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Post-mortem Locus Coeruleus Neuron Count in Three American Veterans with Probable or Possible War-Related PTSD

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Abstract

Objective—Because enhanced CNS noradrenergic postsynaptic responsiveness has been previously shown to contribute to PTSD pathophysiology, we investigated whether war-related posttraumatic stress disorder (WR-PTSD) is associated with a post-mortem change in neuronal counts in the locus coeruleus (LC).

Method—Using post-mortem neuromorphometry, we counted the number of neurons in the right LC in seven deceased elderly male veterans. We classified three veterans as cases of probable or possible WR-PTSD.

Results—All three veterans with probable or possible WR-PTSD were found to have substantially lower LC neuronal counts compared to four controls (three non-psychiatric veterans and one veteran with alcohol dependence and delirium tremens).

Conclusion—To our knowledge, this case series is the first report of LC neuronal counts in patients with PTSD or any other DSM-IV-TR anxiety disorder. Previous post-mortem brain tissue studies of Alzheimer's Disease (AD) demonstrated an upregulation of NE biosynthetic capacity in surviving LC neurons. The finding reported here is consistent with the similar upregulation of NE biosynthetic capacity of surviving LC neurons in veterans who developed WR-PTSD. If replicated, the finding we report here in WR-PTSD may provide further explanation of the demonstrated effectiveness of PTSD treatment with propranolol and prazosin. Larger neuromorphometric studies of the LC in veterans with WR-PTSD and in other stress-induced and fear-circuitry disorders are warranted.

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Keywords

Veterans; War; Fear-circuitry; Locus Coeruleus; Neuropathology

BACKGROUND

For decades, post-mortem human brain tissue studies have made slow but steady contributions to the psychiatric knowledge base. While early work focused on neurochemistry (1), recent post-mortem techniques allow for neuron-counting studies of some of the smaller brain nuclei, such as those found in the brainstem reticular activating system (RAS) (2–4). The locus coeruleus (LC), the noradrenergic arm of the RAS, comprises approximately 23,000 neurons on each side of the brainstem (5) and provides over 70% of the noradrenergic innervation in the central nervous system (CNS) and probably a higher percent of the ascending noradrenergic innervation (6).

There are no published morphometric studies of the LC in war-related posttraumatic stress disorder (WR-PTSD). We wanted to investigate whether chronic WR-PTSD is associated with lower LC neuronal counts. In this preliminary study, we compared the LC neuronal counts of three veterans whose clinical histories were strongly suggestive of a probable or possible WR-PTSD with four veterans of similar age whose clinical histories lacked any signs of WR-PTSD.

METHODS

Institutional Review Board Approval

All procedures were approved by the Institutional Review Board of the Central Arkansas Veterans Health Care System. Post-mortem brain tissue was obtained during autopsy from psychiatric patients and medical control subjects who expired at the Central Arkansas Veterans Health Care System. Consent for autopsy with special provision for use in neuropsychiatric research was obtained post-mortem from next of kin for all subjects.

Patient Selection

All seven patients presented in this paper were identified post hoc. The seven veterans presented here were a part of nine psychiatric and medical controls included in a previous National Institute of Mental Health (NIMH) funded study of pedunculopontine nucleus (PPN) neuropathology in veterans with chronic schizophrenia (4;7). The data on all patients included in the present report were previously published in the above study. The patients were part of the control group in that study since none had any current psychosis, and they had PPN neuronal counts in the normal range for their age (4). In Table 1, we have retained the identification case numbers from the original schizophrenia study for comparison purposes.

Post hoc, we selected three veterans with a clinical history that was indicative of a diagnosis of a chronic probable or possible WR-PTSD. All three of these veterans had past histories of alcohol abuse or dependence. Therefore, we selected one psychiatric control veteran of similar age with a clinical history of alcohol dependence with delirium tremens but with no evident history of posttraumatic stress disorder (PTSD), panic disorder, or GAD. We also selected three medical control veterans of similar age with no evident history of alcohol abuse, anxiety disorder, or any other chronic mental illness in their medical charts.

In an attempt to partly control for the impact of non-specific neurodegenerative conditions on LC counts, we compared these with the number of PPN neurons in these same patients (see Table 1). Projections from the PPN modulate thalamic and locomotive functions. The PPN is comprised largely of cholinergic neurons and is the key component of the cholinergic arm of the RAS. Although physically contiguous with the LC, the PPN is not associated with noradrenergic systems. Therefore, general neurodegenerative conditions would be likely to affect the LC and the PPN equally. In contrast, conditions differentially affecting noradrenergic systems, such as chronic noradrenergic activation, should result in changes to the LC but not the PPN.

