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## **The Effects of Ultrasound, Infrason, and Electroconvulsive Stimulations on Anxiety-Like Behavior in Mice**

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Anxiety is a prevalent mental illness worldwide with a considerable burden to health services. We tried to assess the effects of ultrasound, infrason, and electroconvulsive stimulation on anxiety-like behavior in mice models. In total, 60 male BALB/c mice were included. Our mice were exposed to the urine of cats. Each exposure lasted for 1 hour and was repeated 3 times a day, for 30 days. Then, the mice were allocated to three groups of experimental (ultrasound, infrason, and electroconvulsive stimulation) and one group of control animals, each including 15 mice. The experimental animals received ultra- or infrason .5 hours or 1 electroconvulsive pulse, daily for 10 days. We used a mouse elevated plus maze (EPM) to compare anxiety responses between the experimental and control groups. The outcome measures, percentage of entries to and percentage of time spent on the open arms, were measured. There was a significant effect of the intervention on the percentage of entries into as well as the time spent on the open arms (MANOVA,  $p = .001$ ). Separate analyses

confirmed significant treatment effects on the outcomes (ANOVA, both  $p = .001$ ). Post-hoc tests revealed that ultrasound increased the percentage of entries into and time spent on the open arms. Infrasound did not affect the outcome compared with the no-treatment control. The mice with electroconvulsive stimulation entered the open arms less than controls. Ultrasound stimulations are capable of decreasing anxiety. We did not find any significant anxiolytic effect for infrasound. Our results were not compatible with the application of electroconvulsive therapy for the treatment of anxiety.

**Keywords:** anxiety, ultrasound, infrasound, electroconvulsive stimulation, brain stimulation, anxiety-like behavior

Anxiety is an increasingly prevalent mental illness worldwide and has a considerable burden on health services. People with anxiety have a wide age range. Anxiety may be primary or secondary to a large variety of health problems (Barker, Beresford, Bland & Fraser, 2019). It is associated with functional impairment, and in turn causes further problems for the patient such as fatigue, difficulty in concentration, irritability, muscle tension, and sleep disturbance (Sagliano, Atripaldi, De Vita, D'Olimpio & Trojano, 2019). Further, anxiety is believed to complicate somatic conditions, for example in patients with cardiovascular dysfunction.

A large number of medications have been used for the management of anxiety. However, there is a growing effort in searching for non-invasive and non-medical techniques for the treatment of anxiety (Vicario, Salehinejad, Felmingham, Martino & Nitsche, 2019). This is motivated by the desire to find more effective treatments with fewer side effects and lower risk for addiction and to achieve better outcomes through offering combined therapy. More importantly, the ease of administration is critical in the patient's compliance.

Researchers considered brain stimulation by electromagnetic field as a possibility for anxiety treatment (Tufail, Yoshihiro, Pati, Li & Tyler, 2011). Also, the current stimulation of the brain has favorable potentials for the treatment of psychiatric disorders (Donde, Neufeld & Geoffroy, 2018; Velasques et al., 2014). These techniques are believed to change cortical excitability and the resting membrane potential of neurons (Velasques et al., 2014). Currently, research programs are dedicated to the application of electromagnetic and current stimulation for the treatment of psychiatric disorders such as depressive, bipolar, obsessive-compulsive, and post-traumatic stress disorders (Sagliano et al., 2019). However, there are few reports regarding the effects of ultra- and infrasond stimulations on psychological problems.

The ultrasond wave has been known to have physiological effects on living tissues (Tufail et al., 2011), which can activate or suppress neuronal electrical activity (Tufail et al., 2011). The procedure is noninvasive and provides exact spatial targeting. There is no report suggesting serious threats to human life for the ultrasound technique used as a diagnostic means (Hameroff et al., 2013). Nevertheless, with extreme intensities, ultrasound causes heating and cavitation and is used for ablation of thalamic brain regions to treat chronic intractable pain (Hameroff et al., 2013). Sparse research has been done supporting the application of ultrasound for mood elevation in patients with chronic disease. Ultrasound is believed to have mood-enhancing effects in patients with low back pain (Durmus, Durmaz & Canturk, 2010). Overall, the effects of ultrasound on living organisms are still in preclinical testing and any possible application of the method should yet to be assessed before

carrying out clinical trials (Bystritsky et al., 2011; Ter Haar, 2007).

