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A preliminary examination of cortical neurotransmitter levels associated with heavy drinking in posttraumatic stress disorder

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ABSTRACT

Posttraumatic stress disorder (PTSD) patients have low cortical concentrations of γ-aminobutyric acid (GABA) and elevated glutamate (Glu) as measured by proton magnetic resonance spectroscopy (^{1}H MRS). Alcohol use disorder (AUD) is highly comorbid with PTSD, but the neurobiological underpinnings are largely unknown. We wanted to determine if PTSD patients with AUD have normalized cortical GABA and Glu levels in addition to metabolite alterations common to AUD. We compared brain metabolite concentrations in 10 PTSD patients with comorbid AUD (PAUD) with concentrtations in 28 PTSD patients without AUD and in 20 trauma-exposed controls (CON) without PTSD symptoms. We measured concentrations of GABA, Glu, *N*-acetylaspartate (NAA), creatine- (Cr) and choline-containing metabolites (Cho), and myo-Inositol (mI) in three cortical brain regions using ^{1}H MRS and correlated them with measures of neurocognition, insomnia, PTSD symptoms, and drinking severity. In contrast to PTSD, PAUD exhibited normal GABA and Glu concentrations in the parieto-occipital and temporal cortices, respectively, but lower Glu and trends toward higher GABA levels in the anterior cingulate cortex (ACC). Temporal NAA and Cho as well as mI in the ACC were lower in PAUD than in both PTSD and CON. Within PAUD, more cortical GABA and Glu correlated with better neurocognition. Heavy drinking in PTSD is associated with partially neutralized neurotransmitter imbalance, but also with neuronal injury commonly observed in AUD.

1. Introduction

Among individuals with posttraumatic stress disorder (PTSD), up to 85% suffer from alcohol use disorders (AUD) (Kessler et al., 1995; Baker et al., 2009; Javidi and Yadollahie, 2012). The co-occurrence of these disorders is associated with worse psychosocial and medical outcomes, higher rates of hospitalization and typical substance use-related problems (McCarthy and Petrakis, 2010). Although the recent biological literature on PTSD and AUD has each grown substantially (Volkow and Li, 2005; Spanagel, 2009; Pitman et al., 2012), little is known about the neurobiological underpinnings associated with *comorbid* PTSD and AUD (PAUD). The purpose of this study is to contrast neuroimaging-based brain metabolite concentrations in PTSD patients with and without AUD.

In vivo proton magnetic resonance spectroscopy (^{1}H MRS) is an invaluable tool for non-invasive quantitation of regional brain metabolite levels related to the neuropathology of a disease. ^{1}H MRS has been used to investigate the deregulation of the glutamate and γ-aminobutyric acid (GABA) pathways posited to be involved in the pathophysiology of PTSD (Hageman et al., 2001). In a recent ^{1}H MRS study comparing PTSD patients with trauma-exposed individuals without PTSD symptoms, we found lower GABA levels in the lateral temporal (TEMP) and parieto-occipital cortices (POC), higher glutamate in TEMP cortex, and lower *N*-acetylaspartate levels (NAA, a marker of neuronal viability) in prefrontal cortex (Meyerhoff et al., 2014).

Other brain metabolites such as myo-inositol (mI), creatine- (Cr), and choline-containing compounds (Cho) serve as intracellular

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markers of membrane abnormalities and high-energy metabolism in psychiatric disorders (Vion-Dury et al., 1994). PTSD brain studies have mainly targeted regions with functional (Shin et al., 2001; Shin et al., 2004) and structural abnormalities (Pitman et al., 2012), namely the hippocampus and anterior cingulate cortex (ACC). A meta-analysis of 16 ^{1}H MRS studies that compared PTSD patients with healthy controls (Karl and Werner, 2010) revealed lower left and right hippocampal NAA measures (both NAA relative to Cr and absolute NAA concentration), reduced NAA concentration in the ACC, and higher left hippocampal Cho/Cr. These abnormalities indicate neuronal injury and membrane alterations in regions of the brain associated with memory encoding, fear extinction, and emotional control (Hamner et al., 1999).

