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Alterations in anterior cingulate cortex myoinositol and aggression in veterans with suicidal behavior: A proton magnetic resonance spectroscopy study

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ABSTRACT

Studies investigating the neurochemical changes that correspond with suicidal behavior (SB) have not yielded conclusive results. Suicide correlates such as aggression have been used to explore risk factors for SB. Yet the neurobiological basis for the association between aggression and SB is unclear. Aggression and SB are both prevalent in veterans relative to civilian populations. The current study evaluated the relationship between brain chemistry in the anterior (ACC) and the posterior cingulate cortex (POC), as well as the relationship between aggression and SB in a veteran population using proton magnetic resonance spectroscopy (^{1}H-MRS). Single-voxel MRS data at 3 Tesla (T) were acquired from the ACC and POC voxels using a 2-dimensional J-resolved point spectroscopy sequence and quantified using the ProFit algorithm. Participants also completed a structured diagnostic interview and a clinical battery. Our results showed that the myoinositol (mI)/H2O ratio in the ACC and POC was significantly higher in veterans who reported SB when compared to veterans who did not. The two groups did not differ significantly with regard to other metabolites. Second, verbal aggression and SB measures positively correlated with mI/H2O in the ACC. Finally, verbal aggression mediated the relationship between mI/H2O in the ACC and SB.

1. Introduction

Suicide is the tenth leading cause of death and is a significant public health issue in the United States (CDC, 2015). Suicide is also prevalent among veterans with an average of 18 individuals dying by suicide every day in the United States, which is approximately 18% of suicides in individuals 18 or older (Department of Veterans Affairs, 2009). The high rate of suicide among veterans coupled with limited number of pharmacological treatments highlight the fact that there is an urgent need to investigate the neurobiological underpinnings of suicide in veterans, with the overall goal of identifying objective biomarkers of suicide. These objective biomarkers may help clinicians to accurately predict who is at greatest risk for suicide so that effective targeted interventions can be developed. Suicide attempts (SA) are at one end of a continuum of behaviors commonly referred to as suicide-related behaviors (SB) that include suicidal ideation (SI) and SA (Nock et al., 2008). SI, defined as thinking about, considering or planning suicide and SA, defined as a non-fatal, self-directed, potentially injurious behavior with intent to die, are both significant risk factors for suicide (Baca-Garcia et al., 2011; Isometsa and Lonnqvist, 1998). In the current study, veterans with SI and/or SA were classified as the SB + group and those without SI and/or SA were classified as the SB- group.

The concept of suicide endophenotypes has been used to explore the neurobiological basis of suicide (Mathews et al., 2013). Endophenotypes include neurophysiological, biochemical, and neuropsychological constructs, where heritability and stability (state independence) are important considerations for an ideal endophenotype (Gould and Gottesman, 2006). Aggressive behavior is a construct that meets specific endophenotypic criteria and associations have been widely reported between aggression and suicide risk in case-control studies in clinical populations, cohort studies in epidemiological samples, retrospective studies of individuals who have died by suicide and

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case registries (Mann et al., 1999; Rusch et al., 2008). Aggression is often reported as a concern among veterans (Hellmuth et al., 2012; McFall et al., 1999). Furthermore, it has been shown that veterans with higher aggression scores are more likely to demonstrate SI and SA (Flanagan et al., 2014; Goldstein et al., 2012). However, the neurobiological basis underlying the association between aggression and SB is not clear.

Neuroimaging tools have been increasingly used to characterize the biological factors underlying vulnerability to suicide. Structural and functional alterations have been reported in several brain regions in individuals at risk for suicide as well as in postmortem studies of people who died by suicide (Desmyter et al., 2013). The anterior cingulate cortex (ACC), which has been implicated in cognitive and emotion processing (Carter et al., 1998), has demonstrated differences in individuals with SB. For example, reduced gray matter density in the rostral ACC measured by voxel-based morphometry was observed in MDD patients at high risk for suicide when compared to non high-risk MDD patients (Wagner et al., 2011). In addition, a meta-analysis showed increased dorsal and rostral ACC activation during emotional tasks and reduced activation in these regions during cognitive tasks to be associated with a history of SB (van Heeringen et al., 2014). In a study of combat-exposed veterans, those with SI showed more engagement of the dorsal ACC during error processing as compared to veterans without SI (Matthews et al., 2012). Furthermore, ACC top-down regulation of aggressive impulses has been extensively studied (Siever, 2008; Sterzer and Stadler, 2009) with high trait aggression associated with decreased activation of the dorsal ACC in response to frustration in a study of healthy males (Pawliczek et al., 2013). There are relatively fewer studies that have investigated changes in POC in association with SB and aggression. Using fMRI, hyper-connectivity from the POC to the medial prefrontal cortex (mPFC) and hypo-connectivity in the opposite direction were demonstrated in schizophrenic patients with high risk of suicide compared to healthy controls (Zhang et al., 2013). With regard to aggression, activation of the POC was associated with increasing revenge stimulus intensity in a study of violent criminal psychopaths when compared to healthy controls (Veit et al., 2010). Collectively these studies suggest that the ACC and POC may be neuroanatomical correlates associated with suicide endophenotypes and an increased risk for suicide.

