2022 International Conference on Electrical, Computer, Communications and Mechatronics Engineering (ICECCME) | 978-1-6654-7095-7/22/$31.00 ©2022 IEEE | DOI: 10.1109/ICECCME55909.2022.9988704

Brain Stimulation by noninvasive Transcranial Pulse Stimulation (TPS) improves cognitive Deficits and Mood in Alzheimer's Disease

Ulrich Sprick
Alexius/Josef Clinic
Department for outpatients and day clinics
Neuss, Germany
u.sprick@ak-neuss.de

Martin Köhne
Alexius/Josef Clinic
Medical Director
Neuss, Germany
m.koehne@ak-neuss.de

***Abstract*—Alzheimer's disease (AD) is considered to be a progressive irreversible illness. So far an effective treatment of symptoms in Alzheimer's disease has not yet been found. One of the symptoms often found in AD patients is the significant reduction of executive functions. Furthermore, affective fluctuations and depressive moods occur regularly.**

Transcranial pulse stimulation (TPS) induced by shock waves which were individually navigated according to current MRI-scans induced an amelioration of executive functions and reductions of depressive symptoms in patients with AD.

The application of shock waves with low intensity is a noninvasive procedure with expected low rates of side effects. TPS allows to address the areas to be stimulated very precisely both superficially in the cortex and in deeper parts of the brain. Thus very justified hopes arise that this new method offers new perspectives for the amelioration of deficits in AD to a great extent.

Outpatients of our clinic (59 – 86 years old) received 6 TPS-stimulations over a period of 2 weeks beside the regular state of the art treatment. The AD patients treated with TPS achieved a significant improvement of executive functions measured by the Stroop-test. Patients mood also improved over the 2-week period. We measured depressive symptoms of the patients using Beck's Depression Inventory (BDI) and found a significant reduction of sum scores indicating that depressive symptoms were relieved.

Keywords — Alzheimer's disease, transcranial pulse stimulation, MRI tracking, amelioration of executive functions, relief of depressive symptoms

I. INTRODUCTION

Despite their similarity to ultrasound, shock waves typically have larger pressure amplitudes than ultrasound waves [1]. The latter can be characterized by periodic oscillations with a limited bandwidth (Fig. 1). In contrast, shock waves are characterized by a single positive pressure pulse with a high amplitude, followed by a comparatively small tensile wave (negative pressure pulse) (Fig. 2). The frequency of this pulse may vary from a few kilohertz up to 10 megahertz [2].

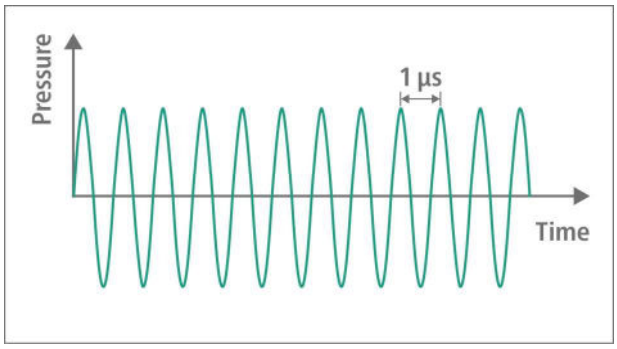

Fig. 1 Typical ultrasound wave with frequent oscillations, positive and negative portions of the wave are equal.

Shock waves stimulate biological processes in the brain and other tissues by mechanotransduction (mechanical stimulation). In order to minimize side effects when used in the human brain focused shock waves of low intensity were used. Fig. 3 shows a typical shock wave distribution as a 3-D pressure plot for superficial areas as well as for deeper areas of the brain [2]. This new therapeutic method of noninvasive brain stimulation allows to reach structures up to 8 cm underneath the cortical surface. In contrast to conventional deep brain stimulation there is no need to open the skull by surgical matters prior to the stimulation.