Research suggests that infrasound waves can alter neural activity in specific brain regions involved in auditory or emotional processing and automatic control. The neuromodulating effects of infrasound occur primarily in the right superior temporal gyrus, anterior cingulate cortex, and right amygdale (Weichenberger et al., 2017). There are few studies on the effects of infrasound on mental health and cognitive processes. Meanwhile, there is conflicting evidence regarding the health outcomes of exposure to infrasound. Some evidence suggests that infrasound exerts a pathogenic influence on the organism (Weichenberger et al., 2017). However, there is other supportive evidence showing favorable cognitive effects on working memory for infrasonic waves (Weichenberger et al., 2015). We did not find any report for the effects of infrasound waves on the level of anxiety.

Electroconvulsive therapy offers long-lasting symptom relief in patients with depression. However, previous works suggested that there is little evidence to encourage its use in people with anxiety, or in the mental health problems where anxiety prevails (Fink, 1982). Recent research indicated that electroconvulsive therapy-related anxiety is common and that the literature provides little guidance for its clinical management. Low methodological quality has been thought to hamper generalization of the conclusions (Obbels, Verwijk, Bouckaert & Sienaert, 2017). Technical challenges need for anesthesia and the expense are other limitations in using electroconvulsive therapy (Shiozawa, Cordeiro, Cho, Trevizol & Brietzke, 2017).

Each of the brain stimulation methods has potentials and limitations, whose exact pattern and magnitude of effects are

uncertain, thus warranting further studies to replicate the results (Tsai, 2015). In addition, evaluation of the external validity is complicated by a lack of uniformity in these studies. We still need more beneficial alternative methods for the treatment of patients with anxiety. Until reliable information about different therapeutic methods is collected, it is difficult to design the best intervention strategy. In the current study, we tried to find if there is any difference in the effects of ultrasound, infrason, and electroconvulsive stimulation on anxiety-like behavior in animal models. Our hypothesis was that the three methods affect mood in mice differently.

### **Method**

In total, 60 male BALB/c mice (mean age of 60 days with the weight range of 25–30 g) were randomly selected from the animal breeding unit at Tehran University of Medical Sciences, Faculty of Veterinary Medicine. They were acclimatized for 1 week before the beginning of the experiment and were maintained at the temperature of  $21 \pm 2$  °C and the humidity of  $45 \pm 5\%$ . The animals were housed per group and had free access to a standard pellet diet and water ad libitum except for the time of exposure. The light source in the animal house was set to provide a 12 h light/12 h dark cycle (07:00 – 19:00 h, light on). The mice were exposed to the stimulations within the light phase of the cycle. We had three groups of experimental and one group of control animals, each including 15 mice.

### **Induction of Anxiety-Like Behavior**

Predator odors can induce fear responses in animals (Takahashi, Nakashima, Hong & Watanabe, 2005). The rats were exposed to cat urine signaling the presence of predator.

Evidence showed that innate fear of predator odor is developmentally regulated and rats of all ages displayed significant freezing to cat urine. Even it has been found that a non-sedating dose of the benzodiazepine chlordiazepoxide injected in rats diminished hiding and increased approach to the cat odor (Ganella & Kim, 2014). We used the predator odor technique to produce mice models of anxiety. Our mice were exposed to the urine of cats fed with meat. Each exposure lasted for 1 hour and was repeated 3 times a day with 4-hour intervals, for 30 consecutive days.

#### **Ultrasound Stimulation**

The mice in the ultrasound group were exposed to constant ultrasound waves of 3000 Hz with the intensity of 7 dB .5 hour for 10 days. The ultrasound waves were generated in the laboratory room through a manufactured device (Touraj Sound Lab, Tehran, Iran). The even distribution of ultrasound waves was controlled using a detector for the course of the research. The device was placed above the cage of the ultrasound group.

#### **Infrasound Stimulation**

Experimental animals in the infrasound group were exposed to infrasound of 17 Hz at the intensity of 7 dB in an infrasonic chamber .5 hours for 10 days. The infrasound waves were generated by an infrasonic radiator.

