Precision Neuromodulation Decreased Brain Atrophy and Increased Connectivity in Key Brain Network in Alzheimer's Patients

Study by Sinaptica scientific co-founders published in Alzheimer's Research & Therapy

Imaging analysis revealed personalized rTMS-EEG preserved structural integrity, enhanced functional connectivity, and slowed atrophy in areas of the Default Mode Network, the primary memory network impacted by Alzheimer's that is targeted by the therapy

Findings support the company's Phase 2 data in Mild/Moderate Alzheimer's showing >80% disease slowing on cognitive & functional endpoints

Cambridge, MA – July 09, 2024 – Sinaptica Therapeutics, Inc., a clinical-stage company leading the development of a new class of personalized neuromodulation therapeutics to treat Alzheimer's (AD) and other neurodegenerative diseases, today announced publication in the journal *Alzheimer's Research & Therapy* of a study using MRI and fMRI neuroimaging analysis to evaluate structural and connectivity changes in the brains of patients with mild-to-moderate Alzheimer's after treatment using a proprietary non-invasive precision therapy. This patented approach to personalized neuromodulation of the Default Mode Network, based on rTMS-EEG technology, referred to as "nDMN", is being developed by Sinaptica.

The publication, titled "Macro and micro structural preservation of grey matter integrity after 24 weeks of rTMS in Alzheimer's disease patients: a pilot study," a sub-study of a larger randomized Phase 2 trial, showed statistically significant slowing in the rate of grey matter atrophy in the Precuneus, which is a key node of the Default Mode Network (DMN), the primary brain network impacted by Alzheimer's disease. The DMN is critical for episodic memory and one of the earliest brain regions to be correlated with amyloid deposits, grey matter loss, and functional connectivity disconnection.

In addition to preserving grey matter at the macro level, detailed microimaging analysis, supported by an independent group, Oxford Brain Diagnostics, also showed that the neuromodulation treatment preserved microstructural integrity of the Precuneus, as measured by AngleR, a proprietary measure of microcortical damage, as well as across regions of the DMN, with high spatial specificity.

Moreover, at a connectome level, treatment increased functional connectivity in the Precuneus, and across the DMN as measured by fMRI, but not in the unrelated areas of the brain such as the motor cortex, pointing to the possibility that nDMN specifically strengthens the target network responsible for memory.

"Brain atrophy is a direct result of Alzheimer's disease, and cognitive impairment directly correlates with both brain shrinkage and diminished connections in the DMN," said Giacomo Koch, MD, PhD, Sinaptica scientific co-founder and primary author of the study. "This is the first pilot study aimed at investigating the neurobiological alterations reflected in structural and functional changes after

multiple sessions of personalized rTMS-EEG targeting the DMN via the Precuneus in Alzheimer's patients. The results provide novel evidence supporting the idea that nDMN may be able to slow down atrophy and increase functional network connections in patients with Alzheimer's disease."

The research design included a subset of 16 patients from the larger Phase 2 trial, evaluated with additional imaging studies. The personalized nDMN treatment protocol consisted of two phases, a daily "intensive" phase with 10 daily sessions delivered in the first two weeks, and a weekly "maintenance" phase with 22 weekly sessions delivered in the subsequent 22 weeks. At baseline and after 24 weeks of treatment, participants underwent structural and functional MRI measurements. The MRI and fMRI measurements were analyzed at three different levels: macro-structural, micro-structural, and functional connectivity changes.

"This imaging data supports the full Phase 2 clinical trial results in Alzheimer's patients that are the foundation of Sinaptica, showing objective evidence that our non-invasive therapy impacts the brain on multiple specific and biologically relevant levels," said Sinaptica CEO Ken Mariash. "It underscores the capability of nDMN, when properly calibrated, to safely induce plasticity, create new connections, slow atrophy, and prevent the DMN from disconnecting, which is a hallmark of Alzheimer's disease."

Sinaptica is building on positive data from the full nDMN Phase 2 study in Alzheimer's, showing statistically-significant slowing of clinical markers of disease progression was seen on the primary endpoint, the Clinical Dementia Rating – Sum of Boxes (CDR-SB), and on a key secondary endpoint, Alzheimer's Activities of Daily Living (ADCS-ADL)—both showing >80% disease slowing—along with two other cognitive measures (ADAS-COG and MMSE) which also showed over 80% disease slowing at six months, as published by the company's scientific co-founders in the journal, *Brain*. The treatment was well tolerated, and no ARIA or serious adverse events were observed in patients treated for six months. The company also has also completed a second Phase 2 study, with a 1-year endpoint, which will soon be published in an upcoming issue of a peer-reviewed journal and presented at CTAD in October. Sinaptica's patented technology has been granted FDA Breakthrough Device Designation, and the company is preparing for a larger Phase 3 clinical trial in Alzheimer's patients at multiple sites.

About Sinaptica Therapeutics

Sinaptica Therapeutics is a clinical-stage neuromodulation therapeutics company leading the development of a new class of personalized therapeutics to revolutionize the treatment of Alzheimer's and neurodegenerative diseases. The company utilizes a patented non-invasive approach to treating Alzheimer's via precision neurostimulation of a key brain network involved in memory, the Default Mode Network. This novel approach slowed disease progression by >80% on all four gold-standard cognitive and functional clinical endpoints in a placebo-controlled Phase 2 clinical study, with results published in the journal, *Brain*. The technology was granted Breakthrough Device Designation by the FDA in 2022 and the company is preparing for a pivotal randomized controlled clinical trial in 2025. Sinaptica's mission is to bring a safe, effective, and non-invasive neuromodulation therapy to Alzheimer's patients that can help to significantly slow the progression of both cognitive and functional decline. Learn more at sinapticatx.com and follow us on LinkedIn and X @SinapticaTX.

The SinaptiStim™ System is for investigational use only. It has not been approved by the U.S. Food and Drug Administration and is not available for commercial sale in any geography.

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