ORIGINAL REPORT

A LONG-TERM INTENSIVE BEHAVIOURAL TREATMENT STUDY IN PATIENTS WITH PERSISTENT VEGETATIVE STATE OR MINIMALLY CONSCIOUS STATE

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Objective: **Persistent vegetative state is regarded as "permanent", if it persists for more than 1 year for traumatic aetiology, or for more than 3 months for other aetiologies. This is also the case for patients in a minimally conscious state. In order to investigate possible improvements after this period we treated and observed 7 such patients over a period of 6 months.**

Design and methods: **An ABA-BAB study design was used, with sensory stimulation and social-tactile intervention as treatment regimes. Changes were documented by clinical evaluation and blind behavioural assessment through video monitoring.**

Results: **Clinical scores improved significantly after treatment. Video assessment also indicated significant changes in the patients' behaviour. During the initial period of therapy, social tactile interaction improved patients' activity, while sensory stimulation impaired activity. During the main part of therapy, both types of treatment yielded similar positive results.**

Conclusion: **This study indicates the possibility of achieving behavioural improvements with regard to the responsiveness of patients with long-lasting persistent vegetative state and minimally conscious state by use of long-term treatment.**

Key words: consciousness; persistent vegetative state; minimally conscious state; sensory stimulation therapy.

INTRODUCTION

Persistent vegetative state (PVS) is defined as "… a clinical condition of complete unawareness of the self and the environment, accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brainstem autonomic functions" (1). The use of the term, "complete unawareness" as a main criterion has been criticized repeatedly because it cannot be operationalized objectively (2–3). Some

years ago a new concept of minimally conscious state (MCS) (4) was introduced, and defined as "… a condition of severely altered consciousness in which minimal but definite behavioural evidence of self or environmental awareness is demonstrated" (5). The concept aimed at a more exact definition of the group of patients who demonstrate weak and inconsistent signs of awareness and had frequently been depicted earlier as "doubtful" PVS or "suspected of being in a PVS". The causes of both PVS and MCS are diverse, and extend from traumatic events, of which motor accidents are the most common, to various non-traumatic events, such as brain anoxia, stroke, poisoning, and degenerative diseases (6).

It is assumed that regaining consciousness is highly improbable if the diagnosis of PVS persists for more than 1 year for head trauma, or 3 months for other aetiologies (7). In the 1990s, the Multi-Society Task Force (MTSF) on PVS stated that the remission rate after the first year is as low as 1.6% (1). However, this result was obtained as a ratio between the number of patients who recovered after 1 year and the initial number of patients with PVS (i.e. including those who died or recovered during the first year). On the other hand, the data are sometimes misinterpreted, such that it is taken that only 1.6% of the patients remaining in PVS after 1 year can recover later. To correct this mistake, Childs & Mercer (8) and Borthwick (9) calculated the corresponding ratio (patients recovered after 1 year/patients in PVS after 1 year) and obtained much higher rates, of 10.6% and 14%, respectively. It should further be noted that all available data are based on rather small samples (i.e. 22 patients in MTSF (1), 25 in Childs & Mercer (8)). A few studies have systematically documented the course of PVS for a time period longer than 1 year (e.g. 10–13). For the diagnosis of MCS, 1 paper reported improvements of up to 5 years (14), and another described a patient who regained consciousness after 19 years (15). It is worthwhile noting that the latter patient became minimally conscious long before the diagnosis of MCS was introduced to the neurological community. Therefore, he would have been diagnosed as "permanent vegetative state" and considered as hopeless, perhaps with fatal consequences.

Most studies describe single cases or small groups, thus providing no basis for estimation of the frequency of occur-

rence of late improvements. None of these studies reported whether the progress was merely spontaneous or if it was a result of therapy.