#### **Electroconvulsive Stimulation**

The mice in the electroconvulsive stimulation group were anesthetized with isoflurane (3% in O<sub>2</sub> at 800 ml/min). The electroconvulsive shock was delivered with an instrument (Duo-Pulse, Ectron Ltd, England) using two saline-soaked skull

electrodes for 2 seconds. The administered current generated tonic-clonic convulsions in our mice lasting 10-20 seconds. We used a stopwatch to control the time taken for induction and the total duration of convulsions. One electroconvulsive pulse was administered to each mouse, daily over a period of 10 days.

### **Randomization and Blinding**

The animals were randomly selected from a population of 2000 male BALB/c mice. We used simple randomization to include 60 mice. At the end of the interval for induction of depression, reserpine-treated mice were randomly allocated to 5 study groups using block randomization. One assessor, blinded to group assignments, tested the mice for depression, before and after the interventions.

### **Outcome Measures**

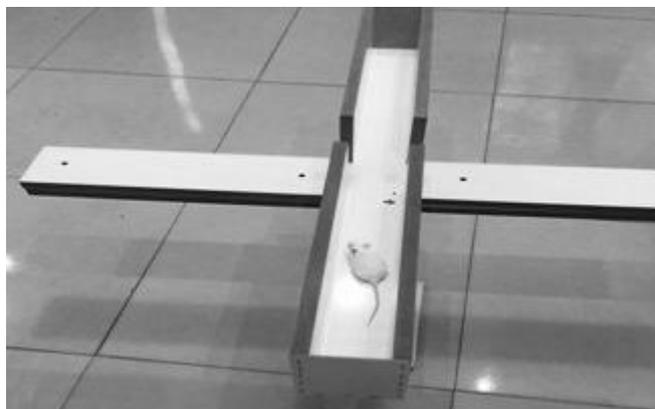
#### **Anxiety**

We used a mouse elevated plus maze (EPM) to compare anxiety responses between the experimental and control groups (Figure 1). Our plus maze was made of wood and consisted of two open and two closed arms each 7 cm wide and 40 cm long arranged to form a plus shape. The two closed arms were enclosed by 10 cm high walls. The apparatus was mounted on a base which elevated it 40 cm above the floor. The animal was placed in the intersection of the four arms of the elevated plus maze and its behavior was recorded for 5 min. Percentage of entries to the open arms was calculated as:

$$\frac{\text{number of entries to the open arms}}{\text{number of entries to the closed arms} + \text{number of entries to the open arms}} \times 100$$

Also, the percentage of time spent on the open arms was calculated as:

$$\frac{\text{time spent on the open arms}}{300} \times 100$$



**Figure 1. Elevated Plus Maze**

We used a 100 W light source placed at 120 cm above the center of the maze. The activity in the open arms showed a conflict between the preferences for protected close areas and the motivation to explore a new environment. Each mouse was placed in the center of the maze facing an open arm. We recorded the number of entries into each type of arm and the time spent in each arm. A mouse was considered to have entered an arm when all four legs were on the arm. An observer, blinded to group assignment, assessed all mice during the study.

Open arms' entries and the time spent on the open arms were positively correlated with the anxiolytic effect of interventions. We considered a significant change in anxiety if both the

number of entries and time spent on the open arms showed a unidirectional change and at least one of them significantly increased or decreased.

### **Ethical Considerations**

The study was carried out in accordance with the Guidelines for the Care and Use of Experimental Animals. The ethics review board of Azad University of Medical Sciences approved the research with the reference number: ir.iau.b.rec.1397.042.

Data are presented as mean (standard deviation) for continuous variables and absolute number (percent) for categories. The data were tested on normality using Kolmogorov-Smirnov test. The mean immobility times for mice were compared using one-way ANOVA and for post-hoc tests, we carried out the Duncan test. Point estimates, 95% confidence intervals, and p-values were calculated. P-values less than .05 were considered significant. Statistical analyses were performed with SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA).