Caseness was determined post-mortem by expert consensus based primarily on information obtained by a psychiatrist following the guidelines of the Diagnostic Evaluation After Death (DEAD) (8). The DEAD uses all available information, including chart review and information obtained from kin. When sufficient information is obtained, the DEAD has been shown to be a valid and reliable instrument (2). The diagnosis of alcohol abuse and dependence relied on the criteria of Feighner et al (9).

It is of note that none of these veterans carried a clinical diagnosis of Parkinson's disease or Alzheimer's disease (AD) in their charts, nor were these diseases evident at post-mortem examination. There was also no clinical evidence of other conditions known to affect the LC, such as multiple system atrophy, progressive supranuclear palsy, or brain stem infarcts in any of these veterans.

Clinical histories

Veteran HB25 (probable WR-PTSD) was a combat veteran who was 68 years old at the time of death. Chart information suggested at least one episode of severe depression treated 24 years prior to his death. Collateral information from the veteran’s wife strongly suggested that the veteran had a history of exaggerated startle response, combat-related nightmares, avoidance of war reminders, avoidance of crowds, restricted range of affect, difficulty concentrating, chronic dysphoria, suicidal thoughts, little to no interest in any social activities, and chronic irritability resulting in difficulties on the job and arrests for fighting. Episodes of rage/violence were also frequently directed towards his family. He had a past history of alcohol dependence; however, it was in remission for 15 years at the time of death. There was no history of panic attacks. Two years before his death, he was admitted to a VA nursing home following a left hemispheric cerebrovascular accident suffered during lung resection due to adenocarcinoma of the lung. No metastases to the brain were noted at autopsy. The presence of a large, old infarct involving most of the left cerebrum in the territory of the middle cerebral artery was confirmed by post-mortem examination. There were also scattered old microscopic infarcts in the right cerebrum. He was taking no medication at the time of his death.

Veteran HB12 (benzodiazepine abuse and probable WR-PTSD) was 68 years of age at the time of his death. He was a combat veteran and served for four years in WWII. This veteran had a diagnosis of benzodiazepine abuse at the time of his death and a history of alcohol dependence that had been in remission for 20 years. He had been hospitalized on several occasions for recurrent unipolar major depression and, as noted in his chart, for “possible panic attacks.” This veteran had a chart diagnosis of Generalized Anxiety Disorder (GAD) dating to the 1960's, which was identified as combat-related on his VA medical record. His anxiety disorder diagnosis was made more than a decade prior to the recognition and DSM formulation of PTSD. It is likely this four-year WWII combat veteran's combat-related anxiety and other symptoms are misdiagnosed manifestations of WR-PTSD.

Veteran HB23 (probable panic disorder and possible WR-PTSD) was 78 years old at the time of his death. History from this veteran’s wife indicated the frequent occurrence of typical spontaneous panic attacks in this veteran (which started in his teenage years preceding his military service). The panic attacks occurred at a frequency of roughly two per week or more and manifested by flushing, profuse sweating, shaking, dyspnea, sudden weakness, and feeling faint. There was a positive history of panic attacks in the veteran’s family. The veteran had a history of alcohol abuse that had been in remission for at least five years at the time of his death. He served as a cook in WWII; and while there was no chart documentation that he experienced severe trauma during the war, he manifested extreme avoidance of war reminders and intense distress when faced with war reminders. In addition, the veteran frequently exhibited insomnia and other symptoms of anxiety. Since this veteran met core PTSD symptoms from each of the three DSM-IV-TR symptom clusters, his post-mortem consensus diagnoses were probable panic disorder *and* possible WR-PTSD.

Alcohol dependent control of similar age: Veteran HB06 (psychiatric control) was selected since he had evidence of alcohol dependence with delirium tremens at the time of his death. He had no history of PTSD, panic disorder, or other anxiety disorders. No combat exposure was noted in his chart. Autopsy revealed acute cerebral ischemia.

Medical controls of similar age: Veterans HB13, HB15, and HB17 (non-psychiatric medical controls) were selected because they had no chart evidence of an anxiety disorder or alcohol dependence. There was no chart evidence of combat exposure. Brain autopsy was within normal limits in these three veterans.

