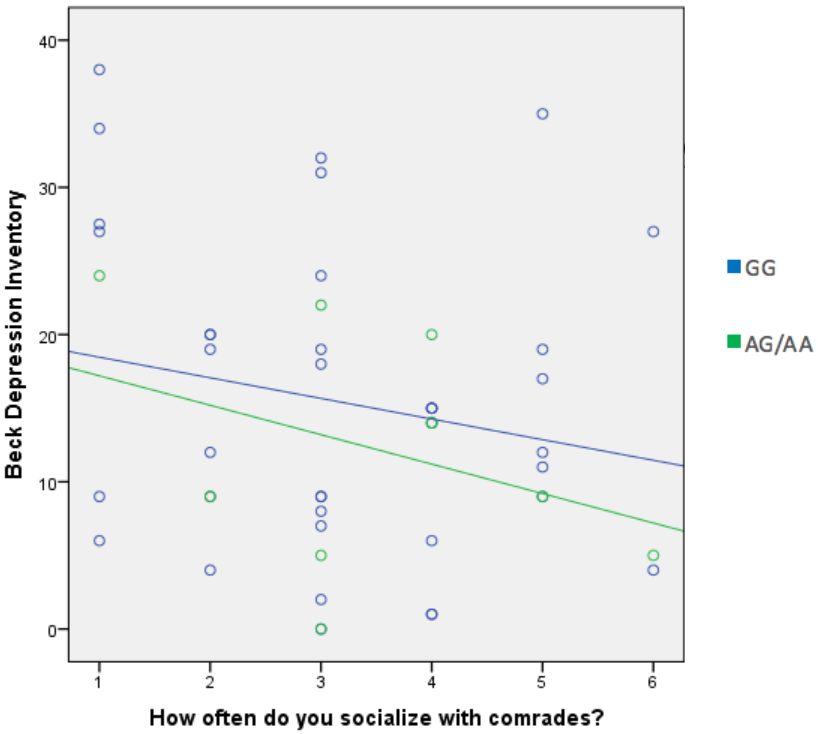
Supplemental Figure 22. Relationship between Post deployment support mean score and Beck depression scores in rs53576 GG genotype versus AG/AA genotype.



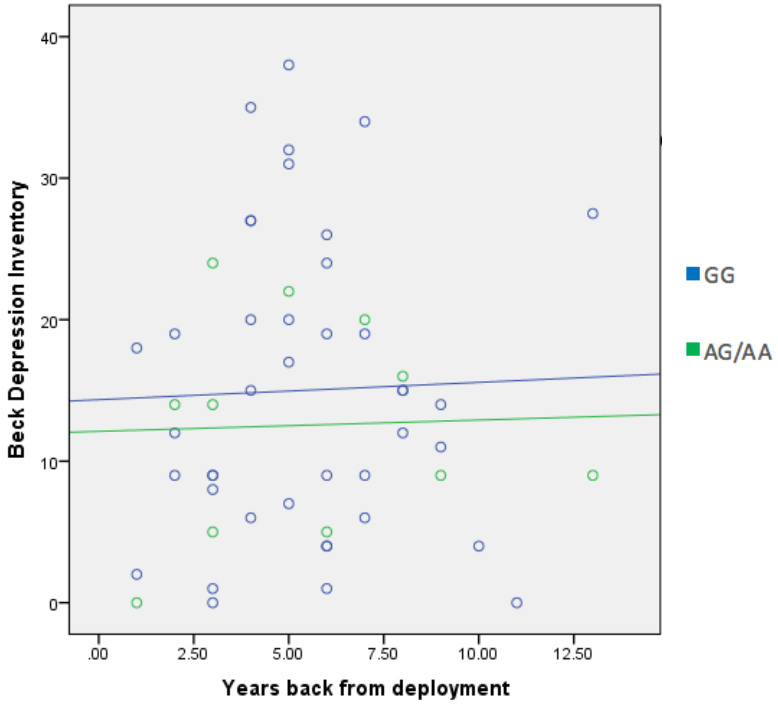
Supplemental Figure 23. Relationship between how close subjects were with their comrades and Beck depression scores in rs2254298 GG genotype versus AG/AA genotype.