To date, there is no effective pharmacological treatment for PVS and MCS. L-dopa can be very efficient, but only in the few patients who exhibit signs of extrapyramidal disorder, such as tremor, rigidity and akinesia (16). Although there is a general consensus that only randomized controlled trials (RCTs) can yield the highest level of evidence concerning the efficacy of a treatment, such trials are particularly difficult in the domain of disorders of consciousness. The only RCT using amantadine vs placebo (17) began after the present study had been completed, and one can estimate that the project encompassing the 10 largest centres in the USA and Germany would require approximately 6 years to recruit the necessary number of patients (18). Furthermore, RCTs have necessary ethical limitations, e.g. the amantadine study had, for ethical reasons, to restrict the treatment time to 6 weeks although it cannot be ruled out that longer treatment would be more efficient (18).

Among the numerous strategies of behavioural therapy proposed for PVS and MCS, most have been based on the principles of sensory stimulation. They have been subjected to meta-analysis by Lombardi et al. (19) and Vanier et al. (20). None of the examined interventions could prove its effectiveness. However, it was not possible to provide compelling evidence that these interventions do not work. Furthermore, the meta-analyses showed that it was nearly impossible to find a common denominator for those interventions. It was criticized that, in most intervention studies, the method was vaguely described, the design was uncontrolled, and the patients were categorized according to heterogeneous criteria. But, most importantly, patients examined in those studies were in the first year of illness. During this time the rate of spontaneous remission can be as high as 50% (21–23), which makes it difficult to prove that a few positive cases were indeed a result of the therapy.

The main questions investigatged by the present study were: Can patients in PVS and MCS improve after 1 year of illness? If yes, does the effect depend on the type of treatment applied? And, does the treatment applied at the beginning of therapy have an effect on the changes that follow. To answer these questions, we used an ABA-BAB design over a period of 6 months, alternating between 2 kinds of treatment: sensory stimulation (SS) and social-tactile intervention (STI). Both treatments were carried out by the same therapist (KS).

METHODS

Patients

After contacting several residential homes, 10 legal caregivers were asked for permission to work with their patients with PV or MCS. Eight of them agreed. Details of these patients' data are shown in Table I. Patient Gamma died in the middle of the course of treatment. Patient Ypsilon experienced intermittent pneumonia, which did not allow for completion of the therapeutic schedule. Furthermore, a surprisingly rapid improvement was observed in the condition of patient Alpha; after a few sessions she communicated with the therapist and relatives. Therefore, the complete course of treatment as intended was carried out with 5 patients. Four of the patients were male, mean age 36.2 years (standard deviation (SD) 8.12 years), and mean time since injury at therapy onset 41.8 months (SD 26.31, minimum 16 months). Three of the 5 patients received at least 1, and up to 6, pharmacological agents, which had negative effects on wakefulness, concentration and mood, or led to hallucinations and confusion (see Table S1 (http://jrm. medicaljournals.se/article/abstract/10.2340/16501977-0653). The effects of medication on particular psychological variables were evaluated on the basis of the official German pharmaceutical compendium, the *Rote Liste* (24). This medication, although partially constraining our therapy intervention, was kept constant over the entire time course of the study.

Diagnosis

Diagnostic assignment was performed (by KS) on the basis of referral letters and reports of relatives and staff. The diagnosis was based on the criteria formulated by Jennett (6) for PVS, and by Giacino et al. (4) for MCS. For ethical reasons no pain stimuli were applied. The diagnostic assignment is plotted in Table III. The original diagnosis was PVS or MCS. In one patient (Alpha) changes during the course of treatment led to a diagnosis of locked-in syndrome.

Therapy procedures

Each treatment block consisted of 48 sessions performed over 8 weeks, at the same time of day, for 6 consecutive days a week, of 30 min duration. All patients received two kinds of treatment, in an ABA or BAB design (see Table II), where A denotes SS, and B denotes STI. Therefore every patient underwent a therapy period lasting for 6 months with concurrent observation. The first block (i.e. A in the ABA design, and B in the BAB design) was regarded as the introductory block. This was followed by two blocks of the main treatment