The total number of control subjects in the original schizophrenia study was nine. Of those, seven are presented in Table 1. The remaining two veterans (HB03, HB22) were not included in this comparison since they were substantially younger (ages 37 and 46, respectively), see Tables 1–3 of Garcia Rill et al. for all available information on these two younger veterans (4).

Laboratory Methods

At autopsy, the brain stem was separated from the remainder of the brain and bisected at the midline. Only the right half of the brain stem was used in the neuronal count studies described here. Immediately after dissection, the right half of the brain stem was placed in a solution of 4% paraformaldehyde with lmM $MgCl_2$ for 4–6 hours, and then it was transferred to 20% sucrose with lmM $MgCl_2$ for 3–4 days. Sagittal frozen sections (60 micrometers) were made to minimize cell-counting errors due to the anteroposterior orientation of the LC. LC neurons were defined as neuromelanin-pigment containing masses enclosed by a cell membrane. Many of the neurons contained a visible nucleus, but neurons without a visible nucleus also were counted. Cholinergic pedunculopontine nucleus (PPN) neurons were identified by processing sections for NADPH-diaphorase histochemistry as previously described (10). This method selectively labels cholinergic mesopontine neurons. Cell counts were performed using a Biographics Image Analysis system. The outlines of the sagittal sections were digitized (at 40x) and the locations of each cell entered (at 100x) and coded. Total numbers of neurons were extrapolated by multiplying the average cell number found in the digitized sections by the total number of sections in which that brain stem nucleus was present, including discarded sections. Correction for split-cell error (11) was used. The individuals making the cell counts were unaware of diagnosis. In all cases at least two individuals carried out neuronal counts in each brain stem, and no individual entered all of the brain stems in a diagnostic group. Inter-observer reliability differed by less than five percent (2;4).

RESULTS

The results are presented in Table 1, which summarizes the available relevant data for all seven deceased veterans.

DISCUSSION

Three veterans with probable or possible WR-PTSD were found to have substantially lower LC neuronal counts compared to four controls (three non-psychiatric veterans and one veteran with alcohol dependence and delirium tremens). Krystal and Duman have recently pointed out that post-mortem studies are sorely needed in PTSD research (12). To our knowledge, this is the first report of LC neuronal counts in veterans with a probable or possible WR-PTSD or with any other DSM-IV-TR anxiety disorder.

It is increasingly recognized that many "noncombat" troops (such as cooks) had been exposed to life-threatening and terrifying combat trauma in the form of artillery attacks, sniper fire, mines, and the carnage of war and, therefore, developed WR-PTSD. It should be emphasized that these veterans died in an era in which VA clinicians were far less sensitive to the multiplicity of war-trauma and the high prevalence of WR-PTSD in noncombat troops. Clinicians, therefore, were likely to make a diagnosis other than PTSD in veterans who had a noncombat MOS (military occupation specialty).

Although no valid inferential statistics are possible in such a small case series, the LC neuronal count in all three veterans with probable or possible WR-PTSD was substantially lower than in the control veterans. Larger post-mortem neuromorphometric studies of the LC in WR-PTSD and other stress-induced and fear-circuitry disorders are warranted.

Confounding factors frequently plague post-mortem studies, especially in psychiatric populations. Replication in a larger sample using this or other cell-counting methods would strengthen the preliminary finding reported here. Age and the presence of neurodegenerative illnesses are known to decrease the number of neurons in the LC (14–17). Limitations that could be addressed include a better match for cause of death, medication, post-mortem interval, and medical and psychiatric co-morbidities.

However, other studies of the LC in normal controls (5) have shown counts similar to the LC counts of the control veterans in our study. Furthermore, the number of cells in the PPN (the cholinergic nucleus adjacent to the LC) were not consistently lower in the three WR-PTSD veterans (2;4). This suggests that there may not have been a general degenerative condition in this region that could account for the lower LC neuronal counts.

Additionally, the fact that the control veteran with alcohol dependence and delirium tremens (HB06) had similar LC neuronal counts to the non-psychiatric (control) veterans suggests that alcohol dependence may not account for the lower LC neuronal count. Furthermore, a study by Halliday et al. found no differences in LC neuronal counts between alcoholics with Wernicke-Korsakoff syndrome and controls (13).

