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Research Article

Modulating the Autonomic Nervous System: Transcutaneous Vagal Neuromodulation Improves Outcomes in Adolescent Post Traumatic Stress Disorder - A Double-Blind Trial

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Abstract

The present study is a double-blind and sham-controlled trial on a pediatric population aged between 15 and 17 years with diagnosis of post-traumatic stress disorder (PTSD). The aim of the research is to propose as gold standard of post-traumatic stress disorder treatment, the combination of cognitive behavioral therapy (CBT) with the transcutaneous vagus nerve stimulation (tVNS). 50 patients were enrolled: (26 female, 24 male) randomly divided into control group (50 patients) who performed CBT and tVNS and placebo group (50 patients) who performed CBT and tVNS in sham mode. All subjects underwent pretreatment (T0) and after three months treatment (T3 months) assessments, monitoring the variation of evening salivary cortisol level (ng/mL) and Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) score. The results obtained highlighted statistically significant difference between the treatment and the placebo group in terms of reduction of evening cortisol and of the PCL-5 rating scale score. Combined treatment with CBT and TVNs is statistically and clinically more effective: placebo mean change post-pre cortisol ng/mL -0.91; p-value < 0.001 and placebo group mean change post-pre PCL-5 19.46; p-value <0.001. Treatment group mean change post-pre cortisol ng/mL -2.12; p-value < 0.001 and placebo mean change post-pre PCL-5 31.46; p-value < 0.001. The obtained data suggest the indication to treat this patient population with the combined CBT tVNS protocol rather than with BCT alone.

Keywords: *Posttraumatic Stress Disorder; Transcutaneous Vagus Nerve Stimulation; Cognitive Behavioral Therapy; Cortisol; Adolescents*

Abbreviations

AMY: Amygdala; CAPS-5: Clinician-Administered Posttraumatic Stress Disorder Scale for DSM-5; CBT: Cognitive Behavioral Therapy; cPTSD: Complex Post-Traumatic Stress Disorder; CRH: Corticotropin-Releasing Hormone; dACC: Dorsal Anterior Cingulate Cortex; HC: Hippocampus; HPA: Hypothalamic-Pituitary-Adrenal; HRV: Heart Rate Variability; mPFC: Medial Prefrontal Cortex; PCL-5: Post-traumatic Stress Disorder Checklist for DSM-5; PTSD: Post-Traumatic Stress Disorder; PVN: Hypothalamic Paraventricular Nucleus; LEC-5: Life Events Checklist for DSM-5; VNS: Invasive Cervical Vagus Nerve Stimulation; tNVS: Transcutaneous Vagus Nerve Stimulation

Introduction

As known in literature cognitive behavioral therapy (CBT) is effective in treating post-traumatic stress disorder (PTSD) [1].

However, as also known the times and efficacy are significantly accelerated and maximized, by introducing an intervention that targets specifically the organic component. These considerations lead to deduce that, with the combination of CBT with transcutaneous vagus nerve stimulation (tVNS), all risk factors such as addictions, social isolation, school dropout, and potential relapses that generate pathologies in adulthood, would be prevented. As known, patients with PTSD have reduced high frequency heart rate variability (HRV) in response to trauma cues, require a longer recovery time, and have higher blood pressure than their non-PTSD peers [2]. HRV in patients who recover from PTSD is indistinguishable from healthy controls. This suggests that negative health consequences of PTSD may be reversible if treatment success is achieved prior to cumulative damage from chronic stress [2]. PTSD may develop following exposure to an extremely threatening or horrific event or series of events [3]. Examples of events that can cause PTSD include violent experiences, war, abuse, natural disasters, and accidents. It is possible that traumatic events are also repetitive. Parental neglect can cause complex post-traumatic stress disorder (cPTSD), because it is a chronic, traumatic condition experienced by the subject during childhood [4,5]. Childhood maltreatment is defined as any act or failure to act of the primary caretaker of the child which provides a risk of emotional or physical harm for the child [6].