Table I. *Demographic data for the included patients*

Patient	Gender	Age at brain damage (years)	Cause of brain damage	Resuscitation time (min)	Time since brain damage (months)	Special rehabilitation unit (weeks)[a]	Diagnosis for residential home
Alpha	Female	33	Ride accident	–	29	24	MCS
Beta[b]	Female	46	Medication overdose	45	22	7	VS
Gamma	Female	62	Stroke	–	34	0	VS
Epsilon[b]	Male	37	Circulatory collapse	30	39	11	VS
Omicron[b]	Male	26	Motor accident	–	83	40	VS
Rho[b]	Male	30	Circulatory collapse	60	49	28	VS
Ypsilon	Male	33	Motor accident	–	126	31	VS
Zo[b]	Male	42	Heart attack	Not documented	16	16	VS

[a]Overall time (after the initial incident) spent in a rehabilitation unit specialized in therapy of persistent vegetative state (VS).
[b]Patients who completed the course of treatment.
MCS: minimal conscious state.

Table II. *Planned and realized treatment of the patients*

Patient	Introductory block	Main block 1	Main block 2	Comment
Alpha	STI	SS	(STI)	Terminated due to diagnosis change
Beta	SS	STI	SS	
Gamma	SS	(STI)	(sS)	Death
Epsilon	SS	STI	SS	
Omicron	STI	SS	STI	
Rho	STI	SS	STI	
Ypsilon	SS	STI	(SS)	Incomplete treatment due to frequent pneumonia
Zo	SS	STI	SS	

STI: social-tactile intervention; SS: sensory stimulation; (): planned but not realized.

(i.e. BA in the ABA design, and AB in the BAB design). The study was approved by the ethics committee of the University of Tübingen School of Medicine.

Sensory stimulation. A modified concept of Fröhlich (25) was used, which was extended with respect to the intensive orientation of the SS according to the patient's response. Initially, the hands and arms of the patients were swept by the therapist's hands. Objects were subsequently presented that allowed somatosensory feedback (e.g. wood), but also those eliciting sounds after touch (e.g. singing bowl, timbrel). The objects were explored by guided movements of the patient's hands, and observed movements of the patient were reinforced. Depending on what the patient did, he or she could actively feel something, produce a sound, be imitated and verbally praised and be informed about what he or she had done. Subsequently, another body part (the other hand, arm, or foot) was stimulated, and changes were reinforced. Everything was done very slowly with numerous breaks and repetitions. The aim of the whole intervention was to initiate an interaction between the patient and the object on demand (e.g. hitting the timbrel).

Social-tactile intervention. We used the method described by Feuser (26), which focuses on building up a dialogue with the patient on the basis of a feedback he or she may be able to register. The patient was held in a seated position in front of the therapist. In this upright position the therapist reinforced the initial movements made by the patient by moving his own body in concert with the patient. For instance, any sign of a voluntary movement exhibited by the patient was reinforced by the therapist. The upper part of the patient's body reclined on the therapist, so that the patient could feel the therapist's body and breathing movements. Patient's movements were commented upon verbally and thereby reinforced by the therapist. During the entire procedure the therapist monitored any possible discomfort of the patient (e.g.

resistance or the increase in spasticity), and if this was observed the posture was changed in order to maintain interaction.

Behavioural assessment

Therapy sessions were videotaped, showing the patient performing standardized interventions together with the therapist (e.g. SS: the patient was asked to use a drumstick with his dominant hand, the patient's hand was guided to use the drumstick for the first third of movement distance; the patient was guided for the whole movement and auditory feedback was provided, etc.; STI: the patient was seated upright in front of the therapist and an invitation to move the upper limb or the trunk voluntary was followed by guided movements). Overall, the clips contain excerpts from the beginning and end of each part of the therapy. Clips of 5-min duration were randomly selected from the first and last weeks of therapy. The therapist did not watch the clips before or during the selection. These clips were shown to 7 independent judges who had not previously seen the patients. Five of them were laymen; one was a neurologist, and one a physician and psychologist who was experienced with similar patients. Each judge scored 6 clips per patient, according to the ABA-BAB design. The clips were randomized so that the judges were blind as to which part and which moment of therapy a given clip presented. The judges were asked to evaluate a set of target behaviours (e.g. thumb movements, hand movements) using a 10-cm visual analogue scale (from 0 cm = none to 10 cm = normal). The set included both active and passive (guided) movements. For analysis of video data the mean rating for all active movements was calculated for each clip.

