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Original Article

Neuromodulatory Impact of Low-Intensity Focused Ultrasound on Early Cognitive Decline

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ABSTRACT

Background: A mild neurocognitive disorder causes problems with memory, attention and thinking skills.. There are not many good ways to treat this that do not need surgery. Objective: To see how active low-intensity focused ultrasound and fake ultrasound affect memory, attention and brain connections in people with neurocognitive disorder. Methods: This study had 76 people, aged 55 to 80. They were split into two groups. One group got ultrasound that targeted parts of the brain related to thinking and memory. The other group got a treatment. They tested the brain functions of the people before the treatment one week after and two months after. Sixty-eight people finished the study. Results: One week after the treatment people who got ultrasound had better memory than those who got the fake treatment. The difference was still there two months later. People who got ultrasound also did better on a test of attention. Their brain connections between the part of the brain and the hippocampus were stronger, than those who got the fake treatment. No serious problems happened. low-intensity focused ultrasound seems to help with memory and attention and makes brain connections stronger.. More studies are needed to be sure. Keywords: Attention; Cognitive Dysfunction; Double-Blind Method; Functional Connectivity; Memory; Mild Neurocognitive Disorder; Non-Invasive Brain Stimulation; Randomized Controlled Trial; Ultrasonic Waves.

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INTRODUCTION

Mild neurocognitive disorder is when someone has a decline in one or more areas of thinking that is more than what is expected as people get older but it does not greatly affect their ability to do everyday things on their own. People with neurocognitive disorder often have problems with memory, attention and decision making which can increase the chance of their condition getting worse and turning into a more serious neurocognitive disorder (1-3). As more people get older the number of people who are experiencing signs of cognitive decline is growing and this is a big challenge for doctors and public health workers. The medicines that are available to help with this condition only provide a help with symptoms and can have bad side effects while things like cognitive training, exercise and lifestyle changes usually require people to keep doing them for a long time and do not always work.

Intensity focused ultrasound is a new way of helping the brain that uses sound waves to target a specific area of the brain. This is different from methods that use electricity or magnets because it can reach the brain without hurting the surrounding tissue. When intensity focused ultrasound is used at the right level it can help the brain without causing damage and it may be able to help the brain cells work better improve communication between brain cells and make the brain more flexible (4,5). Some studies have shown that low-intensity ultrasound can affect how the brain works and how it adapts to things and some studies with

people have found that it can improve cognitive function, brain activity and how different parts of the brain talk, to each other. However these studies have used methods targeted different areas of the brain and looked at different outcomes, which can make it hard to compare them to each other.

Clinical evidence about using ultrasound to change brain activity is still limited. Earlier studies have looked at using ultrasound on the skull or other sound-based methods in people people with Alzheimer's disease and people with brain or metabolism problems (6–10). Some of these studies found thinking or mood results while others mainly looked at if the treatment was safe or if it changed brain activity. These results can't be used for adults with thinking problems because the sound methods are different in frequency how they are sent strength, where they are aimed and how they work. Also few studies have tested if a fake treatment has the same effect as real treatment and looked at both thinking skills and how the brain works together in people who are starting to have memory issues.

The front part of the brain helps with focusing, remembering, checking memory and working with brain parts for memory. The right front part of the brain and nearby areas work with the part of the brain including the hippocampus, when remembering and controlling actions. Problems in these brain areas are linked with thinking problems and early brain changes. Changing activity in the part of the brain might affect thinking skills and how brain parts work together. Repeated ultrasound treatments have shown some hope in people with Alzheimer's disease and new studies suggest that low-level ultrasound might help brain cells grow and repair (11–14). Still the thinking and brain network effects of one ultrasound session in people, with thinking problems are not well known.

This study looked at people with neurocognitive disorder. The study used intensity focused ultrasound on the right inferior frontal gyrus and the part of the brain next to it. The study wanted to see if this treatment was better than a treatment for improving episodic memory in adults with mild neurocognitive disorder.

