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A double-blind pilot study of transcranial ultrasound (TUS) as a five-day intervention: TUS mitigates worry among depressed participants

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ABSTRACT

Transcranial ultrasound (TUS) provides a noninvasive neuromodulation method that has greater spatial precision than existing methods. The present study examined TUS, for the first time, as a potential depression intervention. Twenty-four college students with mild to moderate depression were randomly assigned to an Active TUS Condition or Placebo TUS (no power administered). Participants completed five TUS sessions within seven days. Although depression scores did not change differentially for TUS/Placebo, trait worry decreased in the Active TUS Condition and increased in the Placebo condition. Additionally, those in TUS Active Condition had an increase in global affect over the course of the study, whereas those in the Placebo Condition did not. These results have significant implications for the potential utility of TUS as an intervention for anxiety disorders or worry-related psychopathology, warranting future investigation of the impact of TUS in a larger sample.

1. Introduction

Depression affects an estimated 98 million people in the United States, often leading to substantial personal distress and impairment (Mathers, Boerma, & Ma Fat, 2004). Nearly half of people with depression, or approximately 49 million people, do not respond to traditional antidepressant treatment (Fava, 2003). Additionally, up to 70 % of people with depression have moderate anxiety symptoms, which increase depression severity, suicidality, functional impairment, and likelihood of treatment nonresponse (Fava, 2003; Kessler, Chiu, Demler, & Walters, 2005; Kornstein & Schneider, 2001; Sanderson, Beck, & Ph, 1990). As such, alternative treatments for depression, especially for those who do not respond to existing treatments, are greatly needed. In particular, individuals with comorbid depression and anxiety are at greater risk of treatment non-response (Brown, Shulberg, Madonia, Shear, & Houch, 1996).

Noninvasive neuromodulation presents a promising alternative treatment approach for depression, including treatment-resistant depression. Recent meta-analyses suggest that both transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are efficacious in reducing depression symptoms (Berlim, den Eynde, & Daskalakis, 2013; Berlim, Van Den Eynde, Tovar-Perdomo, & Daskalakis, 2014; Shiozawa et al., 2014; Slotema, Blom, Hoek, & Sommer, 2010). Transcranial ultrasound (TUS), by contrast, is not as commonly used as a neuromodulation methodology, but may hold some advantages over other neuromodulaton approaches that improve depression. Like tDCS and TMS, it is non-invasive. Unlike tDCS, but like TMS, TUS can target regions with precision (Tufail et al., 2010), but TUS can also reach deep targets, unlike TMS (Fini & Tyler, 2017). At higher intensities, TUS can excite neurons in animal brains (Tufail et al., 2010). At lower intensities, it can increase positive mood in healthy humans (Sanguinetti, Smith, Dieckman, Vanuk, Hameroff & Allen, 2013).

Although approximately three studies have shown that TUS can increase positive mood in healthy participants (Hameroff et al., 2013; Sanguinetti et al., 2013; Sanguinetti et al., 2020), it remains unknown whether TUS can improve mood in individuals with depression. As such, this study represents an important advancement from evaluating TUS as a mood enhancer in healthy participants to a clinical tool for those with clinically significant mood disruption. The present study examined the effect of a TUS neuromodulation intervention across five days on subjective mood report and mood symptoms in individuals with mild to moderate levels of depression. The present study represents both the first use of TUS in individuals with depression and the first systematic investigation of daily repeated TUS in humans. This double-blind short-term pilot intervention study was designed to provide

