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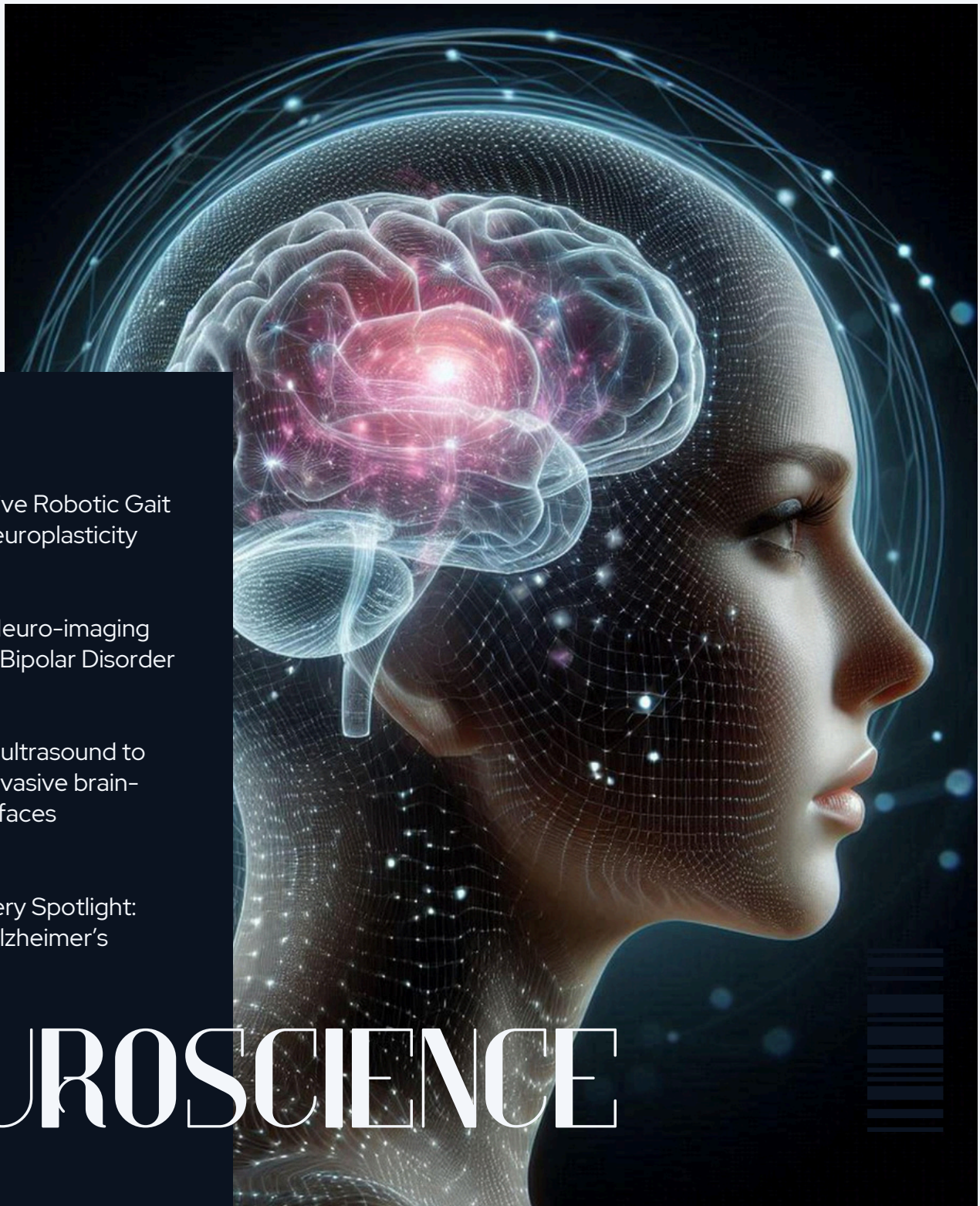

Active VS Passive Robotic Gait Training and Neuroplasticity

Genomic and Neuro-imaging Approaches to Bipolar Disorder

Using Focused ultrasound to improve non-invasive brain-computer interfaces

Recent Discovery Spotlight: Brain Fat and Alzheimer's

NEUROSCIENCE

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Citations for the articles referenced, listed in the order by which they appear in the journal publication.

Yu, Y., Huang, W., Tuerxun, H., Zheng, Y., Su, L., Li, X., & Dou, Z. (2025). Enhanced neuroplasticity and gait recovery in stroke patients: A comparative analysis of active and passive robotic training modes. BMC Neurology, 25, 239. https://doi.org/10.1186/s12883-025-04226-0

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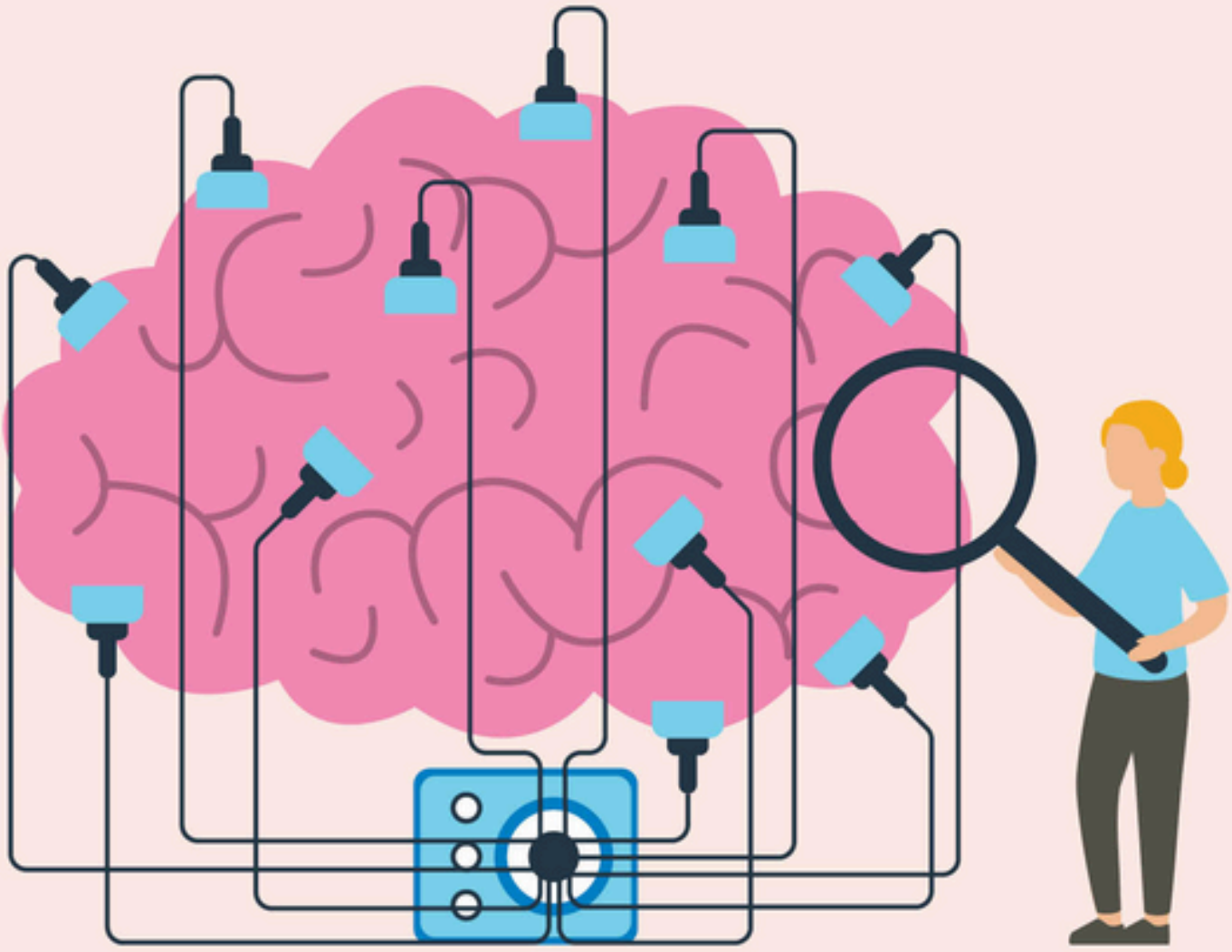
IN THIS ISSUE