Brain metabolite concentrations are also altered in individuals with AUD, primarily in the frontal lobes (Sullivan, 2000; Meyerhoff et al., 2004; Durazzo and Meyerhoff, 2007; Buhler and Mann, 2011; Mon et al., 2012). Using ^{1}H MRS methods identical to those employed in this study, we showed (Mon et al., 2012) lower concentrations of Glu, NAA, and Cr in the ACC of recently detoxified alcohol-dependent individuals compared with non-drinking or light-drinking controls, and normal ACC GABA and mI concentrations; however, metabolite levels in the dorsolateral prefrontal cortex and POC were not abnormal in these alcohol-dependent individuals (Mon et al., 2012).

One ^{1}H MRS study of PTSD investigated the effects of alcohol consumption on brain metabolite concentrations (Schuff et al., 2008). Both PTSD patients with little or no alcohol consumption and PTSD patients with a history of alcohol abuse within the 5 preceding years had low NAA/Cr in the ACC and mesial temporal lobe including the hippocampus. Given that we detected NAA deficits only in heavy drinkers who consumed at least 90 standard alcoholic drinks per month for extended periods (Meyerhoff et al., 2004), this was not necessarily surprising: The alcohol-drinking PTSD patients of the study of Schuff et al. consumed <20 standard alcoholic drinks/month averaged over 5 years and only 34 drinks the month before the study. Such an amount of alcohol consumption is far below what is considered “at risk” or “heavy” drinking according to NIH/NIAAA guidelines (Willenbring et al., 2009).

Therefore, to our knowledge, no research has investigated the effects of heavy drinking on brain metabolite concentrations in PTSD patients with a current AUD diagnosis. This high comorbidity exists, at least in part, because alcohol use may be an attempt to “self-medicate” and/or respond to symptoms such as insomnia, anxiety, and hyperarousal (Leeies et al., 2010; Ouimette et al., 2010). Therefore, we hypothesized that the cortical neurotransmitter imbalances we described in PTSD patients without AUD (Meyerhoff et al., 2014) are attenuated in PTSD patients with AUD. Specifically, we hypothesized that GABA and Glu concentrations would be less abnormal in our comorbid sample than in patients with PTSD only. Additionally, we expected that cortical NAA, typically reduced in individuals with AUD, would also be reduced in patients with comorbid PTSD and AUD (PAUD) compared to both PTSD patients and trauma-exposed controls without AUD (CON). We also explored the degree to which the regional cortical metabolite levels reflected neurocognitive function, PTSD symptoms, and sleep quality.

2. Methods

2.1. Participants

All participants voluntarily provided written informed consent before the study, which had been approved by the human research committees of the University of California San Francisco, the VA Medical Center in San Francisco, and the Department of Defense. All PTSD, PAUD, and non-PTSD (CON) individuals were either trauma-exposed American veterans of war or trauma-exposed civilians recruited at the San Francisco VA Medical Center, from among Northern California United States Army reservists, Army National Guard, or the Mental Health Service of the San Francisco and Fresno VA, regional Veteran Centers and mental health clinics. Exclusion criteria were a history of schizophrenia or schizoaffective disorder, past and current AUD (CON only), AUD and substance use disorder within the past 6 months (PTSD only), suicidal intention, or bipolar disorder as assessed by the Structured Clinical Interview for DSM-IV (First et al., 1998). Medical exclusion criteria included pregnancy, seizure disorders, head injury associated with post-injury memory loss for >24 h or loss of consciousness >10 min, history of stroke or neurodegenerative diseases, HIV infection, or medical instability. Participants were excluded if they were prescribed psychiatric medications or hypnotics within 2 weeks before magnetic resonance imaging (MRI), had any kind of metallic implants, lodged foreign objects, other contraindications for MRI, or likely traumatic reactions to MR scanner noise.