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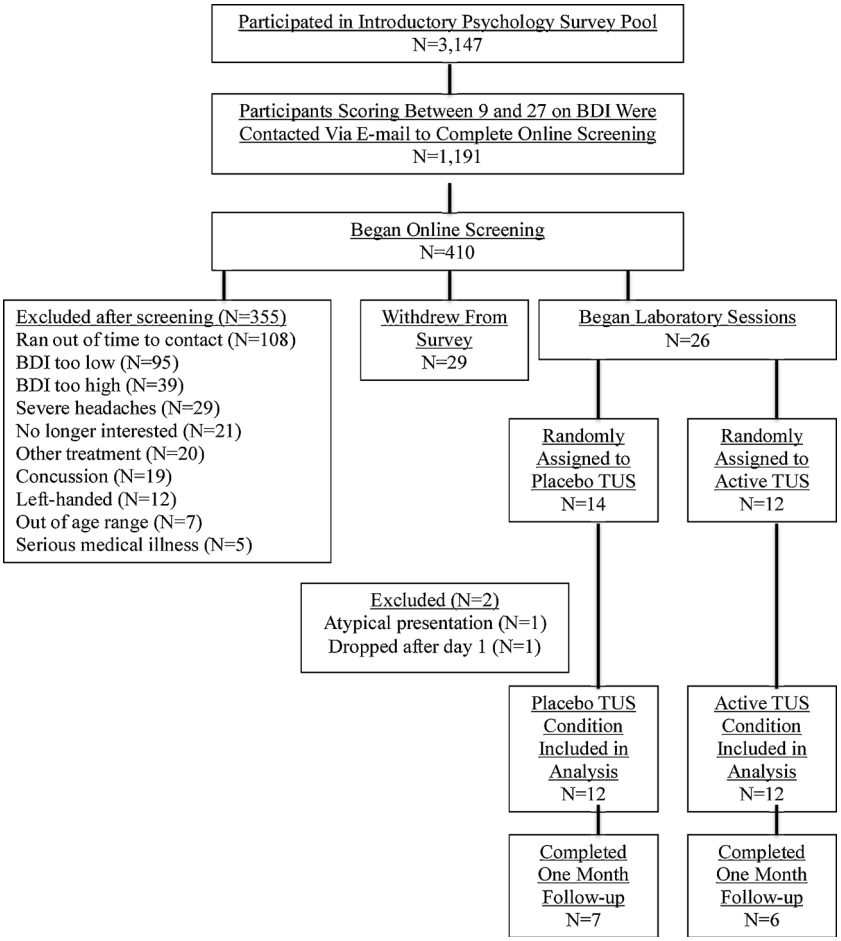

Fig. 1. The above consort chart shows the recruitment procedure and dropout for the present study. Due to matching by age, sex, and BDI level, a number of participants were excluded after screening because they did not match someone else by age, sex, or BDI level. Additionally, one participant who completed the study through to Day 5 was excluded because her BDI scores varied over 30 points, well above 2 SDs of change, due to significant life events during the course of the study. One participant was excluded due to only completing one day of the study.

insight into the feasibility of using TUS as an intervention for depression and has the potential to lead to an effective, noninvasive neuromodulation treatment for mood disturbance.

1.1. Transcranial ultrasound: a novel neuromodulation method

Ultrasound is a sound wave with a frequency higher than 20 kHz, above the range of human hearing . High-intensity ultrasound can produce heat or unstable cavitation (Wu & Nyborg, 2008) and damage cells and tissue, whereas low-intensity ultrasound can stimulate or inhibit muscle and nerve tissues without damage or heat production (Bystritsky et al., 2011). Low-intensity ultrasound has been used safely on biological tissue for therapeutic applications for over 70 years and has been shown not to have lasting bioeffects (Behrens et al., 2001; Busse & Bhandari, 2004; Chaussy & Thuroff, 2003; Cline et al., 1992; Daffertshofer & Hennerici, 2003; Fini & Tyler, 2017; ter Haar, 2007). It has been proposed as a promising therapeutic intervention for neurological and psychiatric conditions because it can excite tissue and safely penetrate the skull with great precision (Bystritsky et al., 2011; Colucci, Strichartz, Jolesz, Vykhodtseva, & Hynynen, 2009).

Hameroff et al. (2013) used TUS for the first time in humans. Fifteen seconds of ultrasound (8 MHz) to the fronto-temporal cortex, opposite the site of pain for chronic pain patients, significantly increased self-reported positive mood compared to placebo at 10 min and 40 min after neuromodulation. Ultrasound images verified the ultrasound had penetrated the skull. This study confirmed that transcranial ultrasound (TUS) can be safely used across the human skull and induce mood changes.

