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Non-invasive brain stimulation to promote alertness and awareness in chronic patients with disorders of consciousness: Low-level, near-infrared laser stimulation vs. focused shock wave therapy

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Abstract.
Purpose: In order to promote alertness and awareness in patients with severe disorders of consciousness (DOC) frontal near infrared laser stimulation (N-LT) or transcranial focused shock wave therapy (F-SWT) might be an option. The study compared both techniques in severe chronic DOC patients.
Methods: Sixteen DOC patients were allocated to two groups (A and B). A three week baseline either followed a frontal N-LT (0,1 mJ/mm^2, 10 min per session), five times a week over four weeks (group A), or a F-SWT (0,1 mJ/mm^2, 4000 stimuli per session) three times a week over four weeks (group B). The primary variable was the revised Coma Recovery Scale (r-CRS, 0–23), blindly assessed.
Results: Both groups improved in the r-CRS over time, but revealed no differences between groups. One patient of group B had a focal seizure in the third therapy week. One patient with akinetic mutism improved most and three patients with global hypoxia did not improve at all.
Conclusions: Both options might be an option to increase alertness and awareness of chronic DOC patients. An akinetic mutism seems to be a positive and severe cerebral hypoxia a negative predictor. Epileptic seizures are a potential unwanted side effect. More clinical studies are warranted.

Keywords: Disorder of consciousness, minimal conscious state, unresponsive wakefulness syndrome, non-invasive brain stimulation, laser therapy, focused shock wave therapy

1. Introduction

The reported incidence and prevalences of DOC patients varies considerably: 0.5 to 2.5 or 4 to 16.8 patients per 100,000 inhabitants, respectively. Craniocerebral traumas and cerebral hypoxias are the most common causes (Ahmadi, 2010). The promotion of alertness and awareness is a prime concern for the neurological rehabilitation of DOC patients. Consciousness is linked to the functional capability of both hemispheres, and the activating reticular system rising out of the brain stem is the neuro-anatomical basis of alertness (Erbguth, 2013; Schnakers, 2009).

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Depending on the clinical findings, a distinction is now made between Unresponsive Wakefulness Syndrome (USW) and Minimally Conscious State (MCS). An MCS patient can, for example, follow a mirror that is moved in front of his or her eye or reproduce simple verbal commands (Ahmadi, 2010; Schnakers, 2009). Akinetic mutism due to a frontal cerebral lesion is differentiated as a further clinical entity (Formisano, 2011). Recognised therapeutic options for the promotion of alertness and awareness include multi-sensory stimulation in the context of a structured rehabilitation, Amantadine (Giacino, 2012), Zolpidem (Du, 2014), and, in case reports, deep cranial stimulation of the thalamus (Schiff, 2013).

A new therapy form is non-invasive cerebral stimulation, for which three options are currently available: transcranial direct current stimulation (tDCS) (Angelakis, 2014; Lesniak, 2014; Thibaut, 2014), near-infrared low-level laser stimulation (N-LT) (Hashmi, 2010; Hesse, 2014; Zivin, 2009) and transcranial shock wave therapy (F-SWT) (Lohse-Busch, 2013).

With respect to N-LT and F-SWT, case histories exist that include reports of the positive effects of a therapy regimen extending over several weeks among both chronic UWS and MCS patients: in addition to an increase in alertness and awareness, there was even an improvement in both ADL competence and mobility in some cases (Hesse, 2014; Lohse-Busch, 2013).

Taking up where these positive reports left off, the present study among chronic DOC patients presenting with a variety of aetiologies compared the effect of four-week therapies involving either N-LT or F-SWT. The primary variable was the internationally accepted revised version of the Coma Recovery Scale (r-CRS, 0–23) (Giacino, 2004). The therapy protocols followed those of the published studies (Hesse, 2014; Lohse-Busch, 2013). Questions of immediate importance for the study were, in addition to the assessment of the effectiveness of the two procedures, safety aspects and the detection of possible predictors.