Data analysis

Diagnostic modifications during therapy were tested by means of a Friedman's rank variance analysis, under consideration of rank binding. For behavioural assessment, inter-rater agreement was evaluated using two measures: Fleiss' kappa coefficient (27) and the intraclass correlation (ICC). Both tests have some deficiencies. The ICC is the ratio between s^2_B and s^2_T, where s^2_T is the total variance of all ratings, and s^2_B is the variance between individual patients or cases. The ICC presumes approximately equal spacing between adjacent scores (28), which can rarely be guaranteed for ordinal data. On the other hand, Fleiss' kappa coefficient can only work with categorical variables and thus disregards the estimated size of the observed improvement or impairment, but simply reduces all scores to the categories of "improvement", "impairment" and "no change". Moreover, all 3 categories are equidistant; that is, the measure disregards the fact that the difference between improvement and impairment is larger than that between improvement and no change.

Because the small set size may decrease the reliability of the parametric techniques, differences between conditions were pairwise compared using the distribution-free Wilcoxon test. Since the variance between the 5 patients is insufficient to attain the conventional significance level, the variance between judgments had to be added to increase the power of the test.[1] Likewise, the variance between judgments was the only source used for the evaluation of changes in single patients, which is the usual approach to single case observations.

Table III. *Course of diagnosis*

Patient	At release to residential home	Relatives/ staff before observation	Observation[a]	After therapy[b]
Beta	VS	VS	VS	MCS
Gamma	VS	VS	MCS	Deceased
Epsilon	VS	MCS/VS	VS	MCS
Omicron	VS	MCS	MCS	MCS
Rho	MCS	MCS	MCS	MCS
Ypsilon	VS	MCS	MCS	MCS
Zo	VS	MCS	VS	MCS

†Observation by KS within a week before therapy started.
[b]Observation by KS after the therapeutic intervention.
VS: vegetative state; MCS: minimally conscious state.

RESULTS

Diagnosis

The changes in diagnoses are shown in Table III. The diagnostic rating changed significantly for both groups

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[1]In theory a non-parametric test can be significant at the 0.05 level only if all 5 patients improve. Four improvements and one no change result in $p = 0.068$, and 4 improvements and one (smallest) impairment result in $p = 0.080$.

(relatives: $\chi^2_{r(corr; \, df = 3)} = 9.69$; $p < 0.05$; staff: $\chi^2_{r(corr; \, df = 3)} = 10.02$; $p < 0.02$). *Post-hoc* tests showed a diagnostic improvement between the time-points "release to the residential home" and "after therapy" ($p = 0.02$ for both the relatives and staff data).

Raters' agreement

The kappa coefficient calculated for nominalized data with 3 categories (improvement, no change, impairment between pre- and post-treatment) was 0.371. The ICC between the 7 raters was 0.660, with the effect of rater being non-significant ($F_{(6,84)} = 2.20$, $p = 0.11$). Given a small effect size of the rater effect (eta-squared $= 0.136$), it may be concluded that the raters' assessments were homogenous. The two expert raters did not significantly differ from any of the lay judges.

Behavioural assessment: introductory treatment

During the introductory part the two kinds of treatment yielded opposite effects: patients who started with STI improved

(Wilcoxon $T_{14} = -5.5$; $p < 0.005$), while those who started with SS were rated as less active at the end of treatment ($T_{21} = 49$, $p = 0.02$). The mean scores ($\pm$ standard error (SE)) for SS were 4.05 ± 0.46 and 2.56 ± 0.45 at the beginning and end of treatment, respectively; for STI they were 1.29 ± 0.26 and 2.89 ± 0.51, respectively. As a result, there was no overall improvement trend during this part.

Because the SS and STI subgroups contained only 3 and 2 patients, respectively, the data could not be analysed by being collapsed across the judgments. At the individual level, significant ($p < 0.05$) improvement was observed in 1 STI patient, and significant ($p < 0.05$) impairment in 2 of the 3 SS patients.

