

Effect of neurosensory stimulation outdoors on acute patients with covert cognition

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Abstract

Background: Sensory stimulation is effective in enhancing the recovery process of severely brain-injured patients with altered consciousness. Recent advances detected covert cognition in patients behaviorally categorized as un- or minimally responsive; a state described as cognitive motor dissociation (CMD).

Objective: Our aim is to determine effectiveness of a neurosensory stimulation approach enhanced by *outdoor* therapy, in the early phases of recovery in patients presenting with CMD.

Methods: Fifteen patients participated in this non-randomized crossover study. We video-recorded a two-phase neurosensory procedure combining identical indoor and

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outdoor protocols and rated observations offline. We measured the frequency of volitional behavior using a behavioral grid.

Results: The outdoor group patients had statistically significant higher scores than the indoor group on seven features of the grid. Conversely, any score in the indoor condition was higher than the outdoor condition.

Conclusions: Although preliminary, this study provides reliable evidence supporting the effectiveness and appropriateness of an outdoor neurosensory intervention in patients with covert cognition, to improve adaptive goal-oriented behavior. This may be a step towards helping to restore functional interactive communication.

Keywords

Neurosensory stimulation; outdoor therapy; cognitive motor dissociation; covert cognition; early rehabilitation

1. Introduction

Rehabilitation strategies for patients in the early phases of recovery after severe brain injury intend to improve attention and stimulate the networks responsible for an individual to have conscious perception of himself and of his environment and adequately interact with it.

One type of intervention uses sensory stimulation, which refers to a variety of methods used to stimulate the senses (sight, hearing, touch, taste and smell) that can considerably vary in form, intensity and number of modalities implied (Oh & Seo, 2003).

Randomized control trials comparing groups receiving the usual care with a sensory stimulation program added are extremely scarce. Despite lack of scientific evidence (Lombardi, Taricco, De Tanti, Telaro, & Liberati, 2002), it is hypothesized that applying a sensory stimulation program will enhance the recovery process and improve the outcomes of severely brain-injured patients experiencing an alteration in consciousness. Decades ago, LeWinn and Dimancescu (LeWinn & Dimancescu, 1978) demonstrated greater improvement in sixteen comatose patients following multimodal sensory stimulation. Similarly, Mitchell (Mitchell, Bradley, Welch, & Britton, 1990) showed that patients receiving coma arousal procedure awakened from coma earlier than controls. A recent randomized controlled trial revealed significant improvements on validated scales dedicated to measure consciousness (Glasgow Coma Scale [GCS] and Western Neuro Sensory Stimulation profile [WNSSP]) after multimodal coma stimulation in comatose individuals with traumatic brain injury (Megha, Harpreet, & Nayeem, 2013).

Disturbances of consciousness may follow acute brain damage, ranging from coma to minimally conscious state. Coma is defined as a state of non-responsiveness to such an extent that one cannot be awakened even when intensively stimulated (Plum & Posner, 1972). Once the patients open their eyes, yet remain unresponsive, they evolve into a vegetative state, more recently described as unresponsive wakefulness syndrome (UWS) (Laureys et al., 2010). UWS patients usually show signs of wakefulness (eye opening, spontaneous breathing, spontaneous reflexive movement), without signs of awareness (responses to commands, attempts to communicate) (Gosseries et al., 2011). Typically, UWS patients gradually recover awareness and enter a minimally conscious state (MCS), in which they are not able to communicate functionally but can achieve reproducible intentional behaviors (Giacino

et al., 2002). However, recent advances in functional imaging techniques have led to the identification of covert cognition in disorders of consciousness (DOC) patients that clinically demonstrate none or limited motor/verbal abilities to respond, yet show forms of command-following during active/passive motor imagery tasks (Edlow et al., 2017); (Goldfine, Victor, Conte, Bardin, & Schiff, 2011); (Monti et al., 2010); (Owen et al., 2006).

A recent systematic review concluded that roughly 15% of patients clinically diagnosed with UWS were able to modify their brain activity on command (Kondziella, Friberg, Frokjaer, Fabricius, & Moller, 2016), supporting the operational definition of “cognitive motor dissociation” (CMD) proposed by Schiff (Schiff, 2015).

A new behavioral assessment strategy, the Motor Behavior tool (MBT) developed by our group (Pignat et al., 2016) and recently revised as a validated stand-alone form, MBT-r (Pincherle, 2018), may enable the early clinical detection of CMD patients. The MBT-r attempts to unveil subtle behavioral evidence of residual cognition, not detected by the neurobehavioral validated scales and was shown to be effective for predicting recovery of consciousness.

To our knowledge, investigating whether sensory stimulation benefits patients presenting with CMD in the acute phase has not been so far explored. Here, We aim to determine the effectiveness of an interdisciplinary neurosensory program in the early phases of recovery in patients categorized as CMD in the context of the therapy outdoors. Furthermore, we will compare the neurosensory approach applied outdoors versus indoors.

