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Efficacy of cervical sympathetic blockade in the treatment of primary and secondary PTSD symptoms: A case series

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ABSTRACT

Background: Post-traumatic stress disorder (PTSD) can develop in individuals following exposure to an overwhelmingly traumatic event. Secondary PTSD is defined as occurring after exposure to a person with primary PTSD, such as an intimate partner. Successful treatment of PTSD symptoms by the use of cervical sympathetic blockade (CSB) has been previously reported to help with symptoms irrespective of PTSD cause.
Objective: To describe the efficacy of CSB in treating symptoms of primary and secondary PTSD in two couples, and visualize CSB impact through neuroimaging.
Methods: Four patients received CSB at C6 and C4 with ultrasound guidance on the right side followed by the left side a day later. PTSD symptoms were evaluated in all patients using the PTSD Checklist (PCL-5) before and after the procedure. Patients underwent SPECT scans acquired using a high resolution Picker (Philips) Prism XP 3000 triple-headed gamma camera, with low-energy high-resolution fan beam collimators, one day before and one week after the procedures.
Results: CSB showed acute benefit for symptoms of primary and secondary PTSD, offering a clinically significant reduction in PTSD symptoms in all four patients. The PCL-5 scores of patients with primary PTSD were reduced from 41 to 7 and from 44 to 6 on the 80-point scale. The PCL-5 scores of patients with secondary PTSD were reduced from 40 to 17 and from 43 to 7 on the 80-point scale. Furthermore, SPECT imaging showed stark increases in activity in the prefrontal pole and thalamus in all patients, and increases in activity in the inferior orbital prefrontal cortex in three of four cases. Modulation of activity in the temporal lobes, orbital prefrontal cortex and basal ganglia was also noted after the procedure.
Conclusion: CSB is a minimally invasive procedure with an excellent safety profile, providing relief of primary and secondary PTSD symptoms. The increase in prefrontal pole, thalamus and inferior orbital activity correlates with the improved symptomatology.

1. Introduction

1.1. Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is a pathological symptomatology which may develop in individuals following exposure to an

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overwhelmingly traumatic event. These patients typically re-experience the events of the trauma through intense, intrusive, and vivid memories, often in the form of waking recollections (flashbacks) and nightmares. Symptoms commonly associated with PTSD are characterized by behavioral, psychological, mood, and sleep factors [1].

The prevalence of primary PTSD among military personnel has been rising steadily over the past decade, as it has in other cohorts. The reason for military-associated symptoms increase is likely multifactorial, with the ongoing psychiatric toll of combat trauma and recurring deployment cycles. The overall, international, lifetime prevalence of PTSD has been estimated by the World Health Organization World Mental Health Surveys at 3.9%, a number which goes up to 5.6% among those exposed to trauma in their lifetime [2]. Among post-deployment US infantry personnel, the PTSD prevalence is considerably higher, averaged at 10–20% [3]. PTSD symptoms have also been identified among wrongfully accused individuals. A systematic review noted that the PTSD rates identified in the wrongfully accused population ranges from 27% to 67% [4].

Secondary PTSD is attributed to exposure to the traumatic experience of a significant other, leading the individuals to develop PTSD symptoms [5]. Secondary traumatization is the stress caused by providing help, or wishing to help, and offering emotional support to a traumatized person. An example of military-related secondary PTSD was described by Dr. Franciskovic, in his study of 56 wives of male veterans diagnosed with PTSD. Among the wives included in the study, 57% had six or more symptoms of secondary traumatic stress, only 5% had none of the symptoms, and 39% of the women met the diagnostic criteria for secondary PTSD [6].

Secondary PTSD has been shown to manifest differently in varying situations. Another study was done comparing 56 wives of combat veterans with 116 wives of former prisoners of war [7]. The latter group reported worse self-rated health and higher levels of secondary traumatization. Furthermore, marital adjustment moderated the relationship between their secondary traumatization and their general health. The experience of living with someone who is experiencing PTSD symptoms is associated with reduced psychological and health measure outcomes.

Recent medical treatment for PTSD has relied heavily on pharmacological modalities. However, these medications are often associated with undesirable safety profiles, leading to the evolution of alternative treatment modalities. Among them is the cervical sympathetic blockade (CSB), targeting the sympathetic nervous system, the utilization of which has been growing in recent years [8].

