Sistema Socio Sanitario
Presidio Ospedaliero di Brescia
Regione Lombardia
ASST Spedali Civili
Università degli Studi di Brescia

CLINICA NEUROLOGICA - UNIVERSITA' DEGLI STUDI DI BRESCIA
UO Neurologia 2 - AZIENDA SOCIO SANITARIA TERRITORIALE degli SPEDALI CIVILI DI BRESCIA
Direttore: Prof. Alessandro Padovani

Title of the study: "Interventional cross-over study to evaluate the efficacy on cognitive performance of alternating current brain stimulation (tACS) in patients suffering from neurodegenerative diseases"

NCT number: Not yet assigned

Date: December 17th, 2019

Sistema Socio Sanitario
Presidio Ospedaliero di Brescia
Regione Lombardia
ASST Spedali Civili
Università degli Studi di Brescia

CLINICA NEUROLOGICA - UNIVERSITA' DEGLI STUDI DI BRESCIA
UO Neurologia 2 - AZIENDA SOCIO SANITARIA TERRITORIALE degli SPEDALI CIVILI DI BRESCIA
Direttore: Prof. Alessandro Padovani

EXPERIMENTAL CLINICAL PROTOCOL

TITLE OF THE STUDY: "Interventional cross-over study to evaluate the efficacy on cognitive performance of alternating current brain stimulation (tACS) in patients suffering from neurodegenerative diseases"

ACRONYM: GammAD

VERSION AND DATE: Version 1.1 of December 17th, 2019

DIVISION WHERE THE RESEARCH IS PERFORMED: Clinica Neurologica, Università di Brescia, Spedali Civili di Brescia

MAIN EXPERIMENTATOR: Prof. Barbara Borroni

INTRODUCTION AND RATIONAL: Brain oscillations are ubiquitous in the human brain and have been implicated in cognitive and behavioral states defined in precisely tuned neural networks. In neurodegenerative disorders, neurodegeneration is accompanied by changes in oscillatory activity leading to the emerging concept of neurological and psychiatric disorders as "oscillopathies". Alzheimer's disease, which accounts for the vast majority of age-related dementias, is characterised by a prominent disruption of oscillations in the gamma frequency band. The restoration of gamma oscillations by neural entrainment in animal models of Alzheimer's disease have shown a remarkable decrease in the pathological burden of amyloid and tau via increased microglial activity, resulting in a significant increase of cognitive performances.
Transcranial alternating current brain stimulation (tACS), is a neurophysiological method of non-invasive modulation of the excitability of the central nervous system that is having an increasingly numerous spectrum of potential therapeutic applications. Recent studies have demonstrated the effectiveness of this method in modulating the natural frequencies of cerebral oscillation, underlying multiple cognitive processes such as verbal memory, perception and working memory.
On the basis of these premises, the treatment with gamma tACS is proposed in patients affected by Alzheimer's disease.
In this randomized, double-blind, sham-controlled, cross-over study, the investigators will evaluate whether a single stimulation with gamma tACS on the posterior parietal cortex can improve symptoms in patients with Mild Cognitive Impairment due to Alzheimer's disease.

Subjects will be randomized in two groups, one receiving a single treatment with gamma tACS (40 Hz) first and the other receiving sham stimulation. After one week the treatments will be exchanged. Patients will be evaluated with neuropsychological tests and neurophysiological measures of cholinergic transmission.

OBJECTIVES: The aim of the study is to evaluate the effects on cognitive performance of tACS in patients suffering from Alzheimer's disease (AD) to identify a possible rehabilitation protocol. The effect of tACS on intracortical connectivity will also be evaluated using the and SAI TMS protocols.

PROCEDURES: Patients followed at the Neurological Clinic with a diagnosis of Alzheimer's disease will be enrolled according to current clinical criteria. Patients will be randomized into two groups:

The first group will undergo a stimulation protocol by means of tACS (real),
the second group will undergo a placebo treatment (sham).

Treatment group:
Each session will consist in the application of a tACS session (real at 3 mA) at the cortical level for the duration of 60 minutes each, during which patients will be subjected to an experimental cognitive task (Face Naming Task). The pre- and post-stimulation effects with tACS will be evaluated; in particular, the effects on cognitive performance will be assessed through the use of dedicated tests (Rey Auditory Verbal Learning Test - RAVLT) and the effects on the neurophysiological parameters of SAI using TMS.