2. Methodology

2.1. Patients

Included in the study were 16 patients at either a stationary care facility for DOC patients ($n = 4$) or at a clinic for neurological rehabilitation ($n = 12$); they were 9 women and 7 men, on average 51 ± 19.9 years old. Clinical findings prior to the beginning of the study revealed that 14 patients suffered from UWS and two from MCS syndrome. Criteria for inclusion were:

- Status CNS lesion (craniocerebral trauma, cerebral hypoxia or multiple cerebral strokes) with a lesion interval prior to the onset of the study of at least 12 months
- Diagnosis of a UWS or an MCS following neurological examination and cerebral imaging
- No epileptic fits in the six months immediately prior to the start of the study, with or without anti-epileptic medication
- No metallic implants in the brain
- No ventriculo-peritoneal or ventriculo-atrial shunt system
- Status post craniectomy without reinsertion of cover
- No cardiac pacemaker
- No oral anticoagulants
- No pregnancy
- No additional administration of alertness-enhancing medications during the study, e.g. Amantadine, L-Dopa or SSRI; a pre-existing medication regimen was continued
- Written consent of the legal guardian to the study, positive votes of local ethics commissions for both procedures were obtained, the devices used were CE-certified.

2.2. Interventions

The patients were assigned to the two groups (A or B) by lottery. The patients in Group A ($n = 8$), analogous to the protocol published by Hesse et al., were treated with the laser therapy in the near-infrared range (N-LT) for 10 minutes at a time, five times a week for four weeks, thus for a total of 20 therapy applications (Hesse, 2013). A CE-certified device ("Power Twin 21", MKW Lasersysteme) was used that had the following properties: wavelength 785 nm, Nogier É, 21 diodes and an energy flux density of 10 mW/cm^2, meaning that each diode emitted an energy of 6 J over a 10-minute period.

Five points were established and marked along a horizontal line at the level of the upper edge of the two fossa sphenoidalis. Each point was stimulated twice, each time for one minute, for which the therapist placed the laser against the skin with a maximum

of contact. The patient wore protective goggles during the session.

Analogous to the protocol published by Lohse-Busch et al., the patients in Group B ($n = 8$) were treated three times a week for four weeks with the focused shock wave (F-SWT), thus corresponding to a total of 12 therapy applications (Lohse-Busch, 2013). 4000 stimuli were applied during each therapy unit. A CE-certified device (Duolith, Storz Medical) was used with the following properties: energy flux density 0,1mJ/mm^2 , 6 Hz, 4000 stimuli, penetration depth of the focus approximately 5.5 cm. 2000 stimuli were applied to each half of the skull. Ultrasound gel was applied in the stimulation region to ensure optimum contact, after which the transducer was guided from the middle of the forehead across the temporal, parietal and occipital bones up to the inion and back again. It took approximately five seconds to cover this distance each time, which meant that the transducer moved back and forth around forty times. The user took care to ensure that the transducer was always in contact with a maximum amount of scalp area, and that it was held at an angle in accordance with the shape of the head. The transducer was tilted by approximately 45° in the area of the inion in order to target the brain stem there. The patient sat in bed in as upright a position as possible; if this was not possible, then his or her head was turned accordingly and held with the aid of a second person.

In addition, the patients received physiotherapy, ergotherapy and/or logopaedia with an average frequency of ten appointments per week for the patients in the inpatient facility for DOC patients and an average of 20 appointments per week for the patients in the clinic for neurological rehabilitation.

2.3. Dependent variables

The primary dependent variable was the reliable and valid revised version of the "Coma Recovery Scale" (r-CRS, 0–23) (Giacino, 2004). A distinction was made between six dimensions: Auditory (0 = no response – 4 = consistent movement to command), Visual (0 = no response – 5 = object recognition) and Motor (0 = hypotonia – 6 = functional object use) function scales, Oromotor/Verbal (0 = none – 3 = intelligible verbalization), Communication (0 = none – 2 = functional: accurate) and Arousal (0 = unarousable – 3 = attention). The assessment was based on the presence or absence of specific response behaviour to standardised sensory or auditory stimuli.

The simplest task checked reflex activities and the most difficult one a consciously executed response behaviour.

Secondary variables were the SMART (0–25) (Gill-Thwaites, 1999) and FOUR (0–16) (Wijdicks, 2005) scales as well as the well-known Barthel Index as a measurement of competence in the activities of daily living (BI, 0–100) (Mahoney, 1965).

The Smart Scale (0–25) checked the five sensory qualities of Taste (essence of vinegar), Vision (examination lamp), Hearing (clapping of hands), Tactile sense (touch or pain stimulation), and Smell (essence of vinegar). A distinction was made between five qualities of answers, depending on the answer or response, respectively, to the stimulus: 1. patient absent or in deep sleep, 2. reflexive, 3. patient withdraws from the stimulus, 4. localisation in the sense that the patient turns to the stimulus or raises his or her hands to fend it off, and 5. is able to distinguish between various stimuli in accordance with corresponding verbal instruction. Depending on the findings, points were assigned per item from 0 (absence of response) to 5 (can distinguish between stimuli).

