



NEUROLITH[®]
Transcranial Pulse Stimulation (TPS[®])
in Alzheimer's Disease

STORZ MEDICAL

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STORZ MEDICAL – Our approach to treating patients with Alzheimer’s disease

STORZ MEDICAL has been using shock waves for the extracorporeal treatment of kidney stones (extracorporeal shock wave lithotripsy, ESWL) since the late 1980s. Today, we also employ shock waves with great success in the treatment of musculoskeletal disorders and pseudarthrosis (extracorporeal shock wave therapy, ESWT), for the stimulation of angiogenesis, in the treatment of wound healing disorders and in angina pectoris therapy (cardiac shock wave therapy, CSWT).

In the mid-1990s, we discovered the effectiveness of shock waves in the treatment of peripheral neurological diseases such as post-trau-

matic spasms, spastic paralysis and polyneuropathy (Dr Lohse-Busch, Bad Krozingen)^{1,2}. 2014 saw the first treatment of Alzheimer’s patients with shock waves. In 2018, Transcranial Pulse Stimulation (TPS®) with the NEUROLITH® system was the first, and hitherto only, procedure of its kind to obtain authorization for the »treatment of the central nervous system of patients with Alzheimer’s disease«.

In view of the initial success rates achieved, neurological diseases such as Parkinson’s disease, stroke and spinal cord injuries will be one of the key areas in our ongoing clinical research and development activities.

Publications:

¹Lohse-Busch, H. et al.: Focused low-energy extracorporeal shock waves with distally symmetric polyneuropathy (DSPNP): a pilot study, NeuroRehabilitation, Vol. 35(2), 227–233, 2014

²Lohse-Busch, H. et al.: Symptomatic treatment of unresponsive wakefulness syndrome with transcranially focused extracorporeal shock waves, NeuroRehabilitation, Vol. 35(2), 235–244, 2014

1989: MODULITH® SL10 for kidney stone treatment (ESWL)



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Applied knowledge in neurology – The TPS® method of action

The clinical symptoms of Alzheimer's disease are caused by a progressive loss of neurons. This results in cerebral atrophy, especially in the cerebral cortex. The progressive death of neurons also leads to the disruption of synaptic connections between nerves. These connections are responsible for the transmission and processing of information. Disrupted information processing is one of the root causes of memory loss.

Based on the knowledge gathered to date, destructive protein molecules that develop outside the neurons and disrupt their function are thought to be the triggering factor in the pathogenesis of Alzheimer's disease. One of these molecules, the beta-amyloid protein, accumu-

lates and is deposited in the brain of Alzheimer's patients, forming structures called plaques which reduce cerebral blood flow and, consequently, interfere with the oxygen and energy supply to the brain cells.

This is where TPS® comes in!

The key mechanism induced by TPS® is mechanotransduction. The stimulation of growth factors, primarily VEGF^{3,4}, not only improves cerebral blood flow, but also promotes the formation of new blood vessels (angiogenesis) and nerve regeneration. An additional effect is the release of nitric oxide (NO)⁵, which leads to direct vasodilation and improved blood circulation.

Publications:

³Yahata, K. et al.: Low-energy extracorporeal shock wave therapy for promotion of vascular endothelial growth factor expression and angiogenesis and improvement of locomotor and sensory functions after spinal cord injury, *J Neurosurg Spine*, Vol. 25(6), Pages 745–755, 2016

⁴Hatanaka, K. et al.: Molecular mechanisms of the angiogenic effects of low-energy shock wave therapy: roles of mechanotransduction, *Am J Physiol Cell Physiol*, Vol. 311(3), C378–C385, 2016