The study also looked at things like attention and how different parts of the brain talk to each other when people are not doing anything. The study checked if people felt uncomfortable during the treatment. The study also checked what happened to the people two months after the treatment.

The people doing the study thought that the real treatment would help people remember things better one week after the treatment. They also thought that the real treatment would help people pay attention better and that it would help parts of the brain talk to each other better. The study used intensity focused ultrasound and the people doing the study wanted to see how it affected episodic memory and other things in adults, with mild neurocognitive disorder.

MATERIALS AND METHODS

This study was done in Pakistan in the Islamabad and Rawalpindi area over six months. It was done with people who have neurocognitive disorder. The study looked at how a single session of intensity focused ultrasound affects these people.

The people in the study had to be between 55 and 80 years old. They had to have neurocognitive disorder and a certain score on a test called the Montreal Cognitive Assessment. They also had to have been taking the medicines for at least three months before joining the study.

Some people were not allowed to join the study. These were people who had depressive disorder, bipolar disorder or some other mental health issues. People with epilepsy that was not controlled or people who had implants in their skulls were also not allowed. If someone had a brain injury that made them lose consciousness for than ten minutes they could not join either.

Before joining the study people were told what it was about and what they would have to do. They then had to agree to join by signing a paper. The study looked at how the people were before the treatment and then again one week and two months after the treatment. The study used machines to look at the brain and see how it was working.

The people in the study went to clinics and health centers to take part. The study was done in a way that neither the people, in the study nor the doctors knew who was getting the treatment and who was not. This was done to make sure the results were fair.

The study had a total of 76 people taking part. The number of people they wanted for the study was figured out from a study on non-invasive neuromodulation in people with early cognitive impairment. In that study 68 people finished all the tests. To account for some people quitting they added a few more to get to 76 people. They split these people into two groups with 38 people in each group. Even though they planned for 76 people the main results of the study are based on the 68 people who finished all the tests.

They used a computer to assign people to one of two groups. One group got intensity focused ultrasound and the other group got fake stimulation. They made sure the groups were balanced by using blocks of four and six people. A statistician who was not part of the study prepared envelopes that said which group each person would be in. This statistician did not know the people, in the study. Was not involved in treating them or testing them. The envelopes were. Numbered and they were only opened after each person finished all the beginning tests.

The people in the study and the ones who checked the results did not know which group they were in. The specialists who gave the tests to see how well people thought and the people who worked with the machine that took pictures of the brain when it was resting did not know what treatment people got. The person who used the ultrasound machine knew what setting it was on. They did not help with checking on people later or looking at the pictures of the brain or doing the statistics. We made sure that everything about the treatment was the same for all groups, like how it took, where people sat, where the device went what they heard and how they talked to the technician so that people would not think they were getting something special and do better because of it. The treatment procedures and all the other things were standardized for the assessments and the resting-state functional magnetic resonance imaging data to reduce bias.