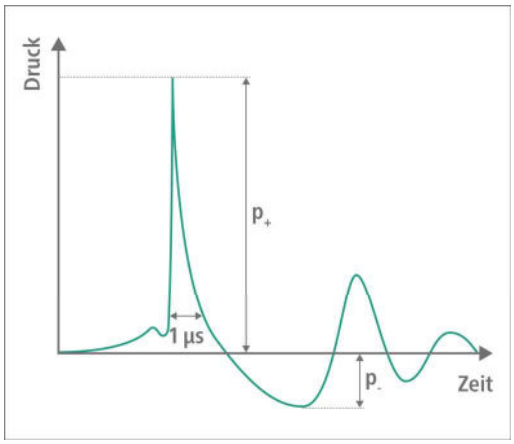

Fig. 2 A shock wave consists of a very short singular pulse. The pressure wave part is followed by a longer counter tension wave. The typical clinical pulse repetition rate ranges from 1-8 Hz.

978-1-6654-7095-7/22/$31.00 ©2022 European Union

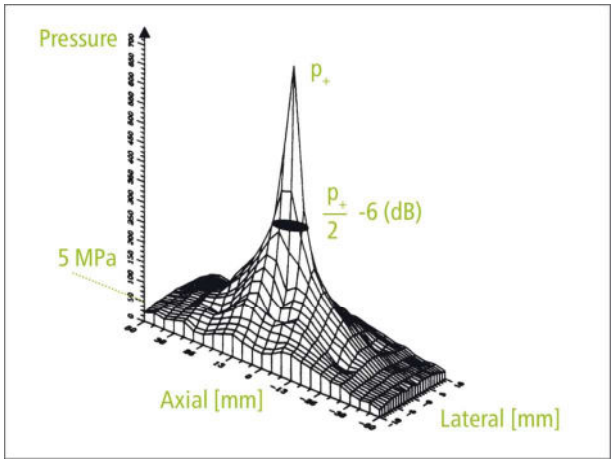

Fig. 3 Distribution of pressure in TPS-pulses

Using the technique of MRI- navigation the accuracy of reaching the target areas is comparable to surgical stereotaxic methods [3]. Fig. 4 shows the 3-D MRI tracking technique with the reference shock wave stimulation handpiece. Pulse parameters may be adjusted depending on the depth and the planned intensity of the stimulation.

First clinical studies with navigated TPS have induced cognitive improvements in patients with AD [4]. Correlating with the cognitive improvement a thickening of the cerebral cortex after TPS-stimulation was described [5].

Even now, the exact working mechanism(s) of TPS are not yet fully understood. It is very likely that the mechanotransduction induced by focused shock waves has influences on cell membranes including ion channels [6]. In addition trophic effects on the brain tissue are generated via an activation of a cascade of (neuro)trophic factors and neuromodulators [7]. All these effects contribute to an induction of adaptive neuroplastic processes.

Fig. 4 TPS is administered by a 3-D MRI tracking technique. The position of the stimulation handpiece is detected by a camera which integrates movements of the head. Parameters of the pulses can be adjusted according to the depth and the planned intensity of the stimulation.

We applied TPS to patients with Alzheimer's disease. AD is a progressive irreversable brain disorder causing dementia. Typical symptoms are increasing impairments of judgement and executive functions as well as cognitive deficits with learning- and memory deficiencies. Impaired orientation becomes manifest. Many patients develop behavioral abnormalities. Changes of affect, restlessness, changes of personality also occur. Sometimes patients also suffer from delusional symptoms or hallucinations. Impairments of speech and speaking are common as well as impairments in the activities of daily living [8,9].

Depressive or subdepressive states cause typical major problems in AD patients. There was one report, that TPS would show antidepressant effects in AD patients [10]. So we investigated antidepressant effects of navigated TPS beside executive functions.

II. METHODS

Twenty-one patients from the outpatient department of our clinic with a confirmed diagnosis of AD of were additionally treated with TPS beside their original state of the art treatment.