The data from all the patients and judges, for the introductory and the main treatment, are shown in Fig. 1.

Behavioural assessment: main treatment

The mean scores ($\pm$ SE) for SS were 2.46 ± 0.44 at the beginning and 3.51 ± 0.45 at the end of treatment; for STI they were 1.94
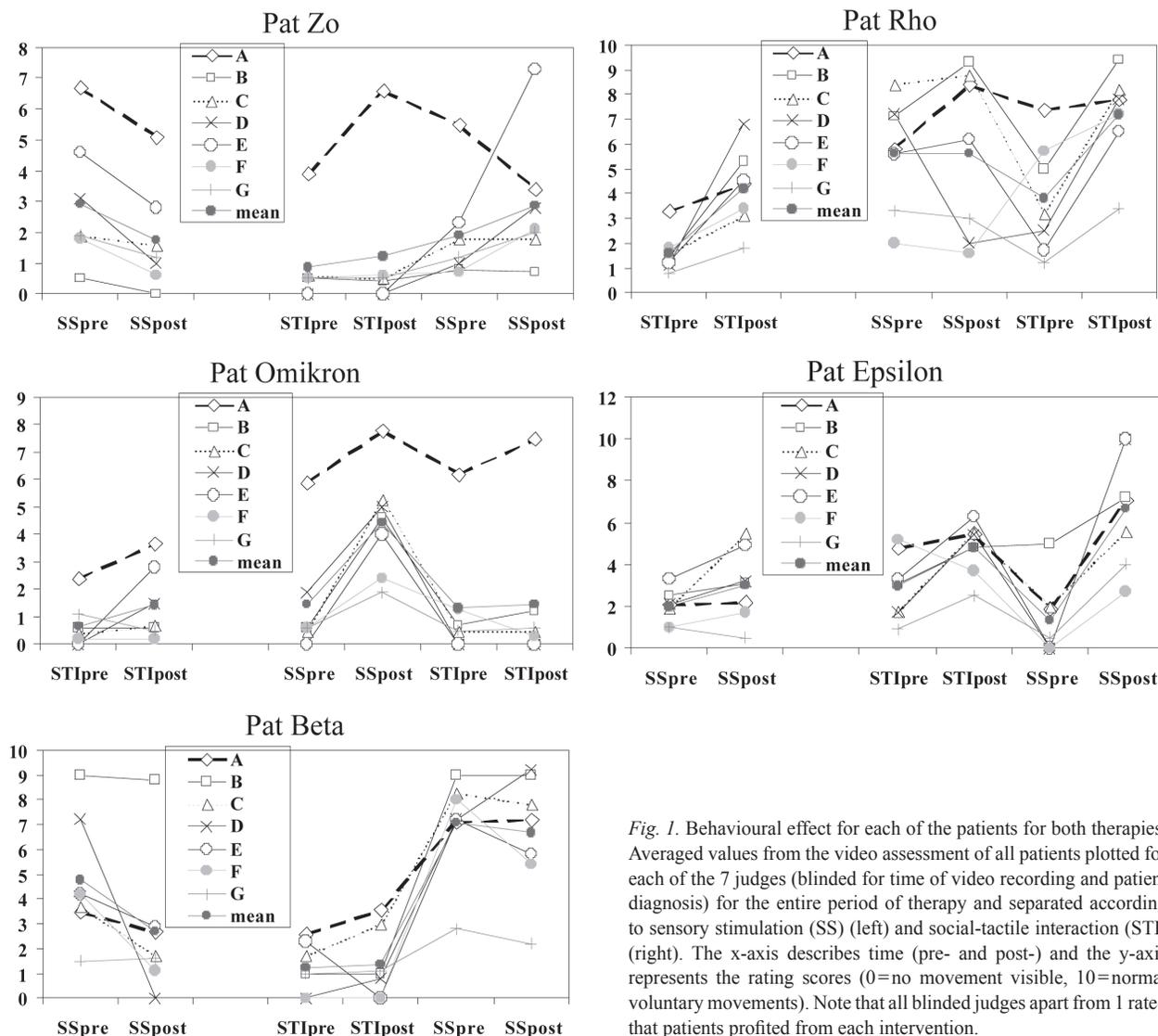

Fig. 1. Behavioural effect for each of the patients for both therapies. Averaged values from the video assessment of all patients plotted for each of the 7 judges (blinded for time of video recording and patient diagnosis) for the entire period of therapy and separated according to sensory stimulation (SS) (left) and social-tactile interaction (STI) (right). The x-axis describes time (pre- and post-) and the y-axis represents the rating scores (0 = no movement visible, 10 = normal voluntary movements). Note that all blinded judges apart from 1 rated that patients profited from each intervention.

