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Research paper

Connectome-based functional connectivity markers of suicide attempt

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ABSTRACT

Background: Functional brain markers of suicidality can help identify at-risk individuals and uncover underlying neurocognitive mechanism(s). Although some converging evidence has implicated dysfunction in several brain networks, suicide-related neuroimaging markers are inconsistent across studies, due to heterogeneity of neuroimaging approaches, clinical populations, and experimental methods.

Methods: The current study aimed to address these limitations by examining resting-fMRI connectivity in a sample of post-9/11 veterans with a past suicide attempt (SA; $n = 16$) compared to a psychiatric control group (PC; $n = 124$) with no SA history but comparable past and present symptomatology, as well as a trauma control group (TC; $n = 66$) of trauma-exposed healthy controls. We used both a novel graph-analytic and seed-based approach to characterize SA-related connectivity differences across brain networks.

Results: First, the graph-analytic approach identified the right amygdala and a region in the cognitive control network (right middle temporal gyrus; MTG) as regional SA-related hubs of dysfunction (HoD), or regions that exhibited a high *number* of SA-related connections. Aberrant SA-related connectivity between these hubs spanned multiple networks, including the cognitive control, default mode and visual networks. Second, the seed-based connectivity analysis that identifies SA-related differences in the *strength* of neural connections across the whole brain further implicated the right amygdala.

Limitations: Small sample size and potential underreporting of SA.

Conclusions: These two analytic approaches preliminarily suggest that the right amygdala and right MTG may be specific neural markers of SA that can be differentiated from neural markers of psychopathology more broadly.

Introduction

Suicide is a major public health crisis worldwide, leading to over 1 million annual deaths globally (World Health Organization [WHO], 2012). Suicide risk is elevated in those exposed to trauma, such as combat veterans, who are twice as likely to die by suicide than US civilians (Kaplan et al., 2007; Kuehn, 2009). Further, since the onset of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), the suicide rate among trauma-exposed veterans more than doubled from estimated rates as low as 10 per 100,000 in 2001 to more than 20 per 100,000 in 2008 and has remained elevated (e.g., approximately 24.8 per 100,000 in 2018; Black et al., 2011; Department of Defense, 2019; Department of the Army, 2010). Current suicide prevention practices are largely informed by the identification and evaluation of suicidal thoughts and behaviors (STBs) and other clinical characteristics. However, self-reports of STBs and clinical symptomatology are limited in their effectiveness to predict future suicide attempts and death by suicide, and individuals who do not disclose thinking of or committing acts of self-harm may not receive

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necessary interventions (Franklin et al., 2016; Nock et al., 2008). Thus, a significant limitation in current suicide treatment and research is the exclusive reliance on self-report to identify at-risk individuals. An alternative approach is to identify complementary, objective neuroimaging-based brain markers of STBs, which have the potential to both help identify the underlying mechanisms and processes that contribute to suicidality and serve as risk signatures of STBs. The goal of the current study is to characterize the resting-state fMRI profiles of post-9/11 veterans with a history of suicide attempt, which could be applied to improve identification of at-risk individuals.

Neuroimaging methods have recently been applied to investigate the neural correlates of STBs, predominantly in the context of major depression, although reliable brain markers have yet to be found (Jollant et al., 2011; Lippard et al., 2014; Schmaal et al., 2020; Zhang et al., 2014). With the recent exponential growth of studies investigating the neurobiology of STBs, some convergent findings have started to emerge. In a recent review paper, Schmaal et al. (2020) reported findings in two broad neural systems associated with STBs across 131 structural and functional neuroimaging studies. On the one hand, STB-related dysfunctional activity and connectivity are found in regions associated with cognitive control, emotional regulation, and decision-making, mainly in cognitive control networks (CCN), such as the dorsolateral, ventral lateral, and dorsomedial prefrontal cortices (dmPFC), as well as the anterior cingulate cortex (ACC). For example, task-based fMRI studies find *decreased* activation in cognitive control regions (e.g., dmPFC and ACC) during emotional processing (e.g., viewing angry faces; Jollant et al., 2008; Olié et al., 2015, though see Pan et al., 2013) and decision-making tasks (e.g., making risky versus safe decisions on the Iowa Gambling Task; Olié et al., 2015) in individuals with a past suicide attempt (SA) and history of depression. On the other hand, dysfunctional activity and connectivity are also frequently observed in regions associated with negative affect and rumination, mainly in limbic, default mode, and salience networks, such as the amygdala, hippocampus, insula, and ventromedial prefrontal cortex (vmPFC). For example, *increased* activation in these regions (e.g., vmPFC and insula) was found during emotional processing (e.g., viewing angry faces; Jollant et al., 2008; Olié et al., 2015) and cognitive control tasks (e.g., continuous performance task; Minzenberg et al., 2015) in individuals with STBs and a co-occurring affective disorder (e.g., depression or bipolar disorder). Further, a recent meta-analysis of 77 neuroimaging studies found significant functional differences in the right amygdala, left hippocampus, and left posterior cingulate cortex (PCC) in those with suicidal behavior (Huang et al., 2020). In addition, resting-state fMRI studies find dysregulated connectivity both within and between these two broad neural systems, particularly in cognitive, limbic, and default mode networks (Kang et al., 2017; Ordaz et al., 2017). For example, studies find *increased* coupling both within the limbic network (e.g., amygdala, insula and orbital frontal cortex) and between the limbic and CCN (e.g., amygdala and middle temporal area; Kang et al., 2017). Moreover, patterns of abnormal neural activity within these two neural systems have even been used to build classification algorithms to predict STBs, which highlights the translational utility of STB-related brain markers (Just et al., 2017).

Although the converging evidence provides a promising preliminary neurobiological framework of STBs, the translational utility of these neurobiological models is limited by the heterogeneity of neuroimaging approaches, clinical populations, and experimental methods across studies. For example, many studies lack an appropriate psychiatric control group with similar rates and severity of psychopathology as their sample with STBs (e.g., Barredo et al., 2019). As a result, it is unclear if brain markers are specific to suicidality or reflect overall psychological distress. Further, some studies that did compare STBs to both psychiatric controls and healthy controls found inconsistent results across the groups. That is, the activation/connectivity pattern of the sample with STBs, though significantly different than psychiatric controls, resembled that of the healthy controls (e.g., Cao et al., 2016; Stange et al., 2019). This inconsistent pattern of results not only limits the ability to reliably differentiate at-risk individuals from the general population but also may reflect uniqueness related to the psychiatric controls rather than those with STBs. Secondly, STBs have been operationalized differently across studies (e.g., suicidal intent/ideation [SI], history of attempt [SA], lethality of attempt). Although these concepts are related, SI is only a modest predictor of SA (Nock et al., 2008) and thus, may have distinct neural underpinnings (e.g., Stange et al., 2019). Additionally, previous studies frequently utilize an *a priori* region-of-interest (ROI) approach (e.g., Jollant et al., 2010; Kang et al., 2017; Olié et al., 2015), which limits conclusions regarding the specificity of results and may artificially inflate cross-study convergence on commonly assessed regions. Despite some converging evidence, a number of studies also implicate regions distributed across the entire brain, including subcortical, sensory, and cerebellar regions (Schmaal et al., 2020; Van Heeringen et al., 2011); thus, substantial heterogeneity exists within the literature. Finally, the majority of suicide research has been completed in samples with major depression. Although these studies elucidate potential abnormalities associated with depression and comorbid STBs, the results may not generalize to other at-risk populations, such as those with trauma-related psychiatric conditions. Few studies have examined the neurobiological basis of STBs in a trauma-exposed cohort (e.g., Barredo et al., 2019; Davis et al., 2019; Matthews et al., 2012). These studies provide evidence of possible transdiagnostic markers of STBs, but differences are also reported. In fact, one study found neurobiological differences in suicidality between those with depression versus post-traumatic stress disorder (PTSD), such that cognitive control and limbic neural markers were more pronounced in those with STBs and PTSD (Davis et al., 2019). Therefore, further exploration of STBs within a trauma-exposed sample may help to advance our understanding of the neural mechanisms of STBs.