With a pre - post design we compared their executive functional skills with the Stroop-test [11] just before the first brain stimulation (t0), after the sixth brain stimulation (t1) two weeks later. Executive functions were measured by the Stroop-test. The Stroop-test is a tool for testing executive functions, especially selective attention processes including conflicts of automatic processing operations (e.g. naming colours with interfering word meaning).

Fig. 5 Example task of the Stroop-test (interfering condition)

Patients with Alzheimer's disease show severe impairments of these executive functions. This sort of cognitive performance is linked to a functioning mediodorsal cortex as a part of the frontal lobe. Patients were asked to name the colours of the written words with interfering meanings which is a difficult task for patients with Alzheimer's disease. Fig. 5 shows an example task from the Stroop-test.

The degree of depressive symptoms was measured with Beck's Depression Inventory (BDI), a standard instrument for the detection of depressive disorders [12].

Twenty-one patients from the outclinic department with a confirmed diagnosis of AD according to the criteria of the actual International Classification of Diseases (ICD 10 : F 00) [13] were additionally treated with TPS beside their original state of the art treatment. All 21 patients completed all treatments and tests.

Patients could be included if an MRI (not older than 3 months) was available as well as a written informed consent to take part.

Patients were excluded if they had a brain tumor (including benign tumors), hemophilia, blood clotting disorders, marcumar therapy or a corticosteroid treatment up to 6 weeks before the first stimulation.

With a pre - post design we compared executive functional abilities and mood of the AD-patients just before the first brain stimulation (t0) and after the sixth brain stimulation (t1) two weeks later.

Pulsed focused shock waves from a NEUROLITH® TPS generator (STORZ Medical, Switzerland) with ultrashort pulses of 3 µs duration, 4 Hz pulse repetition frequency and 0,25 mJ/mm² energy flux density were applicated. A total amount of 6.000 pulses were applied per session (1.000 pulses into the dorsolateral frontal cortex left and right, 1.000 pulses into each parietal lobe and 1.000 pulses into each temporal lobe). Thus 3.000 pulses were applied per hemisphere during each session.

Fig. 6 shows a typical sample of the distribution of the transcranially administered pulses on the screen of the applicator after one session. The green colour indicates that the target areas were stimulated in a medium range.

Fig. 6 Parameters of pulse stimulation and localization of the target areas

III. RESULTS

The results of the Stroop-test (pre vs post comparison) showed that executive functions were significantly ameliorated by the stimulation ($p < 0.05$).

Statistical analysis with the Wilcoxon test showed a significant difference ($p < 0.05$) pre vs post.

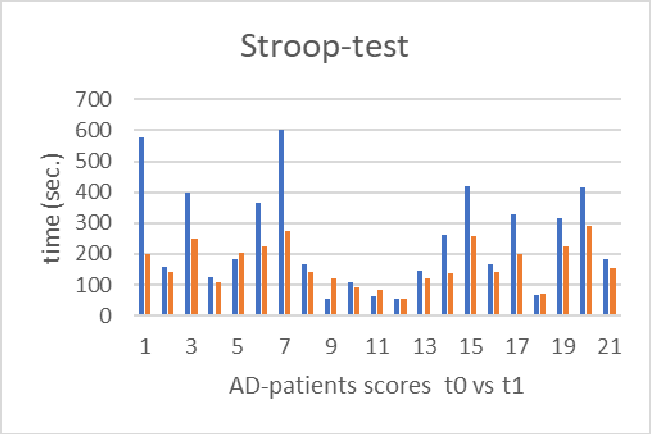

Fig. 7 Results of the Stroop-test. Executive functions improved from t0 to t1. Blue columns show initially longer reaction times compared to orange columns after two weeks of treatment.

Two patients showed an outstanding result by the reduction of test score to half after 2 weeks (from 575 sec to 201 sec, from 602 sec to 276 sec respectively). Group-completer times in the Stroop-test were reduced from 246 sec to 166 sec (mean values).

