J Cancer Surviv
https://doi.org/10.1007/s11764-017-0653-9

Changes in cerebellar functional connectivity and autonomic regulation in cancer patients treated with the Neuro Emotional Technique for traumatic stress symptoms

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Received: 9 June 2017 / Accepted: 7 October 2017

Abstract
Purpose A growing number of research studies have implicated the cerebellum in emotional processing and regulation, especially with regard to negative emotional memories. However, there currently are no studies showing functional changes in the cerebellum as a result of treatment for traumatic stress symptoms. The Neuro Emotional Technique (NET) is an intervention designed to help improve symptoms related to traumatic stress using an integrative approach that combines emotional, cognitive, and motor processing, with a particular focus on autonomic nervous system regulation. In this study, we evaluated whether the NET intervention alters functional connectivity in the brain of patients with traumatic stress symptoms associated with a cancer-related event. We hypothesized that the NET intervention would reduce emotional and autonomic reactivity and that this would correlate with connectivity changes between the cerebellum and limbic structures as well as the brain stem.
Methods We enrolled patients with a prior cancer diagnosis who experienced distressing cancer-related memories associated with traumatic stress symptoms of at least 6 months in duration. Participants were randomized to either the NET intervention or a waitlist control. To evaluate the primary outcome of neurophysiological effects, all participants received resting-state functional blood oxygen level-dependent (BOLD) magnetic resonance imaging (rs-fMRI) before and after the NET intervention. In addition, autonomic reactivity was measured using heart rate response to the traumatic stimulus. Pre/post comparisons were performed between the NET and control groups.
Results The results demonstrated significant changes in the NET group, as compared to the control group, in the functional connectivity between the cerebellum (including the vermis) and the amygdala, parahippocampus, and brain stem. Likewise, participants receiving the NET intervention had significant reductions in autonomic reactivity based on heart rate response to the traumatic stimulus compared to the control group.
Conclusions This study is an initial step towards establishing a neurological signature of treatment effect for the NET intervention. Specifically, functional connectivity between the cerebellum and the amygdala and prefrontal cortex appear to be associated with a reduction in autonomic reactivity in response to distressing cancer-related memories.
Implications for cancer survivors This study contributes to the understanding of possible mechanisms by which interventions like NET may help reduce emotional distress in cancer patients who suffer from traumatic stress symptoms.

Keywords Neuro Emotional Technique · Emotional trauma · Distressing recollections · Cancer · fMRI · Functional connectivity · Cerebellum · Amygdala

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Published online: 19 October 2017

Introduction

As many as one third of all cancer survivors across multiple cancer diagnoses suffer from traumatic stress symptoms [1]. Only a small subset of these patients have symptomatology at the diagnostic level of post-traumatic stress disorder (PTSD) [1, 2]; however, the more typical subsyndromal symptoms in cancer patients have been shown to cause functional impairment and neurological changes comparable to full PTSD [3]. The most common distressing events include the moment of diagnosis or some painful or disturbing aspect of cancer care.

Important questions remain about the brain mechanisms involved in eliciting traumatic memories and subsequent emotional and autonomic reactivity, and how these mechanisms are affected by therapeutic interventions. While the role of the limbic system in emotional processing has been described, several recent studies also implicate the importance of the cerebellum in regulating negative emotions [4]. In addition, the cerebellum appears to have important regulatory control over the autonomic nervous system reactions to negative emotional stimuli [5]. For example, several studies of PTSD patients have shown either abnormal size or activity in the cerebellum as playing a key role in the manifestations of symptoms [6–8]. Given the cerebellum's well-known role in motor regulation, there is potential value in studying an intervention for traumatic stress that utilizes the motor system along with emotional and cognitive processing.