Table 1

DSM-5 criteria for PTSD

Trauma exposure	
Trauma	Actual or threatened violent death, serious injury or accident, or sexual violence
A. Exposure	Via any of the following: 1. Directly exposed to trauma 2. Eyewitness (in person) to others directly exposed to trauma 3. Learning of direct exposure to trauma of a close family member or close friend 4. Repeated or extreme exposure to aversive details of traumatic event (eg, trauma workers viewing human remains or repeatedly exposed to details of child abuse), in person or via work-related electronic media
Symptom groups B to E (symptoms beginning or worsening after the traumatic event)	
B. Intrusion	*≥1 intrusion symptoms:* 1. Recurrent, involuntary, distressing trauma memories 2. Recurrent, distressing trauma-related dreams 3. Dissociative reactions/flashbacks related to trauma 4. Intense or prolonged psychological distress to trauma reminders 5. Marked physiological reactions to trauma reminders
C. Avoidance	*≥1 avoidance symptoms:* 1. Avoidance/efforts to avoid distressing internal trauma reminders (memories, thoughts, feelings) 2. Avoidance or efforts to avoid distressing external trauma reminders (people, places, activities)
D. Negative cognition and mood	*≥2 negative cognition/mood symptoms:* 1. Amnesia for important parts of trauma exposure 2. Persistent, exaggerated negative beliefs about self, others, or the world 3. Persistent, distorted trauma-related cognitions leading to inappropriate blame of self/others 4. Persistent negative emotional state (eg, fear, horror, anger, guilt, shame) 5. Loss of interest or participation in significant activities 6. Detached/estranged feelings from others 7. Persistent loss of positive emotions (eg, happiness, satisfaction, love)
E. Hyperarousal	*≥2 marked alterations in trauma-related arousal and reactivity:* 1. Irritability and angry outbursts with little/no provocation (eg, verbal/physical aggression toward people/objects) 2. Reckless or self-destructive behavior 3. Hypervigilance 4. Exaggerated startle 5. Concentration problems 6. Sleep disturbance (eg, difficulty falling or staying asleep, restless sleep)
Additional criteria	
F. Duration	>1 month
G. Distress/ impairment	Clinically significant distress; social/occupational/other important functioning impairment
H. Not attributable to another disorder	Independent of physiological effects of a substance (eg, medication, alcohol) or another medical condition

Source: Reference 3

Figure 1: *PTSD criteria, DSM-5 [4].*

Description of ICD-11 Posttraumatic Stress Disorder (PTSD) and Complex PTSD (CPTSD)

Trauma exposure: any extremely threatening or horrific event or series of events.

PTSD	CPTSD
Reexperiencing in the here and now • Flashbacks • Nightmares	Reexperiencing in the here and now • Flashbacks • Nightmares
Avoidance of traumatic reminders • Avoidance of internal reminders • Avoidance of external reminders	Avoidance of traumatic reminders • Avoidance of internal reminders • Avoidance of external reminders
Sense of current threat • Hypervigilance • Exaggerated startle response	Sense of current threat • Hypervigilance • Exaggerated startle response
	Affective dysregulation • Increased emotional reactivity • Decreased emotional reactivity
	Negative self-concept • Belief that oneself is a failure • Belief that oneself is worthless
	Disturbances in relationships • Disconnection from others • Difficulty feeling close to others
Symptoms must persist for several weeks. Symptoms must cause significant impairment in functioning.	

Note. *ICD-11 = International Classification of Diseases.*

Figure 2: *Description of ICD-11 post-traumatic stress disorder (PTSD) and complex PTSD (CPTSD) [3].*

Neural circuitry involved in post-traumatic stress disorder (PTSD)

Amygdala activity manages the consolidation of traumatic memories. These reflexes include increased heart rate mediated by projections to the hypothalamus, locus coeruleus and dorsal vagal nerve, increased respiratory rate via parabrachial connections, gastrointestinal distress via dorsal vagal connections, increased startle via projections to the RPC, freezing and social anxiety via projections to the periaqueductal grey, and hypothalamic-pituitary-adrenal (HPA) activation via projections to the paraventricular nucleus of the hypothalamus [7]. The HPA is a key regulator of cortisol production, and abnormalities in the axis can lead to alterations in cortisol levels [8]. Corticotropin-releasing hormone (CRH) production in the hypothalamic paraventricular nucleus (PVN) constitutes a key neuronal mechanism underlying HPA stress response. Chronic stress can activate the HPA axis through heightened stress responses, persistent basal hypersecretion, and adrenal depletion [8]. When glucocorticoid resistance develops, “fight or flight” responses [8]. The hippocampus has a clear role in the extinction, or learned inhibition, of cued fear memories, and that hippocampal disruption might be important for the extinction deficits seen in PTSD [7]. The medial prefrontal cortex, in particular the subgenual prefrontal cortex [7] working in concert with the hippocampus - in providing inhibitory control over threat-related memories and behaviors.

By contrast, the dorsal anterior cingulate cortex (dACC) within the medial prefrontal cortex implicated in increased fear-responding and threat-responding, and are often co-activated with the amygdala during the threat response [7].