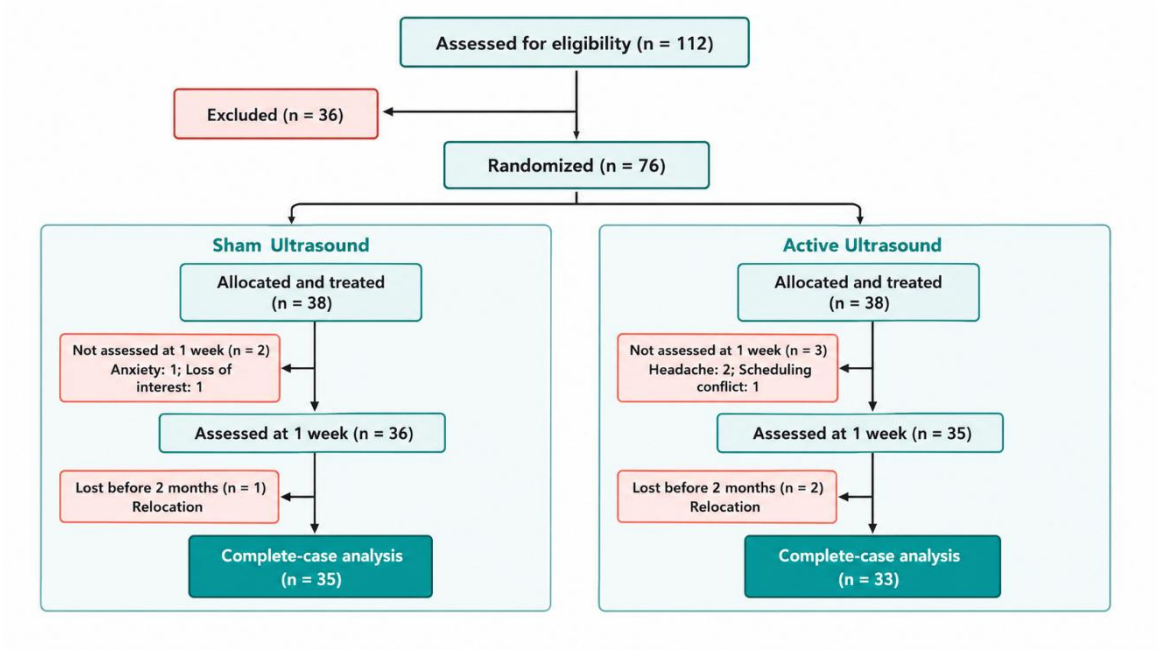

Figure 1CONSORT Flowchart

People in the group got a twenty minute session of low intensity focused ultrasound. This was aimed at the inferior frontal gyrus and the area next to it called the dorsolateral prefrontal cortex. The ultrasound was given at a frequency of 500 kHz. It was also given in pulses that repeated one hundred times per second. The machine was on for thirty percent of the time. The intensity of the ultrasound was point eight watts per centimeter.

The machine that gave the ultrasound was placed in the spot using a special picture of the persons brain. This picture was taken with a magnetic resonance imaging machine. The machine stayed in the spot the

whole time. The people getting the ultrasound were watched to see if they felt bad or had symptoms that would mean the procedure had to be stopped.

People in the group went through the same procedure. The machine was placed in the spot on their brain. Everything else was the same how long it lasted where the machine was the sounds it made and what they saw.. The sham group did not actually get any ultrasound. This was done so that the people in the study would not know if they were getting the thing or not. It also helped to make sure that the study was fair by making everything the same except, for the ultrasound.

The primary outcome was episodic memory one week after stimulation, assessed using the delayed-recall component of the Hopkins Verbal Learning Test–Revised. The principal treatment comparison examined the difference in delayed-recall performance between the active and sham groups after accounting for baseline performance through assessment of changes over time. Delayed recall was reassessed at two months to examine whether the observed response persisted during follow-up.

Secondary outcomes comprised attention, resting-state functional connectivity, and tolerability. Attention was measured using Trail Making Test Part B completion time, with a reduction in completion time indicating improved performance. Resting-state functional magnetic resonance imaging was used to assess functional connectivity between the stimulated prefrontal region and the bilateral hippocampi through seed-based correlation analysis. Cognitive and imaging outcomes were measured at baseline, one week, and two months after stimulation. Immediate tolerability was assessed after the procedure using a visual analogue scale for discomfort. Adverse symptoms, procedure-related withdrawal, and serious adverse events were documented throughout follow-up.

Data was analyzed using IBM SPSS Statistics version 26.0. Continuous variables were shown as standard deviation. Categorical variables were shown as count and percentage. Demographic and clinical details at the start were explained for the groups that were randomly chosen. The way continuous results were spread was checked using the Shapiro–Wilk test and looking at the results that were available.