The Neuro Emotional Technique (NET) is an integrative treatment approach for traumatic stress that combines emotional, cognitive, and motor processing in a standardized format designed to help patients reduce their psychological reactivity to traumatic events and memories. Interestingly, a component of the NET intervention assesses muscle feedback as a gauge of autonomic reactivity. The NET approach also considers body position and activity in the desensitization of traumatic experiences. For example, patients with a traumatic experience around a distressing cancer procedure may have been in an uncomfortable body position during the procedure, and it is encouraged that such physical components of the experience be recalled as vividly as possible, as part of the processing of the traumatic event.

We have previously reported on brain responses to traumatic stimuli pre and post NET in cancer patients utilizing fMRI with arterial spin labeling [9]. Key limbic structures, such as the amygdala and parahippocampus, and the brain stem were observed to have increased activity during traumatic stress activation. Additionally, we demonstrated decreased activation post intervention, and this treatment effect was achieved with three to five, 1-h sessions of NET. An important next step is to examine alterations in functional connectivity among key brain structures involved with emotional regulation to better understand potential mechanisms of therapeutic effect.

Given the multimodal nature of the NET intervention that includes autonomic and motor processes, it is a good candidate for exploring the cerebellum's role in emotional and autonomic regulation. In the present study, cancer survivors with prolonged, symptomatic, distressing, cancer-related recollections received the NET intervention and were compared to a similar group of patients placed in a waitlist control condition. Participants underwent resting-state blood oxygen level dependent (BOLD) MRI before and after the intervention period and also were evaluated for autonomic reactivity based on heart rate changes during elicitation of the traumatic memory. We focused our assessment on the functional connectivity of the cerebellum to the amygdala, parahippocampus, and brain stem to assess the cerebellum's potential role in emotional regulation and autonomic tone. We hypothesized that functional connectivity changes between the cerebellum and emotional and autonomic response centers would correspond with decreased traumatic stress symptoms. A long-term goal is to evaluate functional connectivity changes as a neurological signature of treatment effect.

Methods

Participants

All study participants provided informed consent approved by the Institutional Review Board of Thomas Jefferson University. Subjects enrolled were adult cancer survivors with a distressing cancer-related memory of at least 6 months, but no longer than 3 years, of duration. They were recruited from posted advertisements and via referrals by a physician or social worker at the Sidney Kimmel Cancer Center at Thomas Jefferson University. This study was also posted on clinicaltrials.gov (NCT 02760524). As an initial screening, potential participants were asked to describe their cancer-related recollection and to rate the level of associated distress using the Subjective Units of Distress Scale (0–10), with a score of 7 or higher as the cutoff [10].

The goal was to enroll participants with symptomatic distress from the memory but no other significant Axis I pathology, so all enrolled participants received a Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) [11]. Exclusion criteria included any current Major Mental Disorder, as well as history of post-traumatic stress disorder, major depressive disorder after the cancer diagnosis, and substance abuse or dependence. In addition, potential participants were excluded for use of psychotropic medications within the past month or current use of medications that would interfere with autonomic nervous system measures (benzodiazepines, barbiturates, major tranquilizers). Patients in active cancer treatment were not enrolled but encouraged to call back when they were no longer receiving chemotherapy or radiation.

A total of 25 participants met the full criteria for participation in the study. Two dropped out due to claustrophobia or discomfort undergoing the resting-state BOLD functional MRI (rs-fMRI) scan, which prevented them from participating in the follow-up scan. The remaining 23 participants, 3 men and 20 women, were randomized with 11 assigned to the intervention group (8 females and 3 males with an average age of 59.4 ± 8.4 years) and 12 assigned to the waitlist control condition (12 females and 0 males with an average age of 58.7 ± 8.6 years). Subjects in both groups had a variety of cancer types including breast, thyroid, gynecological, and gastrointestinal. For additional details of the study population, please see our prior publication, however, there were no significant differences between the groups in terms of their disease, treatment, or psychological scores related to the trauma using two-sample Wilcoxon test for continuous or ordinal outcomes and Fisher's exact test for Gender and Ethnicity. Once enrolled, subjects received a battery of psychological measures and the initial MRI scan with rs-fMRI. Participants in the NET intervention arm, received three to five, 1-h sessions given over the course of approximately 1 month. Participants in the waitlist control arm underwent the same "post" measures and fMRI scan approximately 1 month after the initial evaluation. All participants who were placed in the waitlist control group were offered the opportunity to undergo the NET intervention after the study period.