### **Results**

In total, we had 58 mice in our analytical sample ( $n = 13$  for group electroconvulsive therapy, and  $n = 15$  for other groups). Two mice died in the electroconvulsive stimulation group. Table 1 reports the percentage of entries into and time spent on the open arms of the elevated plus maze after the 10-day interventions in the mice model of anxiety. The Kolmogorov-Smirnov test showed that data were normal for all four groups (all  $p > .05$ ). The Levene's test also showed that the groups were homogenous in variances of the data for percentage of entries into and time spent on the open arms [ $F(3, 54) = .40$ ,  $p = .750$ ,

and  $F(3, 54) = 2.29, p = .057$ , respectively]. Using Pillai's trace, our analyses indicated that there was a significant effect of the intervention on percentage of entries into and time spent on the open arms [MANOVA test  $F(9, 162) = 12.50, p = .001, \eta^2 = .41$ ].

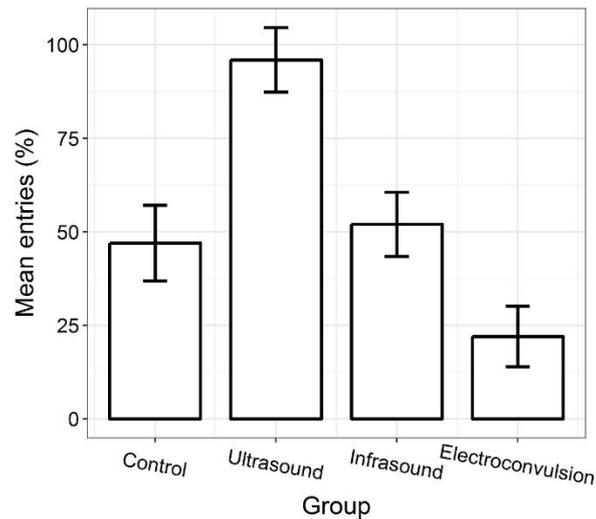
**Table 1**  
**Percent Entries into, and Time Spent on the Open arms of the Elevated plus Maze**

Group	n	Entries into the open	Time spent on the open	P*
		arms (%)	arms (%)	
		Mean (SD) [Minimum, Maximum]		
Control	15	47.3 (20.9) [17.3, 81.7]	40.0 (7.2) [29.0, 53.0]	
Ultrasound	15	96.1 (17.0) [72.3, 130.0]	61.0 (8.0) [52.0, 78.0]	
Infrasound	15	52.2 (17.0) [16.7, 70.0]	44.0 (13.1) [22.0, 64.0]	.001
Electroconvulsive stimulation	13	22.7 (16.7) [1.0, 18.7]	33.0 (16.2) [4.0, 58.0]	

\*MANOVA test

Separate univariate ANOVAs on the outcome variables revealed significant treatment effects on percentage of entries [ANOVA test  $F(3, 54) = 40.78, p = .001, \eta^2 = .69$ ]. Post hoc tests with the Bonferroni correction showed that there were significant differences between the control versus ultrasound ( $p = .001$ ) and electroconvulsive stimulations ( $p = .004$ ). In addition, ultrasound compared with infrasound and electroconvulsive

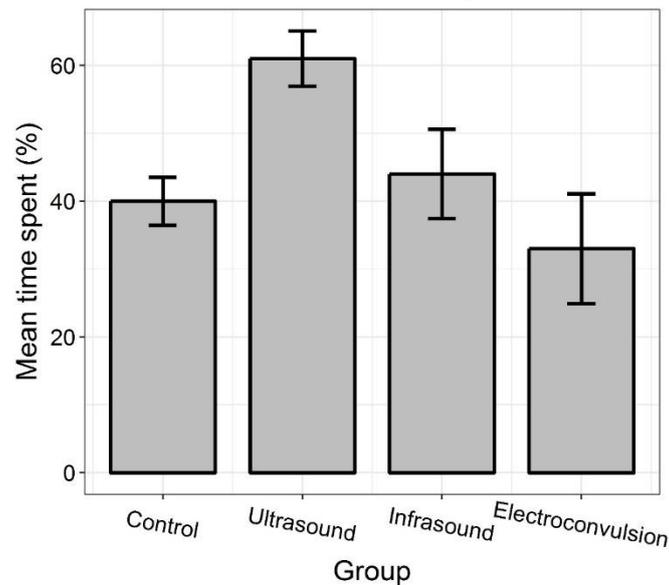
stimulations had significantly different effects on percentage of entries into the open arms (both  $p = .001$ ). The control and infrasound mice were similar in their open arm entries ( $p = .999$ ). In summary, the ultrasound group showed a marked increase in the percentage of entries into the open arms of the elevated plus maze. Infrasound did not affect the outcome compared with no-treatment control. Further, the mice with electroconvulsive stimulation entered the open arms less than controls did (Figure 2).



