Transcranial Pulse Stimulation in Alzheimer's patients:

Whom, how and where to stimulate?

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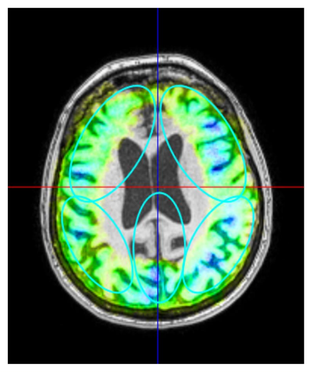
Aims

Transcranial Pulse Stimulation (TPS) uses shockwaves for the treatment of Alzheimer´s patients. Recently, our group published short-term clinical results after the first treatment cycle (Cont et al. 2022). However, many aspects remain unclear concerning patient selection and treatment protocols.

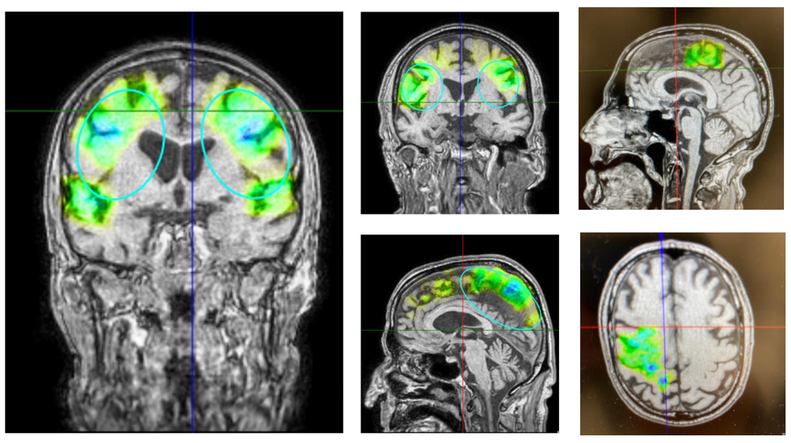
Methods

A consecutive series of 24 patients received TPS using the Neurolith System (Storz Medical). After the initial treatment cycle over 2 weeks patients were scheduled for monthly booster sessions. Safety data and different cognitive scores were assessed over 5-12 months. Individual symptomology, MRI- and CSF biomarker, disease stages, inclusion / exclusion criteria and treatment protocols where registered.



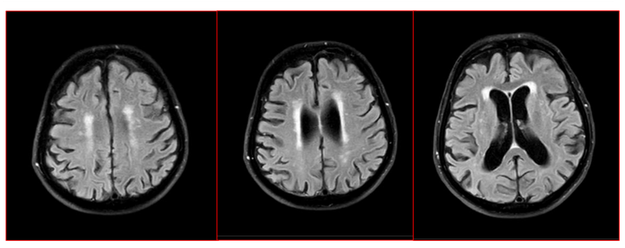
Results

- Standard protocol was 6000 pulses with 4 Hz stimulation of precuneus, bilateral frontal and parietal cortex but was extended to bitemporal cortex and / or motor areas such as SMA, M1, PMC to treat concomitant tremor or hypokinesia.

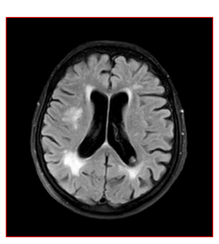


- The treatment was well tolerable with low number of only transient and not severe ADE even in selective patients with minor vascular lesions and platelet aggregation inhibitors.
(From 250 stimulation sessions totally administered: 1.6% drowsiness, 0.8% nausea and headache, and 0.4% jaw pain and earache.)

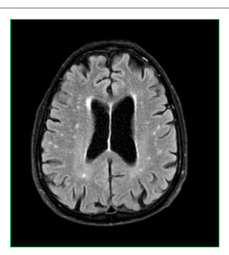
History of TIA and aggressive behavior , SAE Fazekas 2, ASS
Multiple KI, EXCLUDED ➔ TMS



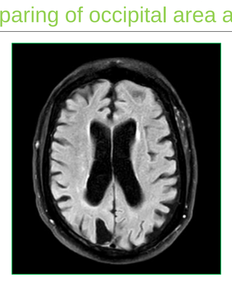
SAE Fazekas 3, ASS
SAE as KI EXCLUDED ➔ TMS



SAE Fazekas 1-2, ASS
Included for TPS



History PCA stroke, SAE Fazekas 1, ASS, Ginkgo
Included for TPS with sparing of occipital area and without Ginkgo



- Cognitive and affective scores improved significantly after the first treatment cycle regardless of symptom severity at baseline and CSF biomarker.

	n	M	SD	df	t	p	Cohens d
MMST- T0	24	16.17	8.042	23	-2.58	.009*	.53
MMST-Post	24	17.29	7.123				
MoCA – T0	24	11.29	6.517	23	-2.24	.018*	.46
MoCA – Post	24	12.33	6.611				
ADAS – T0	23	28.35	13.217	22	2.58	.009*	.54
ADAS - Post	23	26.04	13.227				

TABLE 2 Normalized absolute and relative mean change of the scores for the different groups: Mild cognitive impairment, moderate cognitive impairment, and severe cognitive impairment.

