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Injured brain regions associated with anxiety in Vietnam veterans

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ABSTRACT

Anxiety negatively affects quality of life and psychosocial functioning. Previous research has shown that anxiety symptoms in healthy individuals are associated with variations in the volume of brain regions, such as the amygdala, hippocampus, and the bed nucleus of the stria terminalis. Brain lesion data also suggests the hemisphere damaged may affect levels of anxiety. We studied a sample of 182 male Vietnam War veterans with penetrating brain injuries, using a semi-automated voxel-based lesion-symptom mapping (VLSM) approach. VLSM reveals significant associations between a symptom such as anxiety and the location of brain lesions, and does not require a broad, subjective assignment of patients into categories based on lesion location. We found that lesioned brain regions in cortical and limbic areas of the left hemisphere, including middle, inferior and superior temporal lobe, hippocampus, and fusiform regions, along with smaller areas in the inferior occipital lobe, parahippocampus, amygdala, and insula, were associated with increased anxiety symptoms as measured by the Neurobehavioral Rating Scale (NRS). These results were corroborated by similar findings using Neuropsychiatric Inventory (NPI) anxiety scores, which supports these regions' role in regulating anxiety.

In summary, using a semi-automated analysis tool, we detected an effect of focal brain damage on the presentation of anxiety. We also separated the effects of brain injury and war experience by including a control group of combat veterans without brain injury. We compared this control group against veterans with brain lesions in areas associated with anxiety, and against veterans with lesions only in other brain areas.

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1. Introduction

Anxiety is an emotional response that arises in situations of conflict and uncertainty (Gray, 1982). The symptoms of anxiety include hyperarousal and worry (Bishop, 2007). In stress-provoking situations, the behavioral expressions of anxiety, such as displays of tension, increased agitation and locomotion, and defensive hostile behavior may be observed and reliably quantified in humans (Lippert-Gruner, Kuchta, Hellmich, & Klug, 2006) and other species (Kalin & Shelton, 2003).

In this study, we wished to investigate areas in the brain that when lesioned affect anxiety levels. We used voxel-based lesion-symptom mapping (VLSM) to determine where lesions are associated with higher NRS anxiety ratings. VLSM computes a *t*-value comparing behavioral scores in patients with and without damage to a voxel. It performs a whole-brain, voxel-by-voxel, hypothesis-free analysis, rather than attempting to categorize patients based on lesion location. Because TBI patients have been shown to have increased prevalence and severity of anxiety (Fann, Katon, Uomoto, & Esselman, 1995; Rapoport, McCauley, Levin, Song, & Feinstein, 2002), we expected that the NRS would reveal increased anxiety in veterans with TBI. We used a control group of veterans who did not suffer brain injury, but who otherwise shared a similar war experience.

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Studies have reported increased anxiety and PTSD (a form of anxiety) in those with war experience and TBI. In one study, 74% of Vietnam veterans who experienced combat also reported symptoms of PTSD (Buydens-Branchey, Noumair, & Branchey, 1990). This same study found that longer combat exposure and increased combat intensity were both associated with increased likelihood of PTSD. Also, while 62% of those not wounded in the war reported a lifetime occurrence of PTSD, 92% who suffered physical injuries of any type in the war reported a lifetime occurrence of PTSD. Epstein and Ursano (1994) found that 29% of brain-injured patients were clinically diagnosed with anxiety following their traumatic brain injuries (TBI). Carlson et al. (2010) found increased anxiety disorders and PTSD in war veterans with TBI compared to war veterans without TBI.

While there are factors other than brain damage that can increase anxiety after TBI, including memories of the event that caused the TBI (Epstein & Ursano, 1994), Jorge, Robinson, Starkstein, and Arndt (1993) suggest that anxiety in brain-injured patients may be related to the extent and location of brain damage. Anxiety and fear are mediated at least partially by different brain regions. Fear is a biologically adaptive physiological and behavioral response to an actual or anticipated occurrence of an explicit threatening stimulus (Bishop, 2007). Anxiety is, in many ways, similar to fear, although it is less stimulus-specific, has a slower onset, and is longer lasting (Davis, 1998; Walker, Toufexis, & Davis, 2003). The difference can be portrayed as follows: anxiety occurs during approach or movement toward a dangerous situation and increases awareness and preparedness, while fear occurs during escape from a dangerous situation or threat (Blanchard, Yudko, Rodgers, & Blanchard, 1993; Gray & McNaughton, 2000). Early research found that the destruction of the amygdala and temporal lobes leads to reduced anxiety in both humans and animals. Monkeys who had their bilateral temporal lobe and amygdala removed had no fear of approaching other animals or objects, and were less fearful and hostile toward humans (Kluver & Bucy, 1939; Weiskrantz, 1956). More recent work in humans found that removal of the temporal lobes impaired recognition of vocal fear (Dellacherie, Hasboun, Baulac, Belin, & Samson, 2011). Lesions of smaller regions provide more precise results. Reviews of both animal and human literature report that the bed nucleus of the stria terminalis (part of the extended amygdala; Fox et al., 2010; Walker et al., 2003) is involved in anxiety, and the amygdala is involved in fear (Davis, 1998; Walker et al., 2003). Truitt Johnson, Johnson, Fitz, and Shekhar (2009) found that lesions of interneurons in the anterior and posterior divisions of the basolateral amygdala in rats resulted in increased anxiety-like behaviors.

