The Effect of Non-invasive Transcranial Focused Ultrasound on Depression and the Default Mode Network

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Abstract

Background: Up to 50% of individuals fail to respond to current depression treatments. Repetitive negative thought and aberrant default mode network functional connectivity are considered mechanisms of action in the development and maintenance of depression, which can be targeted using transcranial-focused ultrasound, a novel neuromodulation technique.

Methods: Twenty individuals with diagnosed depression were enrolled in this open-label case series. They completed up to eleven ultrasound sessions within a three-week period. They also completed symptom self-report surveys and interviews before, during, and after treatment.

Hypotheses: It was hypothesized that transcranial-focused ultrasound targeting a major hub of the default mode network, the anterior medial prefrontal cortex, will improve depression symptoms and repetitive negative thought and promote connectivity changes within the default mode network.

Results: There was a significant decrease in depression symptoms and repetitive negative thought after a three-week transcranial-focused ultrasound treatment protocol. Participants with greater decreases in depression symptoms experienced greater decreases in repetitive negative thought. Additionally, there was a significant decrease in connectivity within the default mode network. Two participants dropped after completing week 1 of treatment. One participant met remission criteria after completing week 1 of treatment.

Conclusion: These findings support the potential for transcranial focused ultrasound to be used as an effective and fast-acting treatment for depression. These findings also support the role of the default mode network in the development and maintenance of depression.

Background

Repetitive Negative Thought (RNT) has been identified as a potential maintaining factor in depression, such that those who exhibit higher degrees of RNT endorse greater depression symptoms (Taylor & Snyder, 2021).
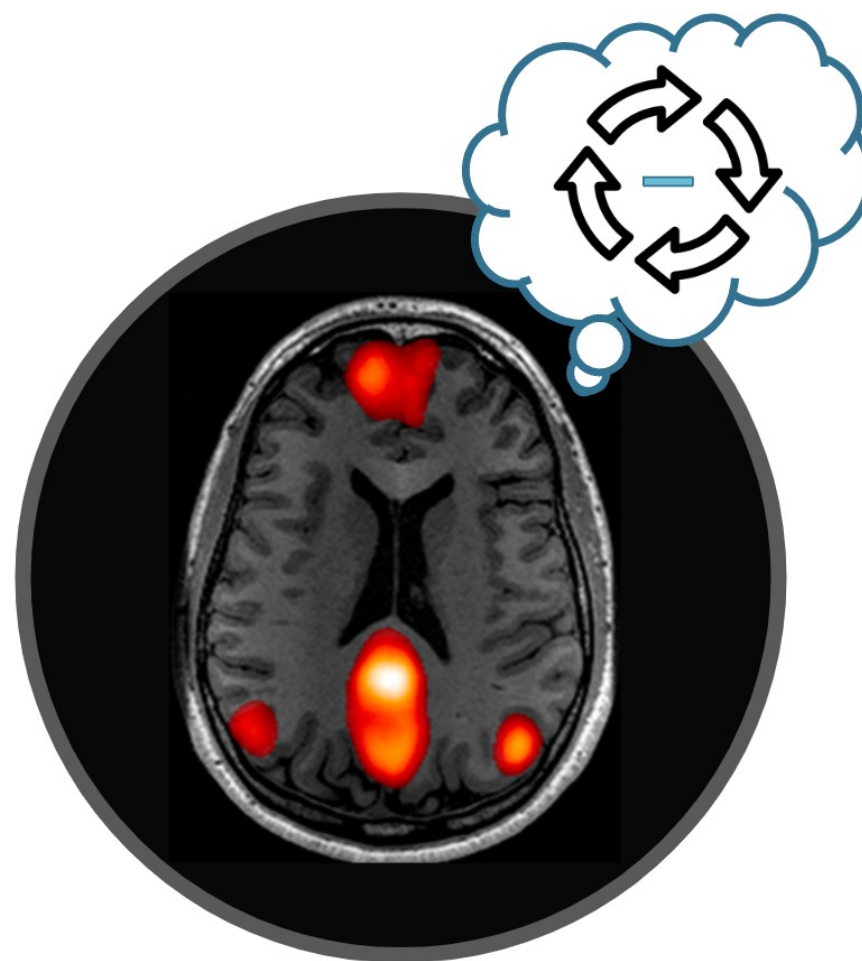
The Default Mode Network (DMN) plays an important role in depression wherein it has been linked to RNT (Sheline et. al., 2010). In depressed individuals, this network appears to be hyper-connected, which, in turn, is thought to promote RNT (Shi et. al., 2015).

