TOUCHPOINT™

# Cortisol Research Study Draft

# A triple-blind, placebo-controlled randomized trial of effect of TouchPoints™ on reducing stress-related cortisol and anxiety during and after the Trier Social Stress Test

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**Abstract:**

The purpose of this clinical study was to determine the efficacy of the *TouchPoints*™ devices for the management of stress and anxiety during and after the Trier Social Stress Test (TSST), a laboratory procedure for reliably inducing stress in human subjects. For this, a randomized, placebo-controlled, triple blind clinical trial of 80 qualified subjects was conducted. Subjects were randomized into two groups, a treatment group (n=40) and a control (placebo) group (n=40). Metrics chosen to assess stress were the *TouchPoint Challenge* (TPC) score, a subjective rating of the level of emotional stress, and salivary cortisol levels obtained before treatment, immediately following the TSST, and 20 minutes following the TSST. Results showed that the treatment group had a statistically greater decrease in the TPC score relative to the control group both immediately following the TSST and 20 minutes after the TSST. Salivary cortisol levels in the treatment group were also lower than the control group at those same time points. These results suggest that *TouchPoints*™ may be effective in reducing stress and anxiety and may lead to reduced inflammation after exposure to stressful situations.

## 1. INTRODUCTION

Stress and stress disorders are responsible for a significant proportion of disability worldwide. Although the term "stress" is used in a wide variety of contexts, it has consistently been demonstrated that individuals with high levels of stress experience impaired physical and mental functioning with more work days lost and a greater utilization of health care services.[i] The total estimated number of people living with anxiety disorders in the world is 264 million.[ii] The Agency for Healthcare Research and Quality found that in 2006, $57.5 billion was spent on mental health care in the Unites States.[iii]

One approach for altering how the brain manages stress and anxiety is through a non-invasive somatosensory-based therapy called eye movement desensitization and reprocessing (EMDR). EMDR is a psychotherapy treatment originally designed to alleviate the distress associated with traumatic memories.[iv] Multiple previous studies have demonstrated a positive therapeutic benefit of EMDR on individuals with high or pathological levels of anxiety or stress[v]. Serin, et al[vi], demonstrated beneficial effects of EMDR utilizing bilateral alternating stimulation showed a statistically significant reduction in the levels of both emotional stress and bodily distress.

Bilateral stimulation is a core element of EMDR and involves a stimulus (visual, auditory or tactile) which occur in a rhythmic, alternating left-right pattern, such as watching a hand or moving light alternating from left to right and back again or listening to tones that alternate between the left and right ears.

TouchPoints are wearable, non-invasive EMDR-based devices to relieve stress using a patent pending technology called BLAST (bilateral alternating stimulation in tactile form). Previous studies have demonstrated reduction in stress levels in as little as 30 seconds using TouchPoints. The purpose of this clinical trial is to determine the efficacy of TouchPoints on the management of stress and anxiety during the Trier Social Stress Test (TSST), a technique for reliably inducing stress in human subjects.

## 2. MATERIAL AND METHODS

### 2.1. Study design and ethics statement

A triple-blind placebo-controlled randomized clinical trial was performed with approval from the research ethics committee (process number 2366732). All patients signed an informed consent form prior to enrollment. The study was conducted at Laboratory of Phototherapy and Innovative Technologies, between January and June of 2018.

### 2.2. Characterization of sample

Eighty participated in the study. Each subject performed the TSST for inducing psychological stress[vii]. The Consolidated Standard of Reporting Trials (CONSORT) flowchart summarizing experimental procedures and subjects are shown in figure 1.

<< Figure 1 >>

#### 2.2.1. Inclusion criteria and exclusion criteria

Inclusion:

To be eligible for study participation, each subject had to satisfy each of the following criteria:

1. Be a male between the ages of 18-35 years old
2. Be healthy, with no illness, injury or disease for the past 30 days
3. Have a self-reported TouchPoints Challenge (TPC) baseline score of 50 or more on 0-100 scale
4. Must rank "Speaking in public" as 4/10 or greater on a Pain/Fear Catastrophizing Scale (PCS) to ensure subjects will experience some anxiety during the test.
5. Be fluent in Portuguese
6. Not currently taking medications for the management of stress/anxiety.
7. Not currently using street drugs (i.e. marijuana)
8. Able to be present for the experimental procedure at a specific time of day
9. Have a Generalized Anxiety Disorder-7 (GAD-7) score of 9 or less.