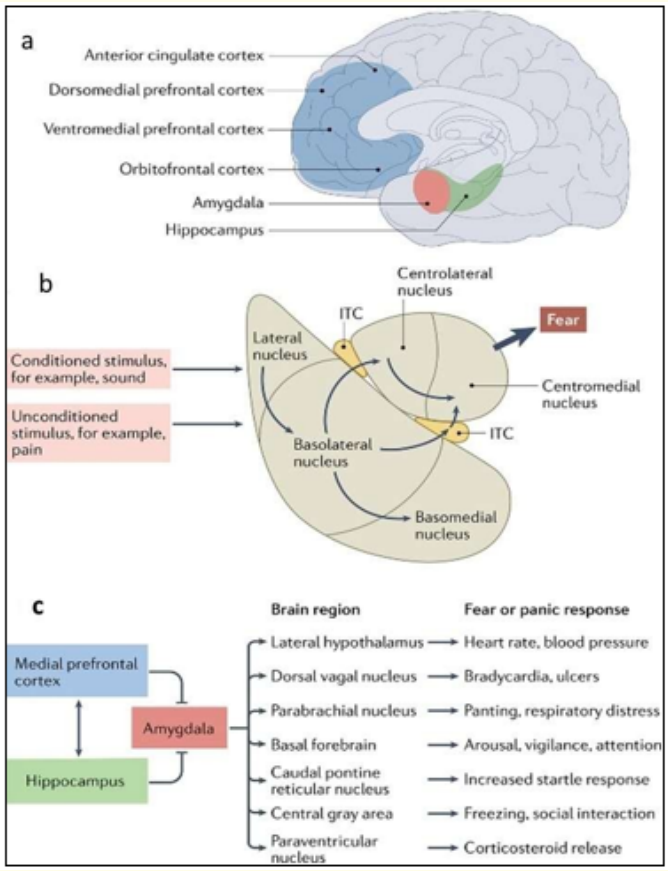

Figure 3: *PTSD cortical-subcortical circuits.*

Neurophysiological findings in PTSD

As shown in the figure 4a, functional MRI individuals with post-traumatic stress disorder (PTSD) have significantly more amygdala activation (orange pixels) in response to the image of a fearful face than do control participants who have experienced trauma but do not have PTSD. As shown in the figure 4b, for examining physiological responses in anxiety and trauma-related disorders is the fear-potentiated startle response [7]. The response of a healthy individual at baseline (black) and in a threat state (red) individuals with PTSD have an enhanced response under both conditions [7]. A structural MRI scan shows smaller hippocampal volume in a participant with PTSD than in a participant without PTSD (Figure 4c) [7]. Blood based biomarkers, such as plasma cortisol, serve as a measure of the hypothalamic-pituitary-adrenal axis response to stress. Individuals with PTSD have a hyper-sensitive hypothalamic-pituitary-adrenal axis response to the cortisol agonist dexamethasone, such that following a dose of dexamethasone, they show a 'super-suppression' of plasma cortisol levels (blue) compared with healthy individuals (green) (Figure 4e) [7].

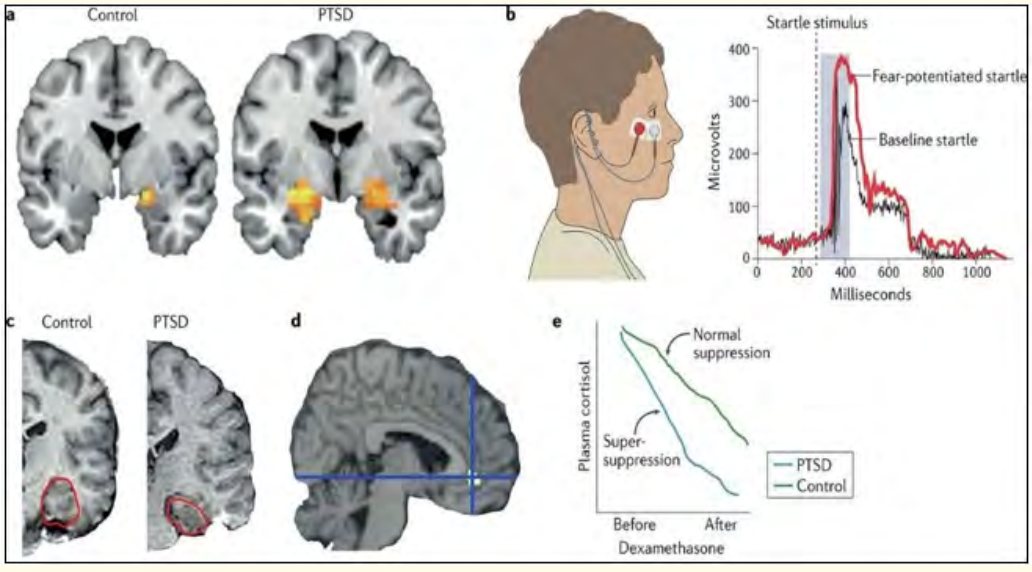

Figure 4: *Neurophysiological findings commonly seen in individuals with PTSD [7].*

Vagus nerve activation using tVNS

Stimulation of the vagus nerve influences biomarkers associated with HPA axis and the autonomic nervous system. Stimulation of the vagus nerve using tVNS therefore acts on symptoms associated with conditions of severe stress [9]. The vagus nerve translates elevated peripheral adrenaline into central noradrenergic activation of memory-relevant brain areas via its projections to the brainstem locus coeruleus the main source of noradrenaline in the brain [10]. This system ultimately projects to memory-relevant brain areas including the basolateral amygdala (AMY), hippocampus (HC) and cortex (e.g. the medial prefrontal cortex; mPFC), increasing noradrenergic transmission and, thus, promoting plasticity in these areas to eventually foster memory establishment [10].