The hierarchical FOUR scale tested the clinical performances of the patient in the four dimensions of eye movement, motor response to a pain stimulus or to a verbal command, brain stem reflexes (pupil and corneal reflex) and breathing. The eye movement dimension investigated the opening of the lid in response to pain, to a loud command and the tracking glance movement (absent or present) by means of a mirror; four points were assigned. The motor response dimension investigated the motor response of the hand to pain stimulus, for which a distinction was made between no response, a stretch response, a flexor response and the localization of pain or an arbitrary hand movement in response to a verbal or gestural command. The brain stem reflexes dimension investigated the pupil and corneal reflex, with a distinction being made between no response, in which case the gagging reflex was also investigated, the positive triggering of one of the two reflexes, the widening and fixing of one of the two pupils and the presence of both reflexes. The breathing dimension distinguished between full respiration, partial respiration, non-intubated with irregular breathing pattern, non-intubated with Cheyne-Stokes breathing pattern and normal breathing.

In addition, patients' family members were surveyed about their estimation of questions of alertness, possible interactions with the patient and emotional

feedback from them before and after the respective four-week intervention.

An experienced researcher, who was blinded with respect to the assignments to the groups, surveyed all of the dependent variables before the therapy and two, four and (as a follow-up) eight weeks after the start of the study. In order to take into account possible fluctuations with respect to alertness and awareness prior to the start of therapy, a baseline with three measurement points was carried out by the same researcher at weekly intervals.

2.4. Statistics

In an initial step, the median of the three baseline values was defined as the starting value on the date T0. The Wilcoxon Test specified a change over time (alpha = 0.05) and the non-parametric Mann-Whitney Test specified a possible difference between the two procedures on the dates T4 and TFU (adjusted alpha = 0.025). The 95% confidence interval was calculated in addition as an interpretation of clinical relevance.

3. Results

Table 1 reproduces the clinical data of the patients in the two groups prior to the start of the study. The number of UWS patients accounted for the majority in both groups. There were, even assuming a limit value of <9 in the r-CRS Score, eight UWS patients in Group A and five in Group B. Patient #4 from Group A differed from the others in that she had suffered a pronounced frontal lesion following SHT and had been diagnosed with a case of akinetic mutism. The aetiologies SHT, cerebral hypoxia and the status following multiple strokes were equally distributed in the two groups.

Fifteen patients completed the intervention, one female patient with UWS (#2) in Group B suffered a one-time focal seizure with secondary generalization in the third week of the intervention after eight specific therapies (Fig. 1). The seizure occurred 32 hours after the last stimulation, at the same time she was being administered a seizure-threshold-reducing antibiotic as a treatment for periodontitis. She had had no corresponding medical history and was transferred from the home to the acute care hospital to stop the seizure. The imaging there showed no change from the prior findings, an anticonvulsant was prescribed for the patient, and the intervention was discontinued in consultation with the attending physician.

Figures 2 and 3 show the individual and Table 2 the mean results of the r-CRS of the two groups (means, SD, 95% confidence interval) (Table 2). The mean (SD) r-CRS score of the two groups improved significantly over time, and no difference arose between the groups at any time. The FOUR and the SMART scales (Table 2) also improved significantly during the intervention, and once again no differences between the groups were displayed. At the time of the follow-up four weeks following the end of the intervention, the improvements of the two groups was at a minimum sustained.

It was assumed that an improvement by four points on the r-CRS scale could not be explained as an improvement in alertness and awareness arising from daily fluctuations (Schiff, 2013; Schnakers, 2009). As confirmation of this threshold, the baseline measurements had revealed a maximum deviation over a three-week period of two r-CRS points. This limit value was achieved by 12 patients: three MCS patients in Group B (it will be recalled that there were no MCS patients in Group A at the start of the study) and nine of the 13 patients with a UWS syndrome at the beginning, six from Group A and three from Group B (Figs. 2 and 3). The greatest improvement (+8 points) was achieved by Patient #4 in Group A with the akinetic mutism following a frontal cerebral lesion. She was the only patient to achieve a relevant improvement of her ADL capability (BI from 0 to 15); ADL competency remained unchanged in all other cases. In the estimation of the speech therapist