A small number of recent follow-up studies have replicated that TUS can increase positive mood in healthy participants. Sanguinetti et al. (2013) found that TUS (2 MHz, 15 s) administered at the prefrontal cortex targeting the right inferior frontal gyrus (rIFG) increased positive mood 15 and 30 min after neuromodulation compared to a placebo that did not change mood. Researchers have shown that the rIFG is implicated in mood and emotional regulation (Phillips, Drevets, Rauch, & Lane, 2003). Additionally, TUS at 2 MHz significantly improved mood compared to TUS at 8 MHz. In a larger study of 51 healthy participants, Sanguinetti et al. (2020) found that 30 s of TUS neuromodulation (0.5 MHz; PRF 40 Hz) targeting the rIFG increased self-reported global affect. Additionally, it was found that resting state functional connectivity (relative to a seed in the rIFG) decreased. These findings suggest that TUS at the right fronto-temporal cortex may be used to increase mood in human participants and reduce resting-state functional connectivity. As such, TUS may have significant potential utility for disorders implicating mood and functional connectivity, such as depression. The present study aimed to, for the first tme, test this potential utility.

1.2. Present study

The present study examined the effect of a five-day TUS intervention on depression and anxiety symptoms in individuals with mild to moderate depression. Consistent with prior research (Sanguinetti et al., 2020), neuromodulation occurred at the right fronto-temporal cortex.

Participants were randomly assigned to an Active TUS condition or Placebo TUS (no power) condition and completed five sessions of Active TUS or placebo administration. Depression severity, impairment due to anxiety, and self-reported mood were examined each day. Worry and rumination were evaluated on day one and day five. Given that TUS has been found to improve mood in humans (Sanguinetti et al., 2020), we predicted that participants exposed to the Active TUS condition would have reduced depressive and anxiety symptoms compared to participants exposed to the placebo condition. In line with prior research, we also predicted that TUS would improve mood in depressed participants and aimed to conduct exploratory item-analysis and moderation analysis to further understand the specific mood effects of TUS and the clinical populations for whom TUS may be most effective. Results in line with prediction would have important significant implications for the potential utility of TUS as an intervention for depression, warranting future work examining TUS as an alternative depression treatment.

2. Method

2.1. Participants

Twenty-four (16 women, 8 men) participants with mild to moderate depression completed the study (M = 18.92, SD = 1.10). Participants who scored between 10 and 25 on the Beck Depression Inventory-II (BDI-II) were recruited from the Introductory Psychology pool at the University of Arizona (see Fig. 1 for consort chart). Mild to moderate depression allowed for investigation of the intervention on a range of severity of depression; however, individuals with severe depression or active suicidality were excluded and immediately referred to resources in the community. Participants were right-handed, fluent English speakers who had no serious medical conditions, head injury, or severe headaches, psychotropic medication use, other treatment. Participants provided informed consent before participation, and the University of Arizona Institutional Review Board approved the protocol.

2.2. Procedure

Eligible participants were invited to join the study and to schedule five laboratory visits via telephone. Participants were randomly assigned to either Active TUS or Placebo TUS (no power) before their first visit. Stratified randomization ensured that participants were matched between conditions by age, sex, and depression severity. Participants completed five laboratory visits within a seven-day span during which they received Active TUS/Placebo at the right fronto-temporal area. At the end of five days, participants were invited to continue for another five days. Only data from the first five days are reported here, as only one participant completed the second five sessions. Participants were reminded that they could withdraw at any time and be compensated for their time.

Researchers and participants were blind to condition assignment. In the placebo condition, the ultrasound probe was placed at the right fronto-temporal area without any power emitted. At each laboratory visit, participants completed a number of state and trait self-report questionnaires as well as receiving Active TUS/Placebo.

Following consent at the first visit, participants again completed a survey of exclusionary criteria. Participants also completed a paper-and-pencil self-report version of the Structured Clinical Interview for the DSM-5 (SCID-5) in which they marked symptoms of depression they currently experience, the number of symptoms they experienced during their worst period of depression, and the number of times they have felt depressed.

At each session, participants completed a standardized measure of state mood before TUS administration. Then, research assistants identified the right fronto-temporal areas using electrode site F8 and placed the ultrasound probe at this area. Both research assistants remained in the room with the participant for the administration period of 30 s of Active TUS/Placebo. After this period, participants were asked to rest for ten minutes without a task and then complete a second mood assessment and then rest twenty minutes without a task and complete a third mood assessment. Participants were monitored via video camera from a next-door room as they rested.