2.2. Clinical assessment

All participants completed a structured clinical interview to yield basic demographic information. PTSD diagnosis and symptom severity were measured with the Clinician-Administered PTSD Checklist (CAPS; Blake et al., 1995), a 30-item structured interview based on the DSM-IV. The CAPS instrument is divided into sections based on typical symptom clusters: Exposure to a traumatic event; Re-experiencing; Numbing and avoidance; Hyper-arousal; Chronology; and Functional impairment. A criterion was considered present if a participant endorsed a symptom with a score ≥ 1 in frequency and ≥ 2 in severity rating. Insomnia was assessed with the Insomnia Severity Index (ISI; Bastien et al., 2001), a valid and reliable self-report measure of perceived insomnia severity. Harmful and hazardous drinking was assessed using the Alcohol Use Disorder Identification Test (Saunders et al., 1993). Alcohol consumption was assessed using the Time Line Follow Back (Sobell and Sobell, 1992) interview, which yielded average drinks consumed over 90 days before the MRI study. To assess the influence of self-reported depressive and anxiety symptoms on regional metabolite levels, we administered the Beck Depression Inventory-II (Beck, 1978) and Beck Anxiety Inventory (Beck et al., 1988) on the day of the MRI examination.

2.3. Neurocognitive assessment

Within 3 days before the MRI study, PAUD participants completed a neurocognitive battery consisting of the following: Trail Making Test A and B (Reitan and Wolfson, 1985), a measure of processing speed and divided attention, Hopkins Verbal Learning Test-Revised (Brandt, 1991), including total recall and delayed recall which measure auditory-verbal learning and memory, and the Balloon Analogue Risk Task (Lejuez et al., 2002), a task-based measure of risk taking. Neither CON nor PTSD participants underwent neuropsychological testing.

2.4. MRI acquisition and processing

MR data were acquired on a 4-Tesla Bruker MedSpec system with a Siemens Trio console (Siemens, Erlangen, Germany) using an eight-channel transmit-receive head coil. Three-dimensional sagittal T1-weighted and 2D axial T2-weighted images were acquired using Magnetization Prepared Rapid Gradient imaging ($1\times1\times1$ mm^3 resolution) and turbo spin-echo ($0.9\times0.9\times3$ mm^3 resolution) sequences, respectively. ^{1}H MRS evaluated 3 volumes of interest (VOIs) known to be associated with PTSD and AUD, the ACC, TEMP and POC. These VOIs were evaluated because the ACC is metabolically abnormal in PTSD (Karl and Werner, 2010) and critically involved in the development and maintenance of all forms of addictive disorders (e.g., Goldstein et al., 2009; Volkow et al., 2012). The TEMP is functionally connected to the hippocampus, and together they contribute to the mesial temporal lobe memory system in humans (Kahn et al., 2008) associated with PTSD (Hamner et al., 1999). The POC has been targeted traditionally in ^{1}H MRS studies to measure levels of the inhibitory neurotransmitter GABA in various populations, and this general brain region has been recently implicated in altered neural activity in PTSD (Sripada et al., 2012; Chen and Etkin, 2013). MRS VOIs were placed over the ACC ($35\times25\times20$ mm^3), POC ($20\times40\times20$ mm^3) and right TEMP ($20\times40\times20$ mm^3), maximizing gray matter content as displayed on the structural MR images. Fig. 1 (top) shows typical VOI locations on T2-weighted MR images, midline for ACC and POC, and always patient right for TEMP. NAA, Cr, Cho, mI and Glu signals were acquired at 12-ms echo time with a Stimulated Echo Acquisition Mode sequence (Frahm et al., 1987). Immediately afterwards, a reference water signal was collected from the same VOI with the same Stimulated Echo Acquisition Mode sequence but without water suppression and used for normalizing all metabolite peak areas across participants. Signals from GABA were acquired from the same VOIs with a J-editing sequence modified for optimal GABA signal-to-noise and improved suppression of water and macromolecular signal (Kaiser et al., 2008). MR images were segmented into gray matter, white matter, and cerebrospinal fluid (Van Leemput et al., 1999) to estimate tissue fraction and cerebrospinal fluid contributions to each VOI. Metabolite and J-edited spectra were processed by operators blind to participant diagnosis to yield metabolite levels in institutional units as peak area ratios relative to the unsuppressed voxel tissue water