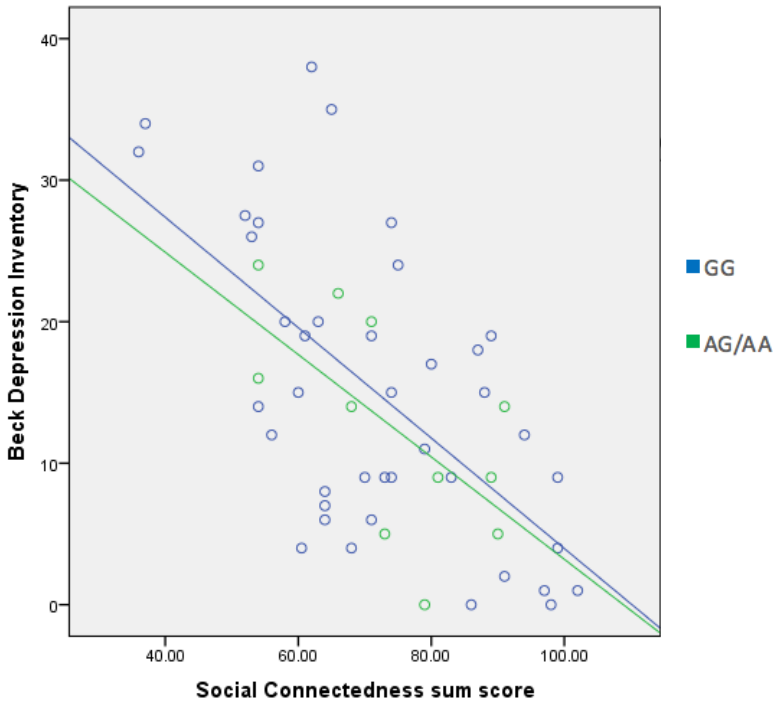
Supplemental Figure 24. Relationship between how much subjects miss their comrades and Beck depression scores in rs2254298 GG genotype versus AG/AA genotype.



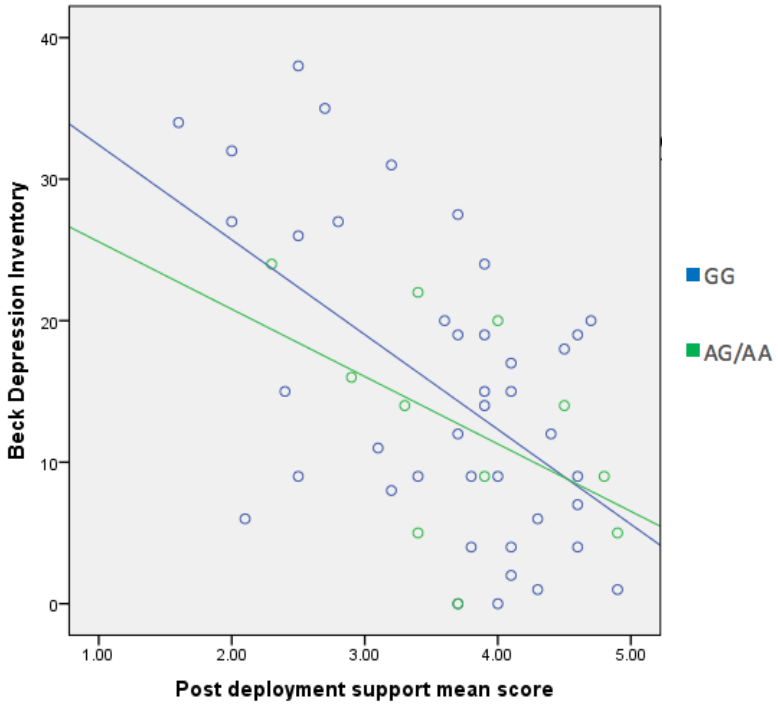
Supplemental Figure 25. Relationship between how often subjects socialize with their comrades and Beck depression scores in rs2254298 GG genotype versus AG/AA genotype.



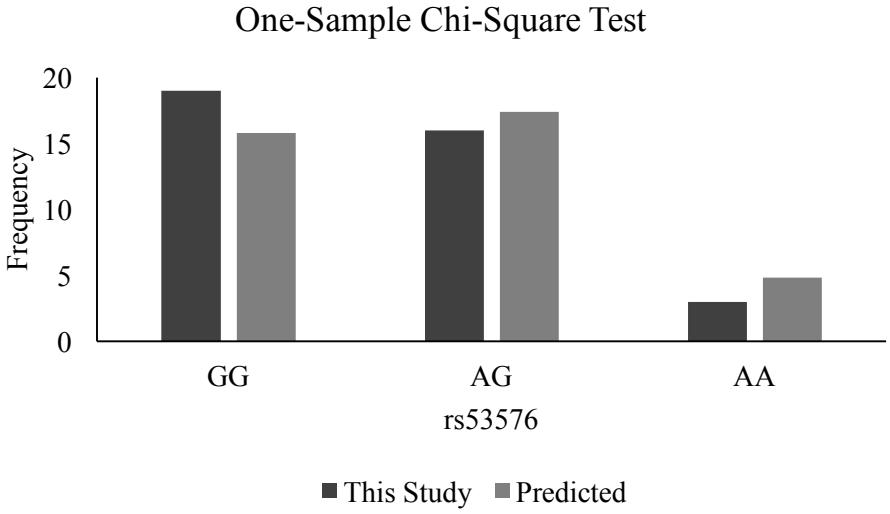
Supplemental Figure 26. Relationship between how long subjects have been back from war and Beck depression scores in rs2254298 GG genotype versus AG/AA genotype.



Supplemental Figure 27. Relationship between Social Connectedness sum score and Beck depression scores in rs2254298 GG genotype versus AG/AA genotype.



Supplemental Figure 28. Relationship between Post deployment support mean score and Beck depression scores in rs2254298 GG genotype versus AG/AA genotype.



Supplemental Figure 29. Differences in genotypic frequencies of the rs53576 gene in subjects identifying as "White" versus European database (p=0.481).