Table 1
Clinical data of all patients at study onset (T0)

	Near- infrared Laser therapy (N-LT)	Focused Shock Wave therapy (F-SWT)
N	8	8
Diagnosis	TBI = 4, Hypoxia = 3, multiple stroke = 1	TBI = 4, Hypoxia = 2, multiple stroke = 2
Syndrome	UWS = 8, MCS = 0	UWS = 6, MCS = 2
Lesion interval [in months]	45.2 (±27.7)	40.1 (±26.6)
Age [in years]	54.1(±20.5) [range: 27–76]	49.0 (±22.6) [range: 21–79]
Sex	5 = female, 3 = male	4 = female, 4 = male
Barthel Index [BI, 0–100]	0.0 (±0.0)	0.0 (±0.0)

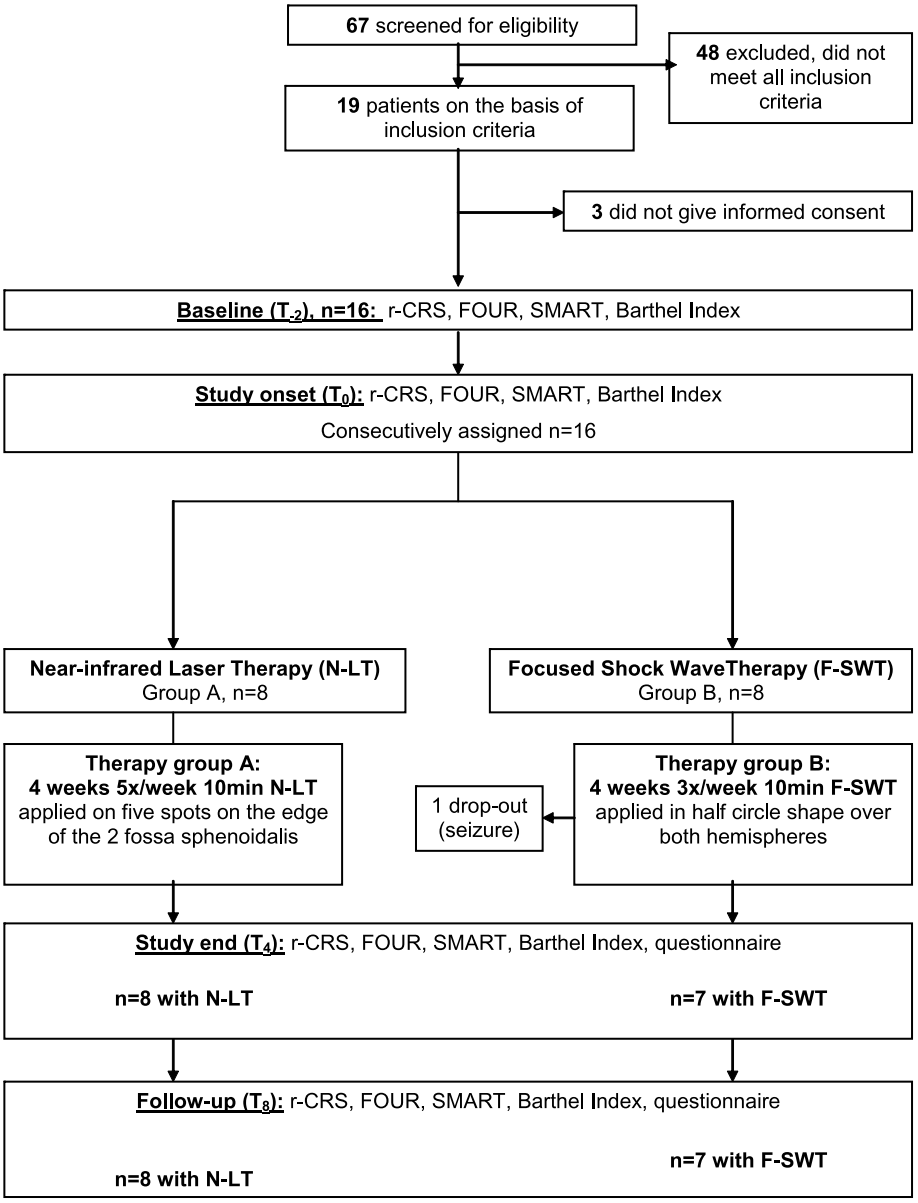

Fig. 1. Flow chart of the study.

and of the family caregivers, three patients (Group A: $n = 1$; Group B: $n = 2$) were able to swallow better and with greater assurance, although it was not possible to remove the PEG tube from any of the three patients. One of the 12 patients (#2 from Group A) began to cry when she saw herself in the large therapeutic mirror in the second half of the intervention period.