Imaging

The MR imaging was performed on a 3-T Philips Achieva scanner using a standard 8-channel head coil. Initially, structural MRI brain images were collected using a T1-weighted Magnetization-Prepared Rapid Gradient Echo (MPRAGE) sequence. The imaging parameters used were: FOV = 25.6 cm, voxel size = 1.0 × 1.0 × 1.0 mm3, matrix size = 256 × 240, TR = 6.44 s, TE = 3.16 s, slice thickness = 1 mm, number of slices = 170, flip angle = 8, and acquisition time = 280 s. Next rs-fMRI data was collected using an Echo Planar Imaging (EPI) sequence. The following imaging parameters were used: FOV = 25.6 cm, voxel size = 2 × 2 × 4mm3, matrix size = 128 × 128, TR = 2.5 s, TE = 35 ms, slice thickness = 4 mm, number of slices = 34, number of volumes = 120, and acquisition time = 300 s. During rs-fMRI the subjects were instructed to close their eyes, keep their heads still, and relax for 5 min.

Functional connectivity post-processing

Connectivity signal is composed of low-frequency components that can be difficult to separate from physiological noise. In an effort to uniquely describe the communication between resting-state networks without the influence of noise contaminants, the following analysis was performed for the acquired functional volumes. This analysis pipeline is well-established and widely used in the fMRI community for evaluating rs-fMRI data. All resting-state data was spatially preprocessed using SPM12 (Wellcome Department of Cognitive Neurology, University College London, UK) in the Matlab environment (Mathworks, Inc). Realignment was initially performed to ensure proper voxel to voxel correspondence within the BOLD time series. The functional volumes were then sliced time corrected to account for timing inconsistencies within the EPI data. Segmentation of gray matter, white matter, and CSF was performed to facilitate the removal (i.e., covary out) confounding temporal factors prior to modeling. Spatial normalization was then performed for each data set and warped to MNI space through a subject-specific deformation field and smoothed using a three-dimensional Gaussian kernel with a FWHM of $4 \times 4 \times 8$ mm^3. This spatial processing rendered the data optimal for additional temporal corrections to highlight the low-frequency resting-state networks of interest for connectivity studies. The Conn toolbox (16a) was integrated into the Matlab environment for component-based noise correction (CompCor) of physiologic and other noise sources inherent to BOLD imaging.

The preprocessed functional volumes from the prior step were imported into the Conn toolbox for the resting-state analysis. Structural volumes were separated into white matter, gray matter, and CSF confounds. A band-pass filter of 0.008 to 0.09 was applied to restrict analysis to a limited frequency window while white matter and CSF confounds were placed in a three-dimensional space. Seed ROIs were defined by the brain regions hypothesized to play a role in regulation of stress-related trauma. These regions included the cerebellum, brain stem, vermis, amygdala, and parahippocampus.

Heart rate response measurement

Prior to scanning, each participant was interviewed to generate a brief written script of his or her distressing cancer-related recollection and a separate brief script of a neutral recollection. It is a standard psychophysiological research method to use scripts as triggering cues for eliciting traumatic stress responses [12]. Further, it is noted that in persons with a prolonged, intense memory of an event, it is unlikely that describing the event in the assessment session will have a significant impact on autonomic arousal or emotional reactivity to the event thereafter [13]. The presence of a control group that received the same assessments controls for this variable.

Next, electrodes were attached to one hand and bilaterally to wrists to measure heart rate. The subject was instructed to sit quietly with eyes closed without moving until stabilization of the heart rate occurred [14]. Data recordings began with a 1-min period of visualizing the neutral image as that script was read. After another 2-min recovery period, subjects were asked to recall their distressing cancer-related image in

response to the previously generated script. Data collection concluded after a 2-min recovery.