Exclusion criteria:
Subject who satisfied any of the following criteria were excluded from study participation:

1. Previously hospitalized for a mental health condition
2. Currently taking any anti-anxiety medication (benzodiazepines, barbiturates, etc.)
3. History of traumatic brain injury
4. History of migraines
5. Diagnosed with post-traumatic stress disorder (PTSD)
6. Diagnosed with dissociative identity disorder.
7. Diagnosed with a chronic pain disease, including chronic fatigue syndrome, fibromyalgia, endometriosis, inflammatory bowel disease, interstitial cystitis diabetic neuropathic pain
8. Diagnosed with a serious mental health illness such as dementia or schizophrenia or had any psychiatric hospitalization in past two years
9. Diagnosed with a developmental disability or cognitive impairment
10. Participated in a clinical study or other type of clinical research in the past 30 days

**Randomization**
Subjects were randomized into two groups: a treatment group and a control (placebo) group (40 subjects per group). Subject allocation to the treatment group was via variable block randomization with varying block sizes of two and four used at random to minimize the likelihood of predicting the next treatment group assignment. Randomization was performed using an automated computerized sequence methodology, insuring that the methodology and the sequence are concealed from the investigator and the subjects.

Concealment will be insured as follows:

1. Each computer-generated randomization sequence is unique and will therefore not be able to be replicated.
2. Randomization occured to either 'Procedure Group A' or to 'Procedure Group B' rather than to a treatment or placebo group. Only the study sponsor knew which assignment (A or B) corresponded to the TouchPoints devices and which corresponded to the mock placebo device. The Sponsor did not reveal this information to any source (investigators, subjects, or study monitor) until the final data analysis was completed.

Both the TouchPoints devices and the mock devices were identical in appearance with the only difference being the lack of tactile response in the placebo devices.

**Figure 1:** The TouchPoints were affixed, one to each wrist, to the volar aspect using wristbands. Wristbands were identical in both groups.

**Interventions**

Each subject randomized to the treatment group or to the placebo group underwent the following intervention:

Treatment group: Subjects randomized to the treatment group performed the TSST with the active TouchPoints devices. The active devices vibrate and has an audible "buzzing".

Control group: Subjects randomized to the control group performed the TSST with a mock (placebo) device. The mock (placebo) TouchPoints devices had the same physical appearance as the actual device, including the appearance of any visible light output. The vibrations were disabled prior to the study via the Bluetooth activation device. Both the real and mock devices emit the same pattern of light when activated so that these two devices would be indistinguishable to both the subject and the investigator. The investigator enabled both the active and placebo devices from a distance using a Bluetooth enabled tablet using the same series of activation steps.

The Trier Social Stress Test (TSST) is a valid and reliable acute stressor used in experimental conditions. It induces stress by requiring participants to make an interview-style presentation, followed by a surprise mental arithmetic test, in front of an interview panel who do not provide feedback or encouragement.[viii] The TSST was employed to induce a stress response to socially evaluative situations. The period of induced stress lasted approximately 15 minutes and was divided into 5-minute components.[ix]

**Outcomes**

Two metrics of stress levels were measured: The TouchPoint Challenge (TPC) score, a subjective rating of the level of emotional stress, and levels of salivary cortisol, a hormone whose release is associated with psychosocial stress.[x]. Measurement for both metrics were taken at three time points for each subject: baseline (pre-treatment), immediately following the TSST, and 20 minutes following the TSST. Salivary cortisol samples were all collected between 11am and 1pm to minimize circadian variations. TPC score measures stress and anxiety on a scale ranging from 0 to 10, with 0 being "no anxiety" and 10 being "the worst anxiety ever".