1.2. *Cervical sympathetic nerve blockade in the treatment of PTSD*

A stellate ganglion block (SGB) involves the injection of a local anesthetic into the area surrounding the stellate ganglion, a sympathetic ganglion located in the neck. A 2017 systematic review including 32 publications found that SGB has significant potential benefit in PTSD patients, particularly in patients unresponsive to conventional treatment options [9]. More recently, in 2020, a large, multisite, sham-controlled, randomized trial was conducted in 113 active-duty service members with PTSD symptoms. The findings revealed that two SGB treatments two weeks apart were effective in reducing PTSD total symptom severity over 8 weeks, with an adjusted mean symptom change two times greater in the SGB group compared the sham group [10].

A review from 2021 aimed to summarize evidence on SGB included 17 published studies and 4 registered clinical trials on patients with PTSD and schizophrenia spectrum disorders [11]. Improvements were observed within 5 minutes of the treatment, and lasted one month or longer. The evidence from clinical trials and case studies supports the use of SGB for treating psychiatric disorders involving dysregulation of the sympathetic nervous system, despite mixed evidence from RCTs. Furthermore, the type of trauma does not appear to affect the efficacy of CSB for PTSD. A 2022 study concluded that CSB is effective in treating PTSD symptoms regardless of gender, trauma type, PTSD-related drug use, suicide attempt, or age [8].

Although it has shown to be safe and effective for the treatment of PTSD, a C6-level right-sided SGB is not always sufficient in clinical practice. As a result, a left-sided SGB may be used as a rescue procedure, if the right-sided SGB does not work. This was shown in a retrospective study with 205 patients treated with a right-sided SGB, 20 patients did not respond to a right-sided SGB with clinical significance. Ten of these patients subsequently received a left-sided SGB, and 90% responded favorably with a PCL-5 mean improvement of 28.3 points [12,13].

In addition to the laterality consideration, the targeting of additional levels has also been suggested to increase the impact of CSB. A retrospective analysis of 147 patients with PTSD compared C6 SGB versus dual CSB at C6 and C4, with ultrasound guidance, on the right and left sides. Not only did both single and two-level CSB show safety and efficacy, but the dual CSB showed greater improvement than the standard SGB in the treatment of PTSD [14].

The objective of this case series is to describe the efficacy of CSB in treating symptoms of primary and secondary PTSD in two couples with different causes of PTSD. The management of PTSD symptoms is assessed through psychometric testing, and cerebral changes resulting from the procedures are visualized through neuroimaging.

2. Materials and methods

2.1. *Patients and setting*

The setting of this case series is the Stella Center located in Chicago. Four patients were included in the case series, two of which were diagnosed with primary PTSD, and two of which were diagnosed with secondary PTSD. Every procedure was performed by the first author. Each patient provided informed consent for the procedure and subsequent publication of their case history.

2.2. Cervical sympathetic block

The patient was given information concerning the risk/benefits of the procedure and a consent form was completed. The patient was positioned comfortably in the supine position, with the head rotated slightly to the left with monitoring per clinic protocol. Sedation was provided by anesthesia personnel with IV propofol.

The skin over the anterior and right-side neck was widely cleaned with chlorhexidine-isopropyl alcohol preparation. Sterile ultrasound gel was applied. The right-side anterior neck was scanned using linear transducer (Mindray Ultrasound, China) from the level of the 7th to the 4th cervical vertebrae in transverse view. Power Doppler was utilized to identify vasculature in the planned needle track. The skin on the lateral neck was anesthetized with 1 ml of 1% lidocaine. Utilizing an in-plane approach, under real-time ultrasound guidance, a 22 Gauge echogenic needle was placed just dorsal to the ventral fascia of the longus coli, medial to the longus capitus, and approximated to the cervical sympathetic chain. After attempted aspiration, while monitoring the patient, 0.5 ml of 0.5% bupivacaine was injected, and after observing the patient for 30 seconds, 7.5 cc of injectate was injected over 1 minute for a total injection volume at C6 level. The same procedure was performed at C4 level. Due to the risk of serious airway compromise with inadvertent bilateral blockade of the recurrent laryngeal nerves, the left-sided SGB was performed 24 hours after the right-sided SGB to allow adequate time for anesthesia effects to subside.