In the current study, we aimed to address these limitations by characterizing neural markers of STBs using resting-state fMRI in a trauma-exposed veteran sample. First, we sought to identify the neural correlates of suicide attempt (SA) in particular, as SA is one of the strongest predictors of future suicidal behavior in both civilian (Christiansen & Jensen, 2007; Nock et al., 2008; Oquendo et al., 2004) and veteran samples (Lee et al., 2018). Next, to identify dysfunctional brain connectivity specific to SA, we focused our analyses on differentiating veterans with a history of SA from a psychiatric control (PC) sample with no history of SA but equivalent levels of psychopathology. As a secondary analysis, we also compared the SA group to a trauma control (TC) group of trauma-exposed veterans with no lifetime or current psychiatric diagnoses of depression or PTSD to clarify if any observed dysfunctional connectivity is SA-specific and not due to unique characteristics of the PC group. Lastly, due to the heterogeneity in neural systems identified across studies, we took two complementary whole-brain approaches to assess the entire connectome and expand our search beyond *a priori* ROIs. Specifically, we applied a novel graph-analytic approach to identify regional hubs of SA-related dysfunction based on patterns of connectivity across the brain. In addition, we examined whole-brain connectivity differences across groups using a comprehensive cortical and limbic parcellation. Although we did not restrict our analyses to specific ROIs, evidence from Schmaal et al. (2020) would predict the results would be localized to regions within the CCN, limbic, and default mode networks. Further, meta-analytic evidence from Huang et al. (2020), focusing specifically on suicidal behavior (suicide attempt or deliberate self-harm) across 77 neuroimaging studies, suggests the right amygdala, left hippocampus, and left PCC, in particular, would be the most likely neural correlates of SA in our study.

Methods

2.1. Participants

Study participants included 377 post-9/11 combat deployed veterans recruited from the Translational Research Center for Traumatic Brain Injury and Stress Disorders (TRACTS) at the Veteran Affairs Boston

Healthcare System (for a detailed description of recruitment, exclusion criterion, and the characteristics of the TRACTS dataset see McGlinchey et al., 2017). Exclusion criteria include moderate to severe traumatic brain injury ($n = 10$), history of neurological illness ($n = 1$), and current diagnosis of psychotic disorders unrelated to PTSD ($n = 2$) according to the Structured Clinical Interview for DSM-IV Axis I Disorders Non-patient Edition (SCID-I/NP; First et al., 1997). Twenty-three participants were later excluded for fMRI quality control (see Supplementary Materials; Esterman et al., 2020). From this larger sample, we selected a final sample of 206 participants who met inclusion criteria for the three clinical groups of interest (trauma controls, psychiatric controls, and those with a past suicide attempt; see Psychiatric Assessment). All research procedures were approved by the Institutional Review Board of Human Studies Research at the VA Boston Healthcare System. Participants provided informed consent and were compensated for their participation.

2.2. Clinical Assessments

2.2.1. Psychiatric Assessment

As part of TRACTS's standard protocol, all participants completed a series of clinical interviews as well as an MRI session at the end of the day. Study procedures have been thoroughly described by McGlinchey et al., 2017. All psychiatric interviews were conducted by a doctoral-level psychologist, and each case was reviewed by at least three doctoral-level psychologists to achieve a consensus diagnosis.

History of suicide attempt was assessed with two measures. Our primary measure was the Beck Scale for Suicide Ideation (BSS; Beck & Steer, 1991), a self-report measure that has shown high internal reliability (Cronbach's alpha = 0.95) in a veteran sample (Gutierrez et al., 2019). As only a subset of participants were administered the BSS (77/206 participants), to more broadly assess a history of SA in our sample, we also used the clinician-administered mood episodes and disorders modules (current and history) of the Structured Clinical Interview for DSM-IV Axis I Disorders Non-patient Edition, as all participants were administered the SCID (SCID-I/NP; First et al., 1997). Lifetime (current and past) mood, anxiety and substance use disorders were diagnosed using the SCID-I/NP. Depression, anxiety and stress severity were assessed by self-report using the Depression, Anxiety and Stress Scale (DASS-21; Henry & Crawford, 2005; Lovibond & Lovibond, 1995). PTSD diagnosis and severity were assessed using the Clinician-Administered PTSD Scale (CAPS-IV; Blake et al., 1995), a semi-structured interview. We also obtained additional demographic and clinical measures that could exacerbate psychiatric disorders or influence functional connectivity (see Supplementary Materials).

2.2.2. Clinical group assignment

Sixteen participants reported a previous suicide attempt (SA). Individuals were included in the SA group if they endorsed a past suicide attempt on either the BSS or the SCID. To isolate the effect of SA, we identified a matched psychiatric control group (PC). First, as all participants within the SA group had a lifetime (current or past) diagnosis of Major depressive disorder (MDD) and/or PTSD, we limited our psychiatric control sample to only include individuals with a lifetime (current or past) diagnosis of MDD and/or PTSD. Next, to ensure that group differences were not observed due to current symptom severity, we further matched the two groups based on current PTSD and depression symptom severity (CAPS-IV and DASS-21), as well as age and education, using a matching algorithm in R Studio ('MatchIt'; Allaire, 2012; Ho et al., 2018). This resulted in a final PC group of 124 participants. Direct statistical comparisons were computed between the SA and PC group to isolate suicide-specific brain markers. In addition, we also compared the SA group to a trauma control group (TC) of trauma-exposed veterans ($n = 66$) with no current or past psychiatric diagnosis of depression or PTSD.