2. Materials and Methods

2.1. Subjects

Eligible patients enrolled in this non-randomized crossover study were adults in the acute or sub-acute phase of brain damage, admitted to the Acute Neuro-Rehabilitation Unit (NRA - Clinical Neurosciences Department, University Hospital of Lausanne, Switzerland) between May 2015 and July 2017. Before admission to the NRA, the patients in the intensive care unit were diagnosed by clinical neurologists and neuropsychologists after repeated testing using the Coma Recovery Scale-Revised (CRS-R) and Motor-Behavior Tool (MBT-r) and clinical details and diagnoses are shown in Table 1. All included patients were clinically stable for transport to a therapeutic garden and had no major medical problems interfering with their safety while outdoors. Eligible patients were screened for the inclusion and exclusion criteria by a neurologist. The experimental protocol (142/09) was approved by the Local Lausanne Ethics Committee and written informed consent was provided by the patients' legal authorized representatives. All included patients underwent a daily 300-minute interdisciplinary program of rehabilitation according to their clinical condition. We used the modified Rankin Scale (mRS) as a clinical outcome measure on NRA admission and on hospital discharge.

2.2. Procedure

The entire study population followed the same protocol with specified activities adapted to each patient's abilities.

We designed a two-phase procedure combining an identical protocol carried out indoors and outdoors. Average length of protocol sessions was 25 minutes (initial rest

and therapy). The protocol order was randomized and both applied the same day with a maximum time of 5 hours (300 minutes) including sessions and time between sessions.

2.3. Interventions

In the initial 5 to 10 minutes rest period, patients were for assessed for pain using the Critical Care Pain Observation Tool (CPOT).

Then, patients underwent either physiotherapy and/or occupational therapy; treatment previously chosen according to the patient's abilities and always aimed at improving the voluntary and/or purposeful behavior of the patient.

All sessions were video-recorded for offline analyses. Two independent blinded and trained investigators reviewed all videos and rated all voluntary and/or purposeful behavior and initiation performance using the behavioral grid described below.

Usual environment effects (e.g. noises, staff, visitors, alarms) were not attenuated but served as background stimulation.

2.4. Measurements

Voluntary and/or purposeful behavior and initiation were measured by a behavioral grid (see supplementary materials), developed by the NRA research team and primarily based on the CRS-R scale (Kalmar & Giacino, 2005). The grid allows behavior counting and prevents a potential training effect as it is observational and repetition of behaviors is not required.

This tool consists of 44 items comprising six sub-scales addressing auditory, visual, motor, oro-motor, communication and attention functions. Scoring is based on the presence or absence of a defined behavioral response to specific sensory stimuli, as for the CRS-R scale. The presence and total numbers of responses (frequency) were

counted as frequency is an indicator of voluntary and/or purposeful behavior and initiation. The instrument has strong inter-rater reliability ($k = 0,9385$) and its content was internally assessed by a panel of recognized experts.

Pain outcome was assessed by the CPOT (Gelinas, Fortier, Viens, Fillion, & Puntillo, 2004) or the Visual Analog Scale (Bijur, Silver, & Gallagher, 2001). The CPOT is designed to score the pain of patients who are not able to report it themselves while the VAS is designed for patients who can. Pain was assessed to ensure the comfort and safety of the subjects during the trial.

2.5. Statistical analysis

Analyses were performed using MATLAB 12.0 (Math-Works, Natick, Massachusetts, USA). This study used a two-way repeated measure Anova design (2X2) with two within-subject factors, expert (expert 1 vs expert 2) and condition (difference in/out vs zero). Given the size of each group, and the non-normality of the groups based on a preliminary Lilliefors test, nonparametric statistics were used throughout. The nonparametric two-way repeated measure ANOVA was performed using bootstrapping (Knebel, Javitt, & Murray, 2011). The subject label was bootstrapped and the within subject condition was permuted within the subject. This approach keeps the intra-subject variance. On each cycle, we calculated the F-values for each randomization. Repeating this for 1000 cycles generates an empirical distribution of F-values from which a corresponding p -value can be obtained by comparison to the original F-values. The only hypothesis is that our data represent the space that we would like to test.

In addition, to avoid multiple testing problems the p -value was adapted using Bonferroni correction.

3. Results

Clinical and demographic characteristics of patients are listed in Table 1. Twenty participants were enrolled in the study. Five patients were excluded from the final sample (one patient withdrew consent, three patients did not undergo the complete intervention and one patient died). Of the included patients, 11 were males and 4 were females with an overall mean age 52.6 ± 17.2 years. The average time from injury was 25.2 ± 10.9 days. Etiologies differed; five (33.3%) suffered a trauma, four various encephalopathies (26.7%), three an intraparenchymal hemorrhage (20%), two a subarachnoid hemorrhage (13.3%), and one an ischemic stroke (6.6%). Initial clinical diagnosis using the CRS-R classified five patients as MCS, three UWS and seven comatose. All but one of the patients were categorized as in CMD state, using the MBT. All included subjects completed at least three sessions of the protocol. On NRA admission, all patients had mRS scores of 5 (severe disability). On hospital discharge, mRS scores ranged from 2 to 5 with a mean of 4 (moderately severe disability). Nine patients recovered consciousness according to the final CRS-R evaluation (defined by functional use of objects and/or functional communication) on discharge,

A summary of the results of the behavior measures is shown in Table 2. Results are presented as mean \pm standard deviation of the difference in the number of behavioral responses between outdoor and indoor conditions.