ACTIVE VS PASSIVE ROBOTIC GAIT TRAINING AND NEUROPLASTICITY

Not all steps are equal: Comparing active and passive robotic walking to uncover the neural signatures of true recovery.



Original Article By: Yu, Y., Huang, W., Tuerxun, Zheng, H.Y., Su, L., Li, X., Dou, Z.
Digest by: Daniella Ling

Every year, millions of stroke survivors are left struggling with basic motor tasks, especially walking. The loss of lower limb function not only undermines independence, but also contributes to long-term disability, social isolation, and a decreased quality of life. In recent years, robotic technologies have emerged as promising tools in rehabilitation, offering consistent and high-repetition training.

This study takes a closer look at the evaluation on how movement alone can rewire the brain or whether recovery is rooted in active participation by comparing two robotic rehabilitation strategies: active-assisted gait training, where the robot supports a patient's efforts to move, and passive training, where the robot moves the limbs with no volitional input from the patient. The central aim is to determine which approach is more effective in restoring walking functions after strokes, and more importantly, which promotes greater neuroplasticity, the brain's ability to reorganize and heal itself.

By combining behavioural assessments with trans-cranial magnetic stimulations (TMS) and functional near-infrared spectroscopy (fNIRS), the study explores how different types of movement training engage the brain and facilitate motor recovery. The study provide insight into why effort matters in rehabilitation, and how technology can be used not just to support our bodies, but in retraining the brain.

Methods

To investigate the impact of active versus passive robotic gait training, the researchers conducted a randomized controlled trial of 45 stroke patients with lower limb motor impairment. Participants were divided into 3 groups: an active-assisted group, a passive therapy group, and a control group receiving standard rehabilitation without robotic assistance.

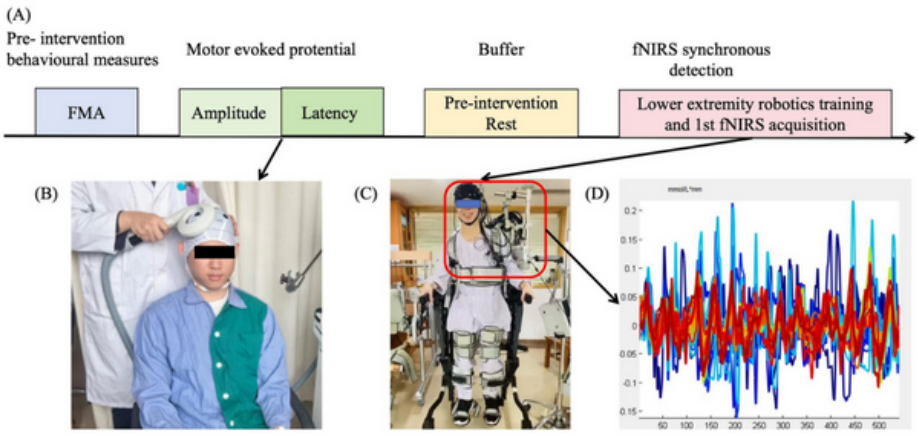


Figure 1: The experimental setup. fNIRS technology was used to detect the real-time hemodynamic signals of patients during intervention. A: Overall experimental process; B: MEP acquistion; C: First completed lower extremity robotics training; D: Collecting fNIRS data