Of the four UWS patients who did not achieve the threshold (two from Group A and two from Group B), three experienced no improvements whatsoever and one patient achieved only two points. The three patients who exhibited no improvement had the lowest initial values (4, 5 or 6 r-CRS points) and the aetiology was cerebral hypoxia following circulatory arrest in two cases and a self-induced insulin coma arising from a suicide attempt in the third case.

The family members/nursing staff reported in 11 cases that the alertness, possibilities for interaction and the emotional feedback from their affected relatives had increased. The family members/nursing staff experienced no change in the other five patients.

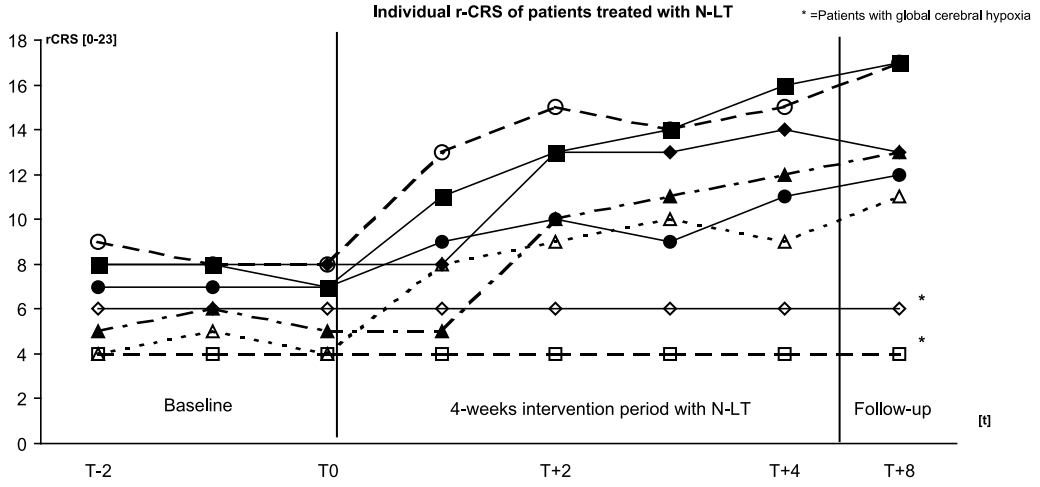

Fig. 2. The graphs show the individual progress of r-CRS among the patients who were treated with N-LT.

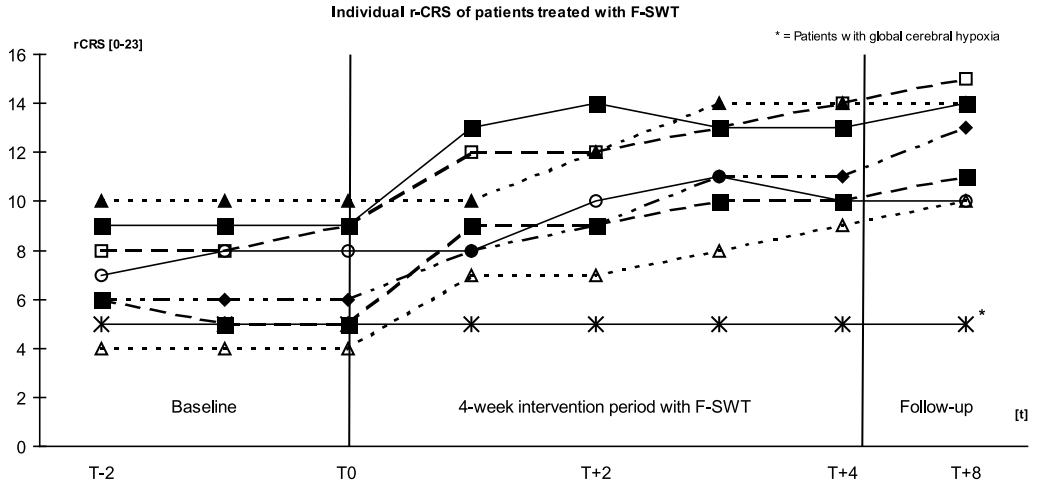

Fig. 3. The graphs show the individual progress of r-CRS among the patients who were treated with S-WT.

