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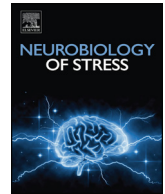
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Shared gray matter reductions across alcohol use disorder and posttraumatic stress disorder in the anterior cingulate cortex: A dual meta-analysis

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ABSTRACT

The considerable comorbidity of posttraumatic stress disorder (PTSD) and alcohol use disorders (AUD) poses a greater public health burden than either condition alone. Although there is a substantial body of evidence linking the direct neurotoxic effect of heavy drinking to gray matter (GM) deficits, as well as a growing body of literature supporting a strong association between PTSD and GM alterations, there is scant research interrogating the direct interaction of the two disorders. In order to generate data-driven, specific hypotheses regarding the overlapping neural substrates of PTSD and AUD, we conducted a meta-analysis of GM volumes in each disorder relative to healthy control subjects. We found shared GM deficits in the anterior cingulate cortex (ACC) across both disorders relative to healthy control participants. These findings suggest that reduced volumes of the ACC across PTSD and AUD may have implications for the development, expression, or treatment of symptoms linked to these frequently co-existing disorders. Recommendations are made for future work aimed at delineating the specific and shared effects of traumatic stress and alcoholism on neural integrity.

1. Introduction

Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) are common, chronic, and disabling mental health disorders, which frequently co-occur. Lifetime rates of PTSD and AUD in the general population are 4.8–6.4% (Blanco et al., 2013) and 29.1% (Grant et al., 2015), respectively. Prevalence of AUD among those with PTSD has been shown to be up to 28% for women and 52% for men (Kessler et al., 2005; Thomas et al., 2010), and rates of PTSD among patients with AUD are 30–59% (Jacobsen et al., 2001). Individuals with both diagnoses have worse treatment outcomes and more psychiatric, medical, legal, and social problems than those with either disorder alone (Driessen et al., 1998). In addition, clinicians report significant challenges in treating these individuals (Najavits et al., 2010). PTSD as it exists with AUD represents an important public health problem, and despite high rates of co-occurrence between PTSD and AUD, the neural substrates related to the specific co-occurrence remain under studied. One reason is that the vast majority of studies examining the impact of PTSD or AUD on the brain exclude for commonly co-occurring mental health disorders. While the study of such rarefied groups of individuals

is essential to delineate the specific processes involved in AUD-only or PTSD-only related sequelae, extending this work to include individuals with co-occurring AUD and PTSD is a necessary next step for our ability to prevent, facilitate diagnosis, and improve treatment of this common comorbidity.

1.1. Structural brain changes in alcohol use disorder

AUD is a chronic relapsing brain disease marked by a maladaptive pattern of alcohol consumption, loss of control over intake, and emotional distress when not using (American Psychiatric Association, 2013). To be diagnosed with an AUD, an individual must meet any 2 of 11 criteria in a 12-month period as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association, 2013). AUD is widespread in the general population and constitutes a significant public health concern. In the U.S., it is estimated that more than 6% of individuals aged 18 and older meet criteria for an AUD (SAMHSA, 2015), and excessive alcohol use is the third leading preventable cause of death in the U.S with a total of nearly 88,000 deaths per year (Stahre et al., 2014).

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Voxel-based morphometry (VBM) offers an automated whole brain measurement technique that uses voxel-wise comparisons of the local concentration of gray matter (GM) between groups (Ashburner and Friston, 2000). Structural neuroimaging studies using VBM have reported that AUD is associated with reduced GM volume in a number of cortical and subcortical regions, including frontal cortical areas (Chanraud et al., 2009; Chanraud et al., 2007; Charlet et al., 2014; Grodin et al., 2013; Heikkinen et al., 2017; Mechtcheriakov et al., 2007; Rando et al., 2011; Segobin et al., 2014; van Holst et al., 2012), cingulate cortex (Chanraud et al., 2009; Charlet et al., 2014; Demirakca et al., 2011; Heikkinen et al., 2017) insula (Charlet et al., 2014; Demirakca et al., 2011; Heikkinen et al., 2017; Mechtcheriakov et al., 2007; Segobin et al., 2014; van Holst et al., 2012), hippocampus (Chanraud et al., 2009; Mechtcheriakov et al., 2007), thalamus (Chanraud et al., 2007; Mechtcheriakov et al., 2007; Segobin et al., 2014; van Holst et al., 2012), and cerebellum (Chanraud et al., 2007; Mechtcheriakov et al., 2007; Segobin et al., 2014). However, there are marked inconsistencies across studies regarding the foci of reduced GM. Sources of inconsistency are multifactorial and can be attributed, although not limited to, demographic characteristics of the sample including age and sex, the presence of comorbid disorders in AUD, differences in acquisition protocols and processing, as well as differences in statistical analyses. In light of some of the inconsistent findings, recent meta-analyses have identified smaller GM volumes most consistently in prefrontal cortical regions, such as the anterior cingulate cortex (ACC), and insular cortex in AUD (Xiao et al., 2015; Yang et al., 2016). A number of studies have reported that the degree of brain volume loss correlates with the rate and amount of alcohol consumed over a lifetime (Brooks et al., 2014; Harding et al., 1996; Segobin et al., 2014). Moreover, there is evidence to suggest that structural GM deficits may persist with abstinence (Demirakca et al., 2011; Fein et al., 2009).

1.2. Structural brain changes in posttraumatic stress disorder

PTSD is characterized by a variety of symptoms, including emotional, cognitive, and physiological abnormalities that arise in a subgroup of individuals following the exposure to a traumatic event (American Psychiatric Association, 2013). While the complex symptomatology of PTSD points to the involvement of numerous brain regions, limbic and frontal areas appear to play a central role in this disorder. In particular, GM volume loss in PTSD subjects has been reported in the ACC (Chen et al., 2012; Felmingham et al., 2009; Nardo et al., 2013; O'Doherty et al., 2017), amygdala (Logue et al., 2018; Morey et al., 2012; O'Doherty et al., 2015; O'Doherty et al., 2017), and hippocampus (Felmingham et al., 2009; Logue et al., 2018; O'Doherty et al., 2017; Thomaes et al., 2010; Zhang et al., 2011). In PTSD, ACC abnormalities are theorized to impede inhibition of overactive amygdala reactivity, leading to an exaggerated response to threat and fear (O'Doherty et al., 2015; Rauch et al., 2006). The hippocampus has also been implicated as a key structure in PTSD pathophysiology due to its involvement in memory function as well as regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis (O'Doherty et al., 2015).