2.3. Self-report assessments

The Visual Analogue Mood Scales (VAMS; Arruda, Stern, & Somerville, 1999) was administered three times per visit (before TUS, 10 min after TUS, and 30 min after TUS). The VAMS provided standardized measures of both self-reported Global Affect, which represents happiness/sadness, and self-reported Global Vigor, which represents anxiety and fatigue. A two item state rumination assessment by Moberly and Watkins (Moberly & Watkins, 2008) was included at the same time points. Trait rumination is past-focused repetitive thought that has been found to both cause and maintain depression (Kaplan et al., 2018) and was hypothesized as a potential treatment outcome. The Beck Depression Inventory-II (BDI-II; Beck, Steer, & Garbin, 1988) and Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006) were administered at the end of each session to assess anxiety and depression symptoms. Researchers monitored questionnaires daily to identify possible adverse effects. Significant changes (10 points on VAMS or four points on negative affect of PANAS or BDI) prompted a consultation in which participant is informed of worsening symptoms before continuing study. During this consultation, researchers also asked about unrelated situational factors. One participant was excluded due to a very significant life event, without investigator knowledge of group assignment to make this decision unbiased by knowledge of treatment condition; other participant life events, living status, and learning status were expected within college students and were controlled for by the double-blind study design.

Trait rumination and trait worry were assessed on the first and last days of the study using the Ruminative Responses Scale (RRS, Nolen-hoeksema, Wisco, & Lyubomirsky, 2014) and Penn State Worry Questionnaire (PSWQ, Brown, Antony, & Barlow, 1992) at the end of each session. One month after participants completed the study, they completed an OASIS and BDI online and answered four questions about their experience in the study.

2.4. TUS parameters

TUS neuromodulation occurred using the Neurotrek U+™, an ultrasound device developed by Neurotrek Inc., Los Gatos, CA. The Food and Drug Administration (FDA) recommends acoustic output below I_{SPTA} of 720 mW/cm^2, a mechanical index (MI) of 1.9, and a thermal index (TI) of 6.0 to avoid heating (Food and Drug Administration, 1999).

The U+™ device was set at a power of 11 %, a frequency of 0.5 MHz, and duration of exposure of 30 s. (For the Placebo condition, power output was 0%.) Prior research has used the same parameters with power at 21 % (Sanguinetti et al., 2020), but a conservative amount of energy (lower power than prior research) was used in this study given that it was the first use of repeated daily TUS in humans. For the present parameters, the estimates for the TI (0.6), MI (0.9), peak negative pressure (MPa = 0.65) as well as the maximum acoustic output (I_{SPTA} = 71 mW/cm^2) and spatial peak pulse-average intensity (I_{SPPA} = 14 W/cm^2) were well below the FDA limits. Lee et al. (2016) used TUS on the sensorimotor and visual brain areas of sheep. They observed minor microhemorrhages when pulses were very frequent (500 or more in minutes) but found no evidence of microhemorrhages when pulses were spaced further apart. As such, this research suggests that caution must be exhibited in spacing of pulses, so the present study utilized only 30 s and repetitions were spaced over at least one day.

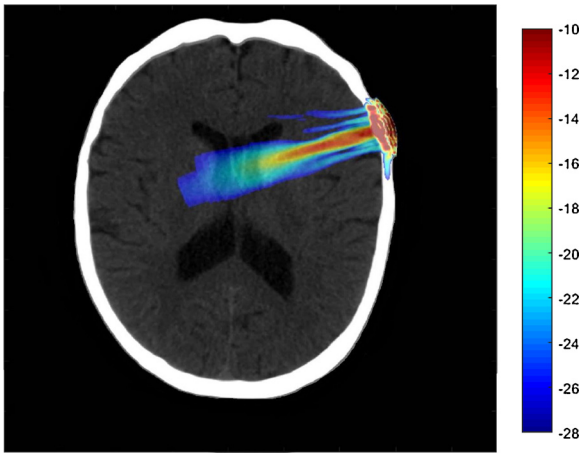

Fig. 2. Fig. 2 shows a simulation of the ultrasound wave propagation through the skull. An acoustic model in a single subject was created to visualize the acoustic wave propagation through the skull accounting for the effect of skull morphology.
It is important to note that the image is not an actual ultrasound administration but simulates one by calculating attenuation through the skull with a K-wave. The model was created using an MRI overlay with a CT scan. The CT scan was selected randomly from an online database (see Methods). The 30 mm transducer was calculated at the F8 (EEG) location.

