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MILITARY/VETERAN TBI

Anhedonia in combat veterans with penetrating head injury

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Abstract Anhedonia is a common symptom following traumatic brain injury. The neural basis of anhedonia is poorly understood, but believed to involve disturbed reward processing, rather than the loss of sense of pleasure. This analysis was undertaken to determine if injury to specific regions of prefrontal cortex (PFC) result in anhedonia. A CT-based lesion analysis was undertaken in 192 participants of the Vietnam Head Injury Study, most with penetrating head injury. Participants were divided into left and right ventrolateral prefrontal, bilateral ventromedial prefrontal, and other injury locations. Anhedonia was measured by self-report in each group using the four-item anhedonia subscale score of the Beck Depression Inventory-II. Individuals with right ventrolateral injury reported greater severity of anhedonia compared to those with injury in the left ventrolateral region. These findings support an association between injury in the right ventrolateral PFC and anhedonia.

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Introduction

Anhedonia is defined as a diminished interest or pleasure in response to stimuli previously perceived as rewarding, and is a symptom in a variety of neuropsychiatric conditions, including depression (Pelizza and Ferrari 2009), bipolar disorder (Tso et al. 2014), Parkinson's disease (Matsui et al. 2013), schizophrenia (Jorge and Starkstein 2005), posttraumatic stress disorder (PTSD) (Nawijn et al. 2015), and traumatic brain injury (TBI) of all degrees of severity (Rao et al. 2007). Anhedonia has known adverse health effects; in depressed older adults, anhedonia (rather than dysphoria) is associated with increased risk of disability or death (Covinsky et al. 2014). In Parkinson disease patients, anhedonia is negatively correlated with quality of life (Matsui et al. 2013). In TBI patients, anhedonia reduces quality of life and may impede rehabilitation (Jorge and Starkstein 2005).

Anhedonia has classically been considered a symptom related to the lost sense of pleasure from a reward (Ribot 1896). The concept of anhedonia has evolved to include dysfunction in both the consummatory or motivational aspects of reward processing (Treadway and Zald 2011). Reward processing is influenced by executive functions that provide resistance to food and drug cravings (Berkman et al. 2011; Berkman et al. 2014), so executive dysfunction may contribute to anhedonic symptoms, as well.

Functional MRI studies of reward processing in MDD have demonstrated correlations between reported anhedonia and activation in ventral striatum and ventromedial (Keedwell et al. 2005) and ventrolateral prefrontal cortex (PFC) (Tremblay et al. 2005). Both of these areas were activated

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by rewarding stimuli, either a personally relevant happy face or dextroamphetamine sulfate. It is possible that injury to these regions of PFC impair reward processing and produce anhedonia. To our knowledge, the relationship between anhedonia and PFC injury has not been demonstrated.

The Vietnam Head Injury Study, a large cohort of brain injured Vietnam veterans, offers an opportunity to identify potential brain regions of interest where damage results in anhedonia. The intent of this study is to guide further hypothesis-driven research on loss of motivation following TBI.

Methods

Subjects

We analyzed data from 192 TBI participants from Phase III of the Vietnam Head Injury Study, which is a long-term follow-up study of veterans mainly with focal penetrating TBI (Raymont et al. 2011). Phase III included 199 male head-injured participants, six of whom were excluded because they did not complete the study measures used in our analyses, and one was excluded because of a finding of parkinsonism, suggesting a neurodegenerative condition. Participants underwent neurological and psychiatric examinations, neuropsychological testing, and brain CT scan (MRI was contraindicated in these patients due to the presence of retained intracranial shrapnel). We focused this study on the subset of tests that were related to our evaluation of anhedonia from our larger clinical and experimental test battery. These were the Beck Depression Inventory-II (Beck et al. 1996), a self-report of depressive symptoms, the Structured Clinical Interview for DSM-IV-TR AXIS I Disorders, Version I/NP (SCID) (First et al. 2002), and the Clinician Administered Post Traumatic Stress Disorder Scale (CAPS) (Blake et al. 1995), a standardized interview to assess for PTSD symptoms. Self-reported anhedonia was measured with a subscale of the Beck Depression Inventory (BDI Anh) (Pizzagalli et al. 2005). This combines the scores of item 4 (loss of pleasure), item 12 (loss of interest), item 15 (loss of energy), and item 21 (loss of interest in sex) in this subscale. Anhedonia was also measured by the response to CAPS item C-4, markedly diminished interest or participation in significant activities, both frequency (CAPS Freq) and intensity of symptoms (CAPS Int).