These measurements were collected by an assessor who was not aware of the group assignment of the subject.

### Statistical analysis

The intention-to-treat analysis was performed *a priori*. The researcher that performed the statistical analysis was blinded to the randomization of subjects to the groups. Data were firstly tested regarding normal distribution using Shapiro-Wilk test and group results were expressed as mean and standard deviation. A two-way ANOVA test was used, followed by Bonferroni *post hoc* test. The significance threshold was set at $p<0.05$. Results presented as mean and standard error of the mean (SEM).

## RESULTS

Eighty healthy, male subjects were recruited and completed all procedures with no dropouts. The average age of 26.21 years old (± 5.38). Table 1 lists the group mean and standard deviation (SD) of the metrics at each of the time points in this study. There were no statistically significant differences between the two groups in the baseline measurements for the two metrics used.

**Table 1:** Outcomes in absolute values.

**TouchPoints Challenge (TPC)**

| *TouchPoints* | *Recruitment* | *Baseline* | *After initial rest* | *After presentation preparation* | *After presentation* | *After math challenge* | *After final rest* |
|---|---|---|---|---|---|---|---|
| M | 8,47 | 6,32 | 1,56 | 2,61** | 3,79**** | 7,18* | 5,15*** |
| SD | 1,68 | 3,17 | 1,59 | 2,23 | 3,15 | 1,96 | 3,25 |
| *Placebo* | | | | | | | |
| M | 8,83 | 7,17 | 2,27 | 4,41 | 6,30 | 8,49 | 6,99 |
| SD | 1,15 | 2,14 | 1,69 | 1,31 | 1,90 | 1,04 | 1,92 |

**Cortisol**

| *TouchPoints* | *Baseline* | *After TPC* | *After final rest* |
|---|---|---|---|
| M | 1,99 | 1,94 | 1,74 |
| SD | 0,91 | 0,93 | 0,97 |
| *Placebo* | | | |
| M | 1,79 | 1,94 | 2,05 |
| SD | 0,93 | 1,03 | 0,94 |

**GAD7**

| *TouchPoints* | *Recruitment* | *Baseline* |
|---|---|---|
| M | 5,79 | 5,41 |
| SD | 6,03 | 5,70 |
| *Placebo* | | |
| M | 6,37 | 5,55 |
| SD | 6,47 | 5,51 |

| Catastrophizing Scale | | |
|---|---|---|
| | *Recruitment* | *Baseline* |
| *TouchPoints* | | |
| M | 2,67 | 3,20 |
| SD | 0,65 | 1,45 |
| *Placebo* | | |
| M | 2,85 | 3,19 |
| SD | 0,62 | 1,01 |

Data are expressed as mean (M) and standard deviation (SD). *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 between TouchPoints and placebo

The results showed that the TouchPoints significantly decreased the stress level of subjects as measured by the TouchPoints Challenge scale both immediately following the TSST and 20 minutes following the TSST (figure 2).