Given that morphological abnormalities are often lateralized or affect only sub regions of a structure, examining subcomponents of specific structures may be informative in understanding the pathophysiology of PTSD. The ACC is comprised of subdivisions, which are involved in distinct cognitive processes and are functionally connected to different brain regions (Bush et al., 2000). The dorsal ACC is believed to play a role in cognitive functions, while the rostral-ventral ACC has been implicated in emotion regulation (Bush et al., 2000). GM volume loss in PTSD has been reported in the left dorsal (Chen et al., 2012) and right dorsal (Kitayama et al., 2006; Thomaes et al., 2010), pregenual (Kasai et al., 2008; Rocha-Rego et al., 2012), and rostral ACC (Felmingham et al., 2009; Nardo et al., 2013), as well as the paracingulate gyrus (O'Doherty et al., 2017). Likewise, while Kasai et al.

(2008) found reduced GM density only in the right hippocampus (Kasai et al., 2008), others report reduced volumes only in the left hippocampus (O'Doherty et al., 2015; Zhang et al., 2011) or bilateral changes (Felmingham et al., 2009; Logue et al., 2018; O'Doherty et al., 2017). In addition, both decreased (Morey et al., 2012) and increased (Kuo et al., 2012) amygdala volumes have been found in PTSD patients. Group differences in sub regions of the frontal lobe that have been identified in PTSD include the middle frontal cortex (O'Doherty et al., 2017), right orbitofrontal cortex (Hakamata et al., 2007; Thomas et al., 2010), as well as the right prefrontal cortex, including the superior, middle, and inferior frontal gyri (Nardo et al., 2013). Geuze et al. (2008) reported reduced cortical thickness in the superior and inferior frontal gyri as well as the superior temporal gyrus.

Structural brain changes in PTSD have also been found outside limbic and frontal regions, including the insula (Corbo et al., 2005; Kasai et al., 2008), precuneus (O'Doherty et al., 2017), occipital cortex (Tavanti et al., 2012), inferior parietal cortex (Eckart et al., 2011), calcarine cortex (Zhang et al., 2011), and middle temporal gyrus (Li et al., 2014). Other studies, however, did not observe significant structural brain abnormalities in PTSD (Eckart et al., 2012; Woon and Hedges, 2009). The question whether these structural abnormalities are a consequence of chronic stress caused by PTSD symptoms or a predisposition to developing PTSD when exposed to a traumatic event, remains to be answered.

1.3. Structural brain changes in comorbid PTSD and AUD

Although there is ample evidence supporting the common clinical overlap between PTSD and AUD, and relatively large bodies of literature describing the impact of alcoholism or traumatic stress on the brain, there has been relatively little work aimed at identifying the unique and overlapping neural circuitry involved in these conditions. In an attempt to generate specific hypotheses about the mechanisms of PTSD and co-existing AUD, the aim of the current study was to conduct a meta-analysis of VBM studies for both PTSD and AUD, and to discern regions which may be highly involved in the development or maintenance of their comorbidity. In particular, we sought to extend existing knowledge of co-morbid PTSD and AUD by 1) examining both AUD-related and PTSD-related GM alterations and 2) identifying common neural substrates of the two disorders. We hypothesized that there would be relative deficits in prefrontal GM volume across both patient groups, and that markers of disorder severity would be negatively related to decreases in GM volume. Therefore, in these analyses, we provide an overview of the GM changes associated with each disorder, a meta-analysis for each condition, and display a meta-analysis of the collective VBM studies across both disorders. We also provide preliminary evidence that measures of disease severity may co-vary with these volumetric differences.

2. Material and methods

2.1. Inclusion of studies

For VBM studies of AUD, a systematic search strategy was applied to find relevant studies that were published between January 2000 and December 2017 in PubMed (<http://www.pubmed.org>), Web of Science (<http://www.webofknowledge.com>), and Science Direct (<http://www.sciencedirect.com>). Based on the terms suggested by Yang et al. (2016), we searched keywords (1) "alcohol dependence; alcoholism; alcohol abuse OR alcohol use disorder;" these keywords were crossed with (2) "voxel-based morphometry" or "VBM" or "morphometry" or "volumetry" or "gray matter" or "structural MRI" (Yang et al., 2016). Reference lists of the identified studies, as well as additional recent reviews (Xiao et al., 2015; Yang et al., 2016) were manually checked for additional studies that might be included.

For VBM studies of PTSD, a systematic search strategy was applied

to find relevant studies that were published between January 2000 and December 2017 in PubMed (<http://www.pubmed.org>), Web of Science (<http://www.webofknowledge.com>), and Science Direct (<http://www.sciencedirect.com>). Based on the terms suggested by Li et al. (2014), we searched keywords “(1) “posttraumatic stress disorder” or “PTSD” or “stress” or “trauma” or “adversity” or “child*abuse” or “maltreatment” or “rape” or “crime” or “violence” or “assault” or “war” or “combat” or “accident” or “disaster”; these keywords were crossed with (2) “voxel-based morphometry” or “VBM” or “morphometry” or “volumetry” or “gray matter” or “structural MRI” (Li et al., 2014).

Inclusion criteria for studies were: (1) for AUD: either an alcohol abuse disorder, alcohol dependence disorder or alcohol use disorder diagnosis, for PTSD: a formal diagnosis of PTSD, based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Statistical Classification of Diseases and Related Health Problems-10th Revision (ICD-10) diagnostic criteria; (2) use of the whole-brain VBM method to analyze GM reduction; (3) direct comparison to a healthy control (HC) sample; (4) clearly reported Talairach or Montreal Neurological Institute (MNI) coordinates of the significant brain areas, (5) thresholds for significance corrected for multiple comparisons or uncorrected with spatial extent thresholds, (6) studies were peer-reviewed, and (7) results that could be found in English. The exclusion criteria for the final meta-analysis were: (1) review or meta-analysis articles; (2) studies that re-analyzed previously published data; (3) studies with no direct comparison between patient and HC (e.g., 3 or more group comparisons), and (4) non-English or unavailable full-text record studies. If the patient group overlapped with previously published results, the largest sample size or the higher quality set was selected. Finally, special care was taken to only include those results that were held to a single statistical threshold. A flow chart illustrating the search strategy for relevant studies included in the meta-analyses can be found in Fig. 1.