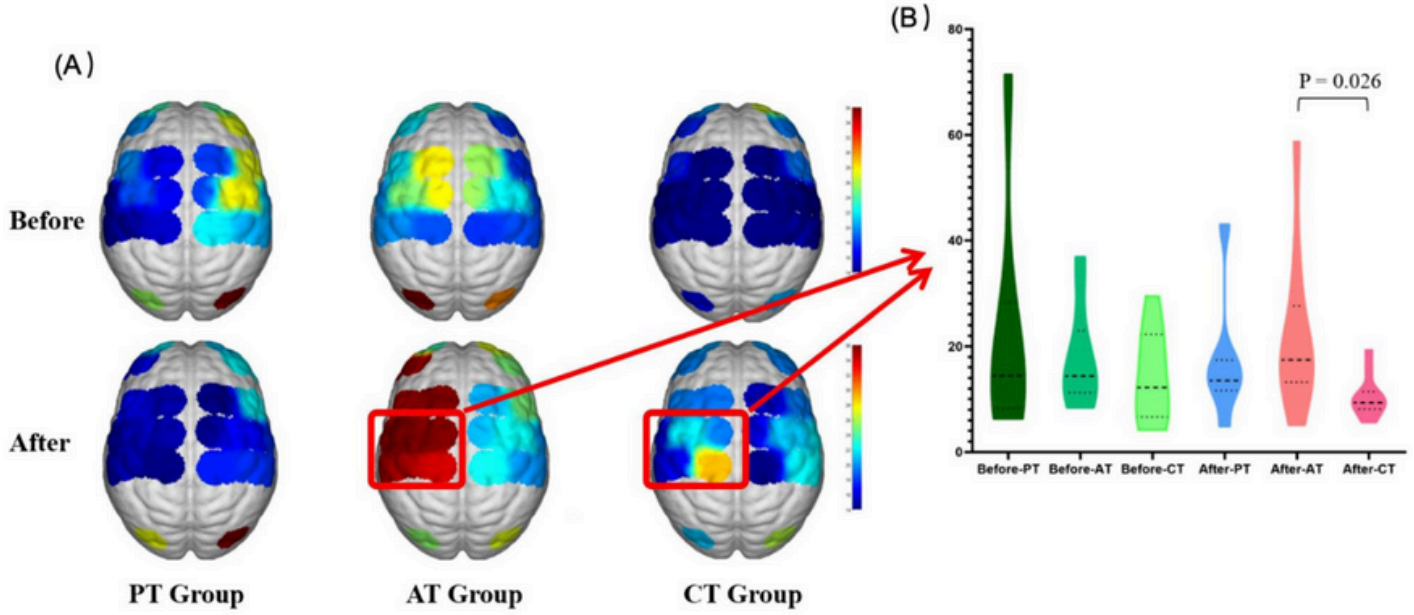
The active-assisted group performed walking exercises with a robotic device that provided partial support, encouraging voluntary movement from the patients themselves. The passive group's limbs however, were moved entirely by the robot. Each intervention lasted for 10 sessions over two weeks, complemented by standard physical therapy.

To assess recovery, the study combined clinical motor function tests with neurophysiological measures of brain excitability (using TMS) and brain activity monitoring (using fNIRS) during walking tasks. This multimodal approach allowed the researchers to link behavioural improvements with underlying changes in brain function.

Findings and Interpretations

To investigate the impact of active versus passive robotic gait training, the researchers conducted a randomized controlled trial of 45 stroke patients with lower limb motor impairment. Participants were divided into 3 groups: an active-assisted group, a passive therapy group, and a control group receiving standard rehabilitation without robotic assistance.

Clinically, motor function was measured using the Fugl-Meyer Assessment for Lower Extremity (FMA-LE). Patients in the active-assisted group achieved higher post-treatment FMA scores than both the passive and control groups, suggesting more meaningful improvements in gait-related function. While the passive group did show some improvement, these changes were ultimately less pronounced, likely due to the reduced role of patient engagement in movement execution.



Neurophysiologically, Motor Evoked Patients (MEPs), a reliable indicator of corticospinal excitability, were recorded using TMS. A significant reduction in MEP latency and increase in amplitude in the active-assisted group indicated greater reactivation of corticospinal pathways. These changes reflect enhanced corticomotor excitability, a marker of functional neuroplasticity associated with voluntary motor recovery. Perhaps most notably, functional brain activation was assessed using fNIRS, which revealed that only the active-assisted group demonstrated statistically significant increases in brain activation, particularly in the ipsilateral primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC). These regions are essential for voluntary motor control, attention, and planning, supporting the notion that active training engages more widespread and functionally relevant networks than passive movement.

Neuroscientific Implications

The results of the study reinforce several key principles of neuroplasticity. First, volitional effort and goal-directed movement are critical for driving changes in the motor cortex. Active-assisted training encourages patients to attempt movement, which recruits motor planning areas such as the premotor cortex and supplementary motor areas, even if the physical movement itself is supported by a robot. This effort-driven activation is thought to trigger Hebbian mechanisms, cells that 'fire wire together', strengthening synaptic connections within the damaged motor network.

Second, sensorimotor feedback plays an essential role in reinforcing these neural changes. During active-assisted walking, patients receive continuous proprioceptive and visual input in response to their efforts, allowing the brain to iteratively adjust and optimize motor commands. This feedback loop is largely absent in passive training, where movement is externally imposed and does not depend on the patient's intention or control.

Third, the study underscores how task-specific and repetitive practice, when combined with cognitive engagement, leads to broader changes beyond the motor cortex. The increased activation in prefrontal areas suggests that active-assisted training also enhances cognitive-motor integration, which is vital for functional recovery in real-world environments.

Clinical Implications and Applications

From a rehabilitation standpoint, the study provides compelling evidence for incorporating active-assisted robotic training into stroke recovery programs, especially for patients who have retained some degree of voluntary motor control. Unlike passive training, which may be appropriate only in the most severely impaired individuals, active-assisted training appears to offer a dual benefit: it strengthens muscle control and stimulates meaningful brain reorganization.

The findings also emphasize the need to move away from purely mechanical repetition in rehabilitation. Technologies that enable patient-driven movement, such as robotic exoskeletons with adjustable assistance, Brain-Computer Interfaces (BCIs) or virtual reality-integrated feedback, may lead to more robust outcomes by fostering neuroplasticity through volitional control and real-time feedback. However, it is important to consider that while promising, the study's small sample size limits the generalizability of the findings. Moreover, only short-term outcomes were assessed, leaving open the question of whether the gains observed are sustained over time or lead to long-term independence in mobility. Additionally, the unequal total therapy duration across groups may have introduced a confounding variable, as the control group received less total movement-based training than the robot-assisted groups.

Future Directions

In conclusion, the study supports the idea that the specific method of rehabilitation delivery matters just as much as how often it is provided. Active engagement, rather than passive repetition, drives the neurobiological changes necessary for meaningful recovery after strokes. Active-assisted robotic training, by requiring effort, supporting volitional control, and amplifying feedback, facilitates greater motor recovery and brain reorganization than passive methods.

Future research should seek to replicate these findings in larger, multi-center trials, and assess the long-term sustainability of neuroplastic changes. There is also a growing need to evaluate the cost-effectiveness of robotic systems in clinical practice, especially in low-resource settings. Additionally, combining active robotic training with other neuromodulatory approaches, such as non-invasive brain stimulation or cognitive motor tasks, may further enhance the potential for recovery.