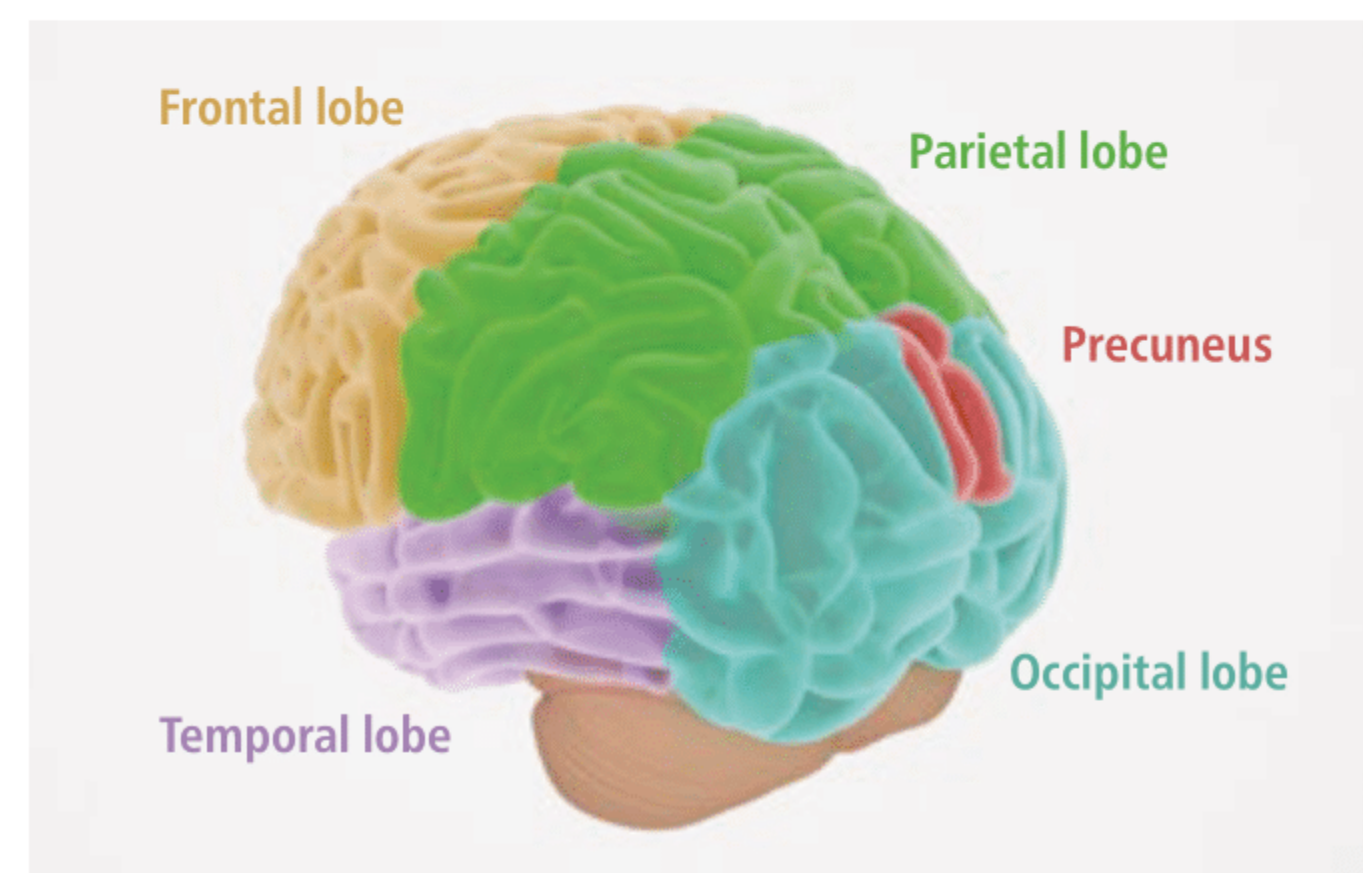
⁵Mariotto, S. et al.: Extracorporeal shock waves: From lithotripsy to anti-inflammatory action by NO production, *Nitric Oxide*, Vol. 12(2), 89–96, 2005

⁶d'Agostino, M. C. et al.: Shock wave as biological therapeutic tool: From mechanical stimulation to recovery and healing, through mechanotransduction, *Int J Surg.*, Dec. 24(Pt B), 147-153, 2015

⁷López-Marín, L. M. et al.: Shock wave–induced permeabilization of mammalian cells, *Phys Life Rev.*, 26-27:1-38, 2018

⁸Wang, B. et al.: Low-Intensity Extracorporeal Shock Wave Therapy Enhances Brain-Derived Neurotrophic Factor Expression through PERK/ATF4 Signaling Pathway, *Int J Mol Sci.*, Feb 16;18(2). pii: E433, 2017

Cerebral regions to be treated



TPS® enables targeted stimulation of cerebral regions.