2.3. Resting-state fMRI acquisition and processing

2.3.1. MRI Acquisition and Processing

Anatomical and 8 or 12 minutes of resting-state MRI scans were acquired on a 3T Siemens MAGNETOM Trio or Prisma (scanner upgrade; Trio: 165/206 participants, Prisma: 59/206) using a 12-channel coil. The number of volumes (240 volumes) collected were matched for all fMRI scans; however, some participants differed in their duration and sampling rate (12-minute scan with a 3 second TR versus 8-minute scan with a 2 second TR) due to unintended operator variability unrelated to any participant characteristics. Post-hoc results demonstrated that controlling for group differences in the proportion of participants with each resting-state acquisition did not impact group differences in functional connectivity (see Supplementary Materials; Supplementary Analyses and Results: MRI Acquisition Group Differences). The brain was parcellated using a 7-network atlas from Schaefer and colleagues (Schaefer et al., 2018) that parses the cortex into 200 nodes (regions) embedded within 7 large-scale cortical networks identified by Yeo et al. (Yeo et al., 2011). In addition, we also extracted the time series of the bilateral amygdala and hippocampus from a subcortical atlas developed by Tullo and colleagues (Tullo et al., 2018), as these regions are commonly implicated in neuropsychiatric disorders, including STBs (Jollant et al., 2011; Lippard et al., 2014; Schmaal et al., 2020). The average time series were extracted from each node (averaged across the set of voxels within the node) and correlated (Pearson) across nodes for a total of 20,706 pairwise correlations. A detailed description of the MRI acquisition, resting-state preprocessing, and brain parcellation are reported in the Supplementary Materials. In addition, as rigor and reproducibility are significant issues of fMRI more broadly (Elliott et al., 2019; Noble et al., 2019), we assessed the Spearman-Brown adjusted split-half reliability of our dataset using two approaches. First, we determined the split-half reliability of the full connectome within each subject to determine the reliability of each individual's connectome. Second, we computed the split-half reliability of each edge (connection) across individuals. The average split-half reliability within each subject (0.86) and across all edges (0.67) were both within the moderate-excellent range (0.6 = moderate, 0.6-0.75 = good, and 0.75-1 = excellent; Cicchetti, 1994). A detailed description of these analyses is included in the Supplementary Materials (see Supplementary Analyses and Results: Connectome Reliability).

2.3.2. Analysis Plan

The overall goal of this study was to identify both regional hubs and seed-based connections that differentiated those with a history of SA from those without a history of SA but a similar history of and current psychopathology. To do this, we took two complementary approaches. First, we applied a novel degree-based approach to identify regions of the brain that most differentiated these two groups (SA versus PC) based on patterns of connectivity across the whole-brain connectome. Second, we used a traditional seed-based analysis, whereby whole-brain voxel-wise connectivity with each seed region (204) was evaluated for group differences. Note that while the hubs analysis identifies regions based on the *number* of connections related to SA based on permutation testing, the seed-based whole-brain analysis identifies regions based on the *strength* of connections related to SA based on whole-brain voxel-wise cluster correction.

Although we were primarily interested in differentiating the SA group from the PC group to isolate suicide-specific brain markers, both the degree-based and seed-based analyses were repeated to differentiate the SA group from the TC group to further determine if group differences were specific to the SA group, in particular, and not due to unique characteristics of the PC group. Finally, all analyses were corrected for multiple comparisons using a Bonferroni correction.

Table 1
Demographic and Clinical Group Differences.

Measure	Suicide Attempt (SA) Group	Psychiatric Control (PC) Group	*P*
N	16	124	
Gender (M:F)	15:1	114:10	.800
Age	31.50 ± 7.85	30.44 ± 6.72	.613
Education	13.25 ± 1.44	13.20 ± 1.66	.902
PTSD Severity (CAPS-IV)	75.69 ± 30.54	71.35 ± 18.79	.587
PTSD (%)	81.25%	91.94%	.166
Current MDD (%)	50.00%	46.77%	.808
Current Anxiety Disorder (%)	37.50%	24.19%	.252
Current Substance Use Disorder (%)	12.50%	16.94%	.652
Current PTSD (%) alone	37.50%	45.97%	.522
Current MDD (%) alone	6.25%	0.81%	.084
Comorbid Current PTSD/MDD (%)	43.75%	45.97%	.867
Medicated (%)	56.25%	54.84%	.915
Antidepressant (%)	43.75%	33.07%	.397
Sedative Hypnotic (%)	12.50%	13.71%	.894
Pain Medication (%)	31.25%	32.26%	.935
Military mTBI (%)	75.00%	56.45%	.156
Lifetime mTBI (%)	87.50%	73.39%	.220
Overall daily life functioning (WHODAS II)	34.00 ± 18.71	28.00 ± 16.09	.250
Estimated premorbid IQ (WTAR)	104.07 ± 11.76	101.93 ± 10.33	.523
Overall Sleep Quality (PSQI)	13.21 ± 3.02	12.43 ± 4.11	.388
Average Pain (McGill)	44.13 ± 25.86	38.66 ± 26.32	.452
Depression Severity (DASS)	15.07 ± 8.55	13.48 ± 9.88	.514
Anxiety Severity (DASS)	12.53 ± 7.91	11.21 ± 8.55	.552
Stress Severity (DASS)	21.60 ± 8.32	19.45 ± 9.46	.364
Average drinks on a drinking day (LDH)	8.20 ± 5.56	6.96 ± 3.68	.412
Combat Exposure	23.57 ± 16.05	19.69 ± 11.41	.393

Note: Mean ± standard deviation, *p*-values are from *t*-test and χ^2 tests comparing the SA and PC group. The two groups were matched by age, education, PTSD severity, and depression severity. CAPS-IV = Clinician Administered PTSD Scale for DSM-IV, MDD = Major Depressive Disorder, Current PTSD alone reflects the percentage of participants who have a current diagnosis of PTSD but not MDD, current MDD alone reflects the percentage of participants who have a current diagnosis of MDD but not PTSD, and comorbid current PTSD/MDD reflects the percentage of participants who have a current diagnosis of both PTSD and MDD. The medicated variable reflects the presence or absence of psychotropic medication, regardless of the specific type. mTBI = mild traumatic brain injury, WHODAS II = World Health Organization Disability Assessment Schedule II, WTAR = Wechsler Test of Adult Reading, PSQI = Pittsburg Sleep Quality Index, DASS = Depression, Anxiety and Stress Scale, LDH = Lifetime Drinking History.

2.3.3. Regional Hubs of Dysfunction (HoD)

We applied a novel graph-analytic, degree-based analysis to identify regional HoD specific to the SA group. Hubs were defined as regions with a greater number of connections across the connectome related to SA than expected by chance. To do this, the connectivity between each ROI (204 in total) and all other regions (203 in total) was compared across groups (two sample *t*-test). For each of the 204 ROIs, this analysis identified the number of connections (range: 0 - 203) that exhibited a significant difference between the SA and PC groups (nominal $p<.05$). We operationalized HoD as regions with a greater number of SA-related connections than expected by chance. To generate a null distribution, group assignment was randomized with respect to participants and then evaluated for group differences in functional connectivity 1000 times. For each randomization iteration, the number of SA-related connections was determined for each ROI. A random distribution was generated for each ROI separately, and regions were considered significant hubs if the observed number of SA-related connections occurred by chance less than 5% of the time in the random distribution. For the significant HoD, follow-up analyses explored the patterns of hyper- and hypo- connectivity across the connectome. This analysis was repeated to investigate group differences between the SA and TC groups.

2.3.4. Seed-based connectivity analyses

To further examine and potentially find converging evidence for the neural correlates of SA, we conducted a complementary series of seed-based voxel-wise whole-brain connectivity analyses. To do this, we selected each ROI in our parcellation (204) as a seed and computed voxel-wise whole-brain correlation maps for each individual. We then contrasted these maps (voxel-wise two-sample *t*-test) across the two groups (SA versus PC and SA versus TC). Significant clusters were determined at a cluster-corrected threshold of 0.05 and nominal threshold of 0.01. For cluster correction, group assignment was randomized 1000 times with respect to participants, and the largest random cluster size was recorded. Observed cluster sizes with the correct assignment (non-random) that occurred less than 5% of random iterations were considered significant (at nominal threshold of $p<.01$).