CT image acquisition and lesion identification

Axial non-contrast CT scans were acquired on a GE Light Speed Plus CT scanner in helical mode. Images were reconstructed with an in-plane voxel size of 0.4×0.4 mm, overlapping slice thickness of 2.5 mm, and a 1-mm slice interval. Lesion location and volume were determined from CT images by manual tracing using the Analysis of Brain Lesion (ABLe) software implemented in MEDx v3.44 (Medical Numerics) (Solomon et al. 2007). As discussed in previous analyses of this dataset (Raymont et al. 2008), a trained neuropsychiatrist (V.R.) performed the tracings, which were then reviewed by an experienced observer (J.G.) who was blind to the results of the clinical evaluations. Lesion volume was calculated by summing the lesion tracings in native space and multiplying by the slice thickness. The CT images for each participant were normalized to a CT template in Montreal Neurologic Institute space using the automated image registration algorithm with a 12-parameter affine fit (Woods et al. 1998) excluding the voxels inside the traced lesion. The resulting normalized lesion mask images were used for subsequent lesion map generation and for defining regions of interest.

Region of interest analysis

Our aim was to explore whether damage to the reward processing pathways in the brain produced anhedonia. Because of the nature of penetrating head injury in this group, no participant had injury exclusively to subcortical regions, such as the basal ganglia, but the majority had frontal injuries. Therefore, to test the hypothesis that injury to ventrolateral and ventromedial PFC produces anhedonia, three regions of interest were chosen, corresponding to right ventrolateral, left ventrolateral, and bilateral ventromedial PFC. These regions were created with ABLe using the Automated Anatomic Labeling (AAL) atlas (Tzourio-Mazoyer et al. 2002) to select cortical areas within each region of interest. The areas corresponding to the left and right ventrolateral regions of interest included lesions in the middle frontal gyrus (orbital part), gyrus rectus, superior frontal gyrus (orbital part), and superior frontal gyrus (medial orbital). Individuals with lesions extending bilaterally were placed in the bilateral ventromedial prefrontal cortex group. The lesion overlay for each of the three groups is illustrated in Fig. 1. Those with lesions not within the regions of interest were placed in a fourth, all-others, group.

To ensure comparability between groups, demographic comparisons of continuous variables were performed using non-parametric testing (i.e., Kruskall-Wallis test, Mann–Whitney U test, or Pearson Chi-square) based on their non-normal distributions. The three region of interest groups and the all-others group were matched on age (p=0.234), handedness (p=0.629), years of education (p=0.291), pre-injury cognitive intelligence as measured by their Armed Forces Qualification Test Scores (p=0.321), frequency of current or lifetime diagnosis of PTSD as determined by the SCID (p=0.692 and p=0.628, respectively), current or lifetime diagnosis of major depressive disorder as determined by the SCID (p=0.732 and p=0.396, respectively), and current and lifetime diagnosis of psychotic disorder (p=0.277 and p=0.823, respectively) (Table 1).