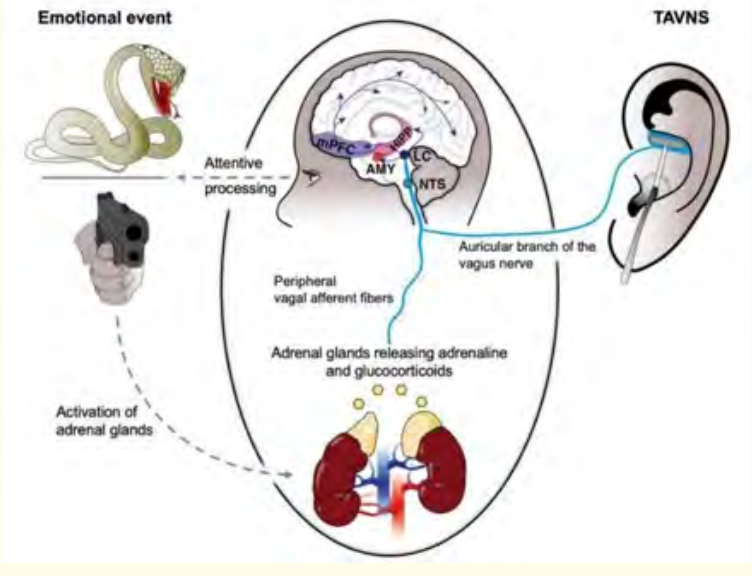

Figure 5: *Vagal afferent brain-body axis guiding emotional memory [10].*

The putative mechanism of action of tVNS is through activation of the nucleus tractus solitarius, which has widespread projections throughout key brain networks involved in emotional regulation and PTSD, and the locus coeruleus. Published pilot fMRI studies have reported BOLD signal alterations in both the nucleus tractus solitarius and the locus coeruleus in the brain stem as well in amygdala activity in response to tVNS as contrasted to a sham stimulation [2]. Alteration of nucleus tractus solitarius activity should increase high frequency HRV, which has been demonstrated with tVNS in healthy controls. Increased high frequency (0.15-0.4 Hz) HRV is associated with improved social function, better health outcomes, and better cognitive function. Conversely, lower RSA is associated with many psychiatric and psychological disorders including major depressive disorder, generalized anxiety disorder, high levels of aggression, and trauma history [2]. NA, acetylcholine and GABA are the most implicated neurotransmitters related to cognitive enhancement following tVNS. Acetylcholine is a key neurotransmitter for memory formation with the majority of neurons in the basal forebrain projecting to hippocampal structures and broad cortical regions. GABA is the primary inhibitory neurotransmitter in the brain, although it also plays a key role in shaping and coordinating excitatory neuronal activity. Modulation of the norepinephrine system is hypothesized to be associated with increases in attentional processing, as well as arousal and memory, acetylcholine in memory encoding; GABA also appears to be a key regulator of resting state networks [9].

Materials and Methods

For the present double-blind and sham-controlled study, 100 patients of both sexes (51 male, 49 female) aged 15 - 17 years were enrolled who turned to Magenta Medical Center, Milan and Cupramedica, Cupra Marittima from 2021 to 2025, because of a diagnosis of Post-Traumatic Stress Disorder (PTSD). They were randomly divided into two groups of 50 people each, through a specific Microsoft Excel feature. Experimental group resulted in 23 females and 27 males, while controls consisted of 26 females and 24 males. After approval of the ethics committee, compilation of the informed consent both for legal guardians and minors, as per the European Community guidelines, all patients were undergoing PCL-5, as a screening method to measure intensity of PTSD symptoms and salivary cortisol levels were monitored. In between, all patients went through Cognitive-Behavioural Therapy (CBT) once a week, combined with Transcutaneous Vagus Nerve Stimulation (tVNS) three times a week. Experimental group received the real treatment, while controls got a sham-mode stimulation. At the end of treatment (T3 months) patients were re-evaluated with PCL 5-and salivary cortisol levels were monitored.

Post-traumatic stress disorder checklist for DSM-5 (PCL-5)

Two of the most widely used PTSD measures are The Diagnostic and Statistical Manual of Mental Disorders, fifth edition [4] versions of the Clinician-Administered posttraumatic stress disorder (PTSD) Scale (CAPS5) [11], a structured interview, mainly used in a clinical way as diagnosis instrument and the PTSD Checklist measures (PCL-5), a self-rated questionnaire, mostly applied as a screening method [12]. It is a 20-item self-rated scale that evaluates symptoms through the four DSM-5 clusters (intrusion, avoidance, negative cognition and mood and hyperarousal). Participants should indicate how much they have been disturbed by each PTSD symptom over the past month, using a 4-point scale (1 = not at all to 4 = extremely), leading to a total symptoms' severity score ranging 0-80. Even though some early studies link a PCL-5 cutoff score between 31-33 with a probable PTSD diagnosis [13], a universally agreed cutoff score for identifying probable PTSD hasn't been found yet, making reliable PTSD diagnosis extremely challenging [14]. The structure being based on DSM-5 allows to have an idea about the symptoms severity score of each cluster individually, by summing the score of the items being part of each cluster separately. The PCL-5 can be administered in different ways, regarding how a Criterion A (exposure) trauma is considered [15] [Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, & Schnurr PP (2013). The PTSD Checklist for DSM-5 (PCL-5). Scale available from the National Center for PTSD at www.ptsd.va.gov.]: avoiding the Criterion A trauma component, with a brief Criterion A trauma evaluation and with the Life Events Checklist for DSM-5 (LEC5) [16], a self-report measure, used to notice potentially traumatic events in an examinee's lifetime, and extended Criterion A trauma analysis. In the present study, PCL-5 was administered to both groups to quantify symptoms severity at T0 and after the tVNS treatment (T3 months).