Results

3.1. Demographics

The SA and PC groups were matched by age, education, and current PTSD and depression symptom severity (see Supplementary Figure 1 for each groups' distributions of the matching variables). Demonstrating the success of this matching approach, no group differences were observed in any demographic variables, including gender, estimated premorbid IQ, or other associated clinical measures, including current rates of comorbid PTSD and MDD (Table 1). Demographic and clinical characteristics of the trauma-control (TC) group are reported in the Supplementary Materials (see Supplementary Table 1).

3.2. SA-related Hubs of Dysfunction (HoD)

The degree-based analysis identified the right amygdala ($p = .007$), part of the limbic network, and the right middle temporal gyrus (MTG; $p = .015$), part of the CCN network, as regional SA-HoD, or brain regions with more SA-related connections across the connectome than would have occurred by chance (see Methods). Functional connectivity between the right amygdala and 34 regions showed significant differences between the SA and PC groups. These regions were distributed across all 7 networks and both hemispheres (Fig. 1A; Supplementary Table 2A). Compared to PCs, the SA group exhibited *hypo*connectivity (i.e., stronger negative coupling versus close to zero coupling in the PC group) between the right amygdala

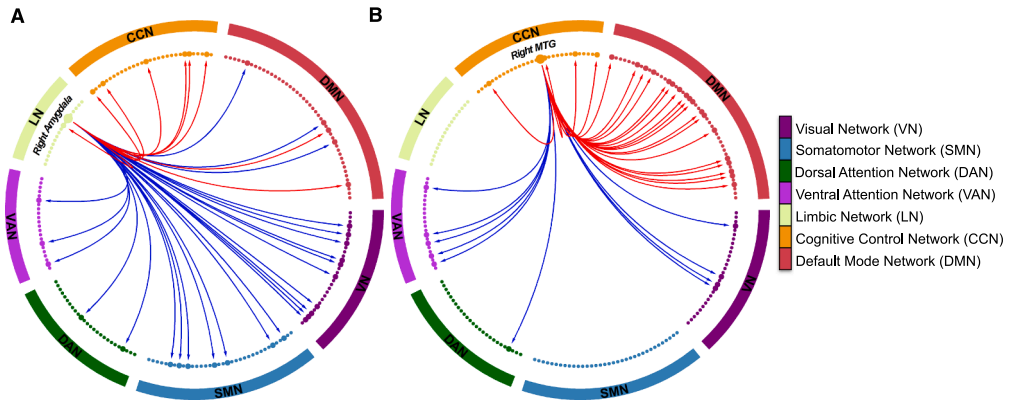

Fig. 1. ROIs within each network with significant hyper- and hypo- connectivity to the SA-related hubs of dysfunction (HoD). A. Arrows connect to points that represent brain regions within each network with significant differences in their connectivity to the right amygdala in SAs compared to PCs. Blue arrows point to regions that are significantly hypo-connected (reduced connectivity) to the right amygdala in SAs versus PCs. Red arrows point to regions that are significantly hyperconnected (increased connectivity) to the right amygdala in SAs versus PCs. The points with no associated arrow reflect the regions within each network with no significant differences in their connectivity to the right amygdala in SAs compared to PCs. **B.** All arrows connect to points that represent regions within each network with significant differences in their connectivity to the right MTG in SAs compared to PCs. Blue arrows point to regions that are significantly hypoconnected (reduced connectivity) to the right MTG in SAs versus PCs. Red arrows point to regions that are significantly hyperconnected (increased connectivity) to the right MTG in SAs versus PCs. The points with no associated arrow reflect the regions within each network with no significant differences in their connectivity to the right MTG in SAs compared to PCs. Additional details regarding the directionality of these group differences in the SAs relative to the PCs and TCs is provided at the network level in Figs. 2 and 3. MTG = middle temporal gyrus; CCN = cognitive control network; DMN = default mode network; VN = visual network; SMN = somatomotor network; DAN = dorsal attention network; VAN = ventral attention network; LN = limbic network.

and regions within the visual, somatomotor, dorsal attention, ventral attention, and limbic networks (Fig. 1A; Fig. 2A-2E). Conversely, the SA group demonstrated *hyper*connectivity between the right amygdala and regions within the CCN (Fig. 1A; Fig. 2F), which was characterized by a reduction in negative coupling compared to the PC group. Notably, the SA group exhibited *both* patterns of connectivity (hypo- and hyper-) between the right amygdala and the default mode network (DMN). Specifically, three regions within the DMN were significantly more *hypo*connected, and tworegions within the DMN were significantly more *hyper*connected in the SA group (Fig. 1A; Fig. 2G). The right amygdala did not survive a conservative Bonferroni correction for 204 ROIs (.05/204 or corrected alpha .00025), although this region was one of three regions recently identified in