The results that were shown included the 68 people who had results at the end. Changes in results from the start to one week and two months were checked inside each group using paired-samples t-tests. Comparisons between groups for results and the changes were done using independent-samples t-tests. Repeated-measures analysis of variance was used to look at the effects of time, treatment group and how time and group interacted across the start one week and two months. When there were comparisons the Bonferroni adjustment was used. The results were shown with differences, 95% confidence intervals, test statistics and two-sided p-values. A p-value less, than 0.05 was considered significant.

The association between change in fronto-hippocampal functional connectivity and change in delayed-recall performance from baseline to one week was explored using Pearson’s correlation coefficient. This analysis was considered exploratory because connectivity change and cognitive change could both be influenced by treatment assignment. Participant discomfort and adverse events were summarized by treatment group, and the occurrence of serious adverse events was documented descriptively.

The study protocol was approved by the institutional ethics review board of the collaborating university hospital. All participants provided written informed consent before any study-specific procedure. Participant information was handled confidentially, and study procedures were conducted in accordance with established ethical principles governing research involving human participants.

RESULTS

A total of one hundred and twelve people took part in this study to see if they could be in it. Of these people thirty-six were not able to be in the study. Seventy-six were split into two groups to get either real or fake treatments. The real treatment is called intensity focused ultrasound.

Five people did not finish the part of the study which lasted one week. Three of these people were in the group that got the treatment and two were in the group that got the fake treatment. The reasons they did not finish were because two people in the treatment group had headaches one person in the real treatment

group had a scheduling problem one person in the fake treatment group was anxious about the treatment and one person in the fake treatment group was not interested anymore.

Seventy-one people finished the part of the study. Then two people from the real treatment group and one person from the treatment group had to leave the study before it was two months old because they had to move away.

So when we looked at all the people who finished the study we had sixty-eight people. Thirty-three of these people were in the real treatment group and thirty-five were, in the treatment group.

In the end eighty-nine point five percent of people finished the two-month study. In the treatment group eighty-six point eight percent of people finished and in the fake treatment group ninety-two point one percent of people finished.

Table 1. Participant Recruitment, Allocation, and Follow-up

Study stage	Active ultrasound, n (%)	Sham ultrasound, n (%)	Total, n (%)
Assessed for eligibility	—	—	112 (100.0)
Excluded before randomization	—	—	36 (32.1)
Randomized	38 (50.0)	38 (50.0)	76 (67.9)
Withdrew before one-week assessment	3 (7.9)	2 (5.3)	5 (6.6)
Completed one-week assessment	35 (92.1)	36 (94.7)	71 (93.4)
Lost between one-week and two-month assessments	2 (5.3)	1 (2.6)	3 (3.9)
Completed two-month follow-up	33 (86.8)	35 (92.1)	68 (89.5)

Percentages for randomized and excluded participants were calculated using the 112 individuals assessed for eligibility. Group-specific withdrawal and completion percentages were calculated using the 38 participants randomized to each group. Overall post-randomization percentages were calculated using all 76 randomized participants. The reasons reported for withdrawal were headache and scheduling conflict in the active group, procedural anxiety and loss of interest in the sham group, and relocation during later follow-up.

Table 2. Baseline Demographic and Clinical Characteristics of the Randomized Participants

Characteristic	Active ultrasound (n = 38)	Sham ultrasound (n = 38)	Total (N = 76)
Age, years	67.9 ± 6.5	68.9 ± 6.9	68.4 ± 6.7
Female sex, n (%)	18 (47.4)	19 (50.0)	37 (48.7)
Education, years	12.3 ± 3.0	11.9 ± 3.4	12.1 ± 3.2
MoCA score	22.6 ± 1.7	22.2 ± 1.9	22.4 ± 1.8

Continuous variables are presented as mean ± standard deviation and categorical variables as n (%). Baseline significance tests were omitted because treatment allocation was randomized. MoCA, Montreal Cognitive Assessment.