Cognitive-behavioral therapy (CBT)

The efficiency of the use of Cognitive-behavioural therapy as a psychotherapeutic method in anxiety disorders and associated conditions is well known in literature [17,18], leading to a symptoms improvement among patients with different conditions, including posttraumatic stress disorder [19]. In Cognitive-Behavioural therapy, both the patient and therapist play an active role in the process, with the aim of changing behaviours and cognitions that causes patient's emotional distress and psychological suffering. During the sessions, the therapist's goal is to evoke relevant information from the patient through their dialogue. Both The therapist and the patient collaborate, developing questions and ideas and testing their hypotheses to find new answers. Cognitive-behavioural therapy techniques for anxiety disorders may be different, such as psychoeducation, implying learning information about the disorder itself and its treatment, symptom management techniques (e.g. relaxation), the aim of which is to reduce the uncomfortable effects of anxiety symptoms, cognitive restructuring, based on the idea that anxiety can be partially linked to interpretations that do not reflect a realistic rating of a situation, worry exposure, involving systematic and repeated exposure to events or situations associated with worry and anxiety and self-monitoring, setting down subjective anxiety and situational information between treatment sessions [20]. The patients involved in the present research attended a CBT session once a week for three months regardless of being part of the experimental group or the controls.

Salivary cortisol levels

Hypothalamic-Pituitary-Adrenal (HPA) axis is the first hormonal mediator of stress responses. One of the most important properties of the HPA axis is the negative feedback signal produced by cortisol. Cortisol is either the molecule that allows the stress reaction or the main inhibitor of HPA axis activity [21]. Also, high morning and nocturnal cortisol levels are risk factors for depression and anxiety disorders [22]. Salivary samples were collected by nursing staff using a salivette swab that were at once analysed by the laboratory.

The normal reference values for evening salivary cortisol (11.00 pm) are 0.6 - 1.6 ng/ml [8]. Salivary cortisol levels were monitored in bot experimental group and controls at T0 and after the treatment (T3 months).

Transcutaneous vagus nerve stimulation (tVNS)

As known in literature, invasive cervical vagus nerve stimulation (VNS) is approved for the treatment of different clinical conditions, such as epilepsies, depression, obesity, and for stroke-rehabilitation. Due to the complexity of procedure (surgery, side-effects and high costs), transcutaneous vagus nerve stimulation (tVNS) has been developed as a more sustainable alternative [23]. Transcutaneous vagus nerve stimulation (tVNS) has shown different clinical benefits, being applied to a wide range of neuropsychiatric disorders, including post-traumatic stress disorder; showing a link to symptoms associated with conditions of serious stress [9]. TVNS exploits the electrical conductivity of the skin and is carried out by applying electrical currents through surface electrodes placed in selected sites, most commonly being the auricular branch of the vagus nerve (auricular or intra-auricular stimulation) and the cervical branch of the vagus nerve in the neck [24]. The present study has provided a stimulation of the cervical branch of the vagus nerve through a complete wearable single piece device that can be directly placed around the neck. The instrument stimulates the vagus nerve by sending electrical impulse to the participants' neck, resulting in a drop-in heart rate and the activation of the parasympathetic nervous system, leading to higher levels of calmness and lower stress-related symptoms. Both groups involved in the research here presented underwent a tVNS three times a week for three months, using the same device previously described. Experimental group received the real treatment, producing the activation of the vagus nerve, while controls got a sham-mode stimulation, during which they could only detect mild non-therapeutic vibrations.

Results and Discussion

This chapter presents the statistical analysis of a double-blind, two-arm clinical trial comparing an active treatment to a placebo for post-traumatic stress disorder (PTSD), as measured by the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) score and salivary evening cortisol levels (measured in ng/mL).

The primary endpoint for efficacy analysis is the change in PCL-5 score and salivary evening cortisol levels score from baseline (pre-treatment) to the end of the study (post-treatment). The paired t-test was used to determine if there was a statistically significant change in salivary cortisol levels within each group from pre-treatment to post-treatment. This analysis accounts for the dependency of the data (each subject serves as their own control).

Intra-group analysis (Paired t-test) evening cortisol levels

Both the placebo group and the active treatment group showed a highly statistically significant reduction in salivary cortisol levels from pre-treatment to post-treatment ($p < 0.001$ for both). The placebo group experienced a mean reduction of 0.91 pm 0.54 ng/mL (Mean -pm SD of the difference). The treatment group experienced a larger mean reduction of 2.12-pm 0.55 ng/mL (Mean-pm SD of the difference). The magnitude of the change is substantially greater than that observed in the placebo group, suggesting a notable effect of the intervention.