Biological effects of TPS®

- Mechanotransduction⁶
- Increase in cell permeability⁷
- Stimulation of mechanosensitive ion channels⁶
- Release of nitric oxide (NO)⁵, which leads to vasodilation, increased metabolic activity and angiogenesis and has an anti-inflammatory effect
- Stimulation of vascular growth factors (VEGF)^{3,4}
- Stimulation of BDNF⁸
- Migration and differentiation of stem cells^{4,6}

TPS

Energy (mJ/mm²) 0.25

Shocks 6000

Frequency (Hz) 4.0

Total shocks 6000

Total energy (J) 49.052

Top

Front

Left

x 2 mm
y -21 mm
z 131 mm

Zoom 14

Transparency

Head 0.1

Handpiece 0.1

007

26.02.2019 10:08
Storz Medical



TPS® non surgical treatment of Alzheimer's disease: an effective and safe procedure

TPS® can stimulate deep cerebral regions, reaching as much as 8 cm into the brain. Owing to the short duration of the TPS® stimulation, tissue heating is avoided. The pulses applied to the treatment area thus develop their maximum clinical effectiveness. TPS® treatment is performed through the closed skull. The patient is not immobilized during the treatment and able to move freely. TPS® treatment has been shown to significantly improve CERAD test performance and to reduce Beck's depression index in patients with mild to moderate dementia. Over 1500 treatments have already been performed using the NEUROLITH® system. No side effects have been reported so far.

TPS® treatment of patients with mild dementia:

The objective of the treatment is to help patients remember the details of conversations better and find objects more easily after putting them away. Another goal is to reduce the impairment of planning and organizational thinking, language expression and orientation.

TPS® treatment of patients with moderate dementia:

The objective of the treatment is to counteract memory decline as well as deterioration of thinking ability and orientation skills, in order that patients can live more independent lives. Additionally, the treatment is designed to help patients communicate more easily with those around them.

Advantages of TPS®

- 6 treatment sessions in 2 weeks
- Outpatient treatment (30 minutes/session)
- Painless and without side effects
- Personalized treatment based on MRI data
- Adjuvant cognitive training not required
- Shaving of the scalp not required
- No immobilization of the patient during treatment