**Figure 2. Entries into the open arms of Elevated plus Maze (error bars represent 95% confidence interval)**

Likewise, separate univariate ANOVA revealed that the percentage of time spent on the open arms was significantly different between the treatment groups [ANOVA test  $F(3, 54) = 15.62$ ,  $p = .001$ ,  $\eta^2 = .46$ ]. Post hoc tests with the Bonferroni correction indicated that there were significant differences between control versus ultrasound ( $p = .001$ ), but not between

control and infrasound ( $p=.999$ ) or electroconvulsive stimulations ( $p = .64$ ). In addition, ultrasound compared with infrasound and electroconvulsive stimulations had significantly different effects on the outcome (both  $p=.001$ ). Electroconvulsive stimulation and infrasound mice were not significantly different in their time spent on the open arms ( $p = .082$ ). The analyses revealed that ultrasound effectively increased the time spent on the open arms of the elevated plus maze. Infrasound did not affect the outcome compared with no-treatment control. The result in the mice with electroconvulsive stimulation was worse than in controls (Figure 3).



**Figure 3. Time spent on the open arms of Elevated plus Maze (error bars represent 95% confidence interval)**

### Discussion

In the present study, we tried to provide evidence to assess the effects of ultrasound, infrasound, and electroconvulsive stimulations on animal models of anxiety. Our evidence rejected

the null hypothesis and the study showed that the treatments are different in efficacy. We used entries into and time spent on the open arms of the elevated plus maze as the scale for anxiety. Anxiety was significantly different in the control group compared with other groups after 10 days of interventions, and the interventions changed the anxiety-like behavior in mice with varying degrees. Overall, our results showed that ultrasound decreases anxiety-like behavior significantly. However, infrasound did not affect anxiety, and electroconvulsive stimulation even increased anxiety-like behavior in mice. Overall, our results are in accordance with some previous findings in the literature.

The mechanisms underlying the development of anxiety are not well-known. In a study on mice models of psoriasis, researchers investigated whether brain-derived neurotrophic factor and tropomyosin receptor kinase B signaling are involved in anxiety- and depression-like behaviors (JiaWen, Hong, ShengXiang & Jing, 2018). The behavioral change was assessed by an EPM, and the biochemical evaluations were carried out using reverse transcription PCR and Western blotting. They found that the anti-anxiety drug fluoxetine increased the expression of brain-derived neurotrophic factor. That study indicated that brain-derived neurotrophic factor plays an important role in the pathological mechanism of anxiety behaviors.

Acoustic energy has been reported to induce revascularization, to modulate cortical function, and to offer neurotherapeutic effects (Gorick, Chappell & Price, 2019; Tsai, 2015). Ultrasound has been used for the treatment of neuropathic pain, essential tremor, and Parkinson's disease with some successful outcomes. The mechanism of action is not yet

well-understood; however, ultrasound has been demonstrated to inhibit monoamine and increase brain-derived neurotrophic factor especially in the hippocampus (Tufail et al., 2010; Zhang et al., 2019). In addition, ultrasound can open the blood-brain barrier and thus increase the permeability to peripheral neurotrophic factor (Scarcelli et al., 2014).

In a double-blind crossover trial study on the effects of ultrasound on brain function, pain and mood changes were compared between two groups of intervention and control using visual analog scales (Hameroff et al., 2013). People (n=31) with chronic pain were recruited from a chronic pain clinic and assigned into two groups. The outcomes were assessed 10 minutes before, plus 10 and 40 minutes after 15 seconds of exposure to either subthermal ultrasound or placebo. The results showed that mood was enhanced 10 minutes ( $P = .03$ ) and 40 minutes ( $P = .04$ ) following the intervention compared with placebo. Subjective pain also slightly decreased at 40 minutes ( $p = .07$ ). It was concluded that transcranial ultrasound is a promising noninvasive therapy for modulating the mental state. Our behavioral evaluations are compatible with the positive effects reported for ultrasound waves.