2.2. Voxel-based meta-analyses

Two meta-analyses of GM differences were performed between (1) alcohol use disordered and healthy subjects and (2) subjects with PTSD and healthy control subjects. We used seed-based d Mapping (SDM; version 5.142) updated to employ anisotropic effect-based algorithms (AES-SDM; www.sdmproject.com). These methods have been previously described in detail elsewhere (Lim et al., 2014; J Radua et al., 2012; J Radua et al., 2014). A tutorial can be found at (<http://www.sdmproject.com/software/tutorial.pdf>), and the steps are summarized briefly here.

(1) Coordinates and effect-sizes of GM differences between patients and controls were obtained from each study's published results. Special care was taken to ensure that the same threshold throughout the brain was applied to all included results. (2) A standard MNI map of the differences in GM was constructed for each study using an anisotropic Gaussian kernel. Anisotropic kernels assign different values to the different neighboring voxels based on the spatial correlation between them, which results in higher effect sizes to the voxels that are more correlated with peaks, and results in maps that are independent of the full width at half maximum values of the included data (J Radua et al., 2014). (3) A map of the effect size variance was created for each study based on its effect size map and sample size. (4) The mean maps were generated via a voxelwise calculation of the random-effects mean of the study maps, weighted by the sample size and variance of each study, and the between study heterogeneity (Lim et al., 2014; J Radua et al., 2014).

A systematic, whole-brain, voxel-based jackknife sensitivity analysis was performed to assess the reliability of the results by iteratively repeating the same analysis, excluding one study at a time, to establish whether or not the results remained significant (Lim et al., 2014; J Radua et al., 2014). Additionally, we assessed whether unexplained between study variability affected our results (Lim et al., 2014; J Radua

et al., 2014). Statistical significance was determined using standard randomization tests, thus creating null distributions from which p-values can be obtained (Lim et al., 2014; J Radua et al., 2012; J Radua et al., 2014). The standard AES-SDM thresholds (uncorrected voxelwise p-value of $p < .005$, extent threshold clusters for ≥ 10 voxels, and z values of greater than or equal to $Z \geq 1$, which are proposed to optimally balance sensitivity and specificity) were used. Meta-regression analyses were used to look for moderators (Joaquim Radua and Mataix-Cols, 2009).

A common critique of the AES-SDM method is that the recommended threshold is too lenient. There are two primary ways to ameliorate this concern: (1) including only studies that use conservative thresholds (e.g., whole brain corrected voxel-wise p-values of $p \leq .05$), or (2) setting our statistical threshold at more stringent levels. As only 8 PTSD v HC and 13 AUD v HC studies met our inclusion criteria, further excluding studies based on the level of statistical threshold seemed to unduly sacrifice our power to detect group differences. While we considered reporting our results at a more conservative threshold at a voxelwise p-value of $p < .001$, the intent of this analysis is to highlight the potential direct, deleterious overlap in GM damage in the presence of the two conditions, therefore it seemed appropriate to be more inclusive of, and bring attention to, their potential additive effects on GM.

2.3. Visualizing overlapping meta-analyses

In order to generate a map of the shared areas of GM increases and decreases relative to healthy control subjects, we multiplied the resulting PTSD v HC and AUD v HC statistical masks, resulting in positive values in all regions where there were non-zero values across both maps. The result is meant to provide a spatial representation of the putative shared neural correlates of GM decreases and increases across both PTSD and AUD. There is no statistical value to these shared coordinates.

3. Results

We identified 13 eligible studies for the present meta-analysis involving AUD v HC, including a total of 456 AUD subjects compared to 522 HC subjects. Table 1 summarizes the primary features of the included investigations and characteristics of the subject cohort in the AUD v. HC contrast. A total of 8 eligible studies were identified for the meta-analysis of PTSD v HC, including 165 PTSD subjects compared to 173 HC subjects. Table 2 shows characteristics of the studies included in the PTSD v HC contrast. None of the PTSD studies allowed for the comorbidity of AUD, and all but one AUD study (E. N. Grodin et al., 2013) excluded for evidence of any concurrent Axis I disorder.

AUD meta-analysis. Subjects with AUD showed significant GM reductions in bilateral middle and anterior cingulate cortices, bilateral insulae and lenticular nuclei, and extending into the left middle frontal gyrus and bilateral superior frontal gyri compared to healthy controls (Table 3). There were no reliable regions wherein AUD subjects had significantly larger GM volumes than HC subjects. We excluded one cluster in the precuneus wherein $AUD > HC$, as (1) its SDM Z-value of 1.001 barely exceeded our set threshold of $Z \geq 1$, (2) a single study included in the meta-analysis contributed to this cluster (Charlet et al., 2014), (3) Charlet et al., 2014 used an uncorrected voxelwise p-value to threshold their results. Fig. 2 shows the reliable regional differences in GM volume in the AUD v HC sample.

Information on average duration of AUD or years of problem drinking was available for 12 of 13 data sets. Using a stringent threshold of $p < .0005$ to minimize spurious findings, duration of drinking (average in years from each study) was significantly negatively correlated within the supplementary motor area extending into BA 6 ($x = -0.7$, $y = 6.4$, $z = 54$; 197 voxels) wherein we also observed significantly decreased volume in the AUD relative to HC subjects.