Moreover, these levels were considerably lower than those used in the study of Sanguinetti et al. (2020) (MI = 1.79, I_{SPTA} = 130 mW/cm^2). Additionally, the U + device was utilized on "experimenter" mode. In this mode, researchers input a sequence of five numbers that turns the ultrasound to power or placebo (unknown to researcher and participant). A PhD-level scientist not directly affiliated with recruitment or subject running (J.L.S.) had access to all conditions of the participants and gave researchers five digit codes.

Acoustic stimulations were performed with k-Wave, a MATLAB toolbox (Treeby and Cox, 2010). In order to simulate the acoustic wave field, an archival CT scan randomly selected from the R.I.R.E. project (http://www.insight-journal.org/rire) was used as a model for the skull. The ultrasound parameters were entered into k-Wave and projected in the skull assuming the transducer was placed perpendicular to the scalp over F8. The speed of sound entered was 1550 m/s, and the brain density was 1030 kg/mˆ3. Fig. 2 displays the stimulated ultrasound wave propagating through the skull. We also calculated the acoustic attenuation through the skull model. There was a 53 % reduction in field intensity through the skull.

3. Data analysis & results

Given the small sample size and pilot nature of the present study, we report all effects where $p < 0.10$ and effect sizes.

3.1. Descriptive statistics

To examine potential group differences at baseline, t-tests were conducted for all major outcome variables (BDI, OASIS, RRS, and PSWQ). There were no significant differences between any outcome variables at day one, $p > 0.191$. Table 1 shows mean and standard deviations for all measures at baseline in both Active TUS and Placebo Conditions.

3.2. Symptom outcome variables

We conducted t-tests on difference scores from the last day of the study to the first day of the study on all major outcome variables. We report all effects where $p < 0.10$. To examine potential change in worry, participants first PSWQ score was subtracted from their last PSWQ score. There was a significant main effect of Condition on PSWQ, $t(20) = -1.742$, $p = 0.97$. Those in the Placebo condition had an increase in worry, whereas those in the Active TUS condition had a decrease in worry. There were no significant main effects of condition on the other outcome variables, $p > 0.255$.

Table 1
Table shows means and standard errors for all baseline measures as a function of condition (Active TUS/Placebo). There were no significant differences between Active TUS and Placebo TUS at any of these baseline measures, $p > 0.191$.

Baseline Measures	Active TUS		Placebo	
	M	SE	M	SE
BDI-II	17.33	1.214	17.00	1.472
OASIS	5.75	0.986	5.50	0.691
PSWQ	57.75	2.758	48.83	2.984
RRS	49.92	2.530	40.92	2.497

3.3. Within-day mood effects

To test change in mood after TUS Power/Placebo, we conducted mixed-design 2 (Condition) by 3 (Time) by 5 (Day) ANCOVAs. Time, a within-subjects factor, was assessed before, 10 min after, and 30 min after Active TUS/Placebo. Day, also a within subjects factor, was also included. For Global Affect, there was a three-way interaction between Condition, Day, and Time ($F(8,15) = 2.452$, $p = 0.064$, $\eta_p^2 = .567$, such that Global Affect increased over the course of days in the Active TUS condition but decreased over days in the Placebo TUS condition. There was no main effect of Condition on Global Affect or interaction between Condition and Time on Global Affect, $p > .598$. There was also no main effect of Condition on Global Vigor or interaction between Condition and Time on Global Vigor, $p > 0.380$.