Group	Mean pre-treatment cortisol (ng/mL)	Mean post-treatment cortisol (ng/mL)	Mean change (post-pre) cortisol (ng/mL)	Paire t-statistic (t)	Degrees of freedom (df)	p-value
Placebo (n = 50)	3.59	2.68	-0.91	-11.97	49	<0.001
Treatment (n = 50)	3.82	1.70	-2.12	-27.52	49	<0.001

Table 1: *Intra-group analysis pre-post treatment.*

Inter-group analysis (Independent t-test on change scores)

To specifically test the efficacy of the experimental treatment, an independent two-sample t-test was performed on the change scores (Post-treatment - Pre-treatment) between the two groups. The null hypothesis (H_0) was that the mean change in the treatment group was equal to the mean change in the placebo group.

The independent t-test comparing the mean change scores yielded a highly statistically significant p-value ($p < 0.001$). This result indicates a significant difference in the reduction of salivary cortisol levels between the experimental treatment group and the placebo group. Specifically, the experimental treatment led to a significantly greater reduction in evening salivary cortisol compared to the placebo.

Analysis	Group 1 (treatment change score) ng/mL	Group 2 (placebo change score) ng/mL	Independent t-statistic (t)	Degrees of Freedom (df)	p-value
Change score comparison	Mean: -2.12 SD: 0.55	Mean: -0.91 Sd: 0.54	-11.53	98	<0.001

Table 2: *Inter group analysis pre-post treatment.*

The overall statistical evaluation strongly supports the efficacy of the experimental treatment in reducing evening salivary cortisol levels. While the placebo group demonstrated a significant reduction on its own (a 0.91 ng/mL mean decrease), the treatment group's

mean reduction (2.12 ng/mL) was statistically and clinically superior ($p < 0.001$). This difference suggests that the effect of the treatment is genuine and exceeds the inherent variability and non-specific effects observed in the control group.