4. Discussion

The N-LT and F-SWT therapies over four weeks each increased the alertness and the awareness of the chronic DOC patients of different aetiologies to comparable extents. An improvement of the r-CRS by at least four points was achieved by 12 of the 16 patients, and the results were at a minimum sustained at the time of the follow-up examination.

The risk of a focal epileptic seizure with secondary generalization exists in connection with the application of both procedures. During the study under review, one patient from the F-SWT group suffered this potential side effect during the third week of therapy. Hesse et al. had also previously reported the provocation of a focal cerebral seizure with secondary generalization in one of five patients who received N-LT (Hesse, 2014). The medical histories in both cases were inconspicuous, and there was no direct connection between the treatment and the seizures; interestingly, both patients had been simultaneously receiving an antibiotic that lowered the seizure threshold. In this context, the simultaneous utilisation of medications that lower the seizure threshold should be checked in individual cases.

Twelve of the 16 patients increased their r-CRS by at least four points, which was not regarded as being an improvement of alertness and awareness that could be explained in terms of day-to-day fluctuations (Giacino, 2012; Rauch, 1944; Schnakers, 2009). It was only for the patient with the akinetic mutism that this resulted in an unambiguously

Table 2
Mean (SD) of the revised Coma Recovery Scale, Four- and SMART Scale as well as the mean differences and 95% confidance intervals (CI) of the deltas T0 to T4 and T0 to T8

Variable	Near-infrared Laser Therapy (N-LT)						Focused Shock Wave Therapy (F-SWT)					
	T-2 Baseline	T0 study onset	T+4 after inter-vention	T+8 Follow-up	95% CI T0–T4	95% CI T0–T8	T-2 Baseline	T0 study onset	T+4 after inter-vention	T+8 Follow-up	95% CI T0–T4	95% CI T0–T8
r-CRS (0–23)	6.4 ± 1.9	6.3 ± 1.9	10.9 ± 4.3	11.6 ± 4.7	4.6 2.2–7.2	5.4 2.3–8.4	6.9 ± 2.0	6.9 ± 2.2	10.8 ± 3.0	11.5 ± 3.3	3.9 2.2–5.5	4.6 2.5–6.7
FOUR Scale (0–16)	10.6 ± 1.1	10.6 ± 1.7	12.8 ± 2.1	13.1 ± 2.4	2.1 0.8–3.5	2.5 1.0–4.1	10.6 ± 1.3	10.6 ± 1.3	12.3 ± 1.8	12.8 ± 2.0	1.6 0.9–2.4	2.1 1.1–3.2
SMART Scale (0–25)	5.4 ± 1.4	5.4 ± 1.5	7.8 ± 2.7	8.1 ± 3.5	2.4 1.0–3.7	2.8 0.8–4.7	6.3 ± 1.1	6.3 ± 1.4	8.5 ± 2.4	9.0 ± 2.9	2.3 1.2–3.3	2.8 1.3–4.2

clinically relevant improvement in that she increased her ADL competence and mobility. The remaining 11 patients remained completely dependent on care; in three cases there was an improvement in swallowing, although this was not sufficient to enable the patient to eat without relying on the PEG tube. The nature of the situation made it difficult to assess the feelings of the patients; one recognizable emotional reaction occurred when one patient began to cry when she saw herself in the mirror. Family members and nursing staff, on the other hand, who had been taking care of their patients for years, expressed themselves positively in 11 cases, emphasising in particular the perceived increase in possibilities for interaction and the greater emotional feedback.

Three UWS patients exhibited no changes in their r-CRS scores whatsoever. On the one hand, they exhibited a low initial r-CRS value (4, 5 and 6 points) and on the other hand had suffered global brain damage as the result of a cerebral hypoxia following circulatory arrest or an insulin coma. Cerebral hypoxia causes diffuse cortical necroses of the brain; in the case of insulin coma, Rauch et al. discussed the fact that it did not cause damage to the brain solely through such complications as seizures or circulatory disorders, but that it also exercised a direct toxic effect on the vascular endothelia and the cerebral parenchyma (Rauch, 1944). Future studies should take into account these two negative predictors as needed.