Non-invasive Transcranial Focused Ultrasound Stimulation (tFUS) is a promising tool for the treatment of depression (Resnik et. al., 2020; Sanguinetti et. al., 2020). tFUS directs a low-intensity (nonthermal) focused ultrasound beam that passes safely through the skull (Fini & Tyler., 2017).

a. Neuronavigation equipment
b. Ultrasound headset
c. Neuronavigation Results
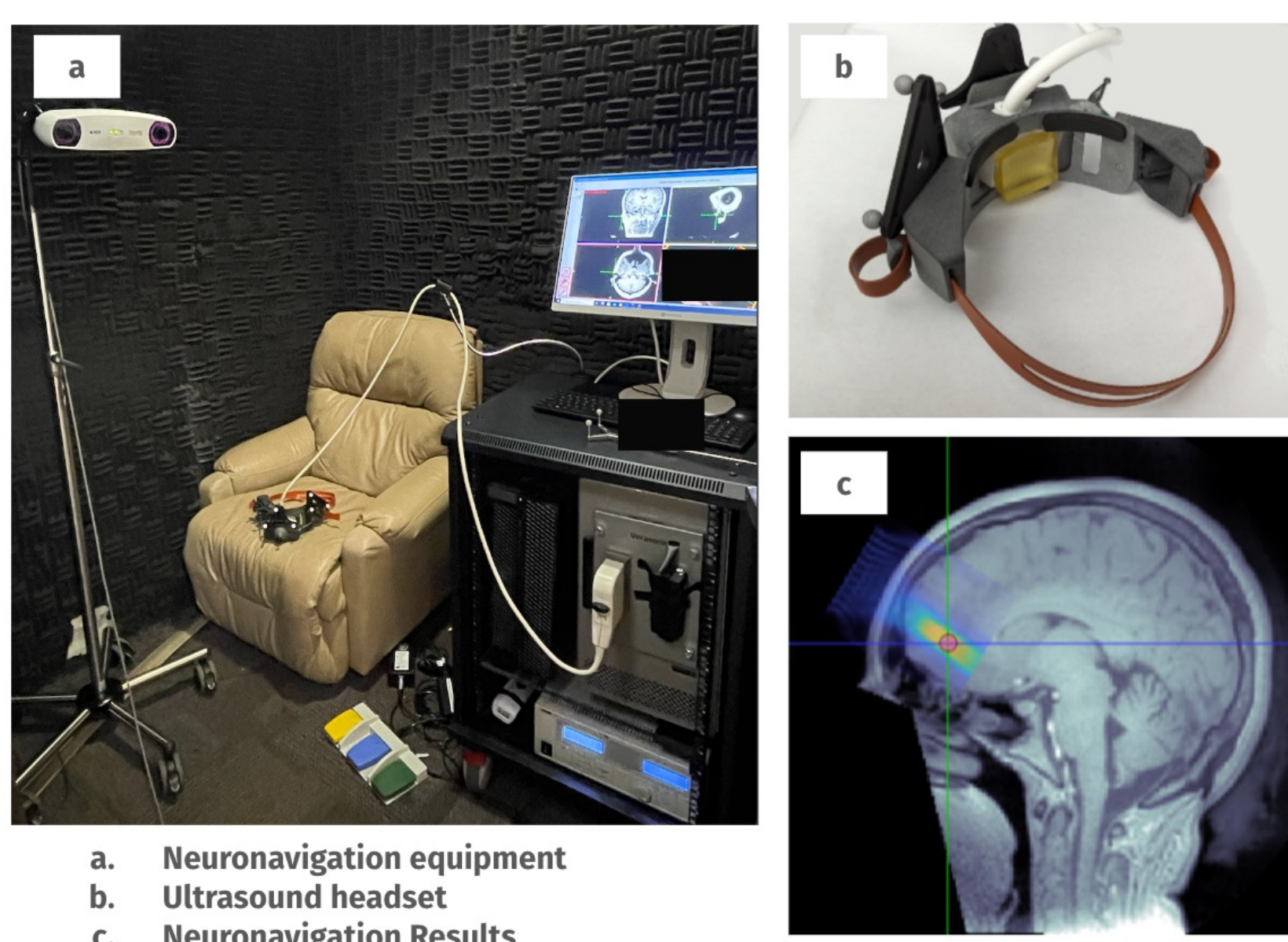
Methods