± 0.35 at the beginning and 3.09 ± 0.53 at the end of treatment. When the variance between judgments was incorporated into the analysis, both pre-post differences were significant at $p < 0.005$. When the data were pooled over all judges, thus leaving only 4 degrees of freedom, the improvement after SS was still significant $(p = 0.043)$. The improvement after STI was not significant $(p = 0.22)$, and the overall improvement showed a trend toward significance $(p = 0.080)$. A similar improvement trend was found when the first assessment was compared with the last assessment regardless of the order in which SS and STI were presented $(p = 0.068$, collapsed over judges).

Although the data appear to be better for SS than STI, the difference between the *change in scores* for the two kinds of therapy was not significant $(p > 0.3)$. At the individual level, 3 of the 5 patients showed a significant $(p < 0.05)$ improvement after SS and 1 patient showed a significant improvement after STI. Whereas in most patients slight but consistent improvement for 1–2 points were obtained after both kinds of treatment, patient Beta demonstrated zero change after STI and worsening after SS. Patient Zo exhibited a slight negative trend after STI, but the largest (3.3 points on average) improvement after SS.

DISCUSSION

The data presented here appear to support the hypothesis of the study; that an improvement as a result of treatment is possible in the so-called "permanent" disorder of consciousness (PVS or MCS). First, there was a significant change in diagnosis (i.e. from PVS to MCS), and secondly, independent judges rated the patients' motor activity significantly higher at the end than at the beginning of treatment. The former finding can be questioned because, although the raw data were obtained from the staff and the patients' relatives, they were integrated into a clinical diagnosis by the therapist herself; therefore, a bias cannot be ruled out completely. The latter finding indicating the improvement in motor activity is more convincing because the 7 judges were completely blind about the condition on the video-recording that they observed and scored.

These results should, of course, be regarded as preliminary and indicative only of improvement, taking into consideration the small sample size and the need for more rigorous evaluation methods. Nevertheless, the fact that 7 judges, including 5 lay-persons and 2 experts, differed only slightly in their estimation of the patients' progress indicates that their scores may have reflected real positive changes in the patients' behaviour during treatment.

An additional problem originating from the small sample was the lack of a complete analysis of variance including all possible factors and their interactions. Of course, random errors of considerable size can always occur in such small samples, and therefore, statistical data presented in the Results section cannot be regarded at face value, but only as indications of trends. The question of the durability of the positive changes noticed by the rater also remains open, because no follow-up was included in the present study. Another bias might be induced by the therapist interacting with the patients on the rated

video. After a considerable period of therapy the induction of motor response might be larger simply because the therapist has accumulated experience with the given patient, and not only due to the increased motor response of the patient.

In contrast to other studies with small samples of patients with PVS, we examined patients who had had this diagnosis for a very long time: 16 months to 10 years. The only patient who did not show any improvement after treatment had a relatively short disease duration of 22 months. Therefore, we believe that the probability of a spontaneous remission was extremely low, and thus, that a control group in studies of this kind is useful but not mandatory.

A further limitation of the present study is the fact that the behavioural improvements observed in video clips do not lead to any conclusion concerning the patients' state of consciousness. Although all judges noticed an improvement in fine motor activity, the method used does not guarantee that the observed movements were, indeed, goal-directed and intended actions. Judges' ratings were not diagnostic instruments, and even considerable dynamics do not suffice to change the diagnosis of PVS. The raters assessing the video evidence might also be biased by the scientist interacting with the patient with respect to the patient's response. We tried to standardize the interaction with the patient and the feedback after voluntary movements, but a stronger feedback might have increased the judges' ratings of the video material. An investigation with highly automated interactions of a person not involved in the therapy might be more objective with respect to this issue. However, video assessment is also an important and widely used strategy to measure patient's behaviour during interaction with the therapist (29). In addition, the subjective assignment of diagnosis is always error-prone, and this relates to one of the main outcome values in the present study, despite the fact that every attempt was made to perform it as accurately as possible.