Subjects who demonstrated autonomic reactivity to the distressing image, as defined by an increase in mean HR of 5% when the distressing image was compared to the neutral image were eligible for the study. This protocol is standard for determining autonomic reactivity to traumatic events [12], and has been used by others [13] as inclusion criteria for studying autonomic reactivity to emotional images. Heart rate response is a standard measurement of stress arousal and they provide a non-invasive objective assessment of autonomic nervous system activity [15].

This same heart rate evaluation of autonomic reactivity was performed after the NET intervention or after the 1-month waitlist control period. Patients who underwent the NET intervention could then be compared to the control group.

Psychological assessments

All assessments were conducted in the same office environment. All participants completed the Posttraumatic Cognitions Inventory (PTCI), Impact of Events Scale (IES), Spielberger State-Trait Anxiety Index (STAI—Form Y) and Brief Symptom Inventory (BSI-18). The PTCI is a 36-item measure of trauma-related thoughts and beliefs [16]. The IES is a well-validated and reliable measure of traumatic stress that has been utilized in clinical studies for over three decades [17]. The STAI Form Y is a 40-item measure which is widely used to determine anxiety in a specific situation and as a general trait [18]. The BSI-18 is an 18-item standardized measure that has been widely used and validated for assessing general distress screening in oncology populations [19, 20]. The measure yields a global severity index that is considered one of the most reliable indicators of psychosocial stress in the literature.

NET intervention

The NET intervention consisted of three to five sessions, 1 h in length each, with a NET-certified, licensed psychologist (AT). Our previous work suggested that 3–5 sessions usually are sufficient for the therapist and patient to feel that the distress of the event has been largely neutralized [9]. Mean intervention dosage for the present study was 4.1 sessions. The focus of the sessions is on the subjective experience of the distressing recollection. The NET protocol consists of standard psychological principles: (1) cognitive (identifying the nature of the thoughts and internal dialog associated with the recollections), (2) emotional (identifying the emotion(s) that the recollection elicits), and (3) behavioral (how the recollections affect actions such as avoidance of accomplishing tasks). During the desensitization aspect of the protocol, while thinking about the traumatic event and the cognitions and emotions associated with it, participants were asked to do simple breathing exercises. The NET intervention also incorporates a biofeedback-based technique called the muscle test to help determine the most reactive features of the traumatic memory [21]. The intervention integrates the use of acupressure points on the wrists that are thought to correlate with specific emotional qualities in the traditional Chinese Medicine system, and they are used during the desensitization step simultaneous with the breathing instructions.

After the participants completed the NET intervention, they underwent the same battery of clinical, autonomic, and fMRI evaluations that they had prior to the intervention.

Statistical analyses

For the final analysis, data from two subjects had to be excluded, one due to substantial movement on the MRI and one due to an inability to get adequate post-intervention heart rate measures due to artifact. For the functional connectivity measures, an intergroup ROI to ROI analysis was implemented to determine statistically significant network connectivity differences between the NET intervention group and controls and between the pre and post scan. The multiple testing adjustment was performed controlling for the family-wise Type I error using the method of Hommel [22].