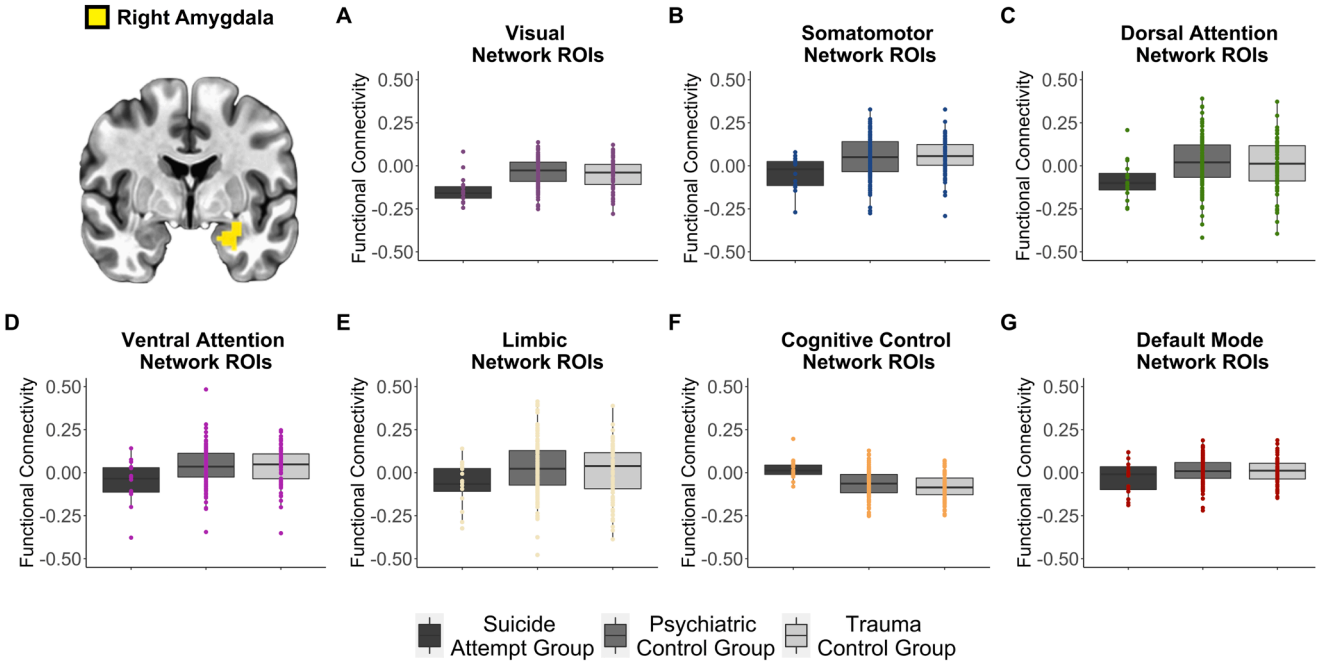

Fig. 2. Functional connectivity between the right amygdala and significant ROIs within each network. Each plot reflects the distribution of the average connectivity between the right amygdala and the select regions within each network with significant differences between SAs and PCs. **A.** Average connectivity between the right amygdala and ten regions within the visual network across the groups. **B.** Average connectivity between the right amygdala and seven regions within the somatomotor network across the groups. **C.** Average connectivity between the right amygdala and two regions within the dorsal attention network across the groups. **D.** Average connectivity between the right amygdala and three regions within the ventral attention network across the groups. **E.** Connectivity between the right amygdala and one region within the limbic network across the groups. **F.** Average connectivity between the right amygdala and six regions within the cognitive control network across the groups. **G.** Average connectivity between the right amygdala and five regions within the default mode network across the groups. Trauma Controls (TCs) are displayed in all plots for descriptive comparison.

a meta-analysis specific to suicidal behavior (Huang et al., 2020).

In addition to the right amygdala, in the second hub, we observed between-group differences in the connectivity between the right MTG and 32 regions that spanned multiple (5 of 7) networks (Fig. 1B; Supplementary Table 2B). In the SA group, the right MTG was significantly *hypo*connected to regions within the visual, dorsal attention, and ventral attention networks (Fig. 1B; Fig. 3A-3C). In all networks, this reflected more negative coupling in the SA group, whereas the PC group exhibited near-zero coupling. In SAs, the right MTG was significantly *hyper*connected (greater positive coupling) to regions within the cognitive control and default mode networks (Fig. 1B; Fig. 3D-3E).

For descriptive comparison, we included trauma controls (TC) in Figs. 2 and 3 to determine if the TCs' connectivity pattern was more similar to PCs than SAs. For TCs, the connectivity pattern between the hub regions and the significant regions within each network appears almost identical to the PCs, suggesting these markers are specific to the SA group. No direct statistical comparisons were computed between the SA and TC groups for the data presented in Figs. 2 and 3; however, to further determine if the right amygdala and right MTG HoDs were specific to SA, we conducted the same hubs analysis comparing the SA and TC groups. The SA versus TC comparison identified identical regional SA-HoD as those identified when comparing SAs to PCs (right amygdala, $p = .010$; right MTG, $p = .049$; Supplementary Figs. 2A-2B and Supplementary Tables 3A-3B). Together, this indicates that the consistent hubs of dysfunction were driven by differences in the SA group relative to both the PC and TC groups.

3.3. Seed-based connectivity analyses

To assess concordance across multiple methods, we further examined connectivity group differences (SA versus PC; see Methods) in seed-based whole-brain voxel-wise connectivity maps for all brain regions in the parcellation. This revealed seven seed regions within the parcellation with significant clusters that differed across groups (cluster corrected $p<.05$; Table 2). Seed regions that exhibited significant between-group differences in the strength of connectivity were located across four networks: visual, dorsal attention, limbic, and cognitive control. Importantly, the right amygdala, previously identified as an SA-related HoD, also demonstrated between-group differences in connectivity with two significant clusters within the visual network: the left cuneus (228 voxels) and left calcarine (74 voxels; Fig. 4). The right amygdala was significantly *hypo*connected to these clusters in the SA group compared to the PC group, which is the same pattern of connectivity previously observed between the right amygdala and significant regions within the visual network identified in the hubs analysis. To obtain the Bonferroni correction resolution of .00025, we repeated the cluster-correction procedure (see Methods) but increased the randomization of group assignment (SA versus PC) to 10,000 iterations and recorded the 10,000 random maximum cluster sizes for the right amygdala. Within this distribution, we observed a cluster size of >= 228 voxels in 4/10,000 iterations ($p = .0004$). Thus, the largest right amygdala-seeded cluster (in the left cuneus) nearly survived Bonferroni correction (which would have required < 3 of 10,000), but was not significant based on the most stringent multiple comparison correction. However, as noted above, this region was one of three regions recently identified in a prior meta-analysis specific to suicidal behavior (Huang et al., 2020).

Secondarily, to determine if the seed regions with significant clusters reflect neural signatures specific to the SA group rather than uniqueness in the PC group, we conducted the same seed-based analyses for all brain regions in the parcellation comparing the SA and TC groups. The results for all SA versus TC group comparisons are reported in the Supplementary

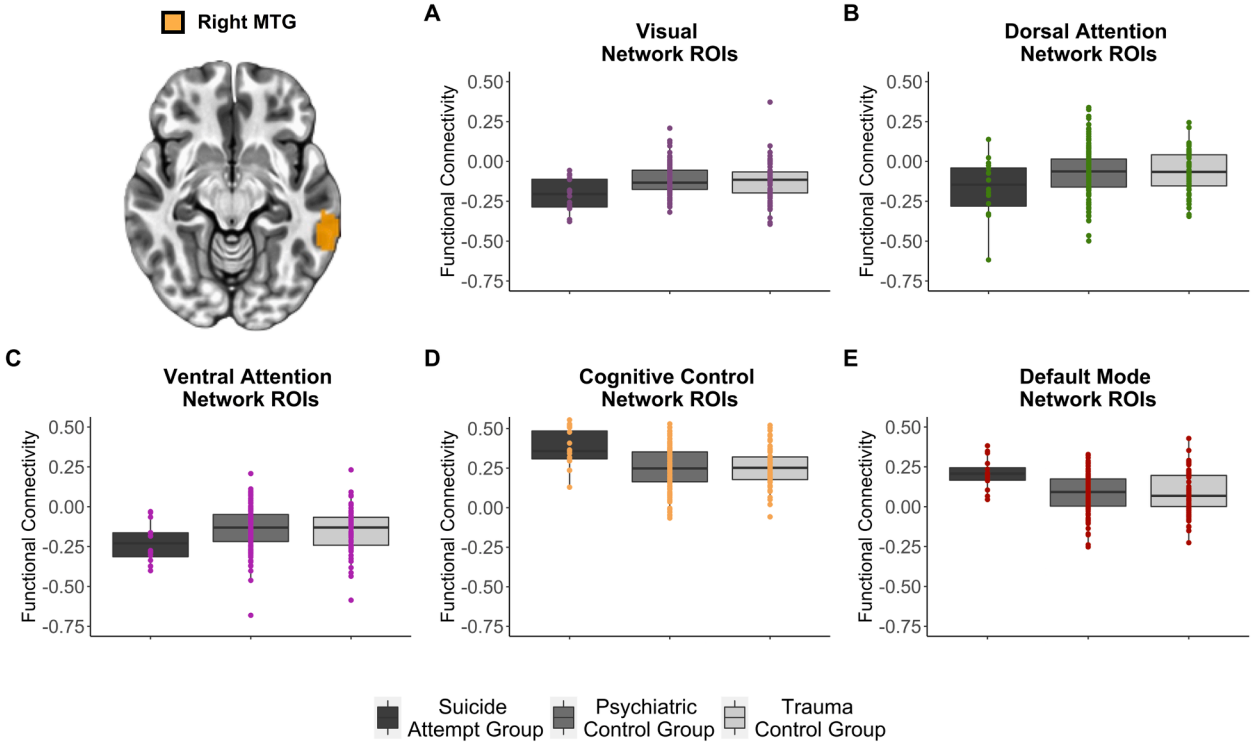

Fig. 3. Functional connectivity between the right middle temporal gyrus (MTG) and significant ROIs within each network. Each plot reflects the distribution of the average connectivity between the right MTG and the select regions within each network with significant differences between SAs and PCs. **A.** Average connectivity between the right MTG and four regions within the visual network across the groups. **B.** Connectivity between the right MTG and one region within the dorsal attention network across the groups. **C.** Average connectivity between the right MTG and five regions within the ventral attention network across the groups. **D.** Average connectivity between the right MTG and four regions within the cognitive control network across the groups. **E.** Average connectivity between the right MTG and 18 regions within the default mode network across the groups. Trauma Controls (TCs) are displayed in all plots for descriptive comparison. MTG = middle temporal gyrus.