A trial study suggested that near-threshold infrasound induces physiological effects and stimulates brain areas involved in auditory processing as well as emotional and autonomic control (Weichenberger et al., 2017). Researchers evaluated the response of the brain for near- and supra-threshold infrasound waves under resting-state fMRI. In the first session, fourteen healthy participants underwent threshold and loudness measurement with different sound pressure levels. In the second session, they underwent three resting-state acquisitions. Analysis of data for regional homogeneity and inter-regional

connectivity revealed that there was greater local connectivity in the right superior temporal gyrus near the primary auditory cortex, in the anterior cingulate cortex, and in the right amygdala during the near-threshold, as compared to both the supra-threshold and the no-tone condition. Also, changes in functional connectivity were observed in the right amygdala with no-tone more than with near-threshold condition and in the right superior frontal gyrus during the near-threshold state. They overall concluded that infrasound has the potential to alter the physiology and connectivity in neural tissues.

Our study did not show any important changes in the anxiety-like behavior of the mice treated with ultrasound. We did not address the questions regarding cellular or molecular effects of acoustic waves on the brain function and structure. In our experiment; physiological change, if any, did not cause significant alterations in the mice's anxiety-like behavior. Any possible significant change caused by increasing the sample size would not seem to be clinically important. Thus, we tend to consider infrasound as unable to provide a substantial therapeutic effect on anxiety in practice.

In a study on 13 healthy participants exposed to infrasound, fMRI was taken while n-back working memory test was carried out. For infrasound, short sinusoidal tone bursts of 12 Hz were administered monaurally. That study showed that infrasound improves the performance. However, there was no correlation between the performance and sum scores of depression, anxiety, and personality assessment scales (Weichenberger et al., 2015).

Electroconvulsive therapy has an established role in the treatment of mood disorders. While the exact underlying mechanism of action is still controversial, animal studies have demonstrated that electroconvulsive therapy is associated with

alterations in the central and peripheral neurotrophin level and immune signaling. It has been suggested that inflammatory stimulation augments neurotrophin expression and mediates antidepressant-like effects (Van Buel et al., 2015). However, a large number of electroconvulsive therapy-treated patients experience anxiety. It has been indicated that anxiety in those patients is underexposed in the literature. In a review study of 31 articles, electroconvulsive therapy-related anxiety was estimated to be present in 14% to 75% of patients. Thus, it seems that anxiety is a prevalent complication of electroconvulsive therapy. We did not find any anti-anxiety effect for electroconvulsive stimulation in our mice. Indeed, our electroconvulsive stimulation group showed anxiety-like behavior more than the control did.

Overall, little information is available about the behavioral effects of acoustic waves on human or animals. To the best of our knowledge, there was no recent study in the literature comparable to ours regarding the comparison of ultrasound, infrasound, and electroconvulsive shock for the treatment of anxiety-like behavior. Our sample was sufficiently large to detect important differences. However, we did not assess the effects of ultrasound combined with other treatment modalities. Studies with factorial designs should determine the combined effect of brain stimulation methods with other known modalities for the treatment of depression. Also, further dose-response studies are required to delineate the optimal therapeutic dose of ultrasound.

Brain stimulation with ultrasound has the potential to be an effective treatment against anxiety. Our study revealed that ultrasound stimulations are capable of mitigating anxiety-like behavior in mice models. Ultrasound is a noninvasive technique

and does not necessitate a high technical and complicated setting nor does it require anesthesia or highly trained staff. We did not find any significant anxiolytic effect for infrason. In addition, our results were not compatible with the application of electroconvulsive therapy for the treatment of anxiety.

### **Highlights**

- Ultrasound reduces anxiety-like behavior in mice.
- Ultrasound has the potential to be studied in clinical research on human anxiety.
- There is no benefit in applying infrason for the treatment of anxiety.
- Electroconvulsive stimulation can increase anxiety-like behavior and should not be considered as a potential treatment for anxiety.

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