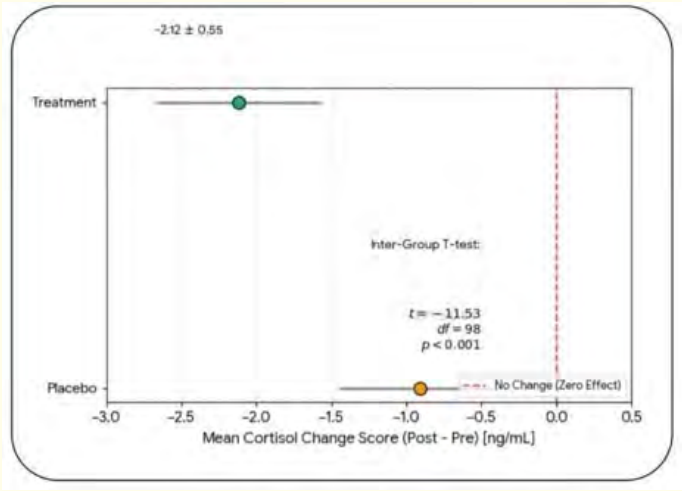

Figure 6: *Mean cortisol charge score ± SD (Dot plot).*

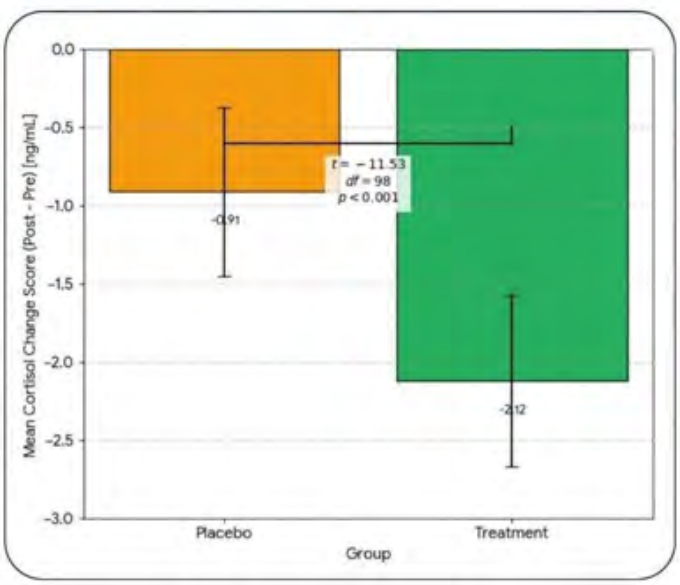

Figure 7: *Comparison of mean charge score ± SD (Inter-group analysis).*

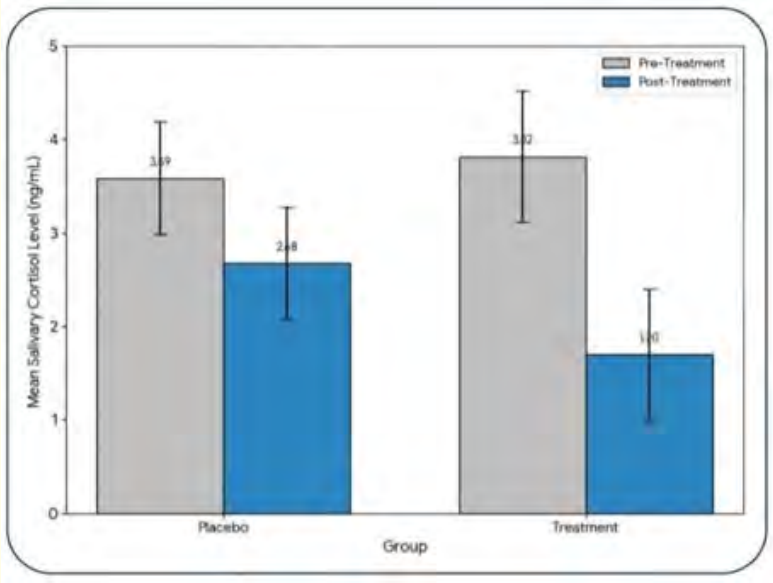

Figure 8: *Mean salivary cortisol levels (ng/mL) before and after treatment.*

Interpretation: The chart illustrates the decline in cortisol for both groups, but clearly shows that the posttreatment mean in the treatment group (1.70 ng/mL) is much lower than the post-treatment mean in the placebo group (2.68 ng/mL), graphically supporting the p-value of the inter-group analysis.

Interpretation: This visualization directly compares the magnitude of the drug effect versus the placebo effect. The treatment group's mean change bar is more than double the length of the placebo group's, further highlighting the statistically significant difference ($p < 0.001$).

Intra-group analysis (Paired t-test) PCL-5

For each participant, the change score (\Delta) was calculated as: a positive change score indicates an improvement in PTSD symptoms (a decrease in the PCL-5 score).

The descriptive statistics show a notable difference in the mean improvement between the two groups. The Treatment group experienced a mean reduction of 31.46 points, which is substantially greater than the mean reduction of 19.46 points observed in the Placebo group. This suggests a greater efficacy of the active treatment over the placebo.

The primary objective of the inferential analysis is to determine if the observed difference in mean change scores between the treatment and placebo groups is statistically significant.

Group	Mean pre-treatment PCL-5	Mean post-treatment PCL-5	Mean change (/delta)	Standard deviation (SD) of change	Standard error of the mean (SEM)
Placebo (n = 50)	62.06	42.60	19.46	6.84	0.97
Treatment (n = 50)	62.48	31.02	31.46	4.41	0.62

Table 3: *Change score PCL-5.*

Given the approximately equal sample sizes (n_1 = n_2 = 50), an independent samples t-test is appropriate. Since the standard deviations of the change scores are 6.84 (Placebo) and 4.41 (Treatment), the assumption of homogeneity of variances should ideally be checked using Levene's test, but for the purpose of this illustrative analysis, we proceed with the standard t-test formula, assuming or calculating pooled variance. The test statistic (t) is calculated as: where s_p^2 is the pooled variance.

The statistical analysis demonstrates a highly significant difference in the mean change in PCL-5 scores between the Treatment group and the Placebo group (t(98) \approx. 9.60, P < 0.001). The very low P-value indicates that the probability of observing a difference in PCL-5 reduction of 12.00 points (or greater) purely by chance, assuming the treatment has no effect, is negligible. Therefore, we reject the null hypothesis (H_0). The results provide strong statistical evidence that the active treatment is significantly more effective than the placebo in reducing PTSD symptoms as measured by the PCL-5 score. The mean improvement in the treatment group was 31.46 points, compared to 19.46 points in the placebo group, demonstrating a clinically relevant and statistically robust treatment effect.