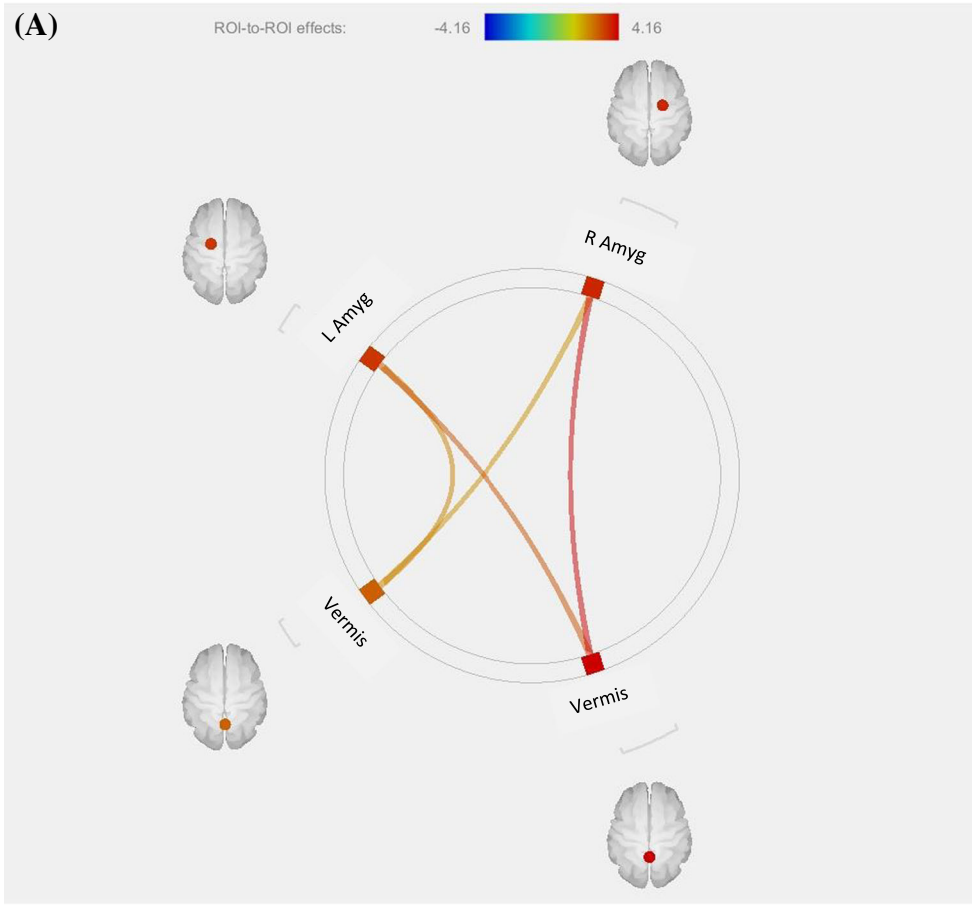
For the heart rate measures separate linear mixed effects (LME) models with the fixed effects of session (pre or post Tx), Tx group (NET vs controls) and their interaction were used to model the absolute changes (HR distress-HR neutral) in heart rate (HR expressed in beats per minute). The difference between treatment groups was tested in terms of the interaction effect (interaction between treatment group and session), which is equivalent to testing the difference in pre-to-post Tx changes between treatment groups. Spearman's rank correlation coefficient was used to evaluate the association between pre-to-post change in IES Score and pre-to-post change in HR differences. The data analysis was performed in *R* [23].

Results

Functional connectivity results

The functional connectivity results showed that the cerebellum had significantly higher connectivity with the amygdala, parahippocampus, and brain stem (see Fig. 1 and Table 1).

Fig. 1 Representative figures showing the change in connectivity between the amygdala (Amyg) regions and the vermis (**a**) and between the left and right cerebellum (Cereb) and the left and right amygdala (**b**)