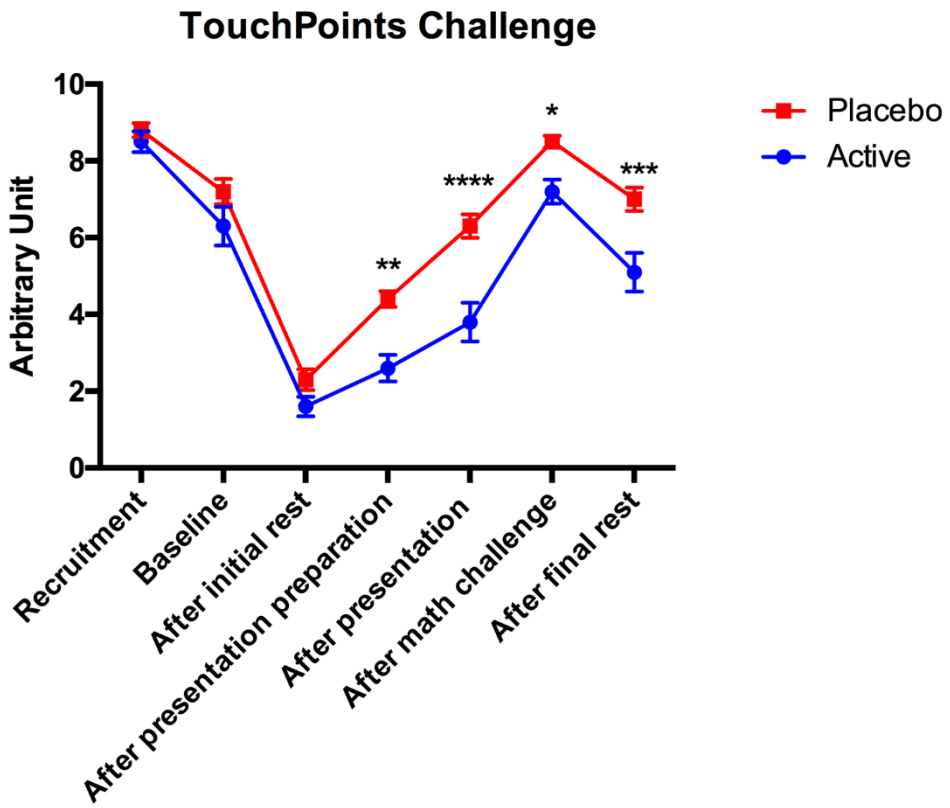


**Figure 2:** Comparison of the TouchPoints scores between the treatment and control groups. Data are expressed as mean and SEM. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 between TouchPoints Classic® and placebo.

Results of the salivary cortisol levels did not reveal any statistically significant difference between groups ($p>0.05$) at the initial time point. Analysis of the change in cortisol levels revealed that the subjects using the TouchPoints had a statistically significant change in cortisol levels between immediately following the TSST to 20 minutes following the TSST compared to placebo (figure 3).

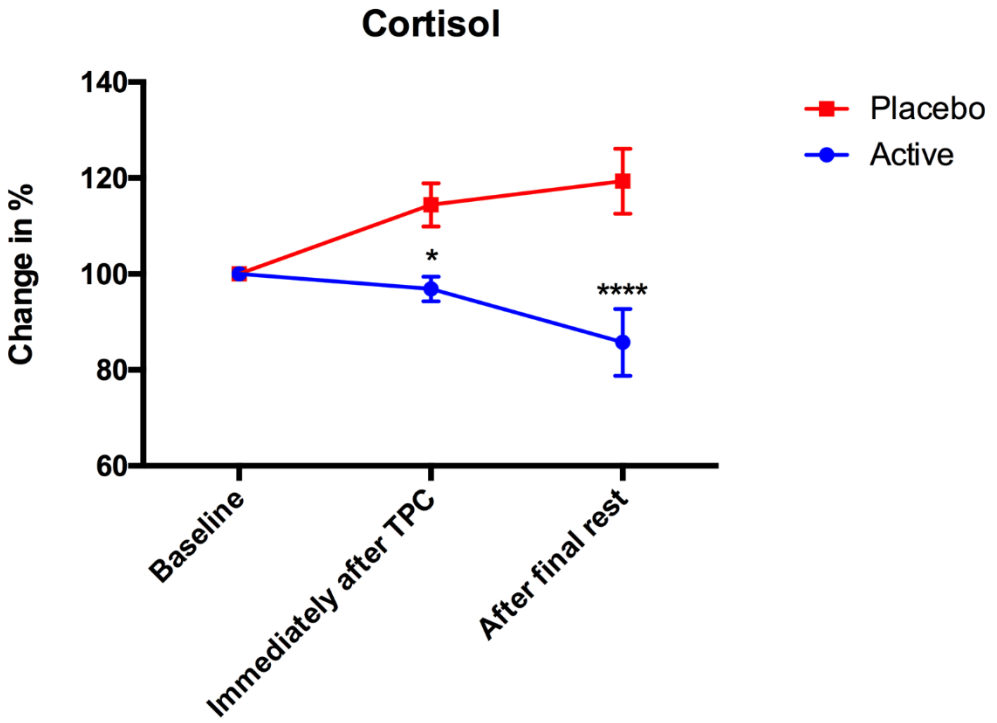


**Figure 3:** Change in cortisol levels between time points for the treatment (active) group and the control (placebo) group. Data are expressed as mean and SEM. *$p<0.05$, ****$p<0.0001$.