Twenty participants with diagnosed depression completed a series of MRI scans, surveys and interviews, and up to 11 tFUS sessions.
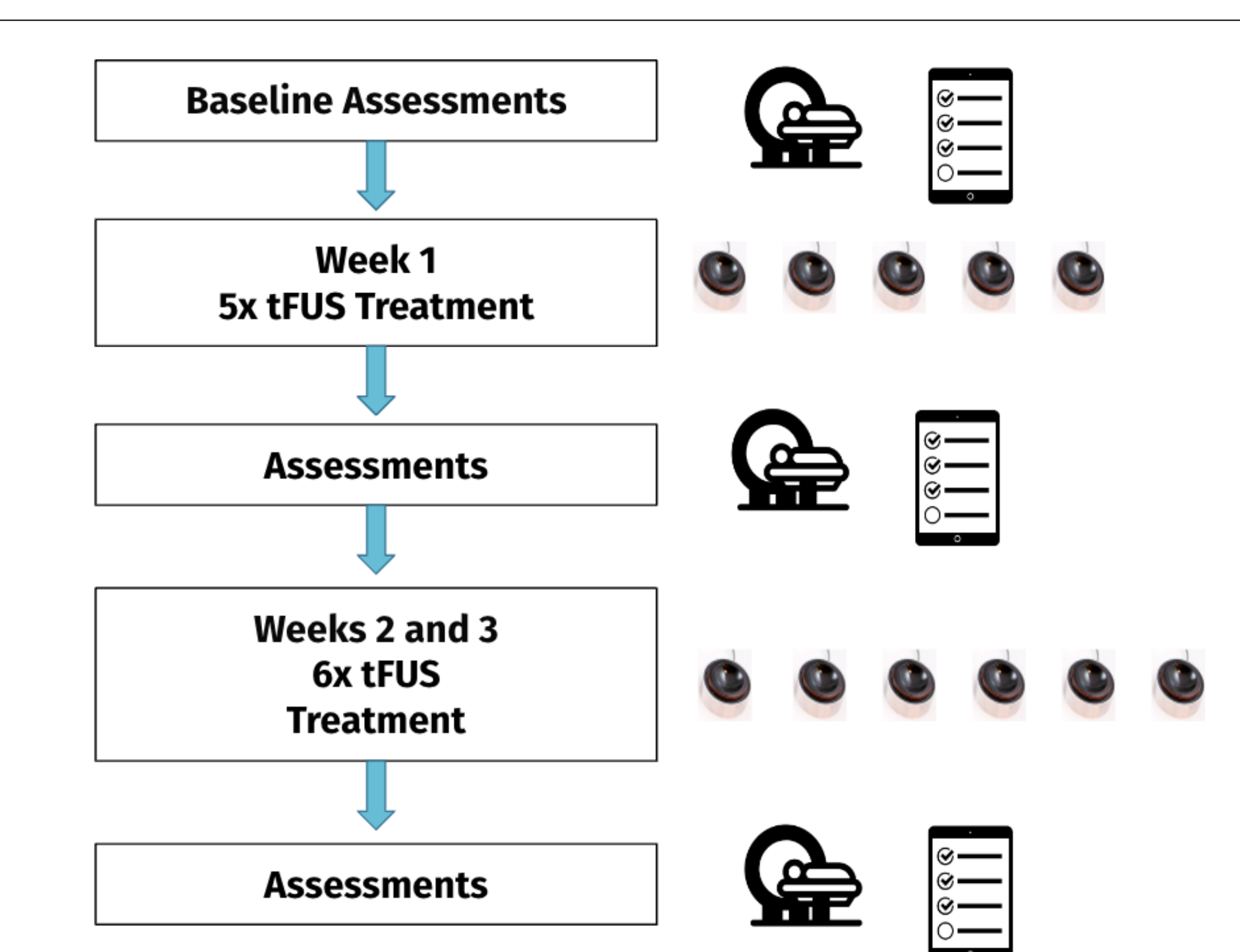
Figure 1. Participants completed baseline assessments, which included the Beck Depression Inventory-II (BDI), the Perseverative Thinking Questionnaire (PTQ), and a functional resting-state MRI scan. Participants completed the same assessments after one week of tFUS treatment before completing six more sessions over two weeks. Finally, participants completed the same assessments after week 3.