(A)
ROI-to-ROI effects:
-4.16
4.16
R Amyg
L Amyg
Vermis
Vermis

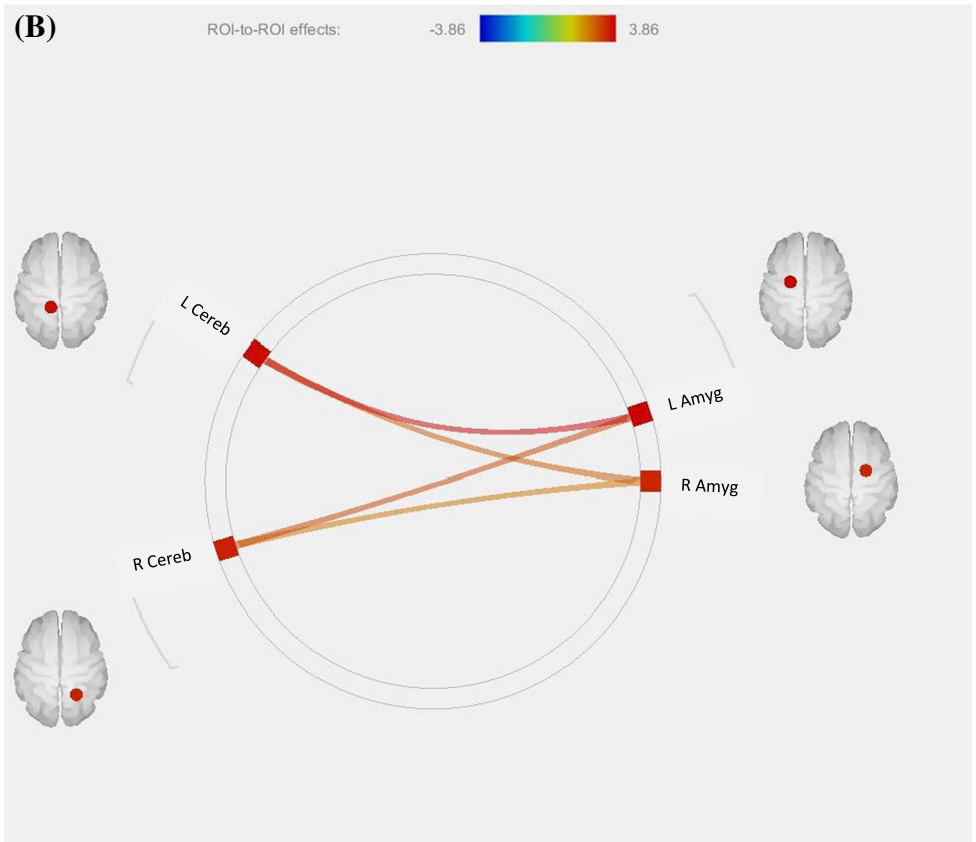

(B)
ROI-to-ROI effects:
-3.86
3.86
L Cereb
L Amyg
R Amyg
R Cereb

Table 1 Areas that had significantly altered functional connectivity between the NET and control group when comparing the initial and follow-up scans

Seed point	Structure	*p* adjusted FW*
L Cereb	L amygdala	0.010
L Cereb	L parahippocampus	0.037
L Cereb	R amygdala	0.037
L Cereb	Brain stem	0.039
R Cereb	L amygdala	0.033
R Cereb	L parahippocampus	0.039
R Cereb	Brain stem	0.039
R Cereb	R amygdala	0.039
Vermis	R amygdala	0.005
Vermis	L amygdala	0.033
Vermis	R parahippocampus	0.039
Vermis	Brain stem	0.039

*The values presented are corrected *p* values after controlling for multiple comparisons

Heart rate response results

When the post-intervention scans were compared to the pre-scans, those subjects who received the NET intervention had significantly decreased autonomic reactivity based on heart rate changes during the traumatic stimulus, compared to controls. Table 2 provides the mean absolute HR differences with corresponding 95% confidence intervals by Tx group and session. The mean pre-to-post changes in absolute heart rate by Tx group are given in Table 3. There were significant differences between Tx groups in terms of pre-to-post changes in heart rate. The mean pre-to-post change in absolute HR difference was significantly lower in the NET group, as compared to waiting list group (difference = − 2.76, 95% CI: -5.28, − 0.23; $p = 0.034$).

Clinical results

The clinical data most relevant to this present analysis, and presented in our previous paper, found that there were significant improvements in the IES scores in the subjects undergoing the NET intervention compared to the control group. In the present analysis, we also found there was a significant association between pre-to-post change in IES Score and pre-to-post change in absolute HR differences (Spearman's rank correlation coefficient = 0.45, $p = 0.047$). In other words, those subjects measuring the greatest decline in heart rate response (i.e., autonomic reactivity) in the post-intervention assessment also reported lower scores on the Impact of Events Scale.