Table 3. Episodic Memory Outcomes in Participants With Complete Follow-up Data

Time point or comparison	Active ultrasound (n = 33)	Sham ultrasound (n = 35)	Mean difference (95% CI)	p-value	Hedges g
Baseline HVLT-R delayed recall	6.2 ± 1.3	6.1 ± 1.4	0.1 (−0.5 to 0.7)	0.760	—
One-week HVLT-R delayed recall	8.9 ± 1.4	7.1 ± 1.6	1.8 (1.1 to 2.5)	<0.001	1.18
Two-month HVLT-R delayed recall	8.2 ± 1.5	7.0 ± 1.7	1.2 (0.4 to 2.0)	0.003	0.74
Baseline to one-week change	+2.7	+1.0	—	—	—

Values are mean ± standard deviation unless otherwise indicated. Positive change indicates improvement in delayed recall. Hedges g was calculated from the reported group means, standard deviations, and sample sizes; positive values favour active ultrasound. The reported 95% confidence interval for the sham-group within-group change excluded zero but was accompanied by a non-significant p-value of 0.08; because these statistics were internally incompatible, that within-group confidence interval and p-value were not reproduced. HVLT-R, Hopkins Verbal Learning Test–Revised; CI, confidence interval.

Table 4. Secondary Outcomes at One Week in Participants With Complete Follow-up Data

Outcome	Active ultrasound (n = 33)	Sham ultrasound (n = 35)	Group differences (95% CI)	p-value	Hedges g
TMT-B change, seconds	−18.4 ± 12.1	−4.2 ± 14.3	−14.2 (−20.8 to −7.6)	<0.001	−1.06
Frontohippocampal connectivity change	+0.21 ± 0.08	+0.03 ± 0.07	0.18 (0.14 to 0.22)	<0.001	2.37

Outcome	Active ultrasound (n = 33)	Sham ultrasound (n = 35)	Group differences (95% CI)	p-value	Hedges g
Post-session discomfort, VAS score	1.2 ± 0.9	0.9 ± 0.8	0.3 (−0.1 to 0.7)	0.140	0.35

Values are mean ± standard deviation. A negative TMT-B change indicates a reduction in completion time and therefore improved performance. Positive connectivity change indicates increased functional connectivity between the stimulated prefrontal region and the bilateral hippocampi. Hedges g was calculated from the reported summary values. For TMT-B, a negative effect size favours active ultrasound because lower completion times indicate better performance. The scale and transformation applied to the functional-connectivity measure were not specified in the available manuscript. TMT-B, Trail Making Test Part B; VAS, visual analogue scale; CI, confidence interval.

Table 5. Reported Inferential and Safety Outcomes

Outcome	Estimate	Statistical result
Time-by-group interaction for HVLT-R delayed recall	$F(2,132) = 14.6$	$p < 0.001$
Correlation between connectivity change and delayed-recall change	$r = 0.52$	$p < 0.001$
Serious adverse events	0	—
Active-group withdrawals attributed to headache	2 of 38 (5.3%)	—
Sham-group withdrawal attributed to procedural anxiety	1 of 38 (2.6%)	—

The analysis of the people in the study and how thingsre related to each other was done for the 68 people who had all the necessary information. The correlation between things should be seen as something to explore further because the treatment people got might have changed the results of both things being measured.

The people in the study were on average 68.4 years old give or take 6.7 years and 37 of them which is 48.7 percent were women. On average the people in the study had 12.1 years of education give or take 3.2 years. They scored 22.4 give or take 1.8 on the Montreal Cognitive Assessment test at the start. The characteristics of the people in the study like age and sex and education were pretty similar between the groups and there was not a big difference in things, like age or sex or education or how well people did on cognitive tests.

The Hopkins Verbal Learning Test Revised scores were much the same for the active group and the sham group at the beginning. The active group had a score of 6.2. The sham group had a score of 6.1.

One week later the active group had a score of 8.9. The sham group had a score of 7.1. The difference between the two groups was 1.8 points. This is a difference.

The active group got better by 2.7 points from the beginning to one week. The sham group only got better by 1.0 point. There was a problem with the numbers for the sham group so we did not use them.