Both before and after the procedure, the patient was specifically informed as to the potential for and signs of life-threatening adverse events, including worsening neck pain which may indicate hematoma formation, and shortness of breath. All procedures were well tolerated, all patients exhibited Horner's syndrome (ptosis, miosis and anhidrosis) within 10 minutes of the injection. The patient was then returned to the supine position and monitored for an additional 30 minutes before discharge.

2.3. Psychometric testing

The PTSD Checklist Version 5 (PCL-5) is a 20-item self-reported questionnaire designed to assess PTSD symptomatology including symptoms of re-experiencing, avoidance, and hyperarousal (Supplementary Table 1). The PCL-5 has demonstrated excellent reliability and validity in primary care settings [15,16]. Nonresponse to the treatment was defined in patients who had obvious Horner's syndrome findings but failed to improve by at least 10 points on a PTSD Checklist Version 5 (PCL-5) [17,18].

2.4. SPECT acquisition and reconstruction methods

SPECT scans were acquired using a high resolution Picker (Philips) Prism XP 3000 triple-headed gamma camera (Picker Int. Inc., Ohio Nuclear Medicine Division, Bedford Hills, OH, USA) with low energy high resolution fan beam collimators. For each procedure, an age- and weight-appropriate dose of 99m Tc–hexamethylpropylene amine oxime (HMPAO) SPECT was administered intravenously at rest and performed a subsequent cognitive task, the Conners Continuous Performance Test (Conners Continuous Performance Test, CCPT-II, Multi-Health Systems, Toronto, Ontario), 3 min after the injection. Approximately 30 min after the injection, subjects were scanned. Data acquisition yielded 120 images per scan with each image separated by three degrees spanning 360°. A low pass filter was applied with a high cutoff and Chang attenuation correction performed. The resulting reconstructed image matrices were approximately $128 \times 128 \times 78$ with voxel sizes of $2.5\ \text{mm} \times 2.5\ \text{mm} \times 2.5\ \text{mm}$ [19,20]. SPECT scans were performed one day before, and one week after CSB.

3. Case reports

3.1. Case # 1

The patient was a 55-year-old male with multiple deployments to combat zones as a member of Special Forces. His years having served as an Operator left him with severe complex PTSD. He reported the following behaviors: inappropriate aggressive responses, rage, hyper-alertness, paranoia, night terrors, physical ailments (high blood pressure and insomnia), problems with memory, and weight gain. As a result of the PTSD and symptoms, the patient reported that the trauma has severely impacted anger outbursts at those he loves, ultimately leading to three divorces and struggles with the fourth marriage. The patient reported feeling worse and an

Table 1
Demographic data and PCL-5 scores of patients.

	Demographic			Baseline		Follow-up		
	Sex	Age (years)	Diagnosis	Time before procedure	PCL-5 score	Time since procedure	PCL-5 score	PCL-5 score difference
Case # 1	Male	55	Primary PTSD	1 month	41	6 months	7	− 34
Case # 2	Female	46	Secondary PTSD	2 days	40	8 months	17	− 23
Case # 3	Male	59	Primary PTSD	2 weeks	44	3 weeks	6	− 38
Case # 4	Female	57	Secondary PTSD	1 week	43	1 week	7	− 36