Placebo group:
In the placebo group, the assembly will be kept the same as that of the real stimulation, however the electric current will be automatically interrupted about 5 seconds after the start of the stimulation, so as to make the placebo stimulation indistinguishable from the real one. The same tests and assessments used during real stimulation will be used.

After 1 week (after a single session of real stimulation or placebo stimulation) the two groups will be inverted (cross over).

INCLUSION CRITERIA:

- Mild Cognitive Impairment due to Alzheimer's disease (according to Albert et al., Alzheimers Dement 2011).

EXCLUSION CRITERIA:

- Cerebrovascular disorders, previous stroke, hydrocephalus, and intra-cranial mass documented by MRI.
- History of traumatic brain injury or other neurological diseases.
- Serious medical illness other than FTD
- History of seizures
- Pregnancy
- Metal implants in the head (except dental fillings)
- Electronic implants (i.e. pace-maker, implanted medical pump)
- Age <18 years

STUDY DESIGN: this is a placebo-controlled, randomized, double-blind, non-pharmacological interventional clinical trial, as neither the patients nor the person who will administer the evaluation tests will be aware of the type of treatment performed, real-tACS or placebo (tACS: placebo tACS = 1 : 1). This is a crossover study, in fact the patients who will carry out the first real stimulation session will carry out a second session with placebo stimulation after 1 week and vice versa. An experimental task (Face Naming Task) will be performed in both sessions.
In consideration of the transient effects of tACS, with a duration of cognitive effects of a few hours after the interruption of stimulation, the study does not provide a long-term follow-up.
Patients diagnosed with Alzheimer's Disease will be included. Each patient will undergo a cognitive assessment with the administration of a dedicated test (Rey Auditory Verbal Learning Test - RAVLT) and analysis of neurophysiological parameters of SAI by TMS before treatment and immediately after. All measures will be repeated after a week by reversing the stimulation from real to placebo and vice versa. In both sessions, a task, the Face Naming Task, will be carried out during the stimulation with tACS, both real and placebo.

END POINTS: The effect of tACS alternating current brain stimulation on the Face Naming Task and RAVLT will be primary outcome measures. The effect of tCAS on SAI measures will be considered as secondary outcome measure.

STATISTICAL PLAN: we will use parametric analyzes (t test) to compare the demographic variables (age and education) of the two groups at baseline. A $p < 0.05$ will be considered significant. To evaluate the effect of the stimulation protocol using tACS on cognitive performance we will use an ANOVA model.
Power analysis: considering that similar studies have not been published, we used data from slightly different studies (both by population and by method of stimulation),

always remaining within the established safety limits (Antal 2017). The "effect size" f (V) was calculated using the direct method. Taking into consideration from the aforementioned studies an effect size equal to a partial η^2 of 0.205, equal to an "effect size" f (V) of 0.5078 and, considering alpha = 0.05 and the power (1-β) = 0.80, the expected sample size is 18 subjects using a repeated measures ANOVA study with two within-subjects factors: both treatment (real vs placebo - crossover study) and time (T0 and T1). The proposed sample size of 20 subjects should be adequate to achieve the main objective of the study.

ETHICAL CONSIDERATIONS (RISK-BENEFIT): tACS is a non-invasive, low-cost and simple to perform method that is having a growing diffusion and an ever-increasing spectrum of potential therapeutic applications.
We hypothesize that tACS can have a positive effect on naming performances in patients suffering from neurodegenerative diseases, such as Alzheimer's disease and frontotemporal dementia, and that tACS can have a positive effect on the normalization of neurophysiological parameters that have been altered in subjects affected by these diseases. neurodegenerative, for which there is still no treatment.
Literature data show that the application of the method according to the current safety guidelines (Iyer, 2005; Nitsche, 2003; Wassermann 2005; Antal 2017) has little relevant side effects, including mild tingling sensation during or after stimulation, moderate fatigue, mild itching sensation at the electrode application points, mild burning or pain, headache, nervousness, nausea, blistering at the electrode application points in more rare cases.
As for the TMS method, it is a non-invasive brain stimulation that allows the study of neurophysiological parameters that can provide information on the pathophysiological mechanisms involved in neurodegenerative pathologies.
Literature data show that the application of the method according to the current safety guidelines has minor side effects: a certain number of subjects participating in TMS experiments (up to 20%) suffer from headache or back pain, due to likely to excessive muscle tension and stiff head and / or neck position during TMS application. These effects are temporary and in most cases do not require any treatment.
Since TMS produces a magnetic field, people with fixed electrical stimulators (e.g. heart stimulators, nerve stimulators, hearing implants) that would not function or be damaged by the magnetic field cannot participate in the study. Also excluded from the examination are those with particular metal foreign bodies (for example splinters, some prostheses, screws and nails) that could move if placed within the magnetic field. Because the effects of TMS on the developing fetus are not known, pregnant women cannot participate in the study.