After two months the active group still had Hopkins Verbal Learning Test Revised scores than the sham group. The active group had a score of 8.2. The sham group had a score of 7.0. The difference between the two groups was 1.2 points.

The difference between the groups was not as big after two months as it was after one week.. The Hopkins Verbal Learning Test Revised scores were still different between the groups.

We looked at how the Hopkins Verbal Learning Test Revised scores changed over time for the group and the sham group. We found that the change was different, for the two groups. This means that the active group and the sham group did not get better or worse in the way.

The people in the study were different after one week when it came to attention. The time it took to complete the Trail Making Test Part B was less for the group it went down by 18.4 seconds on average but for the sham group it only went down by 4.2 seconds. The difference between the two groups was 14.2 seconds, which's a big deal. This is news for the active group because it means they did better on the test.

The connection between the hippocampus parts of the brain was stronger for the active group it went up by 0.21 but for the sham group it only went up by 0.03. The difference between the two groups was 0.18, which's pretty big. This is interesting. We need to learn more about what it means and how we measured it.

When we looked at all the people in the study we saw that the change in how different parts of the brain were connected was related to how well they could remember things after one week. The connection between these two things was moderate which means it is worth looking into. However we need to be careful because the people who got the treatment might have gotten better at both things just because of the treatment. We would need to do analysis to see if the change in brain connection really is related to the change, in memory or if it is just because of the treatment the active group received.

The discomfort people felt after the session was not very high in either group. The active group had a score of 1.2 on the pain scale and the sham group had an average score of 0.9. The difference between the two groups was 0.3 points, which is not a big deal. We did all the math. It is not statistically significant. This means that the difference could have happened by chance. No one had any problems. However two people in the group stopped because they got headaches and one person in the sham group stopped because they were too nervous, about the procedure. We should remember these things when we think about the safety of the session. The active group and the sham group both need to be considered when we look at how safe the session's.