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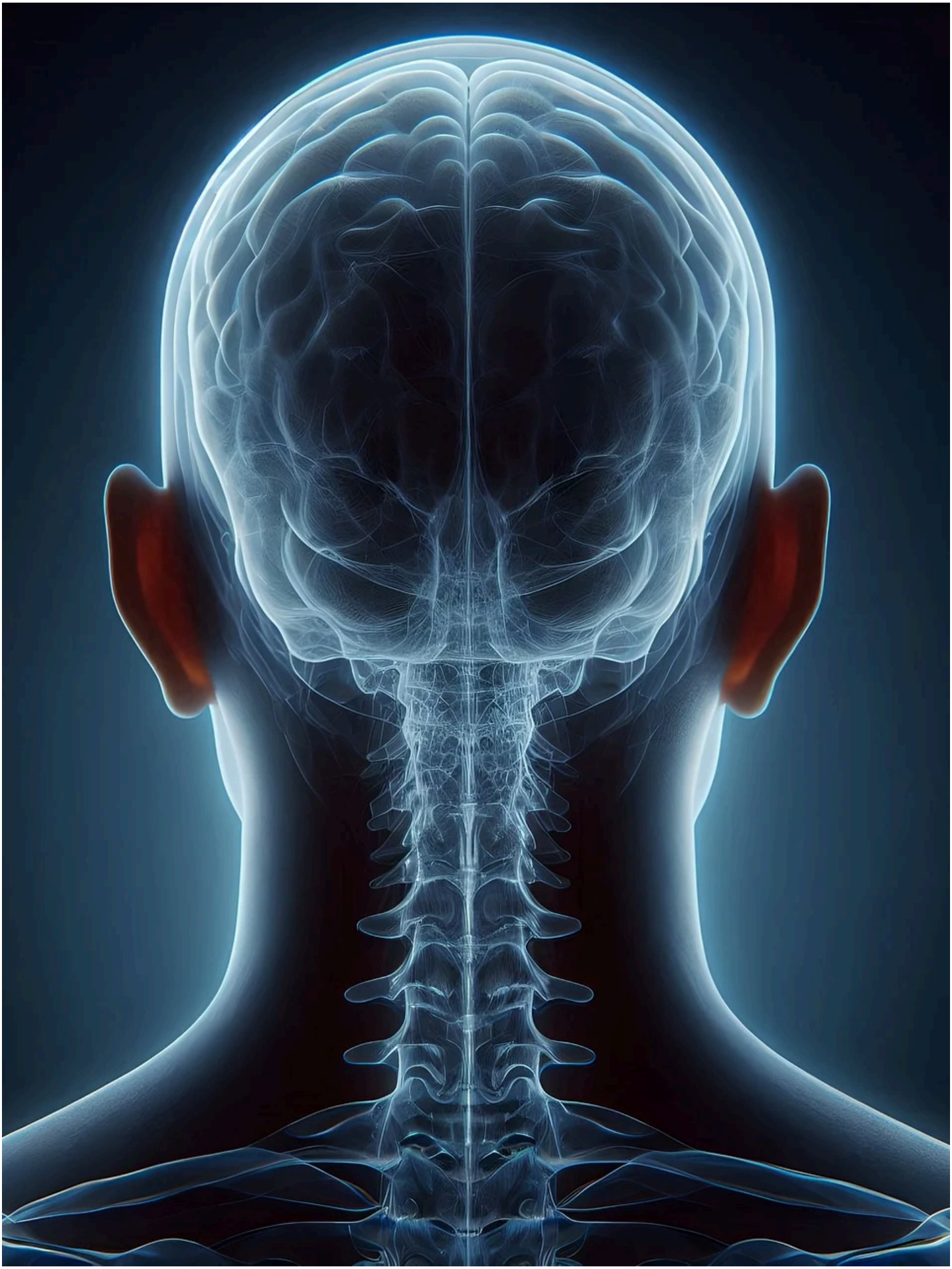
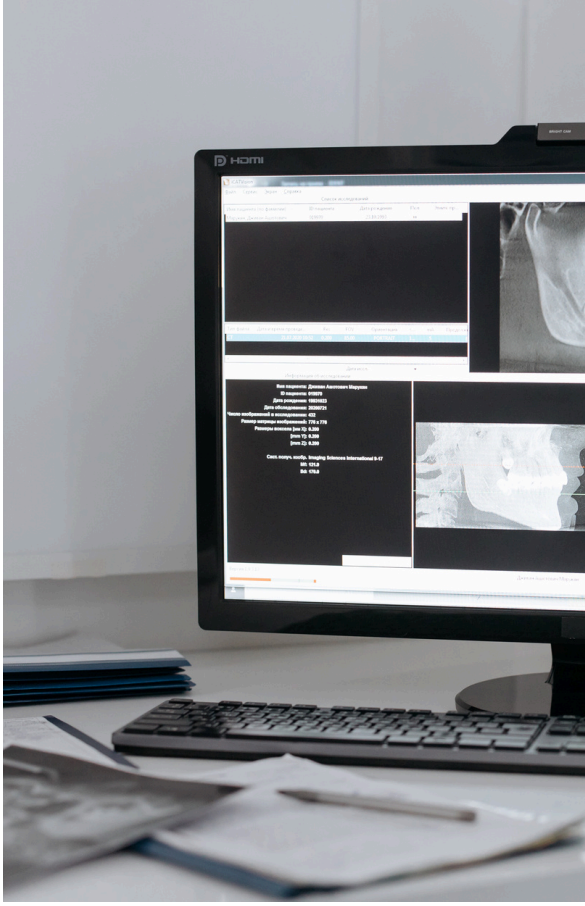