Affective disorder is unlikely to be a confounding factor in our study since a recent study by Hoogendijk et al. reported no association between depression and loss of neurons in the LC in Alzheimer's disease patients (3). Furthermore, Hoogendijk et al. point out the deficits in earlier studies of depression that have suggested such an association (3). Finally, LC neuronal counts in veterans with chronic psychotic illness have been found to not differ from normal controls (2;4). These previous LC neuronal counts from veterans with chronic psychotic illness were higher than those in the three veterans with probable or possible WR-PTSD presented here.

In this study only the right LC was available for neuromorphometry. However, recent bilateral studies of the LC in suicide victims and normal controls (5) have found LC neuronal counts in normal controls that are very similar to those in our study (roughly double our unilateral counts), while those of suicide victims are also similar to the counts in our veterans with probable or possible WR-PTSD. Furthermore, the right LC may be preferred for studies of PTSD (18).

Enhanced CNS noradrenergic postsynaptic responsiveness has been clearly shown to contribute to PTSD pathophysiology (19). The observed decreased LC neuronal number reported here seems paradoxical given that CSF norepinephrine (NE) concentrations (a direct index of CNS noradrenergic activity (20)) and urine MHPG (an indirect index (21)) are both elevated in WR-PTSD during life. It is possible that in our three WR-PTSD veterans, genetic or other pre-deployment factors are responsible for the smaller number of LC neurons. This may result in upregulation of post-synaptic NE receptors which may be a risk factor for PTSD (as is the case with smaller hippocampal size in combat-related PTSD (22)).

However, the most intriguing, and clinically most important possible explanation for our finding, draws on recent studies of antemortem CSF NE and postmortem LC neurochemistry in AD. Despite LC neuronal loss of a magnitude similar to that reported here in WR-PTSD, antemortem NE concentrations are normal or elevated in the CSF in AD (23).

Postmortem brain tissue studies of AD (24) have demonstrated an upregulation of the NE biosynthetic capacity in the surviving LC neurons. The finding reported here is consistent with a similar upregulation of NE biosynthetic capacity in surviving LC neurons following war-trauma-related loss of neurons in the LC of veterans who develop WR-PTSD. If replicated, the finding we report here may provide further explanation for the demonstrated effectiveness of PTSD treatment with the postsynaptic NE beta receptor antagonist propranolol (25;26) and the postsynaptic NE alpha-1 receptor antagonist prazosin (27).

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Orig ID #	Veterans' Primary Diagnoses Post-mortem Consensus	Previous Psychiatric Diagnosis	Primary Infor-mation Source	LC Neurons (Right)	PPN Cholinergic Neurons (Right)	Age Sex Race	Medication at Death	Combat or War Zone Exposure	Psychiatric Service Connection	Brain Weight (gm)	Mental Illness Duration (years)	PMI (h)	Cause of Death	Neuro-Pathology
Veterans with Probable or Possible War-Related PTSD:														
HB 25	Probable War-Related PTSD	Alcohol Dependence. Major Depression. Psychosis	Spouse	**15,177**	14,252	68 M White	None	Combat	No	1,165	35	7.0	COPD	Old Left Hemi-sphere Infarct
HB 12	Probable War-Related PTSD Benzo-diazepine Abuse	Generalized Anxiety Disorder (1960s diagnosis) Alcohol Dependence Recurrent Unipolar Major Depression	Spouse and Chart	**10,586**	8,089	68 M White	Lorazepam Nortryp-tyline Trazodone	Combat	Yes	1,150	29	19.5	CHF	None
HB 23	Possible War-Related PTSD; Probable Panic Disorder	Alcohol Abuse	Spouse	**11,322**	6,924	78 M White	None	War Zone	No	1,400	63	6.0	COPD	None
Psychiatric Control of Similar Age:														
HB 06	Alcohol Dependence with Delirium Tremens	None	Chart	**27,237**	9,407	61 M White	Not known	Unknown	No	1,510	15	6.0	ARDS	Acute Ischemia
Medical Controls of Similar Age:														
HB 13	No Chronic Psychiatric Illness	None	Chart	**19,592**	8,877	61 M White	None	Unknown	No	1,380	N/A	3.5	MI	None
HB 15	No Chronic Psychiatric Illness	None	Chart	**26,107**	9,994	66 M Black	None	Unknown	No	1,360	N/A	3.5	Cancer	None
HB 17	No Chronic Psychiatric Illness	None	Chart	**21,077**	5,945	64 M White	None	Unknown	No	1,130	N/A	21.0	Cancer	None