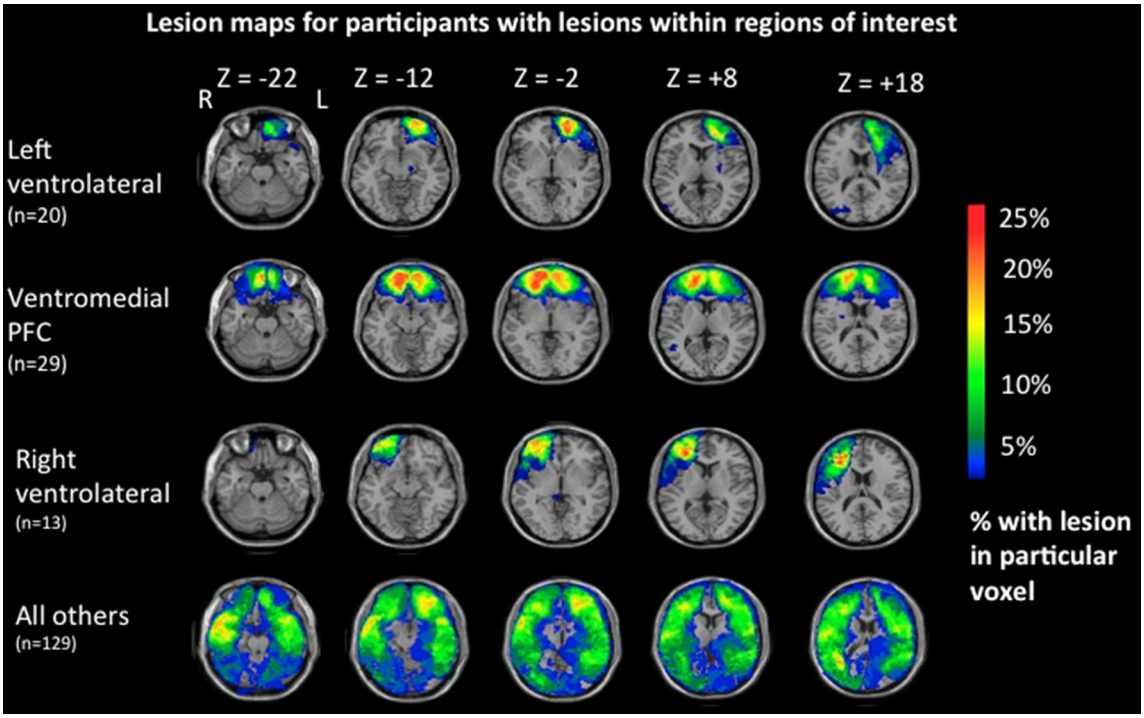

Fig. 1 Lesion maps for participants with lesions within the defined regions of interest. Slice locations are relative to the MNI coordinate system

The bilateral ventromedial group had a significantly higher lesion volume (p=0.014) than the three other groups, but percent lesion volume between left and right ventrolateral regions of interest groups did not differ significantly (p=0.302).

Statistical analysis

We compared the distribution of scores for BDI Anh, Total BDI, CAPS Freq, and CAPS Int across the three regions of interest groups and the all others group by the independent-samples Kruskal-Wallis test. We also tested the correlation between BDI Anh and both CAPS Freq and CAPS Int by Mann–Whitney U test. Statistical significance was set to $p<0.05$ (two-tailed).

After we found that participants with injury to the right ventrolateral PFC had higher scores of BDI Anh compared to others, we compared scores of all 21 items of the BDI-II in the right ventrolateral PFC group to all others was performed. To correct for multiple comparisons, a p value

Table 1 Demographic comparisons between lesion groups

Lesion location	Left ventrolateral	Bilateral ventromedial	Right ventrolateral	All others
Age (years)	57.9 +/− 1.7[a]	58.1 +/− 5.0	57.9 +/− 2.4	58.0 +/− 2.3
Education	14.9 +/− 2.7	14.0 +/− 2.6	14.1 +/− 2.2	14.8 +/− 2.5
Handedness[b]	87	87	71	75
Lesion volume[c]	1.92 +/− 2.04	3.54 +/− 2.31	2.64 +/− 1.87	2.91 +/− 3.49
Pre injury AFQT	60.25 +/− 21.1	53.6 +/− 27.0	63.4 +/− 29.1	62.7 +/− 24.6
Current cases of PTSD	3/20	4/28	3/13	13/133
Lifetime cases of PTSD	9/20	9/28	4/13	41/133
Current cases of MDD	0/20	1/28	0/13	2/133
Lifetime cases of MDD	1/20	3/28	4/13	20/133
Current cases of psychotic disorder	1/20	2/28	0/13	4/133
Lifetime cases of psychotic disorder	1/20	2/28	1/13	5/133

[a] Mean +/− standard deviation

[b] Percent right-handed

[c] As percentage of total brain volume

threshold of 0.002 was established for statistical significance in the BDI-II item analsyis.