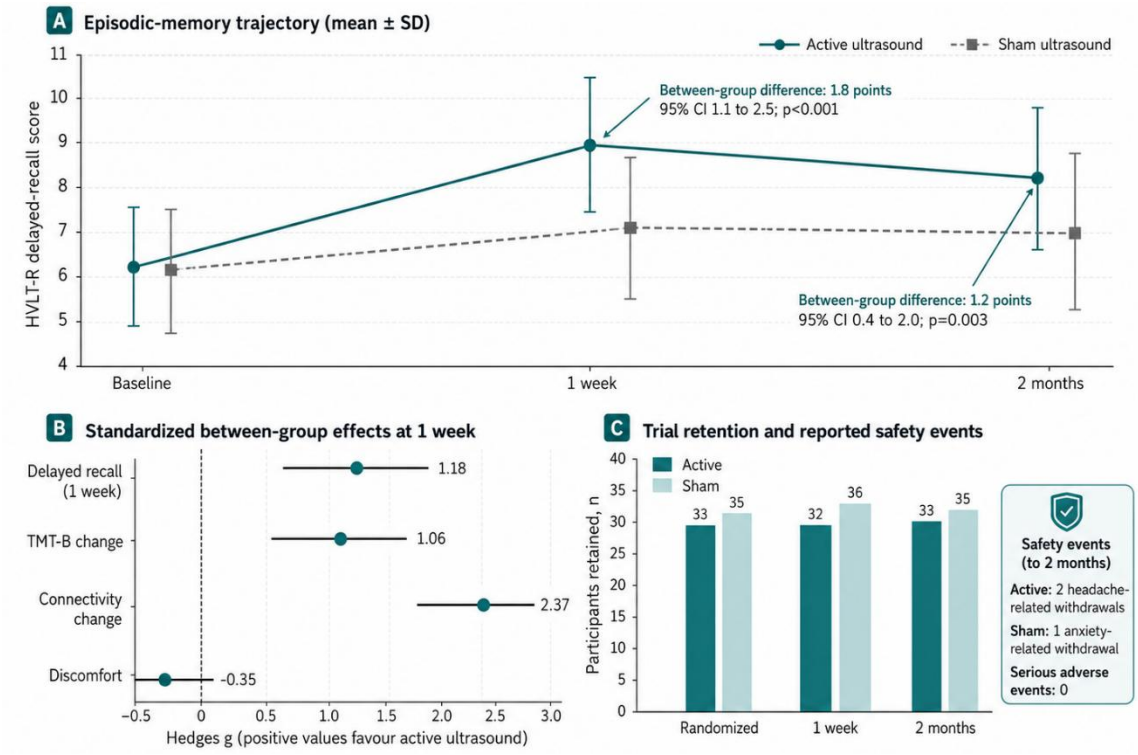

Figure1. Panel A presents mean Hopkins Verbal Learning Test–Revised delayed-recall scores with standard-deviation error bars at baseline, one week, and two months. Panel B presents standardized between-group effects at one week as Hedges g with approximate 95% confidence intervals derived from the reported aggregate means, standard deviations, and sample sizes; positive values favour active ultrasound after aligning outcome direction. Panel C presents participant retention from randomization to two-month follow-up and the principal reported safety events. The active group exceeded the sham group by 1.8 delayed-recall points at one week and 1.2 points at two months. Large standardized effects favoured active stimulation for delayed recall (g = 1.18) and TMT-B improvement (g = 1.06), while the reported connectivity difference produced a very large standardized effect (g = 2.37). Discomfort showed no treatment advantage, and 68 of 76 randomized participants completed two-month follow-up.

DISCUSSION

This study looked at people with problems with their brain function. It found that people who got a kind of ultrasound treatment did better on memory and attention tests than those who got a fake treatment. The people who got the treatment were able to remember things better one week and two months after the treatment. They were also faster at doing tasks and their brain worked better in some areas.

These results suggest that using ultrasound to help the brain might be a way to improve memory and how the brain works. However we need to be careful when looking at these results because not everyone in the study was followed for the time and we are not sure if the improvements are really important.

The fact that peoples memory got better is similar to what we have seen before with kinds of treatments that do not involve surgery. We know that using machines to stimulate the brain can help with memory. This study shows that ultrasound can also help with memory, which's a new and interesting idea. We need to do research to see if ultrasound is a good alternative to other treatments.

The ultrasound treatment is different, from kinds of treatments because it uses sound waves instead of electricity or magnets (15). We cannot compare the treatments directly from this study but the results are promising and suggest that we should keep looking into using ultrasound to help the brain.

The way our brain responds may be connected to how the front and hippocampus parts of the brain work. The right inferior frontal gyrus and the areas around it help us pay attention remember things. Control our memories. If these parts of the brain talk to each other more it might affect how we learn and remember words. We found a connection between how these parts of the brain talk to each other and how well people remembered things after a while. This connection gives us an idea about what might be happening. It does not prove that it is the reason for the improvement in memory.

We need to do analysis to see if the change in how these parts of the brain talk to each other is really the reason for the improvement in memory.

Other studies have shown that we can change how the brain works and how we remember things without cutting into the brain (16). The results are different depending on how we do it and who the people are. Some studies have also shown that using low-intensity ultrasound can affect how the brain cells work and how they talk to each other.

Brain-derived neurotrophic factor is important for how the brain cells adapt and recover. We did not measure it in this study. So we can not say for sure how it works. It is possible.

We should be careful when we interpret the results about how the parts of the brain talk, to each other because we need to make sure we did the analysis correctly.

The decrease in the time it took to complete Trail Making Test Part B suggests that the response wasn't about delayed verbal recall. It might have involved attention or executive processes. This is important because mild neurocognitive disorder often affects connected areas of thinking. However when neuropsychological tests are done again and again people might get better just because they've done the test before. This is called a practice effect. The paper didn't say if they used versions of the test or methods to stop people from learning the answers. Even though the study had a control, which makes it less likely that just practice explains the results there could still be other factors like people guessing what the treatment was or not being fully blinded. Future studies should check if people guessed their group and use test forms when possible.