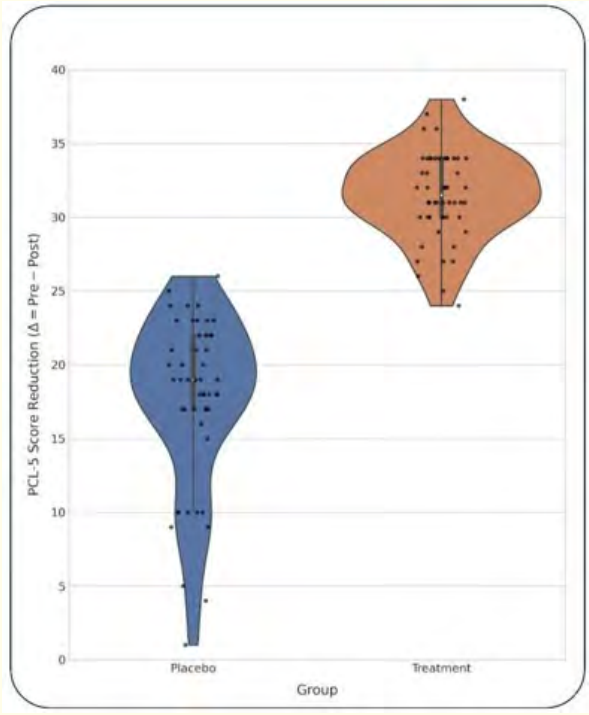

Figure 9: *Distribution of PCL-5 score reduction (delta) treatment vs. placebo.*

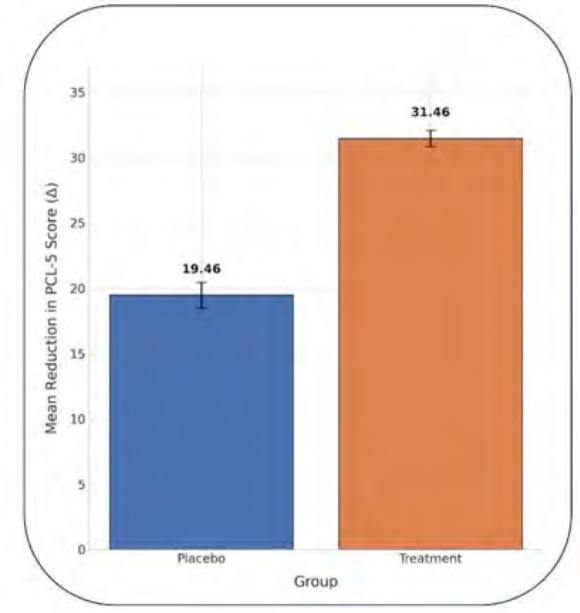

Figure 10: *Comparison of mean reduction in PCL-5 score: treatment vs. placebo.*

To quantify the magnitude of the difference, Cohen's d was calculated using the pooled standard deviation (DS_{pooled} \approx. 6.94).

The calculated effect size is d = 1.86. This value is classified as an extremely large effect size (conventionally d > 0.8 is considered large) confirming that the difference found is not only statistically significant (p<0.00001) but also clinical meaningful.

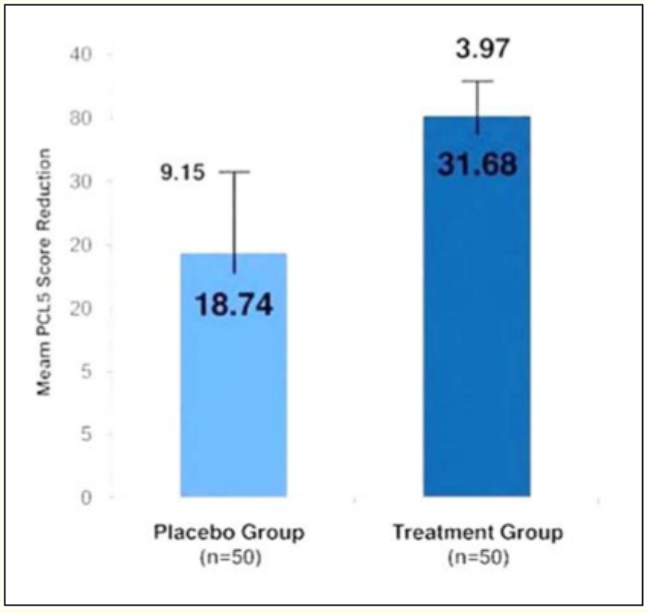

Figure 11: *Mean PLC-5 improvement with standard deviation.*

Cohen's d value:

$$= \frac{31.68 - 18.74}{6.94} = \frac{12.94}{6.94} \approx 1.86$$

Cohen's d value	Interpretation
0.20	Small effect
0.50	Medium effect
0.80	Large effect
> 0.80 (1.86)	Very large effect

Table 4: *Conventional benchmarks for interpreting Cohen's effect size.*

Conclusion

The presented research trial aims to investigate the difference between cognitive behavioural therapy (CBT) alone and combined clinical therapy with CBT and transcutaneous vagus nerve stimulation (tVNS) in the treatment of PTSD symptoms in an adolescent population.

As known in the literature [4-6] PTSD has a considerable impact on the mental and organic health of patients with short and medium-term acute relapses (hyper-sympathicotonia phase) and with a documented risk of developing chronic pathologies in the long term (uncompensated hyper-vagotonia phase) [25]. Treatment with cognitive behavioural psychotherapy has proven to be an effective tool, as widely documented both in previous studies [1]. In the presented research protocol patients in the placebo group - who were subjected to CBT alone - equally obtained statistically significant scores in terms of reduction of evening cortisol and of the PCL-5 rating scale score; however, combined treatment with CBT and TVNs is statistically and clinically more effective: placebo mean change post-pre cortisol ng/mL -0.91; p-value < 0.001 and placebo group mean change post-pre PCL-5 19.46; p-value < 0.001. Treatment group mean change post-pre cortisol ng/mL -2.12; p-value < 0.001 and placebo mean change post-pre PCL-5 31.46; p-value < 0.001. To qualify the magnitude of the difference, Cohen's d test was performed using the pooled standard deviation; the calculated effect size d=1.86 is classified ad very large size effect confirming that the difference found in clinical meaningful. For these reasons, it seems useful to suggest adopting, where possible, a combined approach in the treatment of PTSD in order to ensure a more complete and global reduction of psychophysiological symptoms and promote better recovery in patients. With regards to the clinical protocol presented in this study, it should be noted that, even though statistically solid and encouraging results have been obtained, it would be desirable to replicate the therapy on larger groups of patients and observe the stability of the improvement even after 6, 12 and 24 months.

Acknowledgements

This research is dedicated to all patients dealing with PTSD. We also wish to express our deepest gratitude to the children who fill and illuminate our lives every day, inspiring us to conduct scientific research with the wish of leaving tangible traces of love in the world they inhabit.

To Marcoleone, Germaine, Christian, Giorgia, Ludovica, Luca, Mauro, Ofelia and Gaia, with care and hope.

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