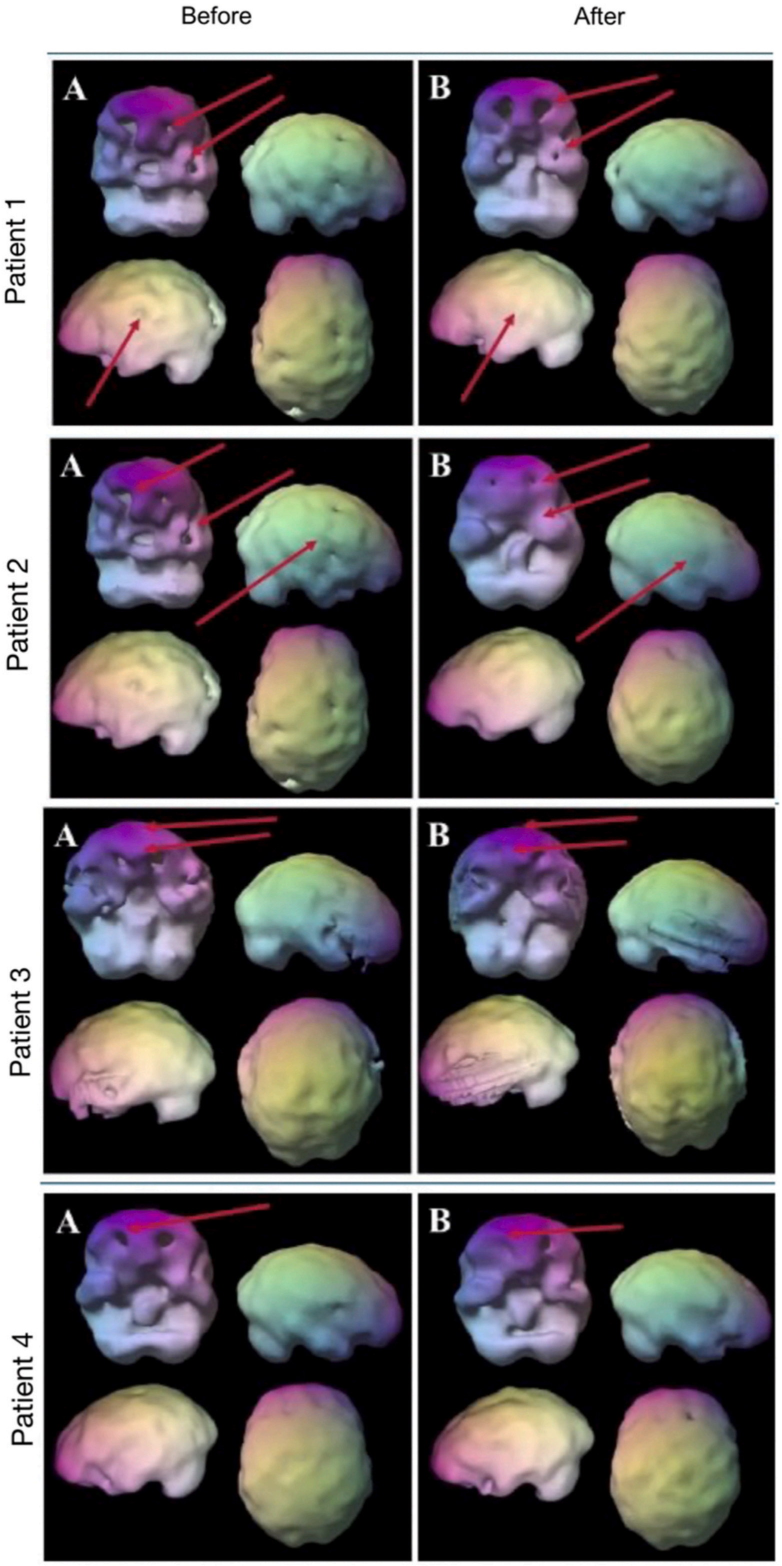

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Fig. 1. Patient 1: SPECT Cortical Scan Before (A) and After (B) Stellate Ganglion Blockade (SGB). The texture of surface is associated with blood flow. Smoother surfaces are associated with better blood flow. Bumpier surfaces are associated with decreased blood flow. 1) Inferior Frontal Lobes demonstrate decreased blood flow after SGB. Such findings are associated with decreased focus and lower impulse control. 2) Left Temporal Lobe demonstrates improved blood flow after SGB. Such findings are associated with decreased anxiety, frustration, anxiety, and stress. 3) Scalloping over Left Parietal Cortex decreases after SGB reflective often associated with decreased brain fogginess. **Patient 2:** SPECT Cortical Scan Before (A) and After (B) Stellate Ganglion Blockade (SGB). The texture of surface is associated with blood flow. Smoother surfaces are associated with better blood flow. Bumpier surfaces are associated with decreased blood flow. 1) Inferior Frontal Lobes demonstrate improved blood flow after SGB. Such findings are associated with improved focus and higher impulse control. 2) Left Temporal Lobe demonstrates improved blood flow after SGB. Such findings are associated with decreased anxiety, frustration, anxiety, and stress. 3) Scalloping over Right Parietal Cortex decreases after SGB reflective often associated with decreased brain fogginess. **Patient 3:** SPECT Cortical Scan Before (A) and After (B) Stellate Ganglion Blockade (SGB). The texture of surface is associated with blood flow. Smoother surfaces are associated with better blood flow. Bumpier surfaces are associated with decreased blood flow. 1) Inferior Frontal Lobes demonstrate improved blood flow after SGB. Such findings are associated with improved focus and higher impulse control. 2) Prefrontal Pole demonstrates increased blood flow after SGB. Such findings are associated with improved executive functioning. **Patient 4:** SPECT Cortical Scan Before (A) and After (B) Stellate Ganglion Blockade (SGB). The texture of surface is associated with blood flow. Smoother surfaces are associated with better blood flow. Bumpier surfaces are associated with decreased blood flow. 1) Bilateral Inferior Frontal Lobes demonstrate improved blood flow after SGB. Such findings are associated with improved focus and higher impulse control.