Results

Participant Demographics

Demographics		N = 20
Age (M/SD)		30.35 (10.04)
Gender (F/M/Other; %)		75 / 20 / 5
Years of education (M/SD)		13.83 (1.93)
Race (%)		
	White	45
	Black	10
	Chinese	5
	Middle Eastern	5
	Indian	5
	Unknown	30
Ethnicity (%)		
	Hispanic	0
	Non-Hispanic	70
	Unknown	30
Employment (%)		
	Full-time	15
	Student	15
	Part-time	45
	Unemployed	25
Baseline BDI-II (M/SD)		38.85 (9.34)
Baseline PTQ (M/SD)		44.35 (6.24)
Baseline HDRS (M/SD)		19.90 (6.34)
Depression onset (Early/Teen/Adult) (%)		55/ 25 / 20

Table 1. Participant demographics. In addition to the information provided on the table, 50% of participants had a comorbid diagnosis (e.g., 85% of participants had comorbid anxiety & stress-related disorders) and 50% of participants were currently on psychiatric medication.
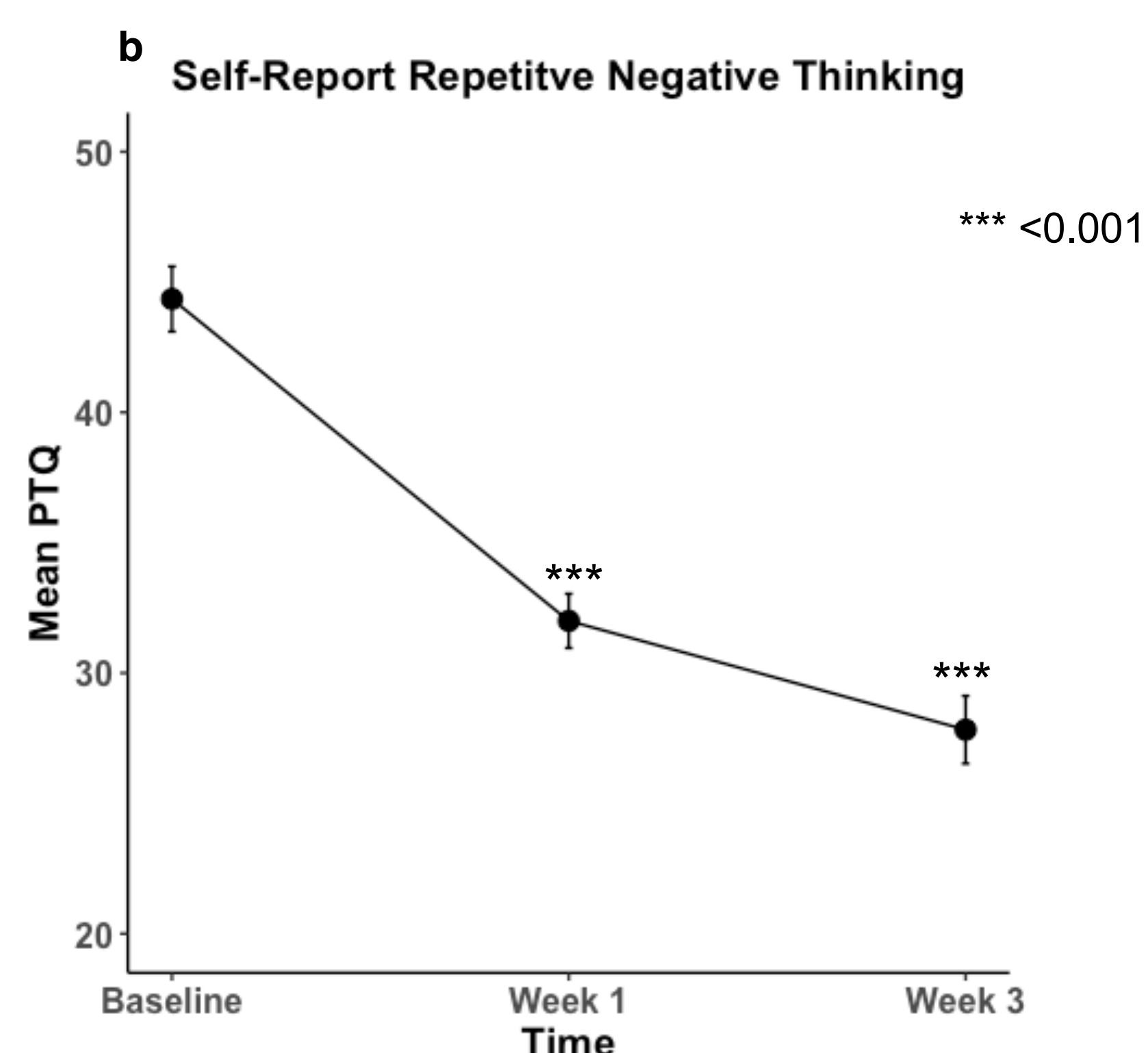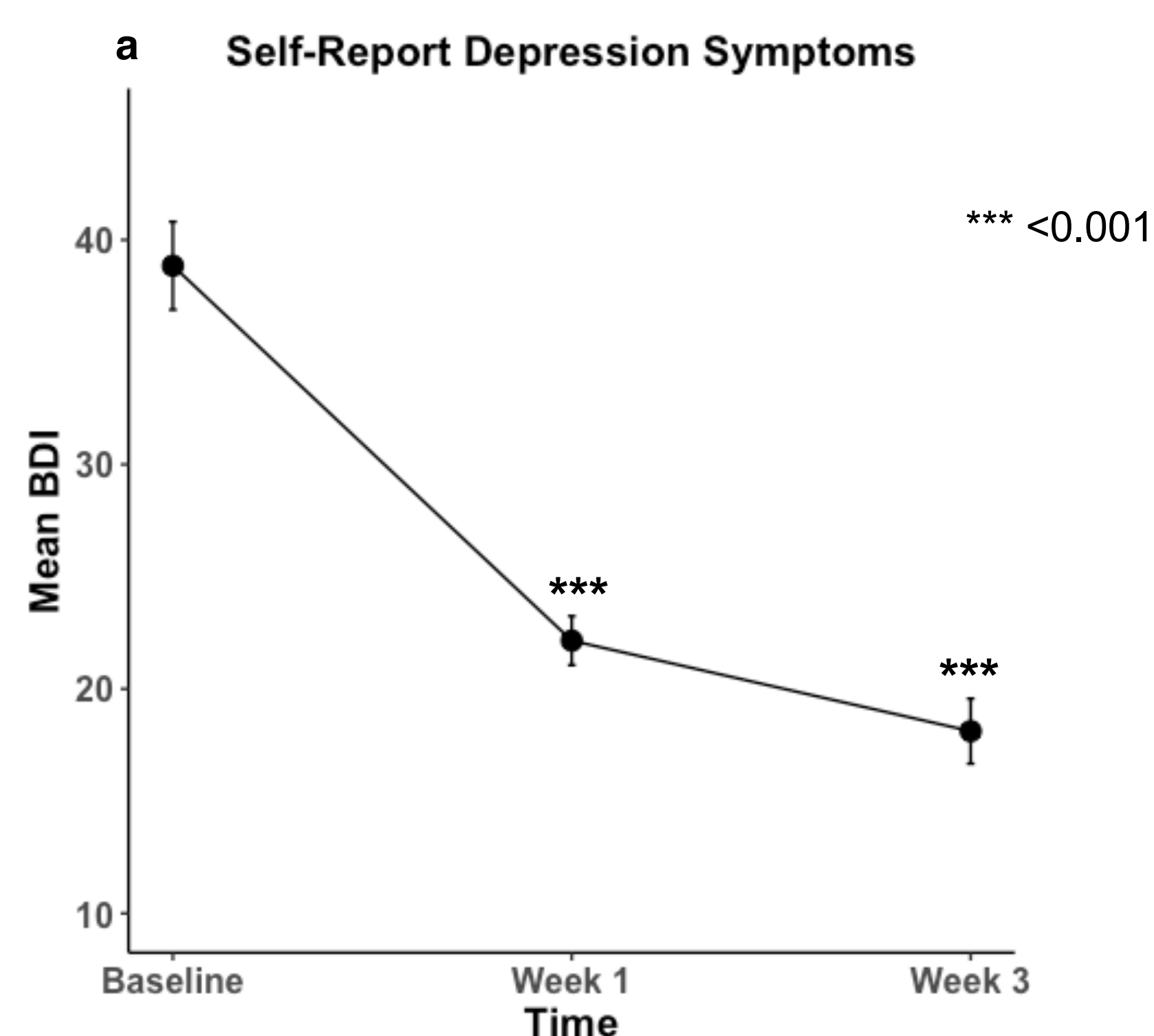
Results