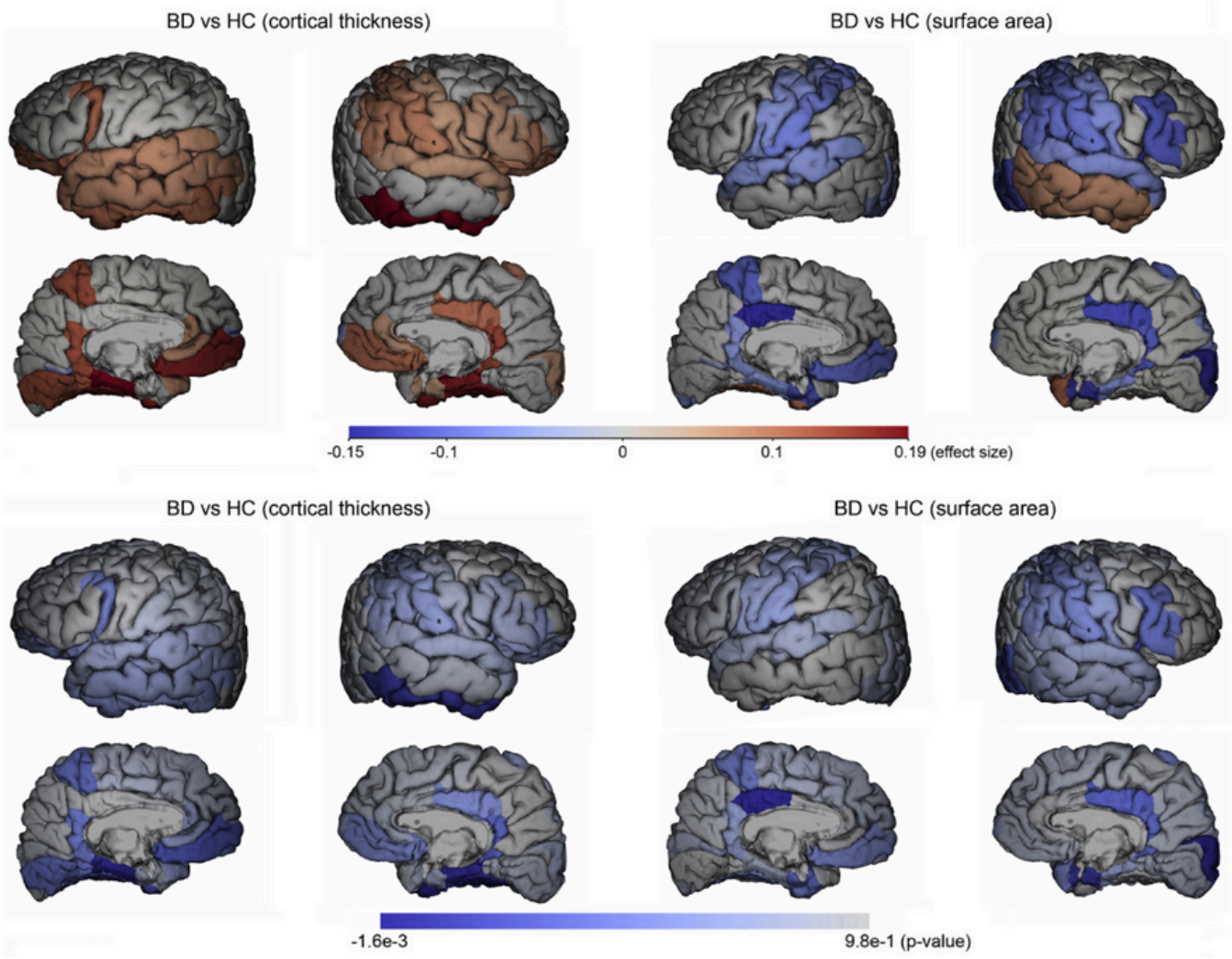
GENOMIC AND NEURO-IMAGING APPROACHES TO BIPOLAR DISORDER



ORIGINAL ARTICLE BY: KOHSHOUR, M.O., PAPIOL, S., CHING, C.R.K., SCHULZE, T.G.
DIGEST BY: JESSICA LU

Bipolar disorder is a chronic, severe and highly heritable mental health condition characterized by recurrent states of mania and depression. Current models suggest that bipolar disorder is a heterogeneous and multifactorial disease. The illness varies widely between individuals and is caused by a combination of factors (genetic, environmental, and epigenetic); individuals with bipolar disorder may have varying types and severities of symptoms, display different patterns of illness, and respond differently to treatment.

Genome-wide association studies (GWAS) in bipolar disorder use large case-control designs to scan the genome for single nucleotide polymorphisms (SNPs) associated with the condition. These studies compare the genetic profiles of individuals with bipolar disorder to those without. Since the first GWAS in 2007, successive studies have identified numerous SNPs associated with bipolar disorder, often within genes involved in brain function, synaptic transmission, and ion channel regulation—such as ANK3, CACNA1C, ODZ4, TRANK1, and FADS2. GWAS have shown that bipolar disorder is highly polygenic, meaning that risk is influenced by many genetic variants, each contributing a small effect.



Polygenic Risk Scores (PRS) summarize an individual's genetic risk by combining these variants, weighted by their effect sizes from GWAS, and have emerged as valuable tools in psychiatric genetics. PRS can predict overall genetic vulnerability more efficiently than analyzing individual variants, utilizing smaller sample sizes and enabling analyses of risk, treatment response, and cross-disorder genetic overlap. PRS have shown genetic overlap between bipolar disorder, schizophrenia and major depression.

Magnetic Resonance Imaging (MRI) is a widely used tool for studying human brain structure and function. Over the past several decades, researchers have found association between bipolar disorder and alterations in the neuroanatomical structure of the brain. Neuroimaging studies show a pattern of reduced cortical thickness in patients with bipolar disorder, and lower volumes in subcortical structures, including the thalamus, amygdala, and hippocampus.

Genome-wide association studies (GWAS) have identified over 120 common genetic variants linked to the disorder. Advances in sequencing technologies, such as whole-exome and whole-genome sequencing, have enabled the discovery of rare genetic variants with potentially larger effects. Polygenic risk scores (PRS) now offer a way to estimate individual genetic risk. Brain imaging studies, particularly using MRI, are also helping to connect genetic findings with structural and functional brain changes. Overall, large-scale genetic studies, combined with imaging and improved statistical methods, are steadily uncovering the complex biological pathways underlying bipolar disorder.

USING FOCUSED ULTRASOUND TO IMPROVE NON-INVASIVE BRAIN-COMPUTER INTERFACES

Original Article by: He, B., Yu, L., Nguyen, C. M., Yang, Y., Zhang, S., Yang, Y., & Deng, Z. D.

Digest by: Nathan Zhuang

Brain-computer interfaces (BCIs) allow people to interact with technology using only their brain signals. While implantable BCIs can produce clear signals, they involve invasive surgeries. In contrast, non-invasive BCIs are safer and more scalable but often suffer from poor signal quality due to the noise and interference that come with reading brain activity from outside the skull. To address this limitation, a recent experiment by He et al. (2024) explored whether transcranial focused ultrasound stimulation (tFUS) could enhance the performance of EEG-based non-invasive BCIs by improving the brain's attention signals and making user intent easier to detect.