TPS® pressure distribution

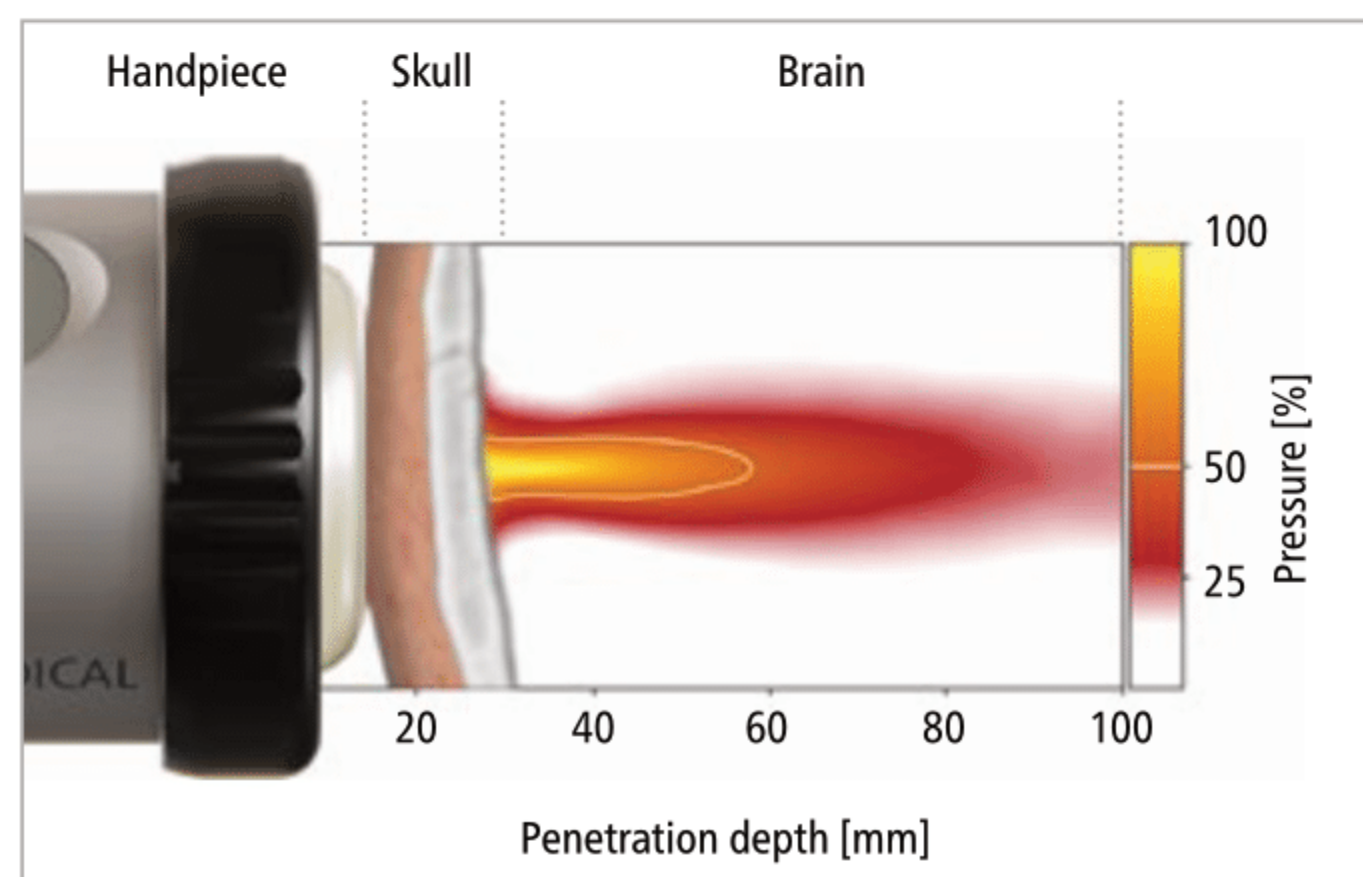


Diagram: improvement