In addition to structural and functional imaging techniques, proton-1 magnetic resonance spectroscopy (^{1}H-MRS) provides a non-invasive means to measure *in vivo* levels of biochemical compounds in brain tissue. ^{1}H-MRS can quantify levels of neurotransmitters such as glutamate, glutamine, gamma amino butyric acid (GABA) as well as molecules involved in membrane and intracellular processes such as total creatine (tCre) that reflects a combined signal of Cre + phosphocreatine (PCr), choline that represents phosphorylcholine + glycerophosphocholine (PC + GPC), N-acetylaspartate (NAA), lactate, and myoinositol (mI) (Bittsansky et al., 2012). MRS studies investigating the neurochemistry of suicide are scarce (Jollant et al., 2016a; Li et al., 2009) and none have been reported on a veteran population. To our knowledge, there have been 2 studies using MRS imaging to investigate the neurochemistry in individuals with SB.

A potential candidate in the ACC and POC that may be linked to both aggression and an increased risk of suicide is mI, an osmolyte that is primarily synthesized in glial cells in the brain (Brand et al., 1993). Although normally considered a glial marker, a few recent studies have suggested that mI may also be localized in neuronal cells (Fisher et al., 2002). Previous studies have linked alterations in mI to suicide. For example, alterations in cortical mI levels have been reported in postmortem analysis of the brains of individuals who died by suicide (Shimon et al., 1997). In addition, postmortem analysis of brains of individuals who died by suicide revealed hypertrophy of astrocytes (Torres-Platas et al., 2011), which may be a relevant finding since mI is found in high concentrations in astrocytes. An MRS study found increased mI/Cre in the dorsal prefrontal cortex in depressed adults with and without SA as compared to healthy controls (Jollant et al., 2016a), although the difference did not survive correction for multiple comparisons. mI signaling may also play a role in aggressive behavior. For example, a genome-wide association study (GWAS) found that a gene coding for the non-tyrosine receptor kinase, Fyn, was significantly associated with anger (Mick et al., 2014). Fyn interacts with inositol signaling pathways to stimulate intracellular calcium release, suggesting that inositol signaling may underlie expression of anger. Furthermore, in another study of medication free youths with severe mood dysregulation characterized by extreme irritability and anger/aggression, mI/Cre levels in the temporal lobe were significantly lower than controls (Dickstein et al., 2008).

The neurochemical basis of SB, especially in the ACC and POC, has heretofore not been explored using MRS imaging. Furthermore, the neurochemical correlates underlying the link between aggression and SB need further investigation. The current study sought to characterize the association between SB, aggression and altered neurochemistry in veterans using an MRS approach. Based on prior evidence (Jollant et al., 2016a), we hypothesized that an increase in mI may be evident in the ACC and POC of veterans with SB, and that changes in mI may be related to aggression, an important suicide endophenotype.

2. Methods

2.1. Participants

Eighty-one veterans (16 females) were enrolled in the study. Participants were recruited from a local VA hospital as well as from the community via flyers and word of mouth. The Institutional Review Boards at the University of Utah and the George E. Wahlen Department of Veterans Affairs (VA) Medical Center approved this study. All subjects provided written informed consent as per the IRB and Declaration of Helsinki. Participants were compensated financially for their time. Exclusion criteria included major sensorimotor handicaps, estimated full scale IQ < 80, history of autism, claustrophobia, electroconvulsive therapy, active neurological disease, and any MRI contraindications.

2.2. Procedures

Participants completed the Structured Clinical Interview for DSM-IV-TR (SCID-IV-TR), a clinician administered, semi-structured interview to determine general adaptive functioning (GAF) as well as current and past mental health symptoms.

Participants also completed a clinical battery including the Columbia Suicide Severity Rating Scale (C-SSRS), Hamilton Rating Scale for Anxiety and Depression (HAM-A, HAM-D) (Hamilton, 1959, 1960) and the Buss–Perry Aggression Questionnaire (BPAQ). The C-SSRS assesses lifetime presence of SI, plans, intensity of ideation and SA. SA includes an actual attempt, an interrupted attempt, or an aborted/self-interrupted attempt. Veterans who reported SI and/or SA were classified as the SB group. Constructs on the C-SSRS have been found to be acceptable internal consistency as well as convergent, divergent, and predictive validity and predict SA in a 24-week follow-up period (Posner et al., 2011). The BPAQ is a 29-item, four-factor instrument that measures physical aggression, verbal aggression, anger, and hostility, with the scales showing good internal consistency and stability over time (Buss and Perry, 1992). The HAM-A and HAM-D are widely used rating scales to measure the severity of anxiety and depressive symptoms respectively. The HAM-D has shown utility in determining the level of depression before, during, and after treatment (Hamilton, 1960). It is based on the clinician's interview with the patient and probes depressive symptoms such as depressed mood, guilty feelings, SB, sleep disturbances, anxiety, and weight loss. Research has demonstrated a validity coefficient of 0.85 (Reynolds and Mazza, 1998). The HAM-A is a rating scale developed to quantify the severity of anxiety symptomatology, and it is often used in psychotropic