	Mild ($N = 4$)	Moderate ($N = 5$)	Severe ($N = 2$)
MMSE	−0.75 (−2.91%)	+1.4 (8.64%)	+0.55 (20%)
ADAS total	+4.25 (18.28%)	+6.4 (20.78%)	-*
ADAS Cog	+1.5 (8%)	+3.8 (14.5%)	-*
MoCA	+0.25 (3.83%)	+1.6 (15.69%)	−1.5 (−60%)

Positive values indicate improvement and negatives values indicate worsening. *For ADAS, the severe cognitive impairment group was N = 1.

The statistical test of hypothesis IV–if TPS effects differed between mildly, moderate, or severely patients–however, showed no significant correlation between baseline MMSE and changes of cognitive scores after treatment.

ADAS total score (non-diagnosed AD group: M improvement = 5.67; AD group: M improvement = 4) and ADAS Cog (non-diagnosed AD group: M improvement = 2.33; AD group: M improvement = 2.2).

MMSE (non-diagnosed AD group: M improvement = 1.67; AD group: worsened slightly, M improvement = −0.13), MoCA (non-diagnosed AD group: M improvement = 1; AD group: M improvement = 0.125).

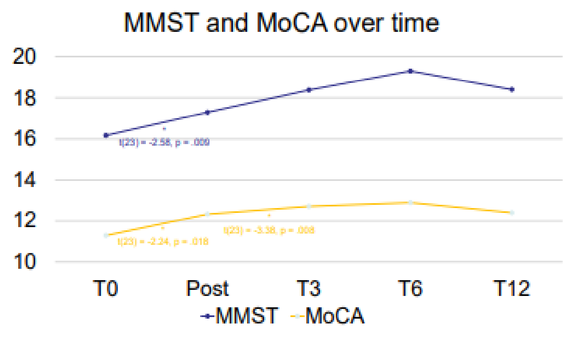
TABLE 1 Demographics of the patients.

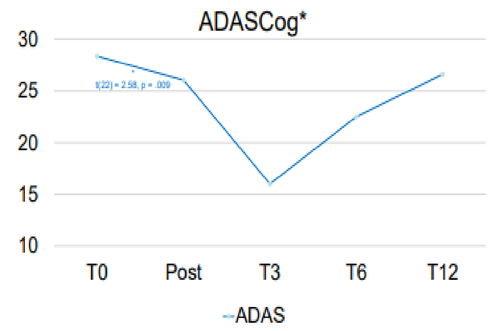
ID	Age	Sex	Cognitive impairment	Biomarker category / diagnosis
1	76	M	Mild	A+T+(N)+ / AD
2	74	M	Severe	A+T+(N)+ / AD
3	77	M	Moderate	Alzheimer's clinical syndrome without biomarkers tested
4	59	M	Moderate	A+T-(N)+[a]
5	60	M	Moderate	A+T+(N)+/ AD
6	65	M	Moderate	A+T+(N)+ / AD
7	61	F	Mild	A+T+(N)+ /AD
8	74	M	Severe	Alzheimer's clinical syndrome without biomarkers tested
9	74	F	Moderate	A+T+(N)+ /AD
10	76	M	Mild	A-T-(N)+[b]
11	72	M	Mild	A+T+(N)+ / AD

Cognitive impairment was defined using the Mini-Mental Status Examination (MMSE): 30–27, no impairment, 26–20, mild impairment, 19–10, moderate impairment, and <10, severe impairment. Diagnostic criteria were assessed according to the NIA-AA criteria. "A" labels biomarker of Aß plaques, "T" labels biomarkers of fibrillar tau, and "N" labels biomarkers of neurodegeneration or neuronal injury (10). Two patients were included with no biomarkers tested. [a]Alzheimer's and concomitant suspected non-Alzheimer's pathological change. [b]Alzheimer's clinical syndrome with non-Alzheimer's pathological change.

The three non-diagnosed AD patients (two patients without biomarkers tested and one with Alzheimer's clinical syndrome with non-diagnosed Alzheimer's pathological change) did show cognitive changes after stimulation in a comparable range as did the AD group ($N = 8$) in most tests. Due to the small sample size, we did not apply statistics. In detail, the mean numbers were as follows:

(Cont et al. 2022)





Preliminary long-term data showed stable effects over months with the selected booster interval. Whereas the t-tests comparing T0 and post stimulation show a significant improvement, a Pearson correlation with MMST for the whole time span (T0, Post, T3, T6, T12) revealed no significant change, thus patients show stable performance ($p = 3.21$ with $r = .057$)

Conclusion

TPS might be an option for Alzheimer's not only in mild cases and regardless of the biomarker constellation und thus maybe for other dementia types. Minor vascular pathology and platelet aggregation inhibitors is generally acceptable. Treatment protocols can extend standard patterns and include e.g. motor areas to address concomitant hypokinesia or tremor. Imaging and electrophysiology biomarkers need to established. Systematic treatment protocols should be tested with a translational approach including basic neuroscience techniques and in comparison to other methods such as electric / magnetic stimulation.

References

Cont, C., Stute, N., Galli, A., Schulte, C., Logmin, K., Trenado, C., & Wojtecki, L. (2022). Retrospective real-world pilot data on transcranial pulse stimulation in mild to severe Alzheimer's patients. Frontiers in neurology, 13, 948204. https://doi.org/10.3389/fneur.2022.948204

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