over 3 months

TPS® boost: 6 treatment sessions in 2 weeks

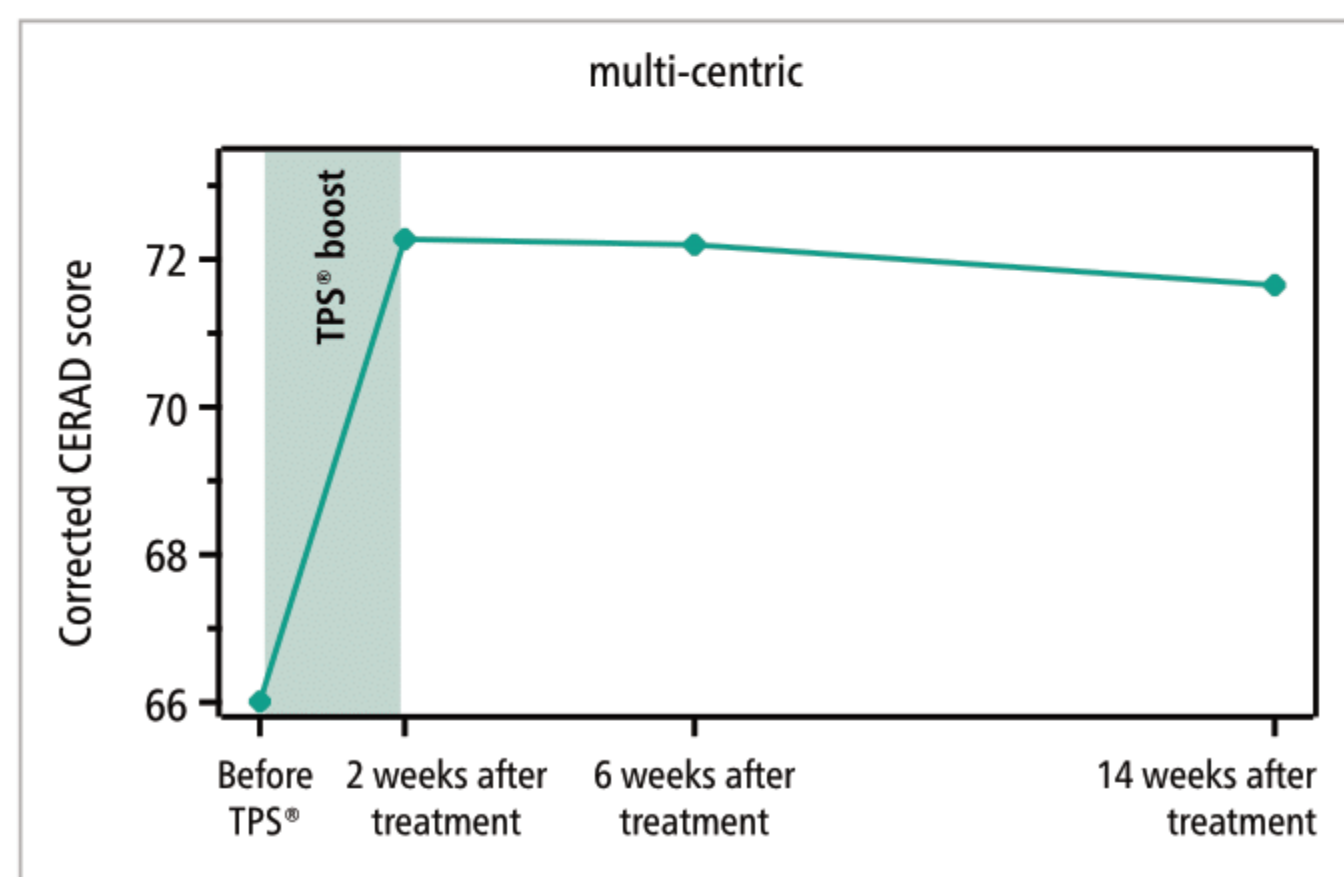