Results

Comparison of BDI, BDI-Anh, CAPS Freq and CAPS Int scores

Across the three regions of interest groups and the all-others group, there was a statistically significant difference in BDI Anhedonia Subscale Scores (p=0.034), but not in total BDI Score (p=0.157). This selective endorsement of anhedonic symptoms is more apparent when comparing the right and left ventrolateral groups, where there is a trend toward greater BDI scores (p=0.080) in the right ventrolateral PFC group, but a highly significant increase in anhedonic symptoms (p=0.014). Between groups comparisons between CAPS Freq and CAPS Intensity were not significant (p=0.997 and 0.934, respectively) (Table 2).

An analysis of individual items of the BDI-II scores in the right ventrolateral group compared to all others revealed significantly higher scores for pessimism (p=0.000), crying (p=0.001), and loss of interest (p=0.001).

Comparison between CAPS and BDI Anh scores

Correlations between CAPS Freq, CAPS Intensity and BDI Anh scores were statistically significant (Spearman's rho of 0.166 [p=0.021] and 0.203 [p=0.005], respectively).

Discussion

The goal of this study was to examine the expression of anhedonic symptoms related to localized TBI. The primary result is that anhedonic symptoms are more pronounced in individuals with damage to the right ventrolateral prefrontal region, than those with wounds to other regions. This finding is consistent with a positron emission tomography study in anhedonic depression, where higher scores on the anhedonic components of the Beck Depression Inventory were associated with decreased regional metabolism in an area of the right hemisphere overlapping with the region demonstrated in our lesion study (Dunn et al. 2002). Among all participants, BDI Anh scores correlated with anhedonia, as measured by the CAPS. The anhedonic symptoms experienced by the individuals in this study are more than simply the result of MDD or PTSD, as these diagnoses were not higher between the groups in the study. However, the right ventrolateral PFC group endorsed more crying suggesting that injury to this region caused more than anhedonia alone.

Interestingly, the right ventrolateral PFC is involved in motivational aspects of reward processing, including drug and food-related cravings. Specifically, the right ventrolateral PFC (right inferior frontal gyrus) is involved in inhibitory processes supporting executive function and in resistance to cravings (Berkman et al. 2011; Berkman et al. 2014). Recent studies illustrate that active inhibition and inhibitory-control training paradigms recruit the ventrolateral PFC, and successful inhibition is proportional with activation in this area (Berkman et al. 2014).

A limitation of this retrospective study is that a categorical, rather than parametric, analysis was chosen, because of the small numbers in the ventrolateral groups. Nevertheless, the highly significant difference between comparable regions in opposite hemispheres warrants further study for clinical correlation.

In summary, our results indicate that injury to the right ventrolateral prefrontal region is associated with anhedonia, and disproportionately so, compared to other mood symptoms. This is consistent with a role for the ventrolateral PFC, especially on the right, in motivational aspects of reward processing. These warrant further investigation with multi-method studies. In addition, these findings support investigation of deep brain stimulation and transcranial magnetic stimulation that may successfully treat this debilitating symptom following TBI. These techniques are discussed further in this special issue.

Table 2 BDI and anhedonia subscale scores between groups

Lesion location	Left ventrolateral	Bilateral ventromedial	Right ventrolateral	All others
BDI total score	8.1 +/−8.0 [a]	9.7 +/−9.1	18.0 +/−14.7	8.4 +/−8.1
BDI Anh subscale score	1.9 +/−1.9	2.4 +/−2.4	4.2 +/−2.6	2.1 +/−2.1
CAPS Freq	0.65 +/−0.75	0.66 +/−0.77	0.62 +/−0.77	0.69 +/−0.87
CAPS Int	0.65 +/−0.75	0.69 +/−0.85	1.0 +/−1.2	0.72 +/−0.87

[a] Mean +/− standard deviation

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Conflict of interest Jeffrey D. Lewis, Frank Krueger, Vanessa Raymont, Jeffrey Solomon, Aron Barbey, Joshua Poore, Kristine M. Knutson, Eric M. Wassermann, and Jordan Grafman declare that they have no conflicts of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

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