increase in symptoms when in large, loud groups. He isolates himself and has continued feelings of unworthiness and never being good enough. He also reported dependency on pharmaceuticals, alcohol, tobacco (smoked for thirty years), and uses marijuana on a nightly basis. It is noteworthy that the patient also has a history of heavy metal poisoning and eight additional spine surgeries. In 2013, he experienced an aborted suicide attempt. He and his wife embraced multiple modalities and practices to combat his PTSD, such as group counseling, cognitive behavioral therapy, and transcranial magnetic stimulation (TMS). One month before treatment, the patient's PCL-5 score reached 41 (Table 1).

Five minutes after the first CSB, he reported feeling refreshed and energized. At the six month follow-up, he acknowledged continued benefits, with a PCL-5 of 7 (baseline score was 41), indicating an improvement of 34 points on the 80-point scale.

Compared to the SPECT scan done 24 hours prior to the procedure (Fig. 1A), there is improved tracer activity in the left anterior temporal lobe, the prefrontal pole, frontoparietal cortex, and left occipital lobe. However, there is more notably decreased activity in the left inferior orbital prefrontal cortex and right occipital lobe. The right temporal lobe again demonstrates mildly decreased activity. The previous scalloping appears slightly less prominent. Additionally, there is less intense tracer activity in the left basal ganglia. The thalamus demonstrates dramatically increased activity (Fig. 1B).

3.2. *Case # 2*

The patient was a 46-year-old female with a history of childhood trauma due to familial physical and emotional abuse. A non-familial sexual assault occurred at the age of 18. The patient also accrued Secondary PTSD during her years married to a traumatized Special Operator. Other notable medical history is endometriosis and fibrosis which led to a hysterectomy in 2000. Two days before the procedure, the patient's PCL-5 score was 40.

Two weeks after the CSB, she reported that she no longer felt she was walking on eggshells, and she no longer spent all her time dedicated to avoiding setting off her husband. She describes that the injections had made her feel empowered, able to do what was needed—or what was wanted—without worrying about backlash. She was experiencing joy again, reveling in happiness, and stated that she is 'super healthy'. The patient's scored 17 on the follow-up PCL-5 test, 8 month following the procedure (baseline score was 40), indicating an improvement of 23 points on the 80-point scale.

Compared to before the procedure (Fig. 1A), her SPECT scan shows is improved tracer activity in the inferior orbital prefrontal cortex and prefrontal pole. However, there is very mildly decreased tracer activity in the occipital lobe and more pronounced decreases in the internal cerebellum. The temporal lobes again demonstrate very mildly decreased tracer activity. Very mild scalloping is again noted. Additionally, the left thalamus demonstrates more intense tracer activity (Fig. 1B).

3.3. *Case # 3*

The patient was a 59-year-old male with PTSD as a result of seven and a half years incarcerated in a federal prison for a crime he did not commit, wrongfully accused of rape and attempted murder. Other notable medical history is a vasectomy in 2006. Extremely depressed, he began therapy; he found it slightly helpful, but it did not truly ease his anxiety, insomnia, nightmares, or outbursts, the worst of his symptoms. The patient usually only gets 3 h of sleep per night as he wakes up approximately every 5 min. He had a hard time eating, being in crowds, and tolerating loud noises. Being alone helps him keep his symptoms under control. The patient reported smoking one pack of cigarettes per day, drinking alcohol daily, and using marijuana. He could not sit unless his back was to a wall. He divorced and re-married, but his PTSD symptoms quickly took a toll on the new marriage, despite attempts at counseling. Two weeks prior to treatment, the patient's PCL-5 score was 44.