Response and remission after tFUS treatment

|	Responded (50% reduction)	Remitted (HDRS <8; BDI<13)
Beck Depression Inventory (BDI-II)	60%	35%
Hamilton Depression Rating Scale (HDRS)	45%	35%

Results

There was a significant decrease in depression symptoms and repetitive negative thought after tFUS treatment

Figure 2. a) Multi-level model assessing change in BDI-II over the course of ultrasound treatment. There was a significant decrease in depression symptoms after ultrasound treatment (Week 1: p < 0.001, Estimate = -16.70, CI: -21.94, -11.29; Week 3: p <0.001, Estimate= -21.41, CI: -26.36, -16.16) **b)** Multi-level model assessing change in RNT over the course of ultrasound treatment. There was a significant decrease in RNT after treatment (Week 1: p <0.001, Estimate= -12.35, CI: -16.40, -8.56; Week 3: p < 0.001, Estimate = -16.47, CI = -20.37, -12.47). Error bars are within-subject.
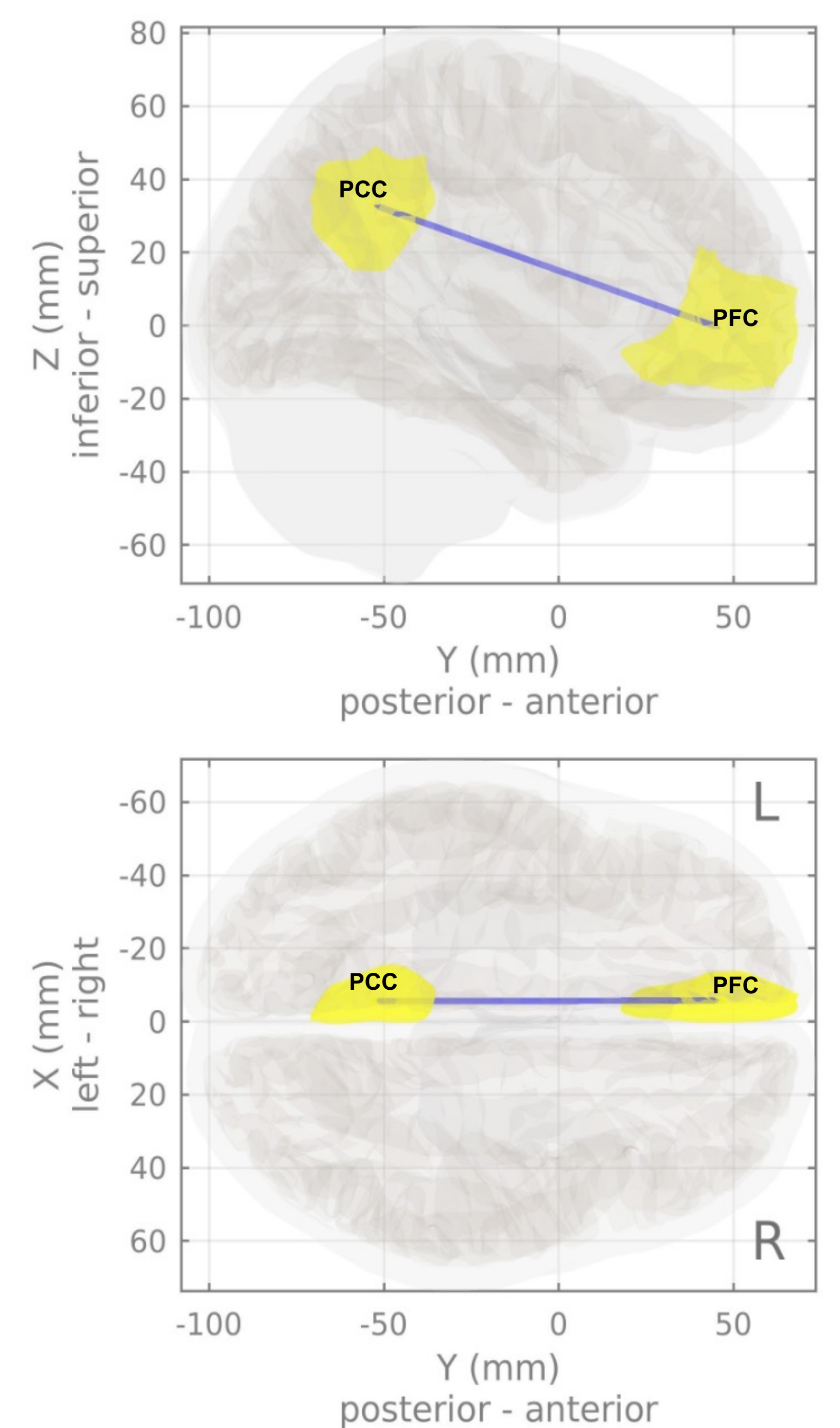
Results