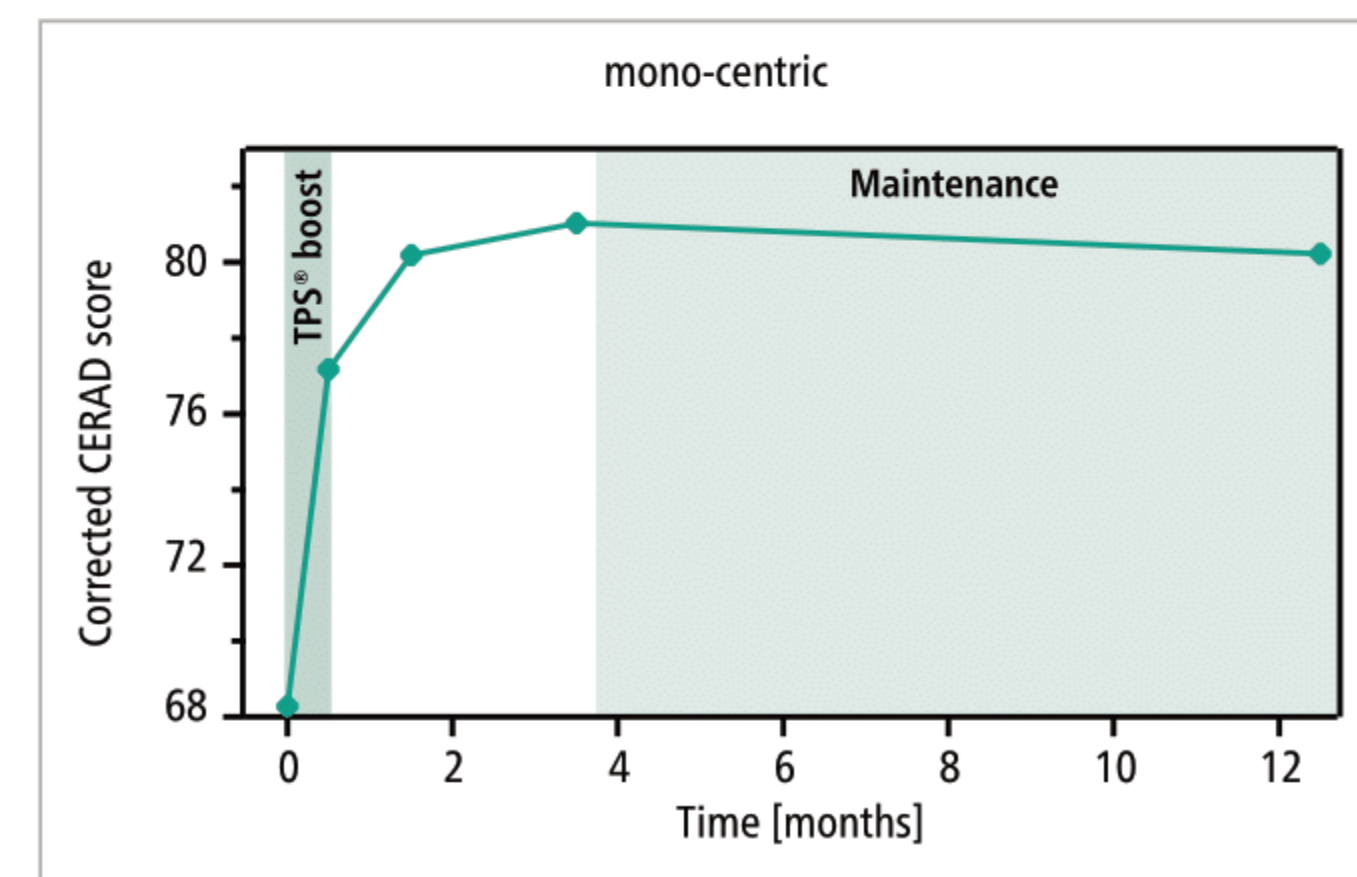
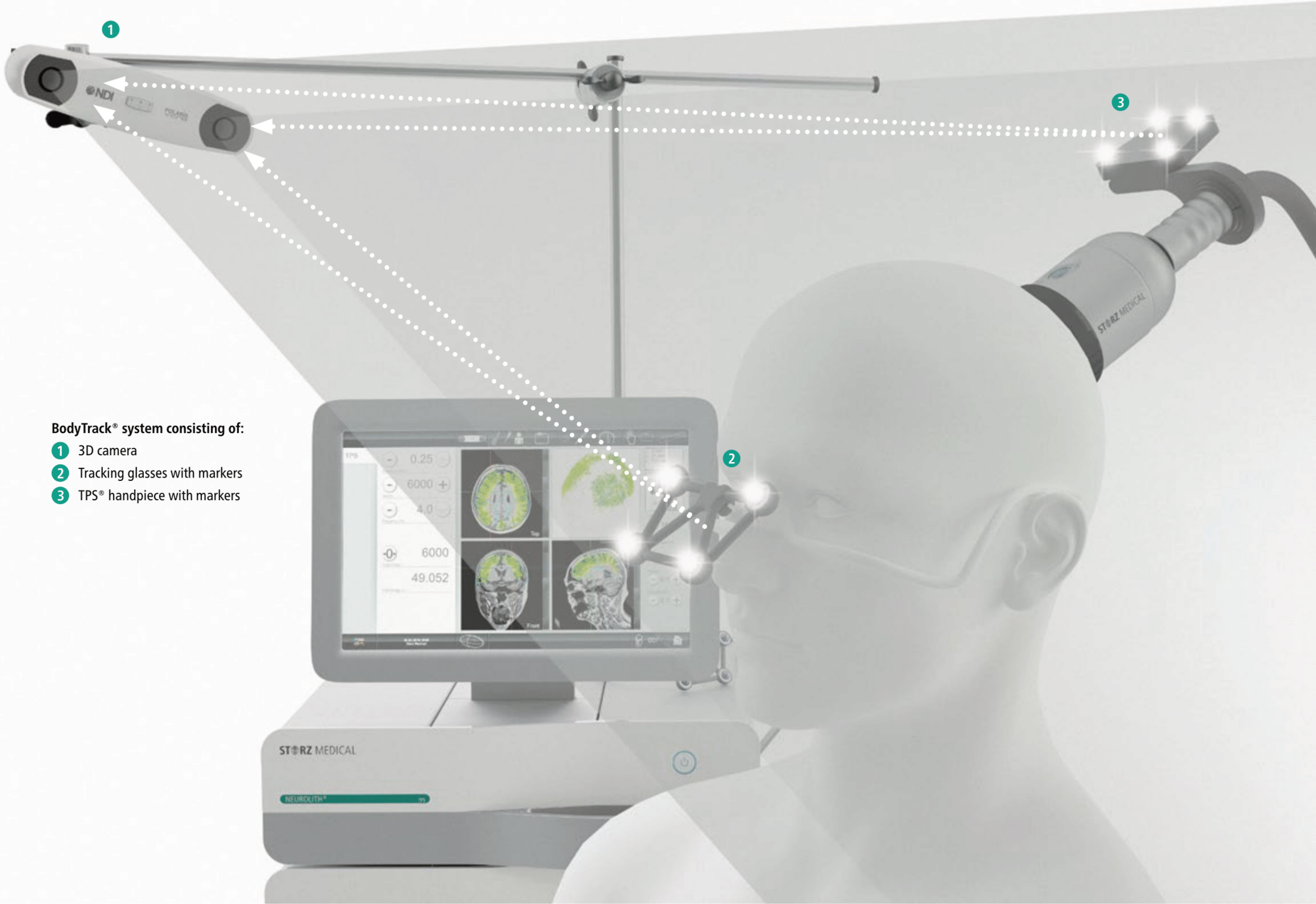