PTSD meta-analysis. Compared to healthy control subjects, the

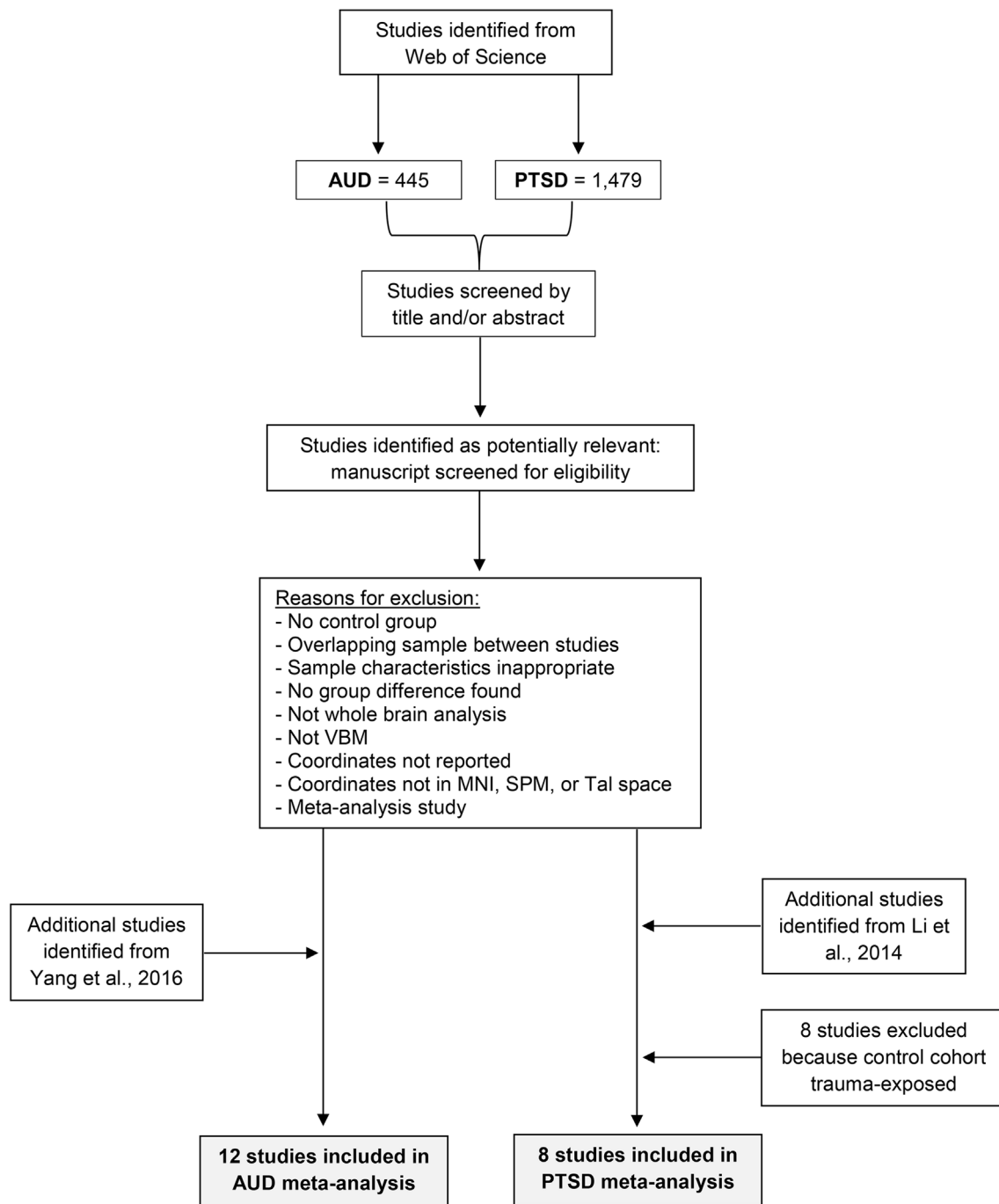


Fig. 1. Flow chart of search strategy and study selection for meta-analyses. Study search and screening procedures repeated for PubMed and Science Direct.

PTSD cohort was found to have significant GM reductions in an overall smaller area of the cortex than the AUD v HC, centered on the bilateral ACC extending rostrally into the ventromedial prefrontal cortex. In addition, analyses revealed an area of relative GM increase in the right supramarginal gyrus (Table 4). These regional differences are presented in Fig. 3.

Information on severity of PTSD symptoms (CAPS-4 total score) was available in 8 of 8 datasets. Again, imposing a stringent threshold of $p < .0005$ to minimize spurious findings, severity of current PTSD symptoms (average from each study) was significantly negatively correlated to a portion of the dorsal ACC ($x = 6, y = 28, z = 34; 48$ voxels), a location within the larger region where we identified significantly less GM volume in individuals with PTSD (PTSD < HC). There were no significant positive correlations between severity of

PTSD and the region that we identified as having significantly greater GM volume in PTSD v HC.

AUD and PTSD overlap. Analyses showed that across AUD and PTSD related GM differences our maps demonstrate an area of shared bilateral GM loss in regions of the ACC, across dorsal and rostral aspects (Table 5). These areas of overlap in significantly reduced GM density are highlighted in Fig. 4.

Jackknife sensitivity analysis in the AUD meta-analysis revealed that the deficits in the bilateral median cingulate/paracingulate gyri and the bilateral insulae/lenticular nuclei/BA 48 were highly robust, as they were replicable in all of the 13 studies (Table 6). Deficits in the left middle frontal gyrus, BA 44 remained significant in 12 combinations of studies. Charlet et al., 2014, the only study which reported increased GM volume in AUD v HC, was judged not to be unduly influential as all

Table 1
Characteristics of AUD vs. HC studies included in the meta-analysis.

Study	Alcohol diagnosis	Criteria	Duration in yrs.	AUD N (% male)	Control N (% male)	Mean age AUD/Control	GM measure	Corrected p-value
Chanraud et al. (2007)	Dependence	DSM-IV	8 (dependence)	26 (100)	24 (100)	47.7/45	Volume	FDR corr. $p < 5 \times 10^{-3}$
Charlet et al. (2014)	Dependence	DSM-IV	N/A	40 (75)	40 (75)	44.9/44.1	Volume	Uncorr. $p < .001$
Demirakca et al. (2011)	Dependence	DSM-IV	12.4 (illness)	50 (54)	66 (51.5)	46.6/45	Volume	FWE corr. $p < .05$
Grodin et al. (2013)	Dependence	DSM-IV	10.3 (heavy drinking)	37 (56.8)	69 (68.1)	40.2/36.6	Volume	Corr. $p < .01$
Jang et al. (2007)	Dependence	DSM-IV	10.3 (illness)	20 (100)	20 (N/A)	43.5/44.5	Density	Uncorr. $p < .001$
Mechtcheriakov et al. (2007)	Addiction	ICD-10-R	> 10 (drinking history)	22 (63.6)	22 (63.6)	53.6/53.7	Density	FDR corr. $p < .05$
Nurmedov et al. (2016)	AUD	DSM-V	7.7 (heavy drinking)	24 (20)	29 (23)	37.45/40.79	Volume	FWE corr. $p < .05$
Rando et al. (2011)	Dependence	DSM-IV	18.62 (alcohol use)	45 (75.5)	50 (56)	38.2/31.14	Volume	FWE corr. $p < .025$
Segobin et al. (2014)	Dependence	DSM-IV	15.15 (alcohol misuse)	19 (89.5)	20 (N/A)	44.4/46.7	Volume	FDR corr. $p < .01$
van Holst et al. (2012)	Abuse/dependence	DSM-IV-TR	11.69 (disorder)	36 (100)	54 (100)	43.2/35.3	Volume	FDR corr. $p < .05$
Wang et al. (2016)	Dependence	DSM-IV	25.25 (alcohol use)	20 (100)	20 (100)	43.95/40.5	Volume	FWE corr. $p < .05$
Wiers et al. (2015)	Dependence	DSM-IV	14.82 (dependence)	22 (100)	21 (100)	42.14/41.95	Volume	FWE corr. $p < .05$
Zois et al. (2017)	Dependence	DSM-IV	10.9 (dependence)	95 (75)	87 (82)	45.9/45.9	Volume	FWE corr. $p < .05$

Notes. FDR = false discovery rate, FWE = family-wise error.