Table 2 Mean absolute HR differences (in beats per minute) between groups (NET group and Control group) and conditions

Group	Session	HR diff	Lower 95% CL	Upper 95% CL
NET	Pre	4.50	2.79	6.20
NET	Post	0.76	− 0.95	2.46
Cont	Pre	3.54	1.83	5.24
Cont	Post	2.56	0.85	4.26

Table 3 Mean pre-to-post changes in heart rate by Tx group (NET versus control)

Measure	Group	Pre-to-post mean change	Lower 95%CL	Upper 95%CL	*p* value
HR diff	NET	− 3.74	− 5.52	− 1.96	0.0003
HR diff	Cont	− 0.98	− 2.76	0.79	0.2613

Discussion

This preliminary study evaluated cerebellar connectivity in relation to limbic and autonomic reactivity in cancer patients receiving NET for traumatic stress symptoms. The results show for the first time that a treatment for traumatic stress changes cerebellar connectivity with limbic structures and the brain stem, and that these changes are associated with reduced symptoms and autonomic reactivity to traumatic stimuli. This data is an important step in understanding the mechanism of treatment effect for the NET intervention.

The cerebellum may be integral to the experience of emotions and the development of emotional memories [24]. In fact, distinct subregions of the cerebellum are believed to be related to negative emotional processing [25, 26]. The potential role of the cerebellum in modulating emotions and autonomic reactivity has been supported by clinical and neuroimaging data [27, 28].

Of particular relevance to the present study, prior fMRI studies show that negative emotional stimuli activate the cerebellum, posterior cingulate, and fusiform gyrus [29, 30]. In addition, reciprocal connections link the cerebellum with brain stem areas containing neurotransmitters involved in mood regulation, including serotonin, norepinephrine, and dopamine [31, 32]. Studies have also suggested that the vermis of the cerebellum may be particularly involved with moderating negative emotions. The mechanism is based in part on how regions of the cerebellum are activated by negative or aversive stimuli independent of regulation of motor or autonomic processes [33]. In fact, the vermis appears to be involved in a number of the processes for forming emotional memories including how memories are acquired [34, 35], how they are stored and retrieved [36], and how they dissipate [33]. These data suggest that the vermis interacts with the limbic structures such as the amygdala during emotional processes

and emotional memory formation. Furthermore, the vermis may function as an interface between incoming sensory stimuli, the emotional state of the individual, and associated motor responses. For these reasons, the NET intervention may be of particular value in helping people regulate negative emotions and associated memories because the mechanism of action of this technique likely affects motor, emotional, and sensory processing.

The cerebellum connects with the limbic structures both ipsilaterally and contralaterally [37]. It has also been found that the vermis may be particularly connected to the limbic structures [38] Using MRI techniques similar to the current study, several resting-state functional connectivity studies have found functional coherence between the cerebellum and amygdala, hippocampus, hypothalamus, insula, and anterior cingulate [39–41]. Furthermore, neuroimaging studies suggest the cerebellum is associated with emotional circuits such that positive emotions are associated with the left cerebral hemisphere and negative emotions are associated with the right hemisphere [42, 43] The vermis and the left cerebellum has also been shown to have increased functional connectivity with the left amygdala during the strong emotion of disgust [44].

An objective of the NET intervention is to help patients become less physiologically reactive to distressing stimuli and to become more capable of choosing alternative responses. An important element of the proposed mechanism by which this would occur is regulation of limbic and autonomic reactivity. Further, the integrated elements of the NET intervention may especially facilitate a cerebellar pathway for modulating responses in the limbic areas, anterior cingulate, brain stem, and autonomic nervous system.

The results from the current study support our hypothesis and suggest that the NET intervention may engage the cerebellum to modulate the psychological and autonomic reactivity experienced in patients with traumatic memories. In our prior work using ASL fMRI, we found that the limbic and brain stem areas were not as reactive to specific traumatic stimuli after NET (9). The current functional connectivity study shows more specifically how this might occur on a neurophysiological level specifically via changes in functional connectivity of the cerebellum and vermis. This has important implications for understanding the neurophysiological effects of the NET intervention.