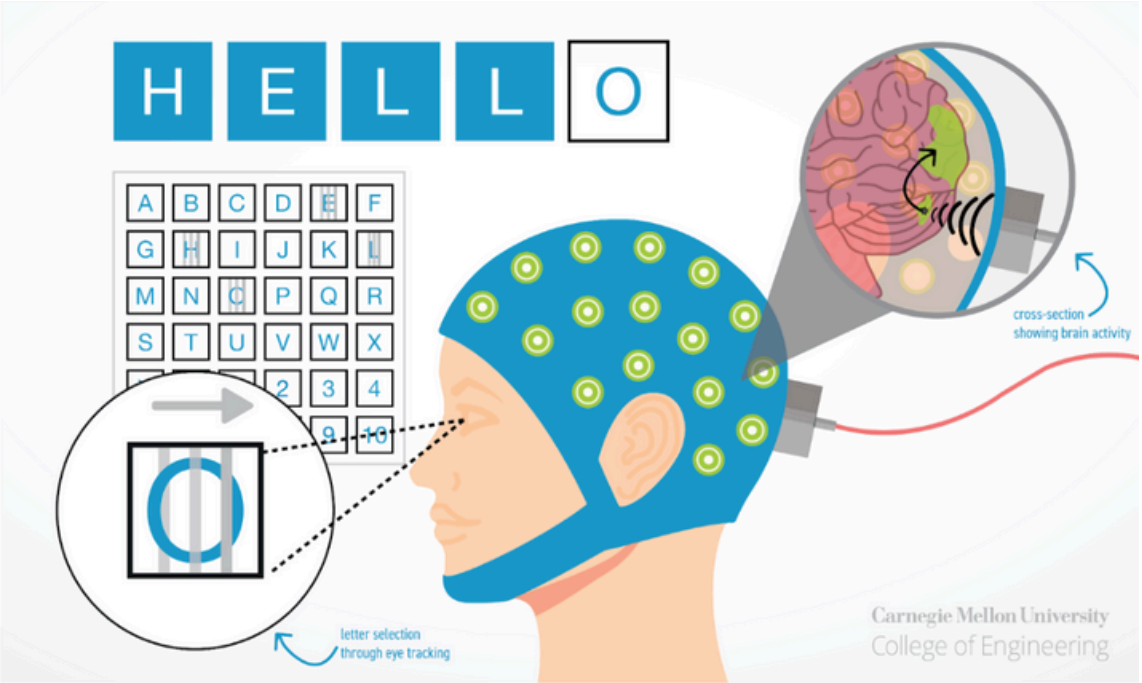


Figure 1: Model of how non-invasive brain-computer interfaces work.

In their experiment, the researchers worked with 25 healthy participants who used a non-invasive BCI speller to type characters on a screen by focusing on rows of flashing letters. While the participants wore EEG caps to record brain signals, the researchers applied low-intensity tFUS to the V5 region of the brain, which is associated with visual motion processing. This was done to enhance attention to visual stimuli, a critical component in improving the performance of speller-type BCIs. Each participant completed multiple sessions, one with tFUS targeting V5 and others with either sham stimulation or no stimulation at all (He et al., 2024).

The results clearly showed that targeted ultrasound stimulation significantly improved BCI performance. When V5 was stimulated with tFUS, participants made fewer errors and showed faster response times compared to all control conditions. EEG data also revealed increased attention-related brain activity in the V5 area, supporting the idea that tFUS helped sharpen the participants visual focus. This not only improved signal clarity but also helped the BCI interpret the participants' intent more accurately. Essentially, the ultrasound gave the brain a boost, improving how clearly the BCI could understand what the user wanted to select (He et al., 2024).

This study is particularly important because it shows that a bidirectional non-invasive BCI is possible. Traditional BCIs only read signals from the brain, but this system also influences brain activity in real time by using ultrasound. That's a major step forward. It also offers a solution to one of the biggest problems with EEG-based systems: the low signal-to-noise ratio caused by recording through the scalp and skull. By stimulating attention networks in the brain, the researchers found a way to make neural signals more consistent and easier for the system to decode, even without any implants (He et al., 2024).

The study used a rigorous experimental design, comparing four distinct conditions: tFUS targeting the geometric center of V5 (tFUS-GC), a non-modulated baseline condition without stimulation, a decoupled-sham condition with tFUS applied off-target to control for possible auditory or placebo effects, and a spatial control targeting the periphery of V5 near the inferior temporal gyrus (tFUS-GP). This cross-over design helped isolate whether the observed improvements were truly due to precise ultrasound targeting or other external factors (He et al., 2024).

To measure effectiveness, the team calculated the Euclidean error the spatial distance between the intended target letter and the letter selected using the BCI system. The results were statistically significant. The mean Euclidean error for the tFUS-GC condition was 13.3 18.4%, which was significantly lower than in the non-modulated (15.5 18.7%; $p < 0.01$), decoupled-sham (16.9 20.8%; $p < 0.05$), and tFUS-GP (17.0 18.2%; $p < 0.001$) conditions. These findings were supported by a linear mixed-effects model and ANOVA analysis. Effect sizes measured with Cohen's showed moderate effects, and Bayes factor analysis revealed a strong overall effect of condition on error rate (median BF = 14.0), confirming the reliability of the findings (He et al., 2024).

The researchers also analyzed how tFUS affected EEG signals. They found significant spatiotemporal differences in EEG topography across the four conditions, particularly between 160 to 230 milliseconds after stimulus onset in the occipital region, which is consistent with known timing of visual attention processing. The N200 component, a brain wave associated with visual attention and decision-making, showed increased power in participants receiving tFUS-GC. Source localization via EEG imaging revealed that this increase was specific to the V5 region, suggesting that the stimulation directly amplified attention-related processing at the source level (He et al., 2024).

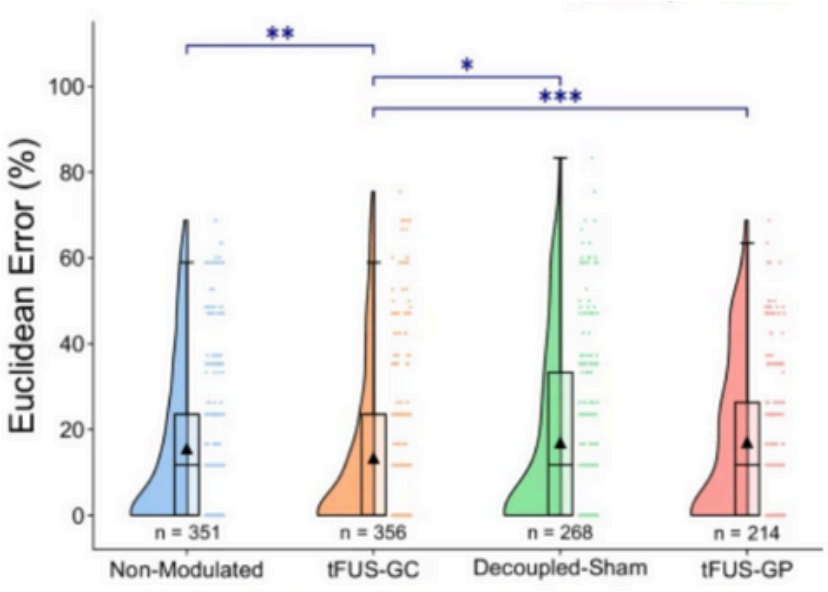


Figure 2: Graphs Taken from the original research paper, highlighting the significant lower amounts of Euclidean Error when under tFUS-GP in patients.

