Cortical and Physiological Modulations Induced by Non-Invasive Brain Stimulation for Anxiety

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Introduction:

In 2019, 301 million people worldwide were diagnosed with an anxiety disorder[1]. Following the pandemic, the prevalence rate of anxiety increased by 25.6%, that's an addition of 76.2 million anxiety disorder cases globally[2].

Since anxiety is the most prevalent mental health disorder, prioritizing health care for anxiety patients has become a priority for citizens and governments worldwide. The gold standard treatment for anxiety is medication and/or cognitive behavioural therapy (CBT). These approaches have limitations in terms of side effects, stigma, access, effectiveness, cost, and requirements of time that in some cases can lead to treatment discontinuation.
In response to the demand for new anxiety treatments, one of the technologies that has yielded encouraging results is non-invasive pulsed brain stimulation (NI-PBS). NI-PBS has been approved as a class II medical device by the FDA for over 40 years, and its safety and efficacy has been well documented in the clinical literature. NI-PBS is the only wearable technology for the treatment of anxiety at home; however, very few patients are aware that it exists.

Up until now, commercially available NI-PBS devices have been too expensive to access and cumbersome to use. New NI-PBS devices are becoming commercially available, ones that are miniaturized, cost effective, and discreet enough to use in public. As wearable devices become more ubiquitous, anxiety patients may start to use NI-PBS in lieu of, or in conjunction with, more standardized treatments like medication and CBT. For that reason, it's important to understand the physiological mechanisms underlying NI-PBS for the treatment of anxiety.

The purpose of the current study was to assess if one 30 minute session of NI-PBS, applied to bilateral mastoid processes, modulated physiological biomarkers associated with anxiety and the perception of anxiety intensity in the healthy sub-clinical population.

Non-Invasive Pulsed Brain Stimulation:

Non-invasive pulsed brain stimulation (NI-PBS) is a type of wearable techeology FDA approved for the treatment of anxiety. It provides a low-level, pulsed electrical stimulation localized behind the ears, thus stimulating the peripheral nerve in this region. Clinical studies show that using NI-PBS once per day for 20-60 minutes for 6 weeks can reduce anxiety symptoms by up to 50%[3]; however, very few people have heard of NI-PBS because up until now, devices have been too cumbersome and expensive.

Our study uses the first miniaturized NI-PBS device called Roga to investigate how NI-PBS modulates cortical and physiological biomarkers associated with anxiety.
There is very little known about the neurophysiological mechanisms underlying the reduction of anxiety symptoms using NI-PBS. There are a few studies showing that NI-PBS can reduce brain activity within the default mode network (DMN) associated with worry and rumination[4]. It can also modulate EEG oscillations: There is no published data on how NI-PBS affects physiological processes associated with anxiety such as heart rate, heart rate variability, or skin conductance.

Fig. 1: NI-PBS device.

Methods:

- Quantitative, open-label study.
- Included healthy participants with moderate or higher levels of anxiety; specifically, those who scored a 9+ on the GAD-7 questionnaire (N = 32, age = 21.03 ± 3.13 years; age range: 18-31 years; 19 females; 13 males).

Protocol:

- The study involved assessing patterns of neural activity using EEG in addition to physiological measures including heart rate, heart rate variability, skin conductance, and subjective perception of anxiety before and after a single 30 minute NI-PBS stimulation session set to 0.5 Hz to a maximum intensity of 500 µA, with electrodes positioned on bilateral mastoid processes.
- Each participant came to the laboratory once. The experiment contained three phases: Pre-Intervention, Intervention, Post-Intervention (see Figure 2).
- Scalp electroencephalography (EEG) were recorded from a 64-channel EEG cap using the international 10-20 system guidelines and an electrode cap from Quik-Cap, Neuroscan, Compumedics, NC (Amplifier was a Synamps 2 by Compumedics Neuroscan). All electrode sites were employed in quantitative analysis. All EEG channels were referenced to linked electrodes placed on the left and right mastoid processes. Vertical and horizontal eye movements were monitored with bipolar recordings above and below the left eye and at the lateral aspect of the left and right eyes respectively. All channels were amplified, low-pass filtered (50 Hz), digitized at a rate of 500 Hz (Neuroscan, Compumedics, NC) and impedance was below 5kΩ. All post-processing of the error related negativity (ERN) and N2 data were performed using Curry® (Neuroscan, Compumedics, NC). Power spectral analysis was performed in MATLAB, and all EEG channels were analyzed. For ERN and N2, measurements included FZ (midline frontal), FCZ (midline fronto-central), and CZ (midline central).

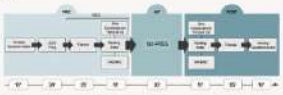

Fig. 2: Experimental procedure.

Results:

TABLE 1: RESULTS PRE- VS POST-NI-PBS

[illegible]	PRE	POST	V OR T(DF)	P
Anxiety Questionnaires				
GAD-7	14.00 ± 0.63	7.47 ± 0.80	V = 476.6	<0.001***
STAI-S	49.00 ± 1.84	42.16 ± 2.15	t(31) = 2.86	0.008**
STAI-T	54.25 ± 1.76	53.03 ± 1.67	t(31) = 0.94	0.35
Flanker ERPs (µV)				
ERN amplitude	-5.29 ± 0.98	-11.86 ± 1.08	V = 499	<0.001***
ERN latency	41.12 ± 3.87	35.38 ± 2.81	t(31) = 1.05	0.30
N2 amplitude	-0.67 ± 0.27	-3.36 ± 0.30	t(31) = 7.14	<0.001***
N2 latency	272.75 ± 6.44	276.25 ± 6.51	t(31) = 0.46	0.65
Absolute Power Spectral Density (10*log_{10}) (uV2/Hz)				
Theta (frontocentral)	5.75 ± 0.61	6.16 ± 0.63	V = 155	0.04*
High beta (frontocentral)	0.85 ± 0.10	0.94 ± 0.10	V = 141	0.02*
Relative Power Spectral Density (10*log_{10}) (uV2/Hz)				
High beta (posterior)	0.03 ± 0.00	0.04 ± 0.00	V = 131	0.01*
Resting Mean Physiological Measures				
SCL (µS)	1.46 ± 0.24	2.32 ± 0.46	V = 91	<0.001***
HR (BPM)	74.99 ± 1.36	73.12 ± 1.42	t(31) = 1.68	0.10
HRV (RMSSD)	41.48 ± 2.54	43.54 ± 2.12	t(30) = -1.20	0.24
HRV (pNN50)	18.61 ± 2.26	21.34 ± 2.05	t(30) = -1.92	0.32

Discussion:

- Similar to past findings, high beta increased after a single NI-PBS session.[4]
- Increased theta power post-NI-PBS may indicate an enhanced state of relaxation and has been shown to increase during meditation.[4]
- Increased ERP amplitudes and beta power may indicate potential cognitive enhancement post-NI-PBS.[10]
- Greater ERNs have also been associated with decreased perceived stress after walking in nature[11] and more broadly in meditators.[12]
- Similar to Feusner et al.'s (2012) findings, an increase in ERN amplitude and frontocentral theta power may reflect a downregulation of the DMN post-NI-PBS.[4,6]

Conclusion:

- A single 30-minute session of NI-PBS reduced perceived anxiety and enhanced cognitive ERPs and brain oscillations associated with deep relaxation (theta) and focused attention (beta). Other physiological measures (i.e. skin conductance) were not modulated as expected.
- Future work should further assess potential physiological changes associated with anxiety as well as potential cognitive effects induced by longitudinal NI-PBS treatment.

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