Table 2
Seed regions within the parcellation with significant clusters that differ between the SA and PC groups.

Seed Network	Seed Region	Cluster Region	Cluster Hemisphere	MNI Cluster Coordinates			Number of Voxels	T_{138}	*P*
				x	*y*	*z*			
VN	Left Middle Temporal Gyrus	Cingulate Gyrus	Right	6	-45	27	154	4.06	.009
	Right Posterior Cingulate	Cingulate Gyrus	Right	9	-15	45	124	3.98	.018
DAN	Left Middle Temporal Gyrus	Lingual Gyrus	Left	-9	-87	-3	97	4.29	.021
LN	Right Amygdala	Cuneus	Left	-12	-78	33	228	4.47	.0004
		Calcarine	Right	15	-69	12	74	5.00	.038
	Right Medial Orbital Frontal Gyrus	Superior Occipital Gyrus	Left	-42	-84	24	119	5.13	.009
CCN	Right Cingulate Gyrus	Cingulate Gyrus	Left	-9	-51	27	114	4.39	.013
	Left Cingulate Gyrus	Middle Temporal Gyrus	Left	-48	-75	9	82	4.69	.028

Note: Each seed region reflects the ROIs from the parcellation with clusters that significantly differed between the PC and SA group. Significant clusters were determined at a cluster-corrected threshold of 0.05 and nominal threshold of 0.01. *P*-values based on cluster threshold randomization algorithm. VN = visual network, DAN = dorsal attention network, LN = limbic network, CCN = cognitive control network.

Materials (see Supplementary Table 4). The SA versus TC comparison identified four seed regions within the parcellation with significant clusters that differed across groups (cluster corrected $p < 0.05$; see Supplementary Table 4). Seed regions that exhibited significant between-group differences in the strength of connectivity were located across the same networks as those identified when comparing the SA and PC groups: visual, limbic, and cognitive control. Of the four significant seed regions, two regions within the limbic network were identical to those identified when comparing SAs to PCs (right medial orbital frontal gyrus and right amygdala), which also demonstrated between-group differences in connectivity to clusters located in the same regions (left superior occipital gyrus and left cuneus, respectively). In addition, the right MTG, the same region previously identified as an SA-related HoD when comparing SAs to both PCs and TCs, also demonstrated between-group differences in connectivity with one significant cluster within the limbic network (cingulate gyrus). The SA versus TC seed-based results further corroborate the specificity of the identified brain markers to the SA group.

3.4. Summary of Results

In sum, we took two complementary whole-brain approaches to assess the neural correlates specific to SA compared to both clinically-matched psychiatric controls and trauma-exposed healthy controls. Both analytic approaches (degree-based and seed-based) and between-group comparisons (SA versus PC and SA versus TC) yielded convergent results. First, the hubs-based approach identified the right amygdala (limbic network) and right MTG (cognitive control network) as SA-related hubs of dysfunction, or the regions that most differentiated the SA group from both the PCs and TCs based on the *number* of connections related to SA. Second, the seed-based approach, which assesses between-group differences in the *strength* of connectivity, also implicated the right amygdala. Specifically, the right amygdala was significantly hypoconnected to a large cluster within the visual network in those with SA compared to both the PC and TC groups. In addition, consistent with these findings, a recent meta-analysis found the *right* amygdala significantly differentiated individuals with suicidal behavior from controls across 77 neuroimaging studies (Huang et al., 2020). Therefore, although the results do not strictly survive the most stringent multiple comparison correction for 204 ROIs (corrected alpha .00025), the convergence not only within this study (across analytic methods and group-wise comparisons) but also across studies (Huang et al., 2020), provides substantial evidence that the results are not likely due to chance. Nevertheless, future work should strive to replicate and extend these preliminary findings in a larger, independent sample to determine the reliability of the right amygdala's association with SA.

Discussion

The aim of the current study was to characterize the neural mechanisms of STBs in post-9/11 combat veterans using resting-state fMRI connectivity. Specifically, we compared 16 individuals with a past suicide attempt to 124 matched psychiatric controls. Secondarily, we further compared the SA group to 66 trauma-exposed controls with no current or past psychiatric symptomatology. Two complementary analytic approaches yielded two primary results. First, the primary graph-analytic approach revealed that the right amygdala and right MTG (in the cognitive control network) were hubs of dysfunctional connectivity that differentiated individuals with SA from both the clinically-matched psychiatric control group (PC) as well as the trauma control group (TC). These regions are consistent with previous research implicating limbic (right amygdala) and CCN (right MTG) dysregulation in STBs (Jollant et al., 2011; Lippard et al., 2014; Schmaal et al.,

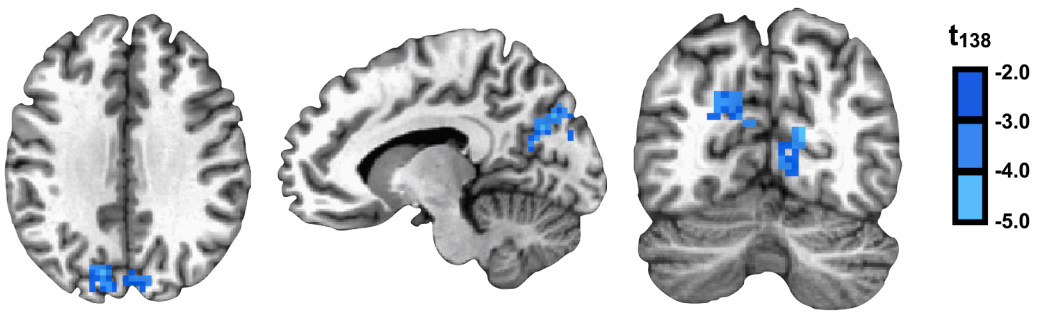

Fig. 4. Right amygdala connectivity differences between suicide attempt (SA) and psychiatric control (PC) groups. Two significant clusters within the visual network (VN) display reduced connectivity with the right amygdala in the SA compared to the PC group.

2020). For these two SA-hubs, patterns of dysfunctional connectivity were distributed across multiple networks and both hemispheres, including the CCN, DMN, and visual network. Secondarily, traditional seed-based connectivity analyses revealed seven regions with connectivity that differed across the SA and PC groups and four regions that differed across the SA and TC groups. Most notably, the right amygdala was *hypo*connected to visual regions in those with SA compared to both PCs and TCs. As the results from SA versus TC comparisons yielded convergent results, and we were primarily interested in comparing the SA group to a clinical-matched psychiatric control group, we focus our discussion on the primary SA versus PC results. Together, these findings support and extend current neurobiological models of STBs and have preliminary translational implications.