The areas observed to have altered functional connectivity have previously been implicated in studies of the brain's response to exposure to traumatic stimuli or memories. The parahippocampal gyrus is known to play an important role in the storage and retrieval of emotional memories [45]. In PTSD patients, exposure to traumatic visual stimuli during fMRI activated the parahippocampal gyri, particularly on the left [46]. These same traumatic stimuli did not activate the parahippocampus in control subjects. In a small study of miners exposed to a traumatic mining accident, fMRI during symptom provocation revealed that PTSD subjects had increased responses in the left parahippocampal gyrus along with diminished responses in the right anterior cingulate gyrus, left inferior frontal gyrus, and bilateral middle frontal gyrus [45].

A systematic meta-analysis of neuroimaging studies of PTSD patients showed that differential activity in the amygdala and parahippocampus distinguished PTSD patients from controls who were and were not exposed to trauma [47]. Interestingly, while this analysis focused on the parahippocampus and amygdala, the data analysis revealed significant findings in the left cerebellum that were essentially not discussed in the paper. Even a small study of Taiwanese adolescents showed that during exposure to earthquake imagery, patients with PTSD had activation in the bilateral cerebellum and left parahippocampal gyrus while the control group did not [45].

A recent FDG PET scan study of veterans with traumatic brain injury with and without PTSD found that cerebellar and amygdala abnormalities are not only frequently associated with physical brain injury, but likely produce symptoms of PTSD [48]. Several volumetric studies have further implicated these same areas with PTSD. The cerebellum, amygdala, and parahippocampal structures have all been found to be significantly affected in individuals with PTSD than in trauma-exposed healthy individuals [8, 45, 49].

The results from the present study also suggest that the NET intervention has the ability to alter the reactivity in the autonomic nervous system, perhaps via the cerebellum. The finding that there is overall decreased heart rate between the trauma and neutral scripts in the NET patients' post-treatment supports the notion that the NET intervention helps "normalize" brain and autonomic reactivity in response to exposure to the traumatic stimuli. And given the clinical response in the NET group, it would seem that these physiological changes underlie the reduced clinical reactivity experienced by the patients.

With regard to potential limitations of this study, it should be noted that the sample size will need to be expanded to fully confirm the functional connectivity observed in these patients. While it is believed that the integrated components of the NET intervention work synergistically to achieve its effect, future studies might try to determine if specific elements are more responsible for the neurophysiological and clinical effects. In addition, future, larger studies can be performed that include analysis of covariables such as gender, age, time since trauma, and other factors. We utilized auditory scripts as triggering cues for eliciting traumatic stress responses but it may be more appropriate to consider other approaches for eliciting emotional reactivity. We used a control group that received the same clinical and neurophysiological assessments as the NET group; however, the next level of investigation could be an

active control group that controls for attention and therapeutic time. Finally, we focused the current study on cerebellar, limbic, and autonomic changes, but it is possible that other brain areas also are involved in the neurophysiological effects associated with the NET intervention.

Conclusion

Overall, the results from this study are the first ever to assess the combined neurophysiological and autonomic effects of an intervention for traumatic stress symptoms in cancer patients. This data suggests that a brief therapeutic course of the NET intervention reduces the reactivity in the autonomic nervous system in large part via altered functional connectivity in the cerebellum. By reducing the brain's reactivity to traumatic memories, the NET intervention appears to diminish distress associated with such recollections and improve emotional self-regulation. This initial study is highly encouraging and emphasizes the need for larger-scale clinical and neurophysiological trials of this potentially important therapeutic approach for cancer patients with traumatic stress.

Funding This study was funded by the One Research Foundation.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the Institutional Review Board of Thomas Jefferson University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent approved by the IRB of Thomas Jefferson University was obtained from all individual participants included in the study.

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