The BDI sum score was reduced by 4.2 points within 2 weeks indicating an improvement of mood (from 16.3 to 12.1 points). The initial mean value of 16.3 showed that there was no major depression according to the ICD 10.

A Wilcoxon signed-rank test was calculated to examine the effects of brain stimulation by TPS on BDI - depression scores. The distribution of differences was symmetrical following visual inspection of the histogram. There was a statistically significant decrease in BDI scores ($Mdn = -4.26$) before TPS t0 ($Mdn = 28.33$), compared to after TPS t1 ($Mdn = 24.07$), $z = 7.43$, $p < .001$, $r = .64$.

There was only a very low rate of side effects. One patient reported temporary headaches in the forehead area. Another reported on transient general fatigue after the stimulation session.

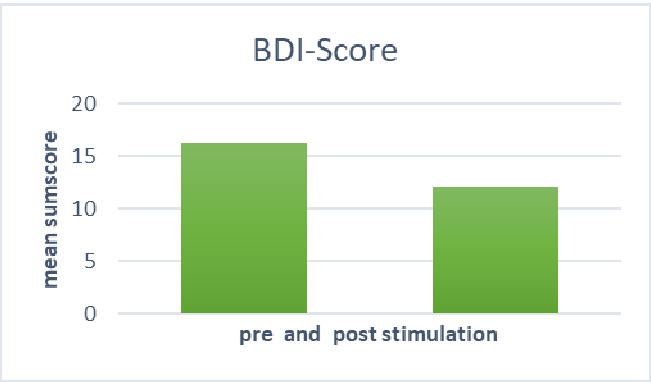

Fig. 8 The BDI-score decreased significantly after 2 weeks of treatment, showing that depressive symptoms subsided after 6 stimulation sessions.

IV. DISCUSSION

The results show that the included AD-patients benefited from TPS. Their cognitive abilities concerning the executive functions measured by the Stroop test significantly improved within the 2 weeks of treatment.

In addition the mood of the patients improved, too and depressive symptoms decreased as could be shown by the significantly decreased score in the BDI.

We observed only very few and transient unwanted side effects (like headaches and fatigue). This suggests that TPS is a safe procedure.

However, it should be noted that there are some limitations. First it has to be considered that the presented sample size was relatively small limiting the generalizability of our results. Due to ethical reasons we did not use a sham control group. It has to be discussed whether the improvements of the patients achieved a long-term or were only of a temporary nature. In our clinic we observed that cognitive deficits as well as positive mood changes after TPS can last at least over two months (unpublished results). Nevertheless in further studies, long-term effects need to be investigated in more detail.

Recently another working group has also reported persistent effects induced by TPS in a clinical trial [14]. Our data confirm the very recent results published by Matt et. al. [10]. They also found that depression can be ameliorated by TPS in patients with AD.

Various factors are discussed regarding the specific working mechanism(s) of action of TPS [15,16,17]. Mechanical effects of TPS on the cell membranes influence ion channels and induce poration in neurons as well as in glia cells [6]. Changes in various neurotransmitter levels have been observed after TPS. While there was an increase of extracellular dopamine and serotonin levels [18] a reduction of GABA-level was described[19]. In addition brain stimulation by TPS may lead to an induction of trophic factors (e.g. brain derived neurotrophic factor BDNF, glial cell line-derived neurotrophic factor GDNF, vascular endothelial growth factor VEGF) [7]. The BDNF contributes to neurogenesis and proliferation of neurons, especially in the hippocampal formation, and to a differentiation of neuronal stem cells. The latter could also be induced by ultrashort pulses in a cell culture [20]. VEGF leads to a significant amplification of vascularization.

There is a recent report on an interesting relationship between activation of microglia by trophic factors with a subsequent reduction of plaques in a rodent model [21]. TPS is capable to induce trophic factors like these.

In a rodent model of dementia TPS induced an increase of nitric oxide (NO)-levels by induction of the enzyme NO-synthetase. It could be demonstrated that the increased NO-levels led to an improvement of induced cognitive dysfunction in learning and memory processes [22].