4 clusters were replicated in its absence.

Jackknife sensitivity analysis in the PTSD meta-analysis revealed that the deficits in the left ACC, paracingulate gyri, and BA 32 were highly robust, as they were replicable in all of 8 studies; deficits in the right supramarginal gyrus, BA 40 were also highly replicable, as they remained significant in 7 combinations of studies (Table 6). The smaller volume of the BA 25 remained significant in 5 combinations of studies, demonstrating less reliability in this region.

For both the AUD vs HC and the PTSD vs HC analyses, an analysis of heterogeneity showed that there was no significant unexplained between-study variability that accounted for the regions in which we found group differences.

4. Discussion

We completed two comprehensive meta-analyses of GM volume in individuals with AUD and PTSD relative to healthy control individuals, and examined the resultant maps for spatial overlap. Consistent with recent meta-analyses comparing GM volume in those with AUD to control individuals (Xiao et al., 2015; Yang et al., 2016), we found relative reductions in bilateral middle and anterior cingulate, bilateral insulae and lenticular nuclei, extending into the left middle frontal gyrus and bilateral superior frontal gyri in those with AUD. These findings implicate the involvement of cortico-striatal limbic circuits in either the vulnerability to engage in, or the direct effects of, problematic alcohol use. Our meta-regressions examining the association between the duration of problem drinking and GM volume did not directly correspond to the regions where we found decreased GM relative to HC. While a more direct measure of total lifetime alcohol consumption would better isolate direct effects of alcohol on GM volumes (Pfefferbaum et al., 1995), other factors reflecting vulnerability or resilience likely contributed to the current results.

Our second meta-analysis revealed significant GM reductions in those with PTSD relative to HC in an overall smaller area of the cortex than implicated by AUD, centered on the bilateral anterior cingulate extending rostrally into the ventromedial prefrontal cortex. We also found an area of relative GM increase in the right supramarginal gyrus. Reductions in medial prefrontal cortex are consistent with existing whole brain meta-analyses of PTSD GM volumes (Li et al., 2014; Meng et al., 2014). Moreover, our meta-regressions indicated that greater PTSD symptom severity was related to smaller GM volumes across studies in the dorsal ACC, underscoring the involvement of this region in active PTSD.

The goal of this investigation was to identify regions of shared GM

loss and sparing in those with either PTSD or AUD. We found spatial overlap in relative GM reductions shared across these meta-analyses within bilateral rostral and dorsal aspects of the ACC, suggesting that both AUD and PTSD disease mechanisms may involve these regions. Our results suggest that reduced volumes of these subregions of the ACC within one, or across both disorders, may have implications for the development, expression, or treatment of symptoms linked to co-existing AUD and PTSD. For example, deficits in these regions may indicate vulnerability for the development of both disorders, and the expression of that vulnerability may vary based upon environmental exposures or other biological variables. Given that our meta-regressions linked greater PTSD symptom severity to smaller GM volumes of the dorsal ACC, we have some preliminary evidence that active PTSD symptoms may, in part, contribute to alterations in dorsal ACC volume. Certainly, only a design that includes individuals with both AUD and PTSD as well as only AUD or PTSD can address whether GM alterations to the ACC are a hallmark of their comorbidity or related to specific factors within either disorder.

As to the mechanism of risk or consequence of smaller ACC volumes in a comorbid population, the ACC and its subregions are integral to a number of emotional, physiological, and behavioral processes that likely play a role in the behavioral correlates of combined PTSD and AUD. Although the ACC is one of the most studied parts of the brain, our understanding of its operations - and subregional operations - is far from comprehensive (Genon et al., 2018). The diverse array of cognitive functions attributed to the ACC include but are not limited to conflict monitoring (Barch et al., 2001; Botvinick and Braver, 2015; Carter et al., 1998; Van Veen and Carter, 2002), error detection (Carter and Van Veen, 2007; Swick and Turken, 2002), as well as task prediction (e.g., error, effort, reward, motivation) and preparation (e.g., decision making, adaptive responding) (Aarts et al., 2008; Botvinick and Braver, 2015; J. W. Brown and Braver, 2005; Chong et al., 2017; Jessup et al., 2010; Silvetti et al., 2013; Vassena et al., 2014a,b). The role of the ACC in the perception and regulation of emotion has also been vigorously investigated (Botvinick and Braver, 2015; Bush et al., 2000; Etkin et al., 2011; Etkin et al., 2006; Phan et al., 2002; Stevens et al., 2011).

A number of functional and anatomical parcellation studies suggest that subdivisions of the ACC and their patterns of connectivity may provide regional specialization to support this diverse array of functions (Balsters et al., 2016; Beckmann et al., 2009; Fan et al., 2016; Glasser et al., 2016; Jin et al., 2018; Neubert et al., 2015; Torta et al., 2013; Yu et al., 2011). Co-activation of dorsal versus rostral ACC and particular limbic structures may relate to their respective roles in the appraisal of

Table 2
Characteristics of PTSD vs. HC studies included in the meta-analysis.

Study	Trauma type	Criteria	CAPS score	PTSD N (%male)	Control N (% male)	Mean age PTSD/Control	AUD exclusion	GM measure	Corrected p-value
Bossini et al. (2017)	Not specified	DSM-IV	75.8	19 (52.63)	HC 19 (78.9)	40/41	N/A	Volume	Montecarlo corr. p < .05
Chen et al. (2012)	Coal mine disaster	DSM-IV	78.7	10 (100)	HC 20 (100)	40.8/37.6	Substance abuse	Volume	FWE corr. p < .05
Cheng et al. (2015)	Wenchuan earthquake	DSM-IV	56.4	30 (70)	HC 30 (70)	26.3/26.2	Alc. abuse	Volume	FWE corr. p < .05
Corbo et al. (2005)	Not specified	DSM-IV	64.71	14 (42.86)	HC 14 (42.86)	33.36/33.29	Alc. abuse/dep.	Density	Corr. p < .05
O'Doherty et al. (2017)	Not specified	DSM-IV	57	25 (48)	HC 25 (48)	34.0/31.7	Substance dep.	Volume	FWE corr. p < .01
Sui et al. (2010)	Rape	DSM-IV	74.45	11 (0)	HC 12 (0)	25.55/26.42	Alc. use/abuse	Density	Uncorr. p < .005
Tavanti et al. (2012)	Mixed	DSM-IV	81.52	25 (32)	HC 25 (32)	38.16/38.08	AUD	Volume	Randomise corr. p < .05
Thomases et al. (2010)	Childhood abuse	DSM-IV-TR	88.5	31 (0)	HC 28 (0)	35.3/35.2	Alc. abuse/dep.	Concentration	Uncorr. p < .001 ^a

Notes.