After the procedure, he describes that his nightmares went away, he sleeps better, his appetite came back, and his anxiety returned to a manageable level. He says he is a changed man. His post PCL-5 score of 6, three weeks later (baseline score was 44), indicating an improvement of 38 points on the 80-point scale.

Compared to the prior scan (Fig. 1A), there is improved tracer activity in the inferior orbital prefrontal cortex, right temporal lobe, the prefrontal pole, and the internal cerebellum. The left temporal lobe demonstrates mildly decreased activity. Very mild scalloping is again noted. There is more intense tracer activity in the right basal ganglia. The thalamus and left basal ganglia again demonstrate severely and moderately increased activity, respectively (Fig. 1B).

3.4. Case # 4

The patient was a 57-year-old female who developed Secondary PTSD after being married for twelve years to a man who was falsely imprisoned for seven and a half years. It was difficult to handle his nightmares, severe startle responses, and inability to be around crowds, as well as watching it affect her kids—they walked on eggshells, making sure they announced themselves before entering rooms, speaking in low tones. When her husband first underwent treatment for his PTSD, she went with him, and it was then that she was diagnosed with Secondary PTSD. Until that moment, she had spent her time focused on her husband, making sure he felt safe and that his reactions to his environment were manageable and safe for her and the family. Her own terrible reoccurring nightmares, hypervigilance, and behavior modifications were ignored, not seeming as important as her husband's issues, not having gone through the trauma he had. Her symptoms increase if someone gets angry or yells, crowds, lots of traffic, and lots of noise. Being alone and isolated or having a drink seemed to decrease her symptoms. She reports waking up three to four times a night and that she just starts thinking. In an attempt to fall asleep better, she uses lavender essential oils. She usually gets four to 5 h of sleep per night but requires seven to feel rested. The patient takes Wellbutrin, but said she is trying to wean off medication. Other notable medical history includes TMJ surgery in 1986 and tubal ligation in 1995. She scored a 43 on the PCL-5 test, a week prior to her procedure.

One week after the CSB injections, she scored a 7 on the PCL-5 (baseline score was 43), indicating an improvement of 36 points on the 80-point scale. Her marriage was rejuvenated, the couple became closer. She no longer worried he was going to commit suicide, his nightmares became better, he was not so jumpy. She says her own nightmares have gone, her hypervigilance is manageable, and she is now calmer, able to talk about her issues without being overwhelmed by emotion, which has made talk therapy much more effective and satisfying for her.

Compared to the scan before the procedure (Fig. 1A), there is improved tracer activity in the inferior orbital prefrontal cortex, right temporal lobe, the prefrontal pole, and the internal cerebellum. The left temporal lobe demonstrates mildly decreased activity. Very mild scalloping is again noted. There is more intense tracer activity in the right basal ganglia. The thalamus and left basal ganglia again demonstrate severely and moderately increased activity respectively (Fig. 1B).

4. Discussion

All patients in this case series had attempted and failed several psycho-pharmacologic interventions; some of them even required prior hospitalization for their psychiatric symptoms. Following sympathetic blockade, all four patients demonstrated a marked improvement in PTSD symptoms, as seen with the PCL-5 scores and comments on daily function. Furthermore, SPECT imaging showed stark increases in activity in the prefrontal pole and thalamus in all patients, as well as increases in the inferior orbital prefrontal cortex in three of four cases. Mild scalloping was also noted after the procedure, as well as modulation of activity in the temporal lobes, orbital prefrontal cortex and basal ganglia.