The present study provides only a very preliminary answer to the question of possible differential effects of the different treatments. A rather strong difference was found in the introductory block, encompassing the first 8 weeks of therapy: while STI enhanced the patients' behavioural repertoire, SS impaired it. In the subsequent period, however, both interventions showed similar effects, and SS even tended to yield slightly higher scores. An important difference is that in SS the patients' movements are prompted, while in STI only spontaneous behaviour is possible. In line with the idea of sensory regulation (30–32), one may speculate that, at the beginning of the therapeutic contact, the requests in SS are recognized by the patient, and thus result in relatively high scores in the initial sessions; however, the entire situation overstrains the patients and leads to subsequent worsening. On the other hand, STI is a more delicate intervention that provides enough time to build up a therapeutic relationship. As soon as the relationship has been established, SS can exert its effect.

The most pronounced and rapid clinical and behavioural improvement was observed in patient Alpha. However, it was so rapid that it cannot be attributed to the treatment and therefore the patient data was removed from the analysis, even though

this exclusion considerably spoiled the statistical trends. Patient Alpha was discharged from hospital with a diagnosis of PVS and further diagnosed as MCS. Because nursing homes do not usually possess good diagnostic facilities, and because the relatives visited patient Alpha only once a month, the patient's ability to communicate was not properly tested for a long time. The present therapist was the first person attempting actively to make contact with the patient. After only several hours of interaction consistent communication was established, indicating that the patient was neither in PVS nor MCS. The medical staff was subsequently given detailed communication instructions, and this led to a rapid improvement in the patient's condition. In addition, the patient was moved to another nursing home, which resulted in an increased frequency of visits from relatives.

Typically for such cases (e.g. (6)), two explanations are possible: either (*i*) a rapid improvement in the course of (or even: due to) the intervention, or (*ii*) a misdiagnosis in which the intervention did not change the patient's condition but merely contributed to the discovery of a means of communicating. Because the apparent improvement was very rapid, and because every case of doubt should be decided contrary to the initial hypothesis, we decided that (*ii*) was correct and (*i*) was not. Although the aetiology did not include a pontine stroke typical for locked-in syndrome, the neuropathology of the injury (head trauma) in this patient entailed a diffuse axonal injury with the involvement of the upper brainstem. Therefore, damage to the pontine structures cannot be ruled out.

Although the high rate of diagnostic errors in PVS is well known and has not changed over the last 15 years (33–35), it is worth noting that, in the case of patient Alpha, the patient was misdiagnosed for over 2 years. It is likely that the diagnosis would have persisted for longer without our intervention, because even during the course of very close and intensive therapist–patient interaction it took more than 1 week to raise doubts about the diagnosis of MCS. Jennett (6) remarks that misdiagnosed patients frequently display only minimal signs of consciousness, which makes "… this high rate of misdiagnosis somewhat less alarming …" (p. 21). We think, however, that the error rate of approximately 40% (33–35) indicates that the extant diagnostic procedures require considerable improvement, including both intensive therapeutic contacts (36), the use of neuroscientific methods (37) or brain–computer interfaces (38).

An additional, often overlooked, problem with patients with chronic PVS/MCS is that because of the lack of hope and negative outcome expectations, not only are they deprived of potentially useful interventions, but they also often receive therapy that they no longer require. Thus, benzodiazepines and mild neuroleptics can sometimes be useful to suppress psychomotor agitation in an acute stage of PVS. However, our patients continued to receive sedatives despite the lack of excitatory syndromes. More active observation and the cessation of redundant pharmacological therapy might contribute to further improvement in patients with long-term severe disorders of consciousness.

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