The big effects found for memory, attention and functional connectivity should be looked at carefully. Effects can seem big if the group doesn't have variation. Also the way they measured connectivity wasn't clear enough to show how big the effect really is in life. Just because something is statistically significant doesn't mean it helps people in their lives. The study didn't look at things like how people can do daily tasks how happy they are with the treatment how they feel about their life how much stress it puts on caregivers how well they take their medicine or if they get worse and develop major neurocognitive disorder. So it's still not clear if the brain changes they found actually made a difference, in how people live.

The memory difference between the groups was still noticeable after two months, which's a good thing. However the difference was not as big as it was after one week. This could mean that the effect of the treatment is starting to wear off or that peoples results are more varied after a time. The study was not meant to figure out how the benefits last or if people need to keep getting the treatment.

Maybe doing the treatment many times will have an effect that lasts longer.. It is also possible that doing it many times could cause more bad side effects or make the treatment less safe. So studies should look at how the treatment is given how strong it is, what it targets and how often it is done before doing bigger studies to confirm the results.

People did not report discomfort right away and it was the same for both groups. No one had any bad side effects.. Two people in the group that got the real treatment stopped because they got headaches and one person in the group that got the fake treatment stopped because they were too anxious. This shows that we should not just look at how discomfort people feel on average to know if the treatment is safe.

Larger studies should keep track of side effects including how bad they are, how long they last if they are related to the treatment when they happen and what happens to the people who get them. They should also have rules for stopping the study if something bad happens and should watch people for a time to make sure they are safe. The group of people, in this study was too small to find any bad side effects that might happen to the brain or ears.

The study had a sham-controlled design. It had concealed allocation. It had blinded outcome assessment (21). It used neuronavigation-informed targeting. It included neuroimaging outcomes. These were strengths. Looking at outcomes at one week and two months gave information about the short-term response. Including connectivity along with behavioral outcomes let us explore if cognitive changes happened with network-level changes.

Several limitations make it hard to understand and apply the findings. The study had a sample from one city. Eight people who were randomized were not in the analysis. The original plan to include everyone was not clear from the results. There was no way to handle missing data. The ultrasound system, how it focused, how it was calibrated how much energy went into the brain the coordinates used, how it was connected and the fake treatment were not fully described. The way images were. Processed was also not good enough. They did not check if the blinding worked. The analysis looked at outcomes but did not explain how to handle that. The diagnosis of neurocognitive disorder did not use biomarkers so we can't say for sure about Alzheimers or other brain problems. Also the change, in HVLT-R was not compared to a way to know if it was important.

Further research must start with replicated studies that are registered in advance. These studies should use defined methods for sound and imaging. Future studies need to include all participants who were randomly chosen in a planned analysis. They should use models that adjust for starting conditions and look at effects. They should share corrected imaging results. Check both how the brain functions and how the mind works. Studies that find the amount of treatment should compare different targets, one time versus multiple times and how often to continue. Grouping people based on how severe their thinking problemsre what might be causing them what their brain scans show, their genes and what medicines they take can help find who will benefit most. These steps are important before intensity focused ultrasound can be used as a regular treatment, for early thinking problems.

CONCLUSION

A single session of low-intensity focused ultrasound that targeted the right inferior frontal region and the nearby dorsolateral prefrontal region showed better results in delayed verbal recall and attentional performance compared to sham stimulation in adults with mild neurocognitive disorder. The differences between the groups were still visible after two months. Active stimulation also led to frontohippocampal functional connectivity but this finding was not the main focus of the study. Because the sample size was small the intervention and imaging details were not fully documented the significance of the results is not clear and the analysis was not complete the findings suggest that carefully designed studies are needed. However these results do not prove that the treatment is effective, in a setting.

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