The right amygdala significantly differentiated veterans with a past suicide attempt from psychiatric controls across two complementary analytic approaches. The graph-analytic approach identified the right amygdala as an SA-related HoD that exhibited abnormal connections to 34 regions distributed across all 7 networks. Notably, the right amygdala displayed a pattern of reduced negative connectivity to regions within the CCN, in line with neurobiological models of STBs that implicate CCN-limbic alterations (Jollant et al., 2011; Lippard et al., 2014; Schmaal et al., 2020). In addition, although limbic-visual dysfunction has not been widely explored or reported in the context of STBs, we found concordance across two analytic approaches revealing the right amygdala to be significantly *hypo*connected (negatively coupled) to visual regions in those with SA (versus near-zero coupling between these regions in PCs; Fig. 2A). Lastly, brain regions distributed across all other cortical networks displayed dysfunctional connectivity with the right amygdala as well, including the somatomotor, dorsal attention, ventral attention, limbic, and default mode networks. These results demonstrate a widespread SA-related connectivity pattern between the right amygdala and regions within every cortical network, which may explain some of the heterogeneity present in the literature, as these differences are not localized to one region or network. However, it also reveals the extensive influence of the right amygdala in relation to differentiating SAs from PCs (and TCs) in this sample. Although neuroimaging studies of STBs have implicated the left, right, and bilateral amygdala (Alarcón et al., 2019; Kang et al., 2017), consistent with our findings, a recent meta-analysis found the *right* amygdala significantly differentiated individuals with STBs from controls across 77 neuroimaging studies (Huang et al., 2020). Research has shown lateralization of amygdala function may be related to a myriad of factors, including gender (e.g., men show greater right amygdala activation) and stimulus type (e.g., right amygdala is more activated by visual than verbal stimuli; Baas et al., 2004). However, the evidence remains inconsistent, and it is unclear how these hemispheric differences may be related to the facilitation of STBs. Thus, future studies should assess potential amygdala asymmetry in relation to STBs. Taken together, these results provide preliminary evidence that the right amygdala may be a key region associated with STBs.

In line with current neurobiological models of STBs, we found that those with SA displayed near-zero coupling between the right amygdala and six regions within the CCN, whereas the PC group exhibited negative coupling between the right amygdala and these regions (Fig. 1A, Fig. 2F). Broadly, amygdala-CCN connections are thought to support emotional regulation and cognitive control (e.g., Banks et al., 2007; Morawetz et al., 2017). Specifically, alternations in the connections between limbic and CCN regions may contribute to STBs via abnormalities in top-down cognitive control and emotional regulation (Jollant et al., 2011; Schmaal et al., 2020). Consistent with this view, one neurobiological model of STBs suggests that dysfunction within limbic-system regions may contribute to enhanced negative and/or blunted positive affect underlying STBs. Our findings are consistent with this model and complement prior work showing diminished coupling between the amygdala and CCN regions in individuals with a past SA and co-occurring affective disorder both at rest (Kang et al., 2017) and while viewing happy and neutral faces (Johnston et al., 2017). Although fMRI studies of emotional regulation in STBs are scarce (Miller et al., 2018 in adolescents with past SI), studies of emotional regulation in healthy participants show a consistent antagonistic relationship between the amygdala and CCN regions (Ochsner et al., 2002; Ochsner, 2004). Therefore, a reduction in negative coupling between the right amygdala and CCN regions may contribute to emotional dysregulation that facilitates STBs.

One unique finding of the present study was that the SA group exhibited altered amygdala-visual connectivity. Specifically, the right amygdala was significantly *hypo*connected to visual regions in those with SA across two analytic approaches, whereas PCs (and TCs) exhibited near-zero coupling between these regions (Fig. 2A). Although visual regions have not been consistently implicated in STBs, such regions demonstrate abnormal activation and connectivity in PTSD samples, often in parallel with dysregulation of the amygdala and paralimbic regions. For example, amygdala-visual connectivity and activation in response to trauma reminder scripts and images differed in individuals with PTSD, suggesting that trauma exposure may alter visual processing and visual imagery (Gilboa et al., 2004; Hendler et al., 2003). At rest, visual regions may be dysregulated in those with PTSD (Misaki et al., 2018), but these results are not typically integrated into neurobiological models (Wang et al., 2016). As few studies have examined STBs in the context of trauma-exposure, it is possible that amygdala-visual abnormalities in trauma-exposed populations facilitate STBs and may reflect differences in mental imagery, a key feature of STBs. Specifically, mental imagery in STBs is characterized by both a preoccupation and perceived vividness of intrusive suicide-related imagery, such as a future suicide attempt or 'flashforwards' (Holmes et al., 2007; Holmes & Mathews, 2010), and this perceived vividness is found to be significantly higher in those with comorbid PTSD (Schultebraucks et al., 2019). Further, these flashforwards also have a significant impact on emotion, as individuals report feelings of comfort from experiencing an 'opportunity to escape' (Holmes et al., 2007). Considering the amygdala's well-established role in emotion (Gallagher & Chiba, 1996; Phelps & LeDoux, 2005), increased negative coupling between the amygdala and visual network in SAs (but not PCs or TCs) may reflect an association between increased suicide-related mental imagery and a reduction in emotional distress associated with suicidal thoughts. However, additional studies are necessary to determine the nature of this relationship.

The second SA-related HoD was the right MTG, which is a region within the larger CCN. The SA group displayed abnormal connectivity between the right MTG and 32 regions distributed across 5 of the 7 networks. Impoverished CCN function is typically associated with impaired cognitive control and increased impulsivity, both of which are commonly implicated in STBs (Nock et al., 2008; Schmaal et al., 2020). Of these 32 right MTG connections, 56% of regions reflected *hyper*connectivity to the DMN, such that those with SA displayed significant positive coupling to the DMN. Negative coupling between the DMN and task-positive CCN regions is thought to support external task-related cognitive control (Chen et al., 2013; Seeley et al., 2007), whereas positive coupling between CCN and DMN supports internal mental processes, such as rumination and mind wandering (Godwin et al., 2017; McVay & Kane, 2010; Thomson et al., 2015). Therefore, positive coupling between the DMN and task-positive right MTG in the SA group may contribute to difficulty disengaging from negative self-focused thoughts or rumination. In fact, studies have found significant positive coupling between the DMN and regions within the CCN during depressive rumination compared to control tasks in individuals with major depression (Zhou et al., 2020). Moreover, this pattern of positive coupling between DMN regions (e.g., posterior cingulate cortex) and CCN regions (e.g., inferior frontal gyrus) has also been reported in individuals with a past SA (Chase et al., 2017). Although the right MTG is less frequently reported than other cognitive control regions, one study found the right MTG to be one of the most discriminating regions in differentiating individuals with STBs from diagnostic controls when actively thinking about suicide-related concepts (Just et al., 2017). Therefore, these results provide preliminary support that this CCN temporal region may be an important contributor to the network's dysregulation in STBs.

