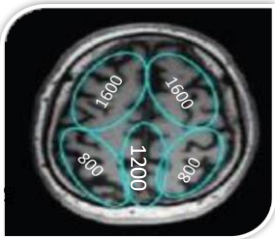


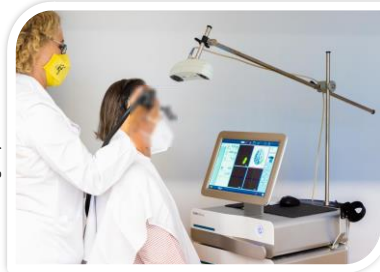
## OBJECTIVE

Recent studies have shown that **Transcranial Pulsed Stimulation (TPS; Neurolith®)** may have beneficial effects on brain glucose metabolism and cognitive function in patients with **Alzheimer's Disease (AD)**. In our study, we expect to confirm the usefulness of TPS on patients with AD at **3 months**.

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## METHODOLOGY

**Study design:** 19 patients (males and females aged 61 to 89) diagnosed with **MCI** due to **AD** or **mild to moderate AD** underwent TPS treatment. Also, to compare the effect of treatment with the natural course of the disease, data from **19 matched control patients** who had not received **TPS treatment** were retrospectively included. The safety, tolerability, cognitive and clinical effects of the TPS therapy vs. control participants have been evaluated.

**Inclusion criteria:** diagnosed of probable AD dementia or MCI due to AD, MMSE > 10, baseline MRI scan excluding other potential causes of dementia, Fazekas score ≤ 2, anticholinesterase drugs or memantine treatments were allowed. Cognitive impairment was screened using MoCA. A comprehensive neuropsychological evaluation was conducted for all patients, before and after treatment.

## Biological effects of TPS

TPS a new tool that allows you to stimulate the brain up to 8 cm depth

- Pore formation, transendothelial openings, better molecules passing-through
- Blood-brain barrier opening
- Microglia activation and AB plaque reduction
- Increased serotonin and dopamine, BDNF and VEGF and NO
- Stem cell proliferation and differentiation
- Reduction of GABA levels

Table 1. Baseline socio-demographic and clinical characteristics of the control and experimental groups.

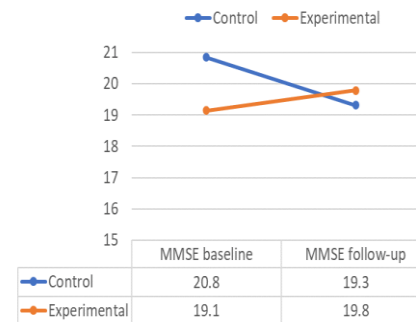
	Total (N=38)	Control (n=19)	Experimental (n=19)	Statistic <sup>§</sup>	Sig
Age (median [IQR])	79.1 [6.5]	79.3 [5.5]	78.9 [7.5]	149	0.358
Education					
Less than Primary Education (n [%])	5 [13.2]	3 [15.8]	2 [10.5]		
Primary Education (n [%])	17 [44.7]	11 [57.9]	6 [31.6]	3.94	0.268
Secondary Education (n [%])	10 [26.3]	3 [15.8]	7 [36.8]		
Tertiary Education (n [%])	6 [15.8]	2 [10.5]	4 [21.1]		
Gender					
Female (n [%])	31 [81.6]	16 [84.2]	15 [78.9]	0.175	0.676
Male (n [%])	7 [18.4]	3 [15.8]	4 [21.1]		
MMSE (median [IQR])	21.5 [5.8]	22 [4.5]	21 [4.5]	151	0.392
GDS-15 (median [IQR])	3 [4.8]	3 [4]	3 [4.5]	164	0.627
STAI trait (median [IQR])	3 [3]	2 [2.5]	3 [3]	121	0.078

<sup>§</sup>Mann-Whitney U for numeric variables and  $\chi^2$  for categorical variables.

No significant differences in baseline characteristics were found between control and experimental groups.

**Figure 2. Differences in MMSE scores between control and experimental groups at 3-month follow-up.**

The figure shows how the **MMSE score** at follow-up **improves** slightly in the **experimental group**, whereas it worsens in the control group. Thus, there is a significant interaction between groups and follow-up.



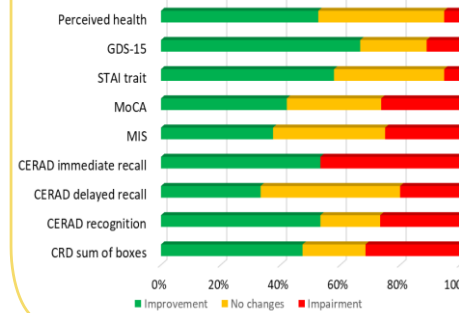
## RESULTS

After treatment, 42% of the patients presented higher scores at the 3-month follow-up, 32% remained unchanged and 26% showed a slight worsening (MoCA test).

In episodic memory, **38% showed improvement** on the 3-month follow-up scores, another 38% remained invariable, and the remaining 25% worsened.

Strikingly, only 11% of the patients reported impairment of **depressive** symptomatology whereas **67% even improved**; three patients showed indeed a relevant reduction. In comparison, during the same follow-up control patients showed a worsening in all domains evaluated.

Figure 1. Percentage of patients undergoing TPS who experience improvement, remain unchanged or show a worsening at 3-month follow-up.



As can be noted, subjective variables (i.e. perceived health, **depression**, and **anxiety**) show a **greater improvement** than cognitive tests. Specific figures are showed in the following table:

	Improvement	No changes	Impairment
CRD sum of boxes	47.4	21.1	31.6
CERAD recognition	53.3	20.0	26.7
CERAD delayed recall	33.3	46.7	20.0
CERAD immediate recall	53.3	0.0	46.7
MIS	37.5	37.5	25.0
MoCA	42.1	31.6	26.3
STAI trait	57.9	36.8	5.3
GDS-15	66.7	22.2	11.1
Perceived health	52.6	42.1	5.3

## CONCLUSIONS

Based on our findings, we can conclude TPS is a **safe** and **effective** therapeutic option for **AD** that benefits cognition and mood. Neurolith® is a neurostimulation treatment especially **useful** in **subjective variables** such as perceived health, depression and anxiety.

The figure shows how the **MMSE score** at follow-up **improves** slightly in the **experimental group**, whereas it worsens in the control group. Thus, there is a significant interaction between groups and follow-up.