A positive effect in acute stroke therapy has been documented for one-time N-LT (Zivin, 2009). N-LT is claimed to enhance cortical mitochondrial energy production by stimulating Complex IV of the respiratory chain, as successfully demonstrated by Lapchak and De Taboada on the rabbit brain (Lapchak, 2010) The authors assume an energy of 10 mW/cm^2 from a penetration depth of 20–30 mm. Cadaver studies confirm that transcranial N-LT reaches the brain (Jagdeo, 2012) Mildly handicapped SHT patients reported that repeated bifrontal N-LT self-stimulation had improved attentiveness and healthy subjects were able to increase their emotional and cognitive abilities in a controlled study (Konstantinovic, 2013). Hashmi et al. applied bifrontal stimulation with N-LT 73 times to a UWS patient. The authors observed an increase in the regional cerebral blood flow and in motor capabilities; the patient reached for his tracheal cannula with this left hand for the first time (Hashmi, 2010). Hesse et al. reported a positive effect on alertness and awareness among five UWS patients who received a six-week N-LT treatment in the area of the forehead;

the improvements in the r-CRS scores corresponded to the those in the present study (Hesse, 2014) Here, too, only one patient with an akinetic mutism was able to reduce his dependency on care.

Focused shock waves are used mainly in lithotripsy and orthopaedic rehabilitation (Coleman, 1995; Mariotto, 2012). Spasticity therapy and the promotion of peripheral nerve regeneration are known indications in neurological rehabilitation. A promotion of angiogenesis and neurogenesis is accepted as the mode of action of bundled ultrasound (Mariotto, 2012). The stimulation of the production of endothelial nitrous oxides and vascular growth factors have been demonstrated in cell cultures. With respect to possible tissue damage caused by the focused energy, it should be taken into account that the energy flux density applied in the present study was lower by a power of 10 than the levels that are applied in lithotripsy treatments, that the therapy source was in continuous movement and that the bones in the skull presumably absorbed the majority of the energy (Coleman, 1995). Whereas it is true that the energy flux density used with F-SWT corresponded to that of N-LT (each of them 10 mW/cm^2), it was, however, more focused and, with 50 mm, penetrated more deeply, according the company that manufactured it.

Lohse-Busch et al. were the first to report on a transcranial application among DOC patients in the case of five patients with disorders of consciousness (Lohse-Busch, 2013). The protocol under review (several weeks' treatment, three times per week with 4000 shock waves per session) was in accordance with the recommendations of the authors. The authors did not report any unwanted side effects; in clinical terms, all of the patients experienced marked improvement in alertness and awareness – and in some cases in swallowing capability and motor function – after several four-week series. The results under review were less pronounced that those reported by Lohse-Busch et al., although those authors had applied several four-week series (Lohse-Busch, 2013).

The nature of the study did not permit a direct comparison with the effectiveness of the third option, namely tDCS. In addition, the results that have been made available regarding t-DCS are inconsistent. In one controlled study, Angelakis et al. reported the positive effect of a one-time tDCS in comparison with a placebo therapy (Angelakis, 2014). They studied a total of 10 subacute patients with UWS or MCS and various aetiologies who were treated in accordance with an A-B or B-A design, respectively (A = verum, B = placebo). The MCS patients improved significantly in the r-CRS with the verum stimulation; there was no unambiguous difference for the UWS patients, a result that was confirmed by Thibaut et al. in another controlled study involving a comparable patient collective (Thibaut, 2014). However, no effect on the t-DCS was exhibited by the controlled study of Lesniak et al., who stimulated 23 chronic patients following SHT using an anodal tDCS via the left dorsolateral prefrontal cortex simultaneously with an attentiveness training program (Lesniak, 2014).

Limits of the study are the small sample size and the concomitant rehabilitation that varied in its extent, depending on the treatment site, a clinic or nursing home for DOC patients. Awareness was also not quantitatively investigated and, in clinical terms, impairments which are either very difficult or even impossible to determine with respect to vision, hearing, communication and motor function may have made the implementation of the testing tasks more difficult. Furthermore, there was no placebo-controlled application or a control group that did not receive non-invasive cerebral stimulation.

In summary, N-LT and F-SWT appear to be of equal value as optional non-invasive cerebral stimulation procedures for promoting alertness and awareness among chronic DOC patients. Patients with akinetic mutism seem to profit the most, while low initial r-CRS scores and global brain damage following cerebral hypoxia appear to be negative predictors. Further studies addressing safety, effectiveness and ethics are warranted.

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