Diagram: improvement over 12 months

TPS® boost: 6 treatment sessions in 2 weeks

Maintenance: 1 treatment every 6 weeks (after 3 months)





BodyTrack® system consisting of:

- 1 3D camera
- 2 Tracking glasses with markers
- 3 TPS® handpiece with markers

BodyTrack® – Treatment documentation in real time

3D visualization for maximum precision, control and safety

The BodyTrack® software is the heart of the patented NEUROLITH® system. Simple and rapid calibration ensures that the shape of the head matches the patient's MRI data. In this manner, each pulse applied can be visualized and documented in real time. Real-time tracking of the handpiece position enables automatic visualization of the treated regions. The use of personalized MRI data allows specific characteristics of the patient's brain to be taken into account. Every time the handpiece position changes, the visualization of the target regions in

the loaded MRI scans is automatically updated. The energy applied is highlighted in colour. The BodyTrack® software is a unique tool for the visualization and control of the TPS® pulses applied and of treatment progress.

Another benefit of the BodyTrack® software is that the user can define patient-specific treatment areas and target regions.

Advantages of the BodyTrack® software

- Use of personalized MRI data
- Visualization of MRI data in 3 planes (axial, coronal, sagittal)
- Coloured visualization of the treatment region
- Real-time visualization of TPS® pulse distribution
- Continuous visualization and documentation of the energy applied and of treatment progress

Manually controlled calibration, steps 1 (red) and 2 (blue)



Manually controlled calibration, step 3 (green)



Real-time visualization of TPS® treatment





NEUROLITH® – The perfect solution to facilitate Alzheimer’s treatment

NEUROLITH® – an innovative system with convincing design features! The special ergonomic shape of the TPS® handpiece minimizes hand fatigue to facilitate treatment working directly on the patient. The coupling surface adapts easily to any shape of head, making the treatment with focused pulses simple and efficient. The NEUROLITH® software includes patient management functionalities with retrievable data and recommended treatment parameters.

The BodyTrack® function supports real-time visualization and documentation of the TPS® treatment. The 3D infrared camera technology ensures high-precision tracking between the handpiece and the tracking glasses. The perfect synergy between state-of-the-art camera technology and the BodyTrack® software enables unprecedented interaction between the doctor and the Alzheimer’s patient.