An important feature of the current study was the use of a psychiatric control group with similar rates and severity of psychopathology to the SA group, as many studies lack an appropriate psychiatric control group (e.g., Barredo et al., 2019). By using resting fMRI to dissociate neural markers of STBs from general psychopathology in a trauma-exposed population, we aimed to better isolate STB-specific neural correlates. Current transdiagnostic neurobiological models of STBs have predominantly been informed by convergent findings from studies investigating STBs in the context of major depression (Jollant et al., 2011; Lippard et al., 2014; Schmaal et al., 2020; Zhang et al., 2014), and few fMRI studies have examined STBs in a trauma-exposed cohort (e.g., Barredo et al., 2019; Davis et al., 2019; Matthews et al., 2012). Thus, given that neuroimaging studies of PTSD observe both transdiagnostic and diagnosis-specific neural correlates (Michopoulos et al., 2015), there may also be important differences in suicide-related brain markers *across* disorders. For example, one study found CCN-limbic STB-related markers (e.g., amygdala and dlPFC) to be more pronounced in the context of PTSD than depression (Davis et al., 2019). Therefore, although CCN and limbic alterations have been implicated in the context of STBs within affective disorders (e.g., depression), we hypothesize that the neural markers observed in the current study may be particularly pronounced for STBs in the context of trauma exposure. Compared to these previous studies, our results share consistencies with non-trauma exposed STB studies (e.g., CCN-limbic dysfunction) as well as novel findings that may be unique to trauma exposure (e.g., limbic-visual dysfunction). However, as no direct comparisons of SA-related neural markers across disorders (e.g., depression versus PTSD) were made in this study, conclusions regarding the transdiagnostic nature of these neural markers are speculative. Future work comparing equivalent imaging methods in a trauma-exposed and non-trauma exposed cohort will help determine the specificity of the current results and may have important treatment implications.

In this study, we attempted to address several methodological limitations in neuroimaging studies of STBs, but some limitations of the present study should be noted. One limitation of this study, and persistent in much of suicide research (Huang et al., 2020), is the small sample of individuals in the SA group ($n = 16$), which hinders interpretation of the results due to an increased likelihood of type I errors. Thus, the current findings should be considered preliminary, as they may not generalize to other independent samples. Nevertheless, the results may provide useful data for meta-analyses to further advance our current understanding of suicide risk, particularly within a trauma-exposed cohort for which neuroimaging studies of STBs are limited. In addition, the SA group was only characterized by the presence or absence of a previous suicide attempt, and additional details about the nature of the attempts were not collected (e.g., date and method of attempt). Therefore, time since the previous attempt and attempt lethality may significantly vary across participants within the SA group. Although our findings differentiate STBs from psychological distress, additional details about participants' attempt history may help to further parse the neural correlates of STBs, as significant differences in the neural correlates of STBs have been reported between high and low lethality suicide attempts (Oquendo et al., 2004). Further, as time since SA may significantly vary across participants, it is unclear if the results reflect a signature of suicide-risk or are a result of the attempt. Clarification of the nature of these SA-related brain markers is necessary, as the conclusions have important translational differences. If the observed SA-related changes are a result of the suicide attempt and were not present prior to the attempt, the hubs may represent targetable regions for suicide-related treatment but lack predictive utility for future STBs. Nevertheless, as those with a past SA are at higher risk for future STBs (Lee et al., 2018), these brain markers may still have some potential utility to inform the identification of at-risk individuals but may not be translatable to individuals with no history of a suicide attempt who attempt in the future. As few fMRI studies have examined STBs in a trauma-exposed cohort, we used a cross-sectional whole-brain approach to differentiate veterans with and without a past SA as a preliminary step. However, considering the current study's limitations, in future work, we plan to take a prospective approach to determine the predictive value of these neural markers in an independent sample (e.g., Lee et al., 2020).

In addition, both measures used to probe suicide attempt history require participants to self-disclose their current and past STBs either via self-report (BSS) or directly to a clinician (SCID). Due to the sensitive nature of suicide, individuals, and veterans, in particular, tend to underreport STBs (Nock et al., 2013). In addition, discrepancies across assessment modalities (written versus verbal) have been observed (Nock et al., 2008). As suicide attempt was only assessed with the SCID (clinical interview versus the written, self-report BSS) in a subsample of participants, underreporting may have been heightened in this study. This raises the possibility that false negative SA cases (those who did not disclose a past SA that occurred) were included in the PC group. However, the matching method used to identify PCs randomly selected a subsample of participants who met specific clinical-matching criteria (e.g., lifetime PTSD or MDD and current PTSD and depression symptom severity). Therefore, the use of random selection limits the likelihood that every possible false negative SA case was included in the PC group. Further, the inclusion of false negative SA cases in the PC group would only weaken our ability to find significant group differences. Thus, the observed group differences would likely be strengthened with a more reliable assessment of SA. Including multiple measures, as well as an objective measure, such as medical records, may help to more reliably identify individuals with a past SA. Additionally, although our analytic approaches extended the scope beyond *a priori* ROIs predominantly identified from studies of STBs and depression, there are limitations to a whole-brain approach. In this study, a data-driven, whole-brain approach required 204 comparisons, which increases the likelihood of type II errors. However, although the results do not strictly survive the most stringent multiple comparison correction for 204 ROIs (corrected alpha .00025), there is substantial evidence of the right amygdala's association with STBs. Namely, the right amygdala was not an isolated result, as the right amygdala was identified as an SA-related brain marker not only across analytic methods (seed--based and hubs-based) but also across group-wise comparisons (SA versus PC and SA versus TC). Further, our results corroborate *a priori* evidence found in a recent meta-analysis that identified the right amygdala to be one of three regions that significantly differentiated individuals with suicidal behavior from controls across 77 neuroimaging studies (Huang et al., 2020) and extend the finding to a different population and set of analytic methods. However, due to the preliminary nature of this study, future research should strive to replicate and extend these results in a larger sample.

The current study expands on previous work by addressing methodological limitations and extending the characterization of STBs-related brain markers to a high-risk sample of trauma-exposed veterans. The results identified two regional SA-related hubs of dysfunction (right amygdala and right MTG) that have widespread effects across networks and hemispheres. These results suggest that the right amygdala and right MTG may be specific neural markers of a past suicide attempt that can be differentiated from neural mechanisms of psychopathology more broadly. However, future studies with larger sample sizes will be necessary to evaluate the significance of these hub regions. This study provides an informative step in advancing our understanding of the neural correlates of STBs in a trauma-exposed sample and highlights the potential presence of both transdiagnostic (e.g., CCN-limbic dysfunction) as well as diagnosis-specific (e.g., limbic-visual dysfunction) SA-related brain markers.

Author Contributions

M.E. and M.A. conceived the study. A.S. conducted the analyses, interpreted the results, created data visualization and wrote the paper. Data analysis was also conducted by M.E., M.A., A.J.R., F.F., and D.R. Data visualization was also conducted by H.P. In addition, M.E., T.E., H. P., J.D., W.M., D.L., and G.M. contributed to data analysis and

interpretation as well as manuscript preparation. C.F. and J.R.F. contributed to data collection and verification. G.M. and M.E. contributed funding.

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Data and material availability

All data associated with this study are in the paper or Supplementary Materials. Full datasets are managed by data use agreements and Freedom of Information Act with the U.S. Department of Veterans Affairs.

Conflict of interests

No authors had competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.11.061.

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