What this means is that not only did participants perform better behaviourally, but their brains were measurably more engaged in the task during stimulation. The ability to non-invasively target a specific brain area and see both improved behaviour and stronger neural engagement is a powerful validation of tFUS as a complementary technique for EEG-based BCIs. Importantly, there were no significant performance differences between the non-modulated, sham, and off-target stimulation conditions meaning that the precise location of stimulation really mattered, and it wasn't just a general arousal or placebo effect driving the results.

Despite the success of this study, several limitations remain. All participants were healthy individuals, so it's unclear how well this technique would work in people who actually rely on BCIs, such as patients with paralysis or severe motor disorders. Also, the study only tested one target regionV5and one type of task focused on visual attention. Applications involving motor control, language, or emotional regulation might require stimulation of other brain areas. Furthermore, the study only tested acute effects within a single session. Longer-term studies are needed to see whether repeated tFUS use remains safe and effective, and whether the brain adapts to the stimulation over time (He et al., 2024).

Moving forward, this technique could be applied in many new ways. Researchers plan to adapt this bidirectional BCI for use in clinical populations, potentially helping non-verbal individuals communicate more clearly or helping paralyzed users regain control over digital devices. There is also interest in stimulating other regions of the brain to support different tasks, like limb control or even mood regulation. Long-term studies will be needed to ensure that repeated tFUS use is both safe and effective, especially since the brain may change in response to chronic stimulation. But even at this early stage, this experiment shows a path forward for non-invasive BCIs that is smarter, faster, and far more precise than what current systems offer.

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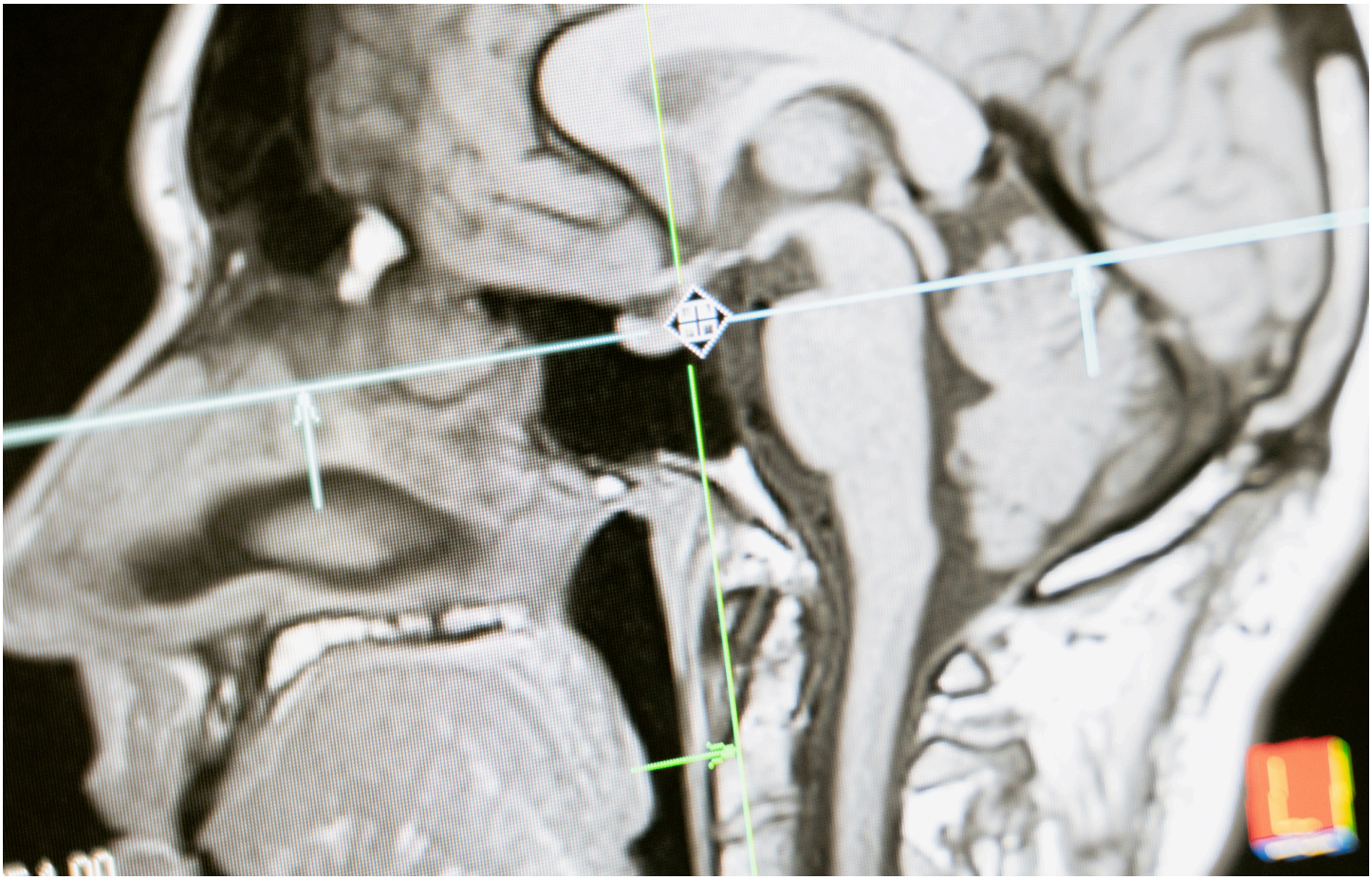


SPOTLIGHT:

Brain Fat and Alzheimer's Disease

THE STORY

For decades, Alzheimer's disease has been explained through two culprits: sticky amyloid-beta plaques and tangled tau fibers. Most drugs in development have targeted these proteins, yet treatments have offered only limited relief.