^a The clusters included reached significance at an uncorrected p < .001 level. FDR = false discovery rate, FWE = family-wise error.

Table 3
Regional differences in GM volumes: AUD vs. HC.

Clusters of ≥ 10 voxels with all voxels SDM-Z ≥ 1 and all peaks SDM-Z ≥ 1						
MNI coordinates						
x	y	z	SDM-Z	P value	Voxels	Brain region
None						
Clusters of ≥ 314 voxels with all voxels SDM-Z ≤ -2.686 and all peaks SDM-Z ≤ -3.119						
MNI coordinates						
x	y	z	SDM-Z	P value	Voxels	Brain region
0	-4	34	-5.083	~0	6024	Left median cingulate/paracingulate gyri
-38	-4	6	-4.377	0.000020623	2944	Left insula, BA 48
34	-4	0	-4.371	0.000020623	2541	Right lenticular nucleus, putamen, BA 48
-46	10	38	-3.089	0.00124377	140	Left middle frontal gyrus, BA 44

Notes. Areas of reduced GM volume in AUD subjects (N = 456) compared to HC subjects (N = 522) from 13 peer-reviewed studies. Voxel threshold: p < .005. Peak height threshold: peak SDM-Z > 1.000. Extent threshold: cluster size ≥ 10 voxels.

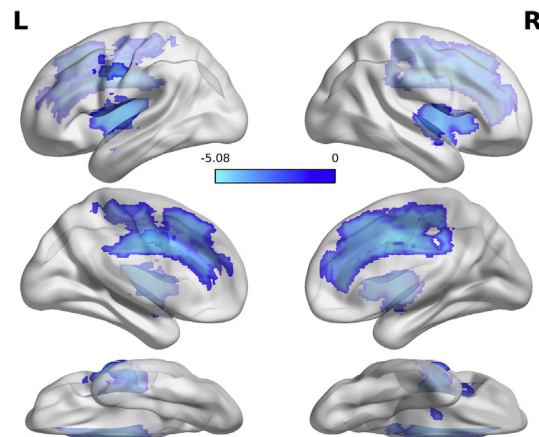


Fig. 2. Areas of significantly decreased GM volume in AUD v HC: bilateral middle and anterior cingulate, insulae, lenticular nuclei, left middle frontal gyrus, superior frontal gyri. Gradient bar represents SDM value. L = left hemisphere, R = right hemisphere.

emotion (e.g., dorsal ACC and anterior insula connectivity) versus more regulatory demands (e.g., rostral/ventral ACC and amygdala connectivity) (Dosenbach et al., 2006; Egner et al., 2007; Etkin et al., 2006, 2011; Giuliani et al., 2011; Seeley et al., 2007). Despite these varied functions, the ACC can be broadly assigned the role of integrating information from multiple sources to assign a value or resolve conflict, and consequently to inhibit or engage in a behavioral response (Etkin et al., 2011; Fitzgerald et al., 2018). Given the design of the current analysis, we may only hypothesize as to how volume decrements across rostral and dorsal ACC may impact clinically relevant behavioral outcomes in these co-occurring disorders.

Neuroimaging findings across PTSD and AUD studies strongly suggest that dysfunction within the rostral and dorsal ACC plays a role in their respective symptomologies. With regard to PTSD, exaggerated response in the dorsal ACC has been consistently observed during fear conditioning and fear extinction (Linnman et al., 2011; Milad et al., 2009; Rougemont-Bücking et al., 2011; Shvil et al., 2014). Several fMRI studies of emotional processing have observed hypoactivation in the dorsal and more rostral regions of the ACC, suggesting that both emotional appraisal and regulation are likely to be impacted (Hopper et al., 2007; Hou et al., 2007; Shin et al., 2005; Simmons et al., 2011; Williams

Table 4
Regional differences in GM volumes: PTSD vs. HC.

Clusters of ≥ 1717 voxels with all voxels $\text{SDM-Z} \geq 0.618$ and all peaks $\text{SDM-Z} \geq 1.117$						
MNI coordinates						
x	y	z	SDM-Z	P value	Voxels	Brain region
52	-46	44	1.117	0.000127137	1717	Right supramarginal gyrus, BA 40
Clusters of ≥ 10 voxels with all voxels $\text{SDM-Z} \leq -1.851$ and all peaks $\text{SDM-Z} \leq -1.986$						
MNI coordinates						
x	y	z	SDM-Z	P value	Voxels	Brain region
2	42	20	-3.115	0.000010967	3118	Left anterior cingulate/paracingulate gyri, BA 32
0	6	-6	-1.986	0.002647817	10	BA 25

Notes. Areas of increased and reduced GM volume in PTSD subjects (N = 165) compared to HC subjects (N = 173) from 8 peer-reviewed studies. Voxel threshold: $p < .005$. Peak height threshold: peak $\text{SDM-Z} > 1.000$. Extent threshold: cluster size ≥ 10 voxels.

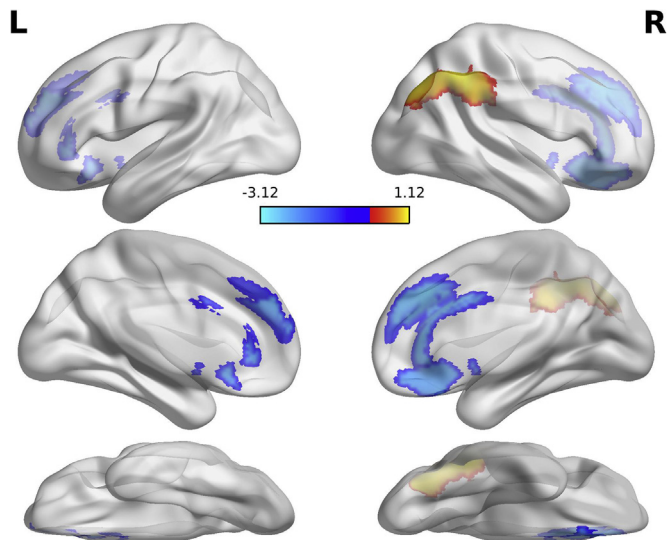


Fig. 3. Areas of GM volume differences in PTSD v HC: GM volume loss in bilateral ACC (blue), GM volume increase in right supramarginal gyrus (yellow/red). Gradient bar represents SDM value. L = left hemisphere, R = right hemisphere. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 5
Size and extent of ACC that is reduced compared to HC in both samples.