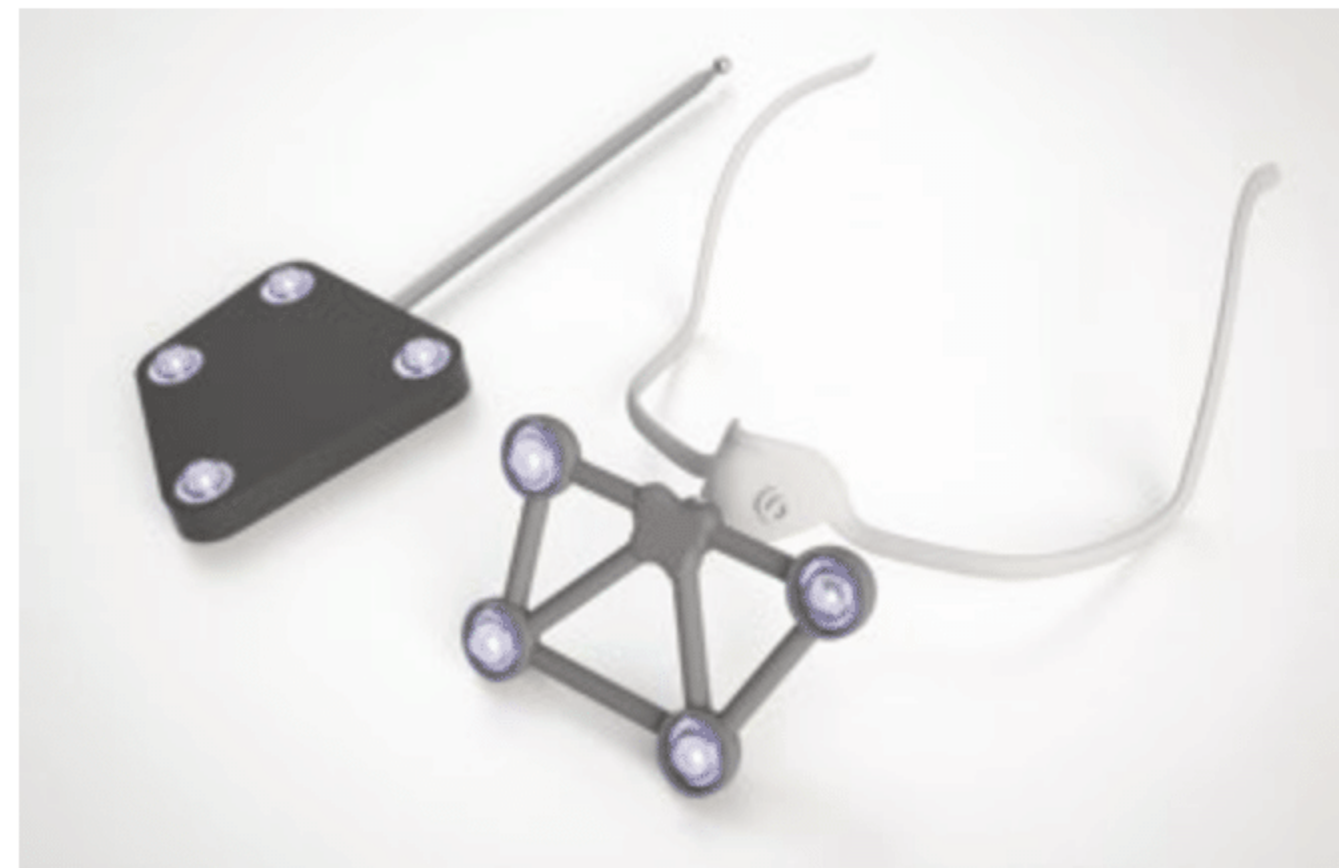
Advantages of the NEUROLITH®

- Focused stimulation of deep cerebral regions
- Personalized 3D visualization of patient’s head
- 3D infrared camera system for precise cerebral tracking
- USB interface for MRI data import
- Patient database

3D camera with patient and handpiece position detection



Calibration probe and tracking glasses with markers



TPS® handpiece with markers





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