We believe that in particular a transient opening of the blood-brain-barrier (BBB) by TPS helps to potentiate the effect of applied pharmaceuticals thus contributing to an improvement of brain functions. Opening of the BBB has been shown in an animal model [23]. This suggests maintaining state-of-the-art pharmacological treatment during TPS-therapy.

Thus, a variety of working mechanisms of TPS are discussed, which have in common that they all induce neuroplastic changes.

In summary, the evaluation of the data showed that TPS as an adjunctive therapy to a state-of-the-art treatment of AD could achieve both an improvement in cognitive executive functions and a reduction of depressive symptoms in AD patients, whereby AD is currently regarded as a disease that is progressive and has irreversible deficits [13].

In addition to its use in AD, we assume that TPS will also represent a new and promising, perhaps even revolutionary therapeutic option for other neurodegenerative diseases in the future, leading to an improvement not only in the symptoms of the disease but also to an improvement in the overall quality of life.

V. ACKNOWLEDGMENT

This observational study was financed by resources of the Alexius/Josef Clinic, Neuss. The authors thank STORZ Medical for providing the figures 1,2,3,4 and 6 for this paper.

REFERENCES

[1] Wess, O., „Physikalische Grundlagen der extrakorporaler Stoßwellentherapie, J. für Mineralstoffwechsel“, 2004, pp. 4-7.

[2] Nowak, P., “Physics: F-SW and R-SW – Basic information on focused and radial shock wave physics” in Multidisciplinary Medical Applications, H. Lohrer and L. Gerdesmeyer, Eds. Level 10, 2014, pp. 28-49.

[3] S. Ning, M. Jorfi, S. Patel, D. Kim and R. Tanzi, “Neurotechnological approaches to the diagnosis and treatment of Alzheimer’s disease”, Frontiers in Neuroscience, 16:854992, 2022, doi:10.3389/fnins.2022.854992.

[4] R. Beisteiner, E. Matt, C. Fan, H. Baldysiak, M. Schönfeld, T. Philippi Novak, A. Amini, T. Aslan, R. Reinecke, J. Lehmer, A. Weber, U. Reime, C. Goldenstedt, E. Marlinghaus, M. Hallett and H. Lohse-Busch, „Transcranial pulse stimulation with ultrasound in Alzheimer’s disease – A new navigated focal brain therapy”, 2019, doi: 10.1002/advs.201902583.

[5] T. Popescu, C. Pernet and R. Beisteiner, „Transcranial ultrasound pulse stimulation reduces cortical atrophy in Alzheimer’s patients: A follow-up study”, Alzheimer’s Dement, 7, e12121, https://doi.org/10.1002/trc2.12121, 2021.

[6] M. Babakhanian, L. Yamg, B. Nowroozi, G. Saddik, L. Boodaghians, P. Blount and W. Grundfest, “Effects of low intensity focused ultrasound on liposomes containing channel proteins”, Scientific Report, 8, 17250, 2018.

[7] W. Lin, R. Chen, W. Lu, S. Liu and F. Yang, „Protective effects of low-intensity pulsed ultrasound on aluminium-induced cerebral damage in Alzheimer’s disease rat model”, Scientific reports, 5, 9671, 2015

[8] R. Radue, A. Walaszek A and S. Asthana "Neuropsychiatric symptoms in dementia". Handbook of Clinical Neurology. Vol. 167. pp. 437–454. 2019, doi:10.1016/B978-0-12-804766-8.00024-8. ISBN 9780128047668. PMID 31753148. S2CID 208230186.

[9] A. Harper, S. Rouch, N. Leland, R. Turner, W. Mansbach, C. Day and L. Terhorst (April 2022). "A Systematic Review of Tools Assessing

the Perspective of Caregivers of Residents With Dementia". *Journal of Applied Gerontology*. **41** (4): 1196–1208. doi:10.1177/07334648211028692. PMID 34229505. S2CID 235758241, 2022.