Now, researchers at Purdue University suggest a surprising twist: fat may be just as important as plaques. Their study reveals that the brain's immune cells, called microglia, can become clogged with fat — leaving them too weak to fight off disease.

By Daniella Ling

At the center of this discovery are microglia, the brain's resident immune cells. Imagine them as janitors and security guards rolled into one: they patrol the brain, clean up debris, and protect neurons from harm.

But in brains affected by Alzheimer's, these microglia are anything but healthy. Chopra's team found that many of them were swollen with fat droplets — tiny storage bubbles normally used for energy. Instead of patrolling, these "lipid-bloated" microglia became sluggish, weak, and ineffective.

The Evidence

- In brain tissue samples, microglia near plaques carried twice as many fat droplets as those farther away.
- These clogged microglia cleared 40% less amyloid-beta than their healthier counterparts.
- The buildup worsened with age and disease progression, suggesting a direct tie to Alzheimer's advancement.

The researchers dug deeper to uncover the "how." They traced the fat accumulation to an enzyme called DGAT2, which catalyzes the last step of turning free fatty acids into long-term fat stores.

In diseased brains, DGAT2 wasn't overproduced — it simply refused to degrade. This left microglia trapped in fat-processing mode, stockpiling energy they couldn't use, and losing their ability to protect neurons.

Turning the Tide:

The team tested two strategies in Alzheimer's animal models: one drug blocked DGAT2's activity, while another promoted its breakdown. Both approaches reduced fat buildup in microglia. More importantly, they restored microglia's ability to clear plaques, decreased inflammation, and improved signs of neuronal health.

For the first time, scientists showed that targeting fat metabolism directly could revive the brain's immune system.

This work supports a bigger idea Chopra calls the "lipid model of neurodegeneration." Instead of viewing fat droplets as harmless byproducts, this model treats them as active drivers of disease.

The concept builds on earlier research:

- Astrocytes, another type of brain cell, have been found to release toxic fatty acids in response to stress.
- Studies with the University of Pennsylvania showed that aging neurons accumulate fat deposits linked to mitochondrial dysfunction.
- Even Alois Alzheimer himself, over a century ago, noted fat droplets in the brains of patients. At the time, these were dismissed as irrelevant. Now, they're being re-examined as possible root causes.

Why It Matters

If lipid buildup is central to Alzheimer's, then therapies could shift away from chasing plaques alone. Future treatments might aim to:

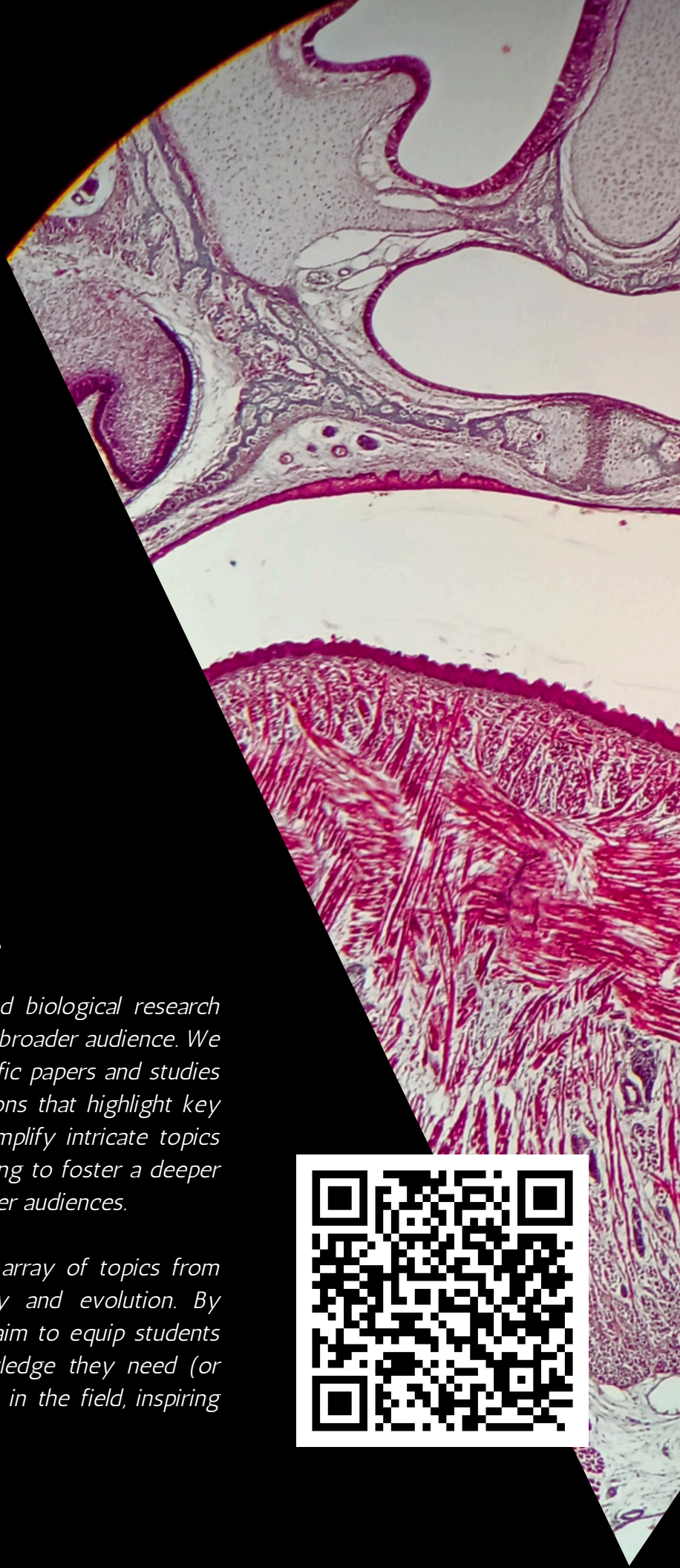
- Balance fat metabolism in brain cells
- Reinforce microglial defences so the brain can heal itself
- Prevent neuroinflammation before symptoms appear

"It's incredibly exciting to connect fat metabolism to immune dysfunction in Alzheimer's," says co-author Palak Manchanda. "Restore microglial metabolism, and you may restore the brain's own defence against disease."

Looking Forward

While this research is still early, it offers hope for a new generation of therapies. Instead of fighting the disease from the outside, scientists could reignite the brain's own resilience by targeting fat.

In the fight against Alzheimer's — a disease that affects more than 50 million people worldwide — this shift could mark a turning point.



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