MNI coordinates						
x	y	z	SDM-Z	P value	Voxels	Brain region
1.1	32.4	25	N/A	N/A	1897	BA 32, 25

Notes. Voxel size $2 \times 2 \times 2$ mm. Extent of cluster max RL (10), min RL (-6), max AP (54), min AP (-4), max IS (46), min IS (-2).

et al., 2006). It is widely held that hyperresponsivity of the salience network (dorsal ACC and anterior insula) and hyporesponsivity in regions important for cognitive control (rostral ACC and other prefrontal regions) may underpin a bias for negative emotional and trauma related stimuli in those with PTSD (Hayes et al., 2012).

With regard to AUD, difficulties with cognitive control and emotional regulation figure prominently into the phenomenology of addictions (e.g., Volkow et al., 2016). Akin to findings in PTSD patients,

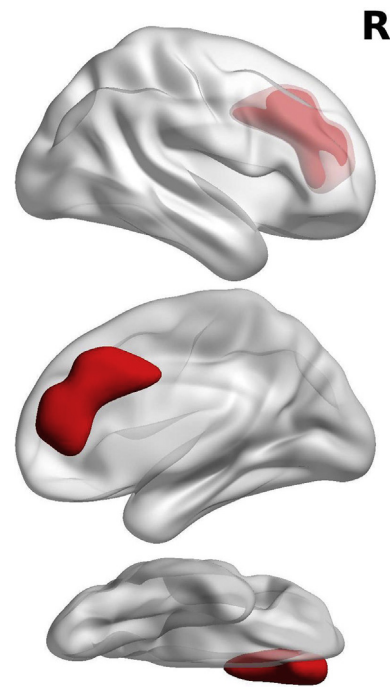


Fig. 4. Areas of overlap AUD v HC and PTSD v HC: reduced GM volume bilateral ACC. Ventral view depicts left and right hemispheric extent of overlap. R = right hemisphere.

neuroimaging studies of AUD also tend to indicate hypoactivation of the ACC in response to stress and negative affective cues, but, without the hyperactivation of limbic structures seen in PTSD (Seo et al., 2013; Wilcox et al., 2016). Therefore, emotional dysregulation in those with AUD alone may stem from deficient prefrontal functioning without exaggerated bottom up neural response (Wilcox et al., 2016). Taken together in the context of the PTSD and AUD literature, our current findings may reflect that smaller volumes across dorsal and rostral ACC could have implications for the effective management of negative mood states and stress triggers in those with both PTSD and AUD. This hypothesis is consistent with evidence that smaller volumes of the dorsal ACC across a range of psychopathologies is related to poorer executive functioning (Goodkind et al., 2015), and that recovery in AUD is also related to rostral and dorsal ACC volume increases with abstinence (Zou et al., 2018). However, Helpman et al., 2016 also found volume decreases in rostral ACC following treatment for PTSD, suggesting the relationship may not be the same across subregions of the ACC, stages of illness, or within PTSD alone compared to PTSD in the context of AUD (Seo et al., 2013; Wilcox et al., 2016).

There have been several recent attempts to unify the functions of the ACC under a single working model that may also provide a more parsimonious, albeit speculative, hypothesis as to how decrements in ACC volume play a role in the development and consequences of comorbid AUD and PTSD (Alexander and Brown, 2011, 2015; Botvinick and Braver, 2015; J. W. Brown and Alexander, 2017; Holroyd and McClure, 2015; Khamassi et al., 2011; Shahnazian and Holroyd, 2018; Silvetti et al., 2011; Vassena et al., 2017). Specifically, the ACC has been robustly associated with generating learning signals during complex executive tasks in uncertain environments, ranging from reward learning to perceptual decision-making and inhibitory function (Aarts and Roelofs, 2011; Behrens et al., 2007; Botvinick and Braver, 2015; Bush et al., 2000; Etkin et al., 2011; Harlé et al., 2014; Holroyd and Coles, 2002; Ide et al., 2013; Kennerley et al., 2011; Wilcox et al., 2016; Shenhav et al., 2013; Somerville et al., 2006). In sum, this conceptualization suggests a prominent role of both rostral and dorsal aspects of the ACC in adaptive decision making, in that continuous

Table 6
Jack-knife sensitivity analysis for each significant cluster.

AUD v HC				
Studies	L median cingulate/paracingulate gyri	L insula, lenticular nucleus, putamen, BA 48	R insula, lenticular nucleus, putamen, BA 48	L middle frontal gyrus, BA 44
Chanraud et al. (2007)	Y	Y	Y	N
Charlet et al. (2014)	Y	Y	Y	Y
Demirakca et al. (2011)	Y	Y	Y	Y
Grodin et al. (2013)	Y	Y	Y	Y
Jang et al. (2007)	Y	Y	Y	Y
Mechtcheriakov et al. (2007)	Y	Y	Y	Y
Nurmedov et al. (2016)	Y	Y	Y	Y
Rando et al. (2011)	Y	Y	Y	Y
Segobin et al. (2014)	Y	Y	Y	Y
van Holst et al. (2012)	Y	Y	Y	Y
Wiers et al. (2015)	Y	Y	Y	Y
Wang et al. (2016)	Y	Y	Y	Y
Zois et al. (2017)	Y	Y	Y	Y
PTSD v HC				
Studies	R supramarginal gyrus, BA 40	L anterior cingulate/paracingulate gyri, BA 32	BA 25	
Bossini et al. (2017)	N	Y	Y	
Chen et al. (2012)	Y	Y	N	
Cheng et al. (2015)	Y	Y	Y	
Corbo et al. (2005)	Y	Y	Y	
O'Doherty et al. (2017)	Y	Y	N	
Sui et al. (2010)	Y	Y	Y	
Tavanti et al. (2012)	Y	Y	Y	
Thomaes et al. (2010)	Y	Y	N	

feedback in the form of a prediction error or learning signals via the ACC to lateral prefrontal regions shapes subsequent behavior (Alexander and Brown, 2011, 2015; J. W. Brown and Alexander, 2017; Holroyd and McClure, 2015; Khamassi et al., 2011; M. Silvetti et al., 2011; Vassena et al., 2017). Therefore, damage or alteration to the structural integrity of the ACC would contribute to impaired adaptive behavior, putatively via the disruption of ACC feedback to the prefrontal cortex (Grodin et al., 2017).