We conducted two follow-up analyses to explore the significant interaction between Condition, Day, and Time on Global Affect. First, because Global Affect includes both items related to happiness and anxiety, we wanted to examine items related to happiness separately from items related to anxiety to further understand any potential impact of TUS on mood. We computed two composite variables (State Happiness = [(happy) - (sad)] and State Anxiety = [(tense) - (calm)]. We again conducted mixed-design 2 (Condition) by 3 (Time) ANCOVAs with these variables. For State Happiness, we did not find a significant main effect of Condition or a significant interaction between time and condition, $p > 0.409$. For State Anxiety, there was no significant main effect of Condition or interaction between Time and Condition, $p > 0.163$.

Second, we examined Condition by Time interactions for each of days one through five. Based on the results of Sanguinetti et al. (2013; 2020), we expected changes in Global Affect on day one of the study. Given this study represents the first systematic use of TUS repeated over days, however, we did not have a prediction about whether this effect would be sustained on days two through five. We found that there were significant Condition by Time interactions on Day 1, 3, and 4. On day 1, there was a significant interaction between Time and Condition on Global Affect, $F(2, 21) = 3.941$, $p = 0.035$, $\eta_p^2 = 0.273$, such that those in the TUS Active Condition had a significant increase in Global Affect compared to those in the Placebo Condition. Global Affect decreased for those in the TUS Active condition at thirty minutes, suggesting that mood change occurred at 10 rather than 30 min. On day 3, there was a significant Condition by Time interaction such that there was an increase in Global Affect in the Placebo Condition but Global Affect did not change in the Active TUS Condition, $F(2, 21) = 3.341$, $p = 0.055$, $\eta_p^2 = 0.241$. On the other hand, there was also a significant Condition by Time interaction on day 4, such that those in the Active

Table 2
Exploratory analysis of individual differences was conducted using ANCOVAS. Table 2 shows the parameter estimates for the interaction between each moderator variable and Condition (Active TUS/Placebo). Four different moderators (BDI, OASIS, RRS, and PSWQ) were examined for all four major outcome variables. BDI is a measure of depression symptoms, OASIS is a measure of overall severity of anxiety, RRS is a measure of rumination, and PSWQ is a measure of worry. High and low groups were identified for each of these measures as participants below or above the mean.

	High BDI	Low BDI	High OASIS	Low OASIS	High RRS	Low RRS	High PSWQ	Low PSWQ
N	13	9	9	13	11	11	14	8
BDI								
B	−3.633		*−8.682*		*−12.654*		2.700	
P value	0.409		*0.027**		*0.006**		0.558	
η_p^2	0.040		*0.256*		*0.369*		0.021	
OASIS								
B	0.003		*−4.048*		−2.349		−1.178	
P value	0.999		*0.054**		0.335		0.598	
η_p^2	0.000		*0.202*		0.055		0.017	
RRS								
B	1.117		2.564		8.982		4.637	
P value	0.808		0.586		0.090		0.334	
η_p^2	0.004		0.018		0.160		0.055	
PSWQ								
B	0.149		2.763		8.657		1.800	
P value	0.982		0.666		0.248		0.788	
η_p^2	0.000		0.011		0.078		0.004	

TUS Condition had an increase in mood but those in the Placebo Condition decreased mood, $F(2, 21) = 2.697$, $p = 0.091$, $\eta_p^2 = 0.204$. There were not significant Condition by Time interactions on Day 2 and 5, $p > .302$.

As expected, there was no main effect of Condition on Global Vigor at day one only, $F(1,22) = .899$, $p = .353$, $\eta_p^2 = .039$. There was, however, a small interaction of Condition and Time on Global Vigor, $F(1,22) = 1.772$, $p = 1.82$, $\eta_p^2 = .075$, such that those in the Active TUS had significantly decreased Global Vigor compared to the Placebo condition after TUS administration.

We also conducted mixed-design 2 (Condition) by 3 (Time) ANCOVAs for each of the individual items on the VAMS. There were no significant main effects of Condition or Condition by Time interactions, $p > 0.164$.

3.4. Moderation by individual differences

Additionally, exploratory analysis of potential moderators was conducted using ANCOVAs (see Table 2 summary). First, we examined OASIS level as a potential moderator. We found that OASIS level on day one (split into high and low anxiety groups at the mean) moderated the relationship between Condition and BDI, $F(1, 17) = 5.855$, $p = 0.027$, $\eta_p^2 = .256$, as well as OASIS, $F(1, 17) = 4.304$, $p = 0.054$, $\eta_p^2 = 0.202$. OASIS level did not moderate the relationships between Condition and RRS or PSWQ outcome, $p > 0.586$. The high OASIS group had lower BDI and OASIS scores in the Placebo compared to Active, whereas the low OASIS group had lower BDI scores in the Active compared to Placebo and minimal change in BDI score between Active and Placebo.