PERSONAL DATA PROCESSING:
The data will be processed in compliance with Legislative Decree 196/2003 and subsequent authorizations and additions and with the European Regulation n. 679/2016 relating to the protection of privacy and used for the purposes pursued by the study.

DETECTION OF ADVERSE EVENTS: The Principal Investigator will promptly communicate to the Provincial Ethics Committee of the Province of Brescia any adverse event induced by the method.

BIBLIOGRAPHY:
1. Berger H. Über das Elektrenkephalogramm des Menschen. Arch Psychiatr Nervenkr. 1929;87(1):527-570.
2. Schnitzler A, Gross J. Normal and pathological oscillatory communication in the brain. Nat Rev Neurosci. 2005;6(4):285-296.
3. Fries P. Neuronal Gamma-Band Synchronization as a Fundamental Process in Cortical Computation. Annu Rev Neurosci. 2009;32(1):209-224.
4. Koenig T, Prichep L, Dierks T, et al. Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging. 2005;26(2):165-171.
5. World Alzheimer Report. The Global Impact of Dementia: an analysIs of prevalence, incidence, cost and trends. 2015. https://www.alz.co.uk/research/world-report.
6. Iaccarino HF, Singer AC, Martorell AJ, et al. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature. 2016;540(7632):230-235.
7. Adaikkan C, Middleton SJ, Marco A, et al. Gamma Entrainment Binds Higher-Order Brain Regions and Offers Neuroprotection. Neuron. 2019;102(5):1-15.
8. Martorell AJ, Paulson AL, Suk H, et al. Multi-sensory Gamma Stimulation Ameliorates Alzheimer's-Associated Pathology and Improves Cognition. Cell. 2019;177(2):256-271.e22.
9. Herrmann CS. Human EEG responses to 1-100 Hz flicker: Resonance phenomena in visual cortex and their potential correlation to cognitive phenomena. Exp Brain Res. 2001;137(3-4):346-353.
10. Herrmann CS, Rach S, Neuling T, Strüber D. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front Hum Neurosci. 2013;7:279.
11. World Alzheimer Report. The Benefits of Early Diagnosis and Intervention. 2011. https://www.alz.co.uk/research/world-report.
12. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework:

Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535-562.

13. Benussi A, Alberici A, Cotelli MS, et al. Cortico-spinal tDCS in ALS: A randomized, double-blind, sham-controlled trial. Brain Stimul. 2019;12(5):1332-1334.
14. Benussi A, Di Lorenzo F, Dell'Era V, et al. Transcranial magnetic stimulation distinguishes Alzheimer disease from frontotemporal dementia. Neurology. 2017;89(7):665-672.
15. Benussi A, Cosseddu M, Filareto I, et al. Impaired long-term potentiation-like cortical plasticity in presymptomatic genetic frontotemporal dementia. Ann Neurol. 2016;80(3):472-476.
16. Benussi A, Alberici A, Ferrari C, et al. The impact of transcranial magnetic stimulation on diagnostic confidence in patients with Alzheimer disease. Alzheimers Res Ther. 2018;10(1):94.
17. Benussi A, Dell'Era V, Cantoni V, et al. Discrimination of atypical parkinsonisms with transcranial magnetic stimulation. Brain Stimul. 2018;11(2):366-373.
18. Benussi A, Gazzina S, Premi E, et al. Clinical and biomarker changes in presymptomatic genetic frontotemporal dementia. Neurobiol Aging. 2019;76(2019):133-140.