Those with a greater decrease in depression symptoms experienced a greater decrease in repetitive negative thought
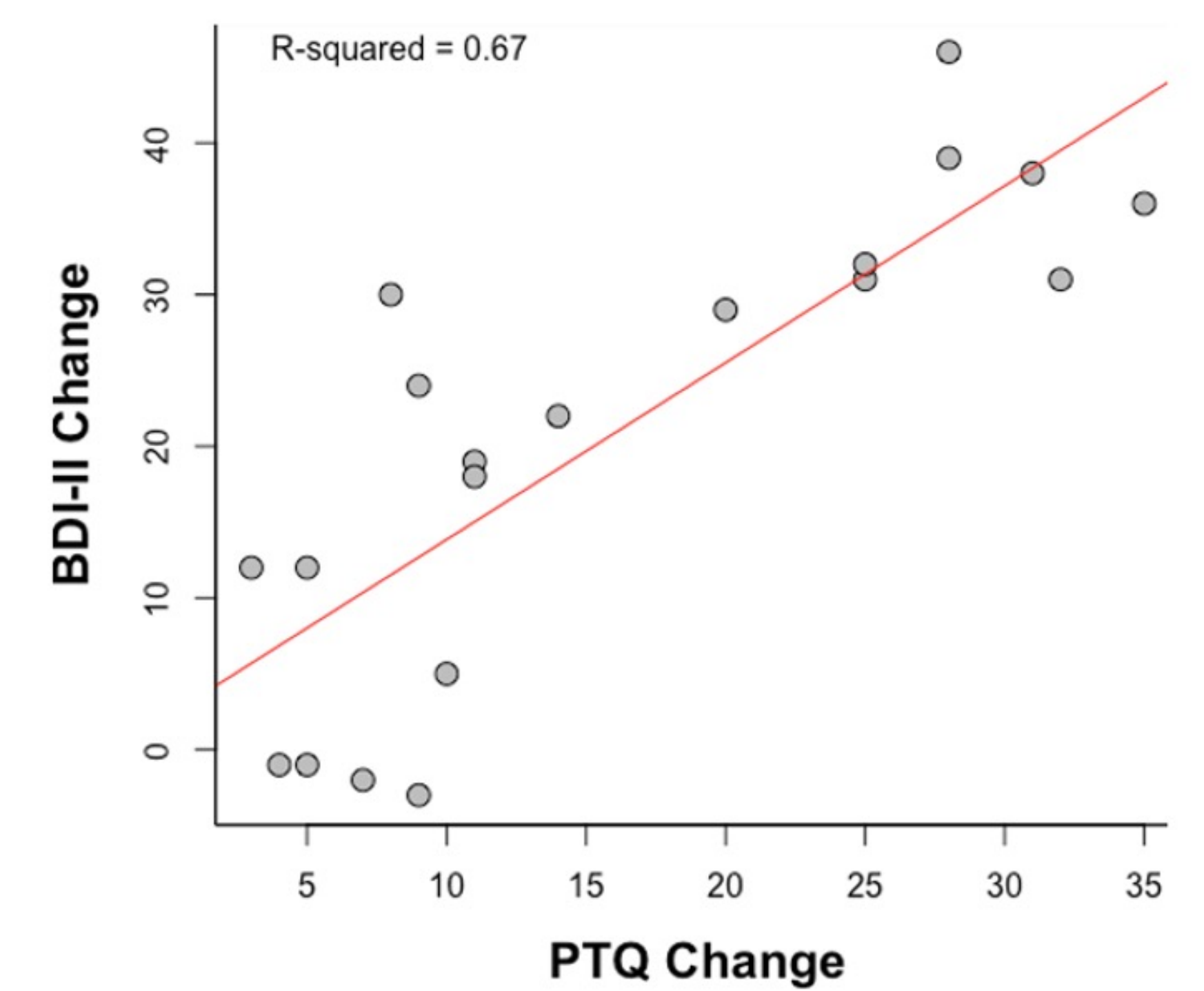
Figure 3. Linear regression between depression symptom change (baseline - week 3) and RNT change (baseline - week 3). There was a significant, positive relationship between change in depression symptoms and change in RNT. Those who experienced greater decreases in depression symptoms experienced a greater decrease in RNT (R^2 = 0.67, F = 36.84 (1, 18), p < 0.001).

There was a significant decrease in connectivity within the DMN after tFUS treatment

Prefrontal Cortex (PFC)

Posterior Cingulate Cortex (PCC)

Figure 4. Spatial Pairwise Clustering analysis assessing connectivity changes within the the DMN from baseline to end of week 3. Results were thresholded using a combination of a cluster-forming p < 0.01 connection-level threshold and a familywise corrected p-FDR < 0.05 cluster-mass threshold. There was a significant decrease in connectivity within the DMN, between the prefrontal cortex and posterior cingulate cortex (p_{fdr} = 0.029, T = -4.40)

Conclusion & Next Steps

After Ultrasound treatment:

- 45% - 60% of subjects responded to treatment and 35% met remission criteria.
- Participants' depression symptoms and RNT decreased after treatment
- Those with a greater decrease in depression symptoms experienced a greater decrease in RNT.
- There was a significant decrease in connectivity within the Default Mode Network.

tFUS holds promise as an effective treatment for depression

A randomized controlled trial with a larger sample and sham control group is required to confirm findings.

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