The rationale of targeting two levels of the cervical spine, C4 and C6, particularly in the case of single-level SGB-resistant PTSD, involves the vasculature of different regions of the brain. All sympathetic afferent fibers supplying the brain originate from the spinal cord (primarily T-2 to T-4), and pass through the stellate ganglion following the arterial supply, before ascending to the superior cervical ganglion [21]. The stellate ganglion sympathetic fibers typically follow the vertebral artery to the brain, unlike the superior cervical sympathetic ganglion which follows the internal carotid artery [22]. Both of those arteries supply different regions of the brain. This would explain how dual blockade of the sympathetic system may produce a more intense “rebooting” of the brain, thereby leading to increased pruning and clinically greater reduction of PTSD symptomatology [8,23]. Although the mechanism of action for CSB in PTSD has yet to be elucidated, one leading hypothesis suggests that the decrease in nerve growth factor levels following cervical sympathetic blocks leads to reductions in norepinephrine, and deactivation of the hyper-aroused status of the sympathetic nervous system present in pathologic states [24].

The neuroimaging analysis showed increased activity in the prefrontal pole and thalamus of all patients. A number of studies have described stress-induced modulations in volume and activity of the thalamus, as well as enhanced connectivity in the pathways formed by the superior colliculus, pulvinar, mediodorsal thalamus and amygdala in PTSD patients [25]. In addition, animal studies have linked the thalamus-amygdala pathway to visual fear processing. In non-PTSD trauma survivors, it is hypothesized that trigger exposure in everyday life desensitizes the thalamus-amygdala pathway. Failure of this process may be related to a functional defect in an atrophy of the thalamus. Recovery of the thalamus volume and activity may correspond to improvement in PTSD symptoms.

The involvement of the prefrontal cortex in PTSD pathophysiology, along with the hippocampus and amygdala, has also been previously established by neuroimaging studies [26–29]. The orbitofrontal cortex (OFC) region contains extensive connection to the limbic and sensory systems. The OFC receives projections from multiple sensory modalities, including the primary olfactory cortex, gustatory cortex, secondary somatosensory cortex, and the superior/inferior temporal lobes (conveying visual information). There are also inputs the limbic system, including the medial dorsal nucleus of the thalamus, the amygdala, perirhinal cortex, entorhinal cortex, insula, and hypothalamus. The OFC sends reciprocal efferent projections to the amygdala, entorhinal cortex, perirhinal cortex, and hypothalamus. In addition, there are outputs to the basal ganglia, and projections to the periaqueductal grey area and ventral tegmental area. Within this network, the OFC is thought to add contextual meaning and value to an event, and make constructive task-oriented actions for that specific condition. Furthermore, the OFC will inhibit those actions that are not promoting optimal gain to complete that task. Through its connection to the amygdala, the OFC plays a key role in regulation and tolerance of frustration. Self-control, poise, and emotional tolerance become active participants in making optimal decisions. If the OFC is not functioning properly, optimal decision making and contextual interpretations may become distorted, misaligned, and misconstrued. In such states, an individual is more prone to make impulsive, non-reflective, and erroneous decisions. In addition, such subjects struggle to control their feelings becoming more angry, tense, and irritable. Improved blood flow to the OFC and frontal lobes is associated with improved concentration, less impulsivity, better decision making capacity, and increased executive functioning. With that comes better control over emotions and intrusive thoughts. Thus it is conceivable that the prefrontal cortex activation noted would correlate with improved symptoms of PTSD.

One limitation of our study is the variation in time points at which baseline and follow-up PCL-5 scores were obtained from the patients. Furthermore, this was an uncontrolled case study, which limits our ability to form causal inference. To analyze the neuroimaging changes and determine how they may result from the procedure, a larger cohort with longer follow-ups would be necessary.

5. Conclusion

As described in prior case studies, CSB appears to be both safe and efficacious in the treatment of PTSD symptoms. Given that none of the patients presented in this case series were psychotropic naive and, indeed, several were resistant, further weight can be given to the hypothesis that CSB is beneficial for treatment of non-responders to single-level SGB. Although the mechanism of action for the procedure's efficacy remains under study, the findings argue for the case of long-term neuronal changes. In order to elucidate how these results stem from the procedure, further testing is necessary. It is important to design a randomized controlled trials to investigate the procedure's impact on the observed results as randomization will help minimize bias and establish a cause-and-effect relationship between the procedure and the outcomes. It is fundamental to also conduct longer follow-ups for these patients to see further changes on the imaging scans performed.

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Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix A. Supplementary data

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