Given this conceptual model of adaptive or reinforcement learning, the clinical correlates of PTSD and AUD suggest that failure to adjust behavioral responses accordingly in the face of changing stimulus values leads to problematic, perseverative behavior. In the case of PTSD, failure to adjust a disproportionate fear response to stimuli formerly coupled with danger, drives hyperarousal and avoidance (Graham and Milad, 2011; Jovanovic et al., 2012) serving to maintain PTSD symptoms (Marshall et al., 2006; Schell et al., 2004). This diminished top-down influence and flexibility in adaptive decision-making is further consistent with the hypothesis that a compromised ACC in trauma-exposed individuals can lead to disinhibition of an overactive amygdala, leading to an exaggerated response to threat and fear (O'Doherty et al., 2015; Rauch et al., 2006). In the case of AUD, inability to adjust a motivational-salience response to stimuli formerly coupled with alcohol is thought to contribute to problematic drinking patterns (Field et al., 2008; Robinson and Berridge, 1993; Sjoerds et al., 2013; Valyear et al., 2017) and undermine cessation efforts (Koob and Volkow, 2010; Naqvi and Bechara, 2010; Paulus et al., 2009). Therefore, the mechanisms of failed adaptive learning may provide important treatment targets for co-morbid PTSD and AUD. However, to date, there are only few objective inquiries testing the predictive utility of ACC function in AUD (Park et al., 2010; Reiter et al., 2016; Sebold et al., 2014, 2017) and PTSD populations (V. M. Brown et al., 2018; Cisler et al., 2015), and none in individuals with comorbid PTSD and alcoholism. Our findings suggest that the role of the ACC in directing goal-driven behavior may further our understanding of the mechanisms driving the intersection of alcohol abuse and PTSD.

Findings from the present meta-analysis should be interpreted with

caution, as it is problematic to draw conclusions about causality based on volumetric abnormalities in PTSD and AUD. Other factors should be taken into account when examining this cause and effect relationship. For instance, exposure to trauma may lead to a dysregulation of stress signaling pathways, which can, with chronic stress exposure, lead to neuronal synaptic and spinal loss, and may contribute to prefrontal cortex volume deficits in PTSD (Arnsten, 2009), while alcohol-related neurotoxic effects may interact to increase vulnerability to psychopathology. Histories of trauma, including trauma experienced in early life, are often present in individuals who develop AUD later in life (Stewart, 1996). A portion of the overlap in ACC GM volume reductions in both disorders may therefore reflect a common path of trauma exposure. Alternatively, results from the present meta-analysis are consistent with a large meta-analysis indicating diminished ACC volume in subjects compared to healthy controls across a variety of mental health disorders (Goodkind et al., 2015). In the context of this larger work, relative reductions of ACC may not be specific to AUD as it exists with PTSD, but instead may present a shared neural substrate common to a number of psychopathologies. Finally, whether decreased GM volume exists as a precursor or as a result of mental health disorders remains a challenging question to address. Longitudinal, cross diagnostic work may ultimately best address the neural basis of mental health psychopathology.

Several methodological and conceptual differences between studies included in this meta-analysis should be taken into consideration. The wide variance in selection of control groups (e.g., accounting for trauma exposure, occasional alcohol use vs alcohol abstinence, etc.), the limited presence of genetic controls in studies (e.g., twin studies), as well as the range of imaging and normalization methodology used, could account for inconsistent findings between studies. In addition, these methodological differences make it difficult to draw solid conclusions on causality of volumetric abnormalities in patients compared to healthy controls (Li et al., 2014). Furthermore, our review of the literature revealed some areas of concern that should be addressed in order to expand our understanding of how PTSD and AUD may interact. While we found that all included PTSD studies excluded for alcohol and

substance use disorders, it is uncommon for AUD studies to track or report on the number of AUD subjects who have been exposed to trauma. As there is a high level of trauma exposure in those with heavy drinking (Schwandt et al., 2013; Stewart, 1996; Windle, 1994), and trauma exposure itself is linked to GM structural alterations (O'Doherty et al., 2015), there may be additional GM variance due to trauma exposure that is un-accounted for in AUD studies. However, in order to not further complicate the potential relationship between trauma exposure without PTSD and brain morphology, we excluded studies with trauma-exposed control cohorts. AUD studies should therefore assess for and track risk factors such as exposure to childhood trauma to better explain the source of variance in studies. Likewise, PTSD studies should assess exposure to early life stressors or trauma that occurred prior to and in addition to the trauma directly linked to the onset of PTSD. In addition, tracking alcohol consumption, in particular problematic drinking or AUD, in PTSD studies would provide valuable information regarding the effects of both disorders on the brain.

The present meta-analysis is limited by the relatively small number of studies that met inclusion criteria. Studies were carefully selected in order to not introduce unnecessary variance and to maximize reliability of study findings (a detailed account of inclusion criteria can be found in Fig. 1 and section 2.1). In particular, by excluding studies with trauma-exposed control cohorts, the number of eligible PTSD studies was reduced by 50% highlighting the need to assess trauma exposure in control subjects. Moreover, several excellent studies carried out GM volume analyses in patient cohorts with PTSD and AUD but did not include a table of results as these were not the main outcome variable of the research.

For future research, the present work points to the importance of targeting the ACC in the investigation of the neural mechanisms responsible for the development, persistence, and remission of AUD and PTSD related symptoms. In those with co-existing AUD and PTSD, research should not only employ tasks that reliably invoke regions of the ACC, but should include analyses that probe the interaction of ACC modulatory regions and limbic and extra-limbic structures, including the amygdala, insula, and hippocampus as these regions are directly involved in the clinical symptomology of both disorders (Gilpin and Weiner, 2017). Rather than examining the direct effect of task activation on the ACC, investigating the connectivity within these circuits may allow us to better understand the effect of abnormal ACC function in comorbid AUD and PTSD. Finally, this investigation highlights the lack of research focused on the interaction of PTSD and alcoholism on a neural level. Future studies that include direct comparisons across those with PTSD, AUD, and their comorbidity can better address the mechanisms of risk and resilience to these stress-related disorders.

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Conflicts of interest

None of the authors have any conflicts of interest to declare.

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