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## DISCUSSION

Excessive stress is a common complaint in modernized countries, which negatively affects quality of life. Chronic stress has a negative effect on multiple brain functions, causing impairment of many executive skills, including working memory, decision making and attentional control[xi]. Excessive stress can also cause physical symptoms, including headaches, insomnia, reduced immune function, aches and pain. Previous work has demonstrated that repeated social and physical stressors are associated with changes in the amygdala that often results in clear social avoidance[xii].

Multiple previous studies have shown that techniques utilizing biofeedback, neurofeedback and noninvasive brain stimulation are effective in mitigating stress and anxiety. Pharmacotherapies such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors have the most evidence to support their usage [xiii]. Several side effects of SSRIs have increase in frequency including sexual dysfunction and sleep disturbance.[xiv]

Techniques for reducing stress and anxiety by non-pharmacological methods can potentially make a greater impact on quality of life and stress-related morbidity. Devices such as the TouchPoints do not have adverse drug interactions or reported side effects. Previous work by Landin-Romero, *et al* showed

physiological changes in stress levels associated with successful eye movement desensitization and reprocessing (EMDR) therapy. [xv] Several clinical trials have shown positive effects of EMDR in adults with autism spectrum disorder[xvi], depression[xvii], and post-traumatic stress disorder[xviii],[xix]. Serin, et al. was able to reduce ($p<0.0001$) levels of emotional stress and sensations of bodily distress in a group of 1109 in 30 seconds.

TouchPoints™ is a non-invasive way to mitigate stress using a EMDR-based method called BLAST (bilateral alternating stimulation in tactile form) that reduces brain electrical activity in the salience network[xx]. The aim of this study was to evaluate the effects of TouchPoints on stress induced during the Trier Social Stress Test (TSST), assessed by salivary cortisol levels and subjective rating of emotional stress levels at multiple time points.

Results showed that TouchPoints had a statistically significant difference on both measures over placebo, both immediately following the TSST and at 20 minutes following the TSST, indicating the active device was reducing stress during the active portion of the TSST and this effect persisted following the TSST.

Cortisol is a hormone that helps to maintain glucose levels, reduce inflammation, and regulate metabolism. Moreover, since cortisol is stable in saliva, it can be collected between short intervals to look at a time-dependent response[xxi]. When evaluating the effects of the TouchPoints™ on salivary cortisol levels, there were no statistically significant differences between the two groups on initial assessment. Analysis of the change in cortisol levels between time points, there was a statistically significant ($p<0.05$) difference seen between immediately following the TSST and after the twenty-minute rest following the TSST when compared to the placebo ($p<0.0001$). There results show a noticeable downward trending of the cortisol levels in the treatment group that was not present in the control group. This may indicate a beneficial effect of the TouchPoints™ in stabilizing cortisol and returning subjects to a normal baseline after a stress response.

## LIMITATIONS

The study only evaluated male volunteers due to the variability in cortisol measures in females related to menstrual cycle and the use of oral contraceptives. Another limitation to be considered is the metrics used to evaluate stress in this study, which only evaluate some of many aspects related to stress. Further studies must advance on this limitation and also must investigate the chronic effects of the use of TouchPoints™.

## CONCLUSION

TouchPoints were effective in reducing subjective emotional stress levels as well as physiological stress as evaluated by cortisol levels. This suggests that the BLAST technology in TouchPoints may provide a non-invasive, portable means of managing stress in real time situations when other treatments may not be available or practical. Further research is needed to evaluate these effects and to compare them to other conventional methods for reducing stress.

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