Other brain regions involved in anxiety include the hippocampus (in animals: Barkus et al., 2010; and in PTSD patients: Bossini et al., 2008), insula (Simmons, Strigo, Matthews, Paulus, & Stein, 2006; Uchidi et al., 2000), medial prefrontal cortex (PFC) (in rats: Blanco et al., 2009) and the orbitofrontal cortex (Kringelbach & Rolls, 2004; Milad & Rauch, 2007).

Anxiety levels may also be affected by the hemisphere of the lesions. From the same cohort as the current study, those TBI veterans with right orbitofrontal lesions reported higher anxiety than those with left orbitofrontal lesions and controls (Grafman, Vance, Weingartner, Salazar, & Amin, 1986). In patients with both closed head injury and depression, those with right hemisphere lesions were more likely to have anxiety in addition to their depression (Jorge et al., 1993). Patients with tumors in the right hemisphere had higher anxiety than those with tumors in the left hemisphere (Mainio et al., 2003).

The picture is not so simple however. Using the same cohort as the current study, Koenigs et al. (2008) found that veterans with lesions in vmPFC and amygdala were less likely to have PTSD, while those with posterior lesions had a rate similar to controls.

2. Material and methods

2.1. Subjects

Veterans were drawn from Phase III of the W.F. Caveness Vietnam Head Injury Study registry (VHIS), a longitudinal study of brain-injured veterans, mainly with focal penetrating injuries, and uninjured combat control veterans (Raymont, Salazar, Krueger, & Grafman, 2011). In Phase I, 56% of brain-injured veterans were working compared with 82% of control veterans (Schwab, Grafman, Salazar, & Kraft, 1993). Equal percentages of brain-injured and control veterans were living with their wives (74%). Phase III (2003–2006) was conducted at the National Naval Medical Center in Bethesda, MD. The veteran population offers a number of methodological advantages including its large sample size, relative uniformity, and access to pre-injury data for comparison with post-injury performance.

One hundred and eighty-two brain-injured male combat veterans and 51 uninjured combat veterans with CT scans for whom the NRS was completed were included in this study. The TBI and control groups did not differ significantly in age or level of education (see Table 1). All subjects gave informed written consent in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All study procedures were approved by Institutional Review Boards at the National Naval Medical Center and the National Institute of Neurological Disorders and Stroke.

2.2. CT-imaging and lesion identification

MRIs were precluded as many of the veterans had retained metal shrapnel in their heads; therefore axial CT scans were acquired. These were performed without contrast in helical mode on a GE LightSpeed Plus CT scanner, and images

Table 1
Comparison between veterans with TBI and control veterans on means and standard deviations for demographic information and neurobehavioral scores, and medians and mean ranks for anxiety and depression scores.

Variable	Veterans with TBI	Control veterans	Statistics (2-tailed)
Age (years)	58.32 ± 3.09	59.08 ± 3.52	$t(231)=1.50$; $p=.14$
Education (years)	14.74 ± 2.59	15.25 ± 2.50	$t(228)=1.24$; $p=.22$
Post-injury AFQT percentile score	52.71 ± 25.01	67.96 ± 22.04	$t(227)=3.94$; $p<.001$**
WMS-III working memory primary index percentile score	49.19 ± 28.37	62.70 ± 27.76	$t(225)=2.99$; $p=.003$*
NRS anxiety (medians)	1.00	1.00	$U=4087$, $z=1.55$, $p=.12$
NPI anxiety (medians)	0	0	$U=3830$, $z=0.72$, $p=.47$
State anxiety **scaled** scores (medians)	48.00	49.50	$U=4407$, $z=0.64$, $p=.52$
Trait anxiety **scaled** scores (medians)	51.00	54.50	$U=4135$, $z=1.34$, $p=.18$
SCID: PTSD lifetime prevalence (medians)	2.00	2.00	$U=3777$, $z=2.23$, $p=.03$*
SCID: Major depressive disorder lifetime prevalence (medians)	1.00	1.00	$U=4194$, $z=1.35$, $p=.18$
BDI total score (medians)	6.00	9.00	$U=4079$, $z=1.47$, $p=.14$

Armed Forces Qualification Test. BDI = Beck Depression Inventory. NPI = Neuropsychiatric Inventory. NRS = Neurobehavioral Rating Scale. PTSD = Post-traumatic stress disorder. SCID = Structured Clinical Interview for DSM Disorders. U = Mann-Whitney. WMS-III = Wechsler Memory.

* Significant at $p=.01$
** Significant at $p=.001$