Second, we examined whether self-reported trait rumination (RRS) moderated the relationship between condition and outcome. We found that there was a significant interaction between RRS level (split into high and low groups at the mean) and condition on BDI outcome, $F(1, 17) = 9.935$, $p = 0.006$, $\eta_p^2 = 0.369$, and RRS outcome, $F(1, 17) = 3.243$, $p = 0.090$, and $\eta_p^2 = 0.160$. Those in the low RRS group had higher BDI and lower RRS after Placebo compared to Active, whereas those in the high RRS group had higher BDI and lower RRS after Active compared to Placebo. RRS did not moderate either PSWQ or OASIS outcomes, $p > 0.248$.

Finally, we found that self-reported worry (high and low groups at the mean of PSWQ) did not moderate the relationship between condition and outcomes, $p > 0.334$ nor did self-reported depression (high and low depression groups at the mean of BDI), $p > p > 0.409$.

3.5. One-month symptom follow-up

Thirteen participants (seven in the Active TUS condition, six in the Placebo condition) completed the online follow-up that included BDI, OASIS, and four questions regarding enjoyment and self-experienced mood change during the study. We conducted t-tests to examine group differences in perceived 1) enjoyment participating in the study 2) mood improvement from participating in the study 3) reduction in uncontrollable, negative thoughts from participating in the study and 4) recommendation of the study to others. Participants in the Active TUS condition were significantly more likely to enjoy participating in the study ($M = 4.29$, $SD = 0.488$) than those in the Placebo condition ($M = 3.67$, $SD = 0.516$), $t(11) = 2.221$, $p = .048$. There were no other significant group differences ($p > .545$). We conducted ANCOVAs to test the difference between groups at one-month follow-up after adjusting for baseline symptoms. There were no significant main effects of condition on BDI, $F(1, 12) = .196$, $p = .667$, $\eta_p^2 = .019$, or OASIS, $F(1, 12) = 4.422$, $p = .062$, $\eta_p^2 = .307$, at one month follow-up. There were no significant main effects of condition on BDI, $F(1, 12) = .196$, $p = .667$, $\eta_p^2 = .019$, or OASIS, $F(1, 12) = 4.422$, $p = .062$, $\eta_p^2 = .307$, at one month follow-up.

4. Discussion

The present study was the first examination of TUS as a potential intervention for depression and the first systematic investigation of repeated use of TUS over days. The present study found that active delivery of TUS (Active TUS condition) compared to Placebo decreases worry after five sessions in individuals with depression. Additionally, individuals who received active TUS compared to Placebo had increased happiness over the days of the study. In contrast to these treatment effects seen over days, there was inconsistency in mood change within each session. For example, on days one and three happiness increased in the TUS compared to Placebo. By contrast, happiness decreased in TUS vs. Placebo on day four and no significant within day mood effects were seen on days two and five

This study suggests that TUS may have beneficial effects on mood and worry when used repeatedly in participants with depressive symptoms. Further investigation is warranted as to the effects of TUS within day versus over repeated daily use. Importantly, even moderate levels of anxiety and worry increase depression severity and likelihood of nonresponse to traditional depression treatment (Fava, 2003; Kornstein & Schneider, 2001). As such, a novel, noninvasive

neuromodulation treatment that can reduce anxiety symptoms in individuals with depression could be used in conjunction with existing depression treatments to increase likelihood of treatment response. If TUS can reduce worry in depressed participants, it may help these participants to be able to better focus on intervention techniques and thus increase treatment response. These findings may also have significant implications for individuals with comorbid depression and anxiety. Future research may also investigate the impact of TUS on worry in singular anxiety and worry-related disorders, such as Generalized Anxiety Disorder (GAD). Such findings may have significant implications for the potential development of a novel effective, portable, and low-cost intervention for multiple psychological disorders.