[10] E. Matt, G. Dörl and R. Beisteiner, „Transcranial pulse stimulation (TPS) improves depression in AD patients on state-of-the-art treatment", Alzheimer's Dement., 2022, 8:e, 12245, https://doi.org(10.1002/trc2.12245.

[11] J.R. Stroop, "Studies of interference in serial verbal reactions", J. Experimental Psychology, vol. 18, 1935, pp. 643-662.

[12] A. Beck and R. Steer, Beck Depression Inventory, The Psychological Corporation Inc., 1987.

[13] H. Dilling, W. Mombour and M. Schmidt, "Internationale Klassifikation psychischer Störungen – ICD 10 Kapitel V (F), Verlag Hans Huber, Bern, 1991.

[14] E. Matt, L. Kaindl, S. Tenk, A. Egger, T. Kolarova, N. Karahasanovic, A. Amini, A. Arslan, K. Saricicek, A. Weber and R. Beisteiner, „First evidence of long-term effects of transcranial pulse stimulation (TPS) on the human brain", J Transl. Med. 15, 20(1), 26, 2022, doi: 10.1186/s 12967-021-03222-5.

[15] W. Tyler, S. Lani and G. Hwang, "Ultrasonic modulation of neuronal circuit activity", Current opinion in neurobiology, 50, 2018, pp. 222-231.

[16] A. Bystritsky and A. Korb, "A review of low-intensity transcranial focused ultrasound for clinical applications", Current Behav. Neurosci. Reports, 2, 2015, pp. 60-66.

[17] D. Miller and J. O'Callagham, "New horizons for focused ultrasound (FUS)-therapeutic applications in neurodegenerative diseases", Metabolism, 69, 2017, pp. 3-7.

[18] B. Min, P. Yang, M. Bohlke, S. Park, D. Vago, T. Maher and S. Yoo, "Focused ultrasound modulates the level of cortical neurotransmitters: Potential as a new functional brain mapping technique, International Journal of Imaging Systems and Technology, 21, 2011, pp. 232-240.

[19] P. Yang, K. Kim, W. Lee, M. Bohlke, S. Park, T. Maher and S. Yoo, "Transcranial focused ultrasoundto the thalamus is associated with reduced extracellular GABA levels in rats", Neuropsychobiology, 65, 2012, pp. 153-160.

[20] J. Zhang, N. Kang, X. Yu, Y. Ma and X. Pang, "Radial extracorporal shock wave therapy enhances the proliferation and differentiation of neural stem cells by notch, PI3K/AKT and Wnt/ß-catanin signaling", Scientific Report, 7, 2017, 15321, doi: 10.1038/s41598-017-15662-5.

[21] G. Leinenga and L. Götz, „Scanning ultrasound removes amyloid-ß and restores memory in an Alzheimer's disease mouse model", Science translational Medicine, 7, 278ra33-378ra, 2015.

[22] K. Eguchi, T. Shindo, K. Ito, T. Ogata, R. Kurosawa, Y. Kagaya, Y. Monma, S. Ichijio, S Kasukabe, S. Miyata, T. Yoshikawa, K. Yanai, H. Taki, H. Kanai, N. Osumi and H. Shimokawa, "Whole-brain low-intensity pulsed ultrasound therapy markedly improves cognitive dysfunctions in mouse models of dementia – Crucial roles of endothelial nitric oxide synthase, Brain Stimulation, 11 (5), 2018, pp. 959-973, doi: 10.1016/j.brs.2018.05.012.

[23] N. Lipsman, Y. Meng, A. Bethune, Y. Huang, B. Lam, M. Masellis, N. Herrmann, C. Heyn, I. Aubert, A. Boutet, G. Smith, K. Hynynen and S. Black, "Blood-brain-barrier opening in Alzheimer's disease using MR-guided focused ultrasound", Nature Communications, 9, 2336, 2018, doi: 10.1038/s41467-018-04529-6.