Prior research found that a single dose of TUS can increase Global Affect in humans up to 30 min later (Sanguinetti et al., 2020). In the present study, we found that TUS increased Global Affect at 10 but not 30 min after administration on the first day. We propose that this shorter-lived mood effect may be due to the reduced power in the present study. In prior research, the U+™ device was set at a power of 21 %, a frequency of 0.5 MHz, I_{SPTA} of 130 mW/cm2, and duration of exposure of 30 s. In the present study, we opted for caution and lower intensity (I_{SPTA} = 71 mW/cm^2) because of the repeated neuromodulation sessions.

The lower power of ultrasound used in the present study (compared to prior research e.g. Sanguinetti et al., 2020) may have contributed to shorter-lived mood effects. It is also worth noting, that the present study included participants with mild to moderate depression and prior research included only healthy participants. As such, future research will need to explore the potential optimal parameters, considering both safety and efficacy, for a TUS intervention as well as differential population effects.

Contrary to prediction, TUS did not reduce depression or anxiety severity over the course of the intervention. Given the lower power use in the present study compared to previous work, however, the possibility remains that repeated delivery of higher power TUS may hold a role in the treatment of depression. Moreover, the positive impact of TUS on worry and happiness in a population with mild to moderate depressive symptoms suggests that future research may be fruitful in uncovering the needed parameters and population for an effective mood intervention.

Additionally, the results suggest several potential moderators of the impact of TUS on change in symptoms. In particular, individuals with lower impairment due to anxiety and trait rumination levels appeared to have a larger reduction in depressive symptoms in response to the intervention. These results may suggest that those with lower levels of anxiety and trait rumination may benefit more from the intervention in terms of reduction of depression symptoms specifically. As such, additional research with an increased sample size to identify for whom and this intervention may be most effective is warranted.

The present study suggests that TUS has promise as a potential intervention, or a part of an intervention package, for individuals with comorbid diagnosis of depression and anxiety. The small sample size of the present work underscores the need for further research, and specifically for studies designed to identify the optimal parameters of the intervention and to determine for whom the intervention would work best.

4.1. Limitations and future directions

The power delivered by the TUS transducer in the present study was substantially lower than in previous studies, perhaps leading to a potentially suboptimal TUS intervention. As such, future research is needed to identify the ideal TUS parameters to maximize efficacy while ensuring safety. Another important note is that the TUS focal beam may have targeted slightly different areas due to individual differences in brain structure. Future researchers may examine both optimal power and individual differences in TUS targeting the rIFG. Additionally, we administered five sessions within a seven-day period. We found acute mood responses on day one and three as predicted but found effects contrary to our prediction on day four. Future research may investigate the optimal length of time between administrations.

Finally, participants were recruited based on depression but not anxiety symptoms. The relatively restricted range of depression in the present study allowed for a homogeneous population for a pilot study. Future large-scale research may include a range of psychopathology symptoms, from non-existent to severe to examine how TUS parameters may impact mood in different populations.

The small sample size of this study represented a significant limitation for evaluating for whom the treatment may work. This study represents a potential proof-of-concept that repeated TUS use may reduce worry. Future research may utilize a transdiagnostic approach and target worry within the context of varying psychopathology. Large-scale future research may allow for further moderator analyses that provide insight into which populations may benefit most from TUS. In particular, based on our finding that TUS reduces anxiety, future research may focus on recruiting individuals based on anxiety symptoms and including additional empirically validated measures of anxiety and worry. The present findings suggest that more research examining TUS as a potential intervention for depression and anxiety is warranted. This work has the potential to lead to a portable, low cost, and non-invasive treatment for comorbid anxiety and depression.

Contributors

Authors SR, JS, and JJBA designed the project. Author SR analyzed the data and prepared the manuscript, under the supervision of JJBA. Author JT developed the TUS + device. Author CD developed Fig. 2. All authors have approved the final article.

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Ethical statement

The study was approved by the Institutional Review Board at the University of Arizona and meets all guidelines for ethical conduct and report of research.

Declaration of Competing Interest

JT is a co-founder of IST, LLC, as well as inventor on issued and pending patents covering noninvasive neuromodulation methods and devices. Other authors have no conflicting interests to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.npbr.2020.06.004.

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