Outdoor group patients had a significantly higher frequency score than the indoor group on seven items of the grid. During intervention, subjects in the outdoor condition exhibited significantly higher scores for specific items of the auditory, visual, motor and oro-motor function sub-scales. Conversely, any score in the indoor condition was higher than in the outdoor.

Amongst the eight auditory responses, three of them were observed more frequently outside including, “reaction to a simple command” ($p<0.001$), “eyes oriented toward an auditory stimulus” ($p<0.005$) and “reaction when addressed by own name” ($p<0.001$).

On the other hand, only one of the eight visual-behavior items, “exploration/fixation of an individual on command” ($p<0.001$) was more frequent in the open-air. .

Two of the eight motor “spontaneous movement related to an object/task/individual” ($p<0.001$) and “movement on command” ($p<0.001$) and one of the seven oro-motor components, “swallowing” ($p<0.001$) were more frequently observed during outdoor therapy.

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The highest frequencies of activity in the outdoor condition was observed for the “movement on command” item of the motor sub-scale (mean difference = 2.38).

We observed no statistically significant differences in items of communication and attention sub-scales between the outdoor and indoor conditions.

We found no evidence of unintended effects in any subject, including no differences in mean VAS/CPOT scores between conditions.

4. Discussion

The purpose of the study was to evaluate the effectiveness of an interdisciplinary neurosensory approach in the context of outdoor therapies for improving the recovery of volitional behaviors and interaction abilities in patients presenting with CMD.

Overall, the results show a significant effect of the therapies outdoors compared to therapies indoors with a higher number of observed voluntary purposeful behaviors and movement initiation when stimulated outdoors.

The improvement in patients given neurosensorial stimulation in an open-air environment may be attributed to the well-recognized and documented restorative effects of nature on cognitive, emotional and physical functioning (for a review see, (Maller, Townsend, Pryor, Brown, & St Leger, 2006)). Integrative frameworks such as the « biophilia hypothesis » by Wilson (Wilson, 1984), that is “the innately emotional affiliation of human beings to other living organisms”; or the « concept of therapeutic landscapes » (Gesler, 1992) focusing on everyday landscapes believed to contribute to healing, both endorse the therapeutic benefit that interaction with natural elements may have on human health.

The effectiveness found in the present study can also be explained based on the « attention restoration theory » (ART) proposed by Kaplan & Kaplan (Kaplan & Kaplan, 1989) which suggests that nature can restore the attentional capacity. This theory is based on a cognitive view separating attention into two parts: the non-demanding « involuntary attention » passively capturing important stimuli; and the restricted « directed attention » requiring a continuous voluntary engagement directed by executive function processes, ultimately resulting in mental fatigue. Exposure to direct or indirect inferences to nature allows disengaging (by means of a combination of four qualities) and helps the directed attention capacities to recover. Empirical evidence of ART is mostly descriptive and based on observations of human-nature interactions and analysis of quantitative data. Nonetheless, a recent systematic review supports the impact of exposure to nature environments on attention, though concludes about the uncertainty regarding which aspects of attention may be affected (Ohly et al., 2016).

In varying cases of ill health including neurological diseases, small but reliable evidence across studies supports nature-assisted therapies as an effective and

appropriate intervention (see the review of (Annerstedt & Wahrborg, 2011)). In a pioneering study, Ulrich (Ulrich, 1984) demonstrated that even simply viewing certain types of nature fosters improvements in clinical outcomes. Patients whose windows faced a park recovered faster after a surgery than patients whose windows faced a brick wall, in terms of reduced length of stay and pain medication. Similarly, Jonasson et al. (Jonasson, Marklund, & Hildingh, 2007) described favorable experiences working in a training garden in patients with neurological damage. Descriptive categories were used as outcomes and qualitatively showed the capacity of gardens in improving the voluntary activity and functional ability of the patients, especially when they considered the activity as useful and meaningful.

The coma following brain injury produces sensory deprivation (Ansell, 1991), thus in order to prevent such additional detrimental effects on the already damaged brain, the rationale for treatment leads to enrich the environment and promote neural plasticity (Di & Schnakers, 2018). Interventional approaches resort to variations of multisensory stimulation such as multimodal stimulation of the senses (Canedo et al., 2002), music therapy (Formisano et al., 2001); (Magee, 2007), or verticalisation protocol using a tilted table with an integrated stepping device (Krewer, Luther, Koenig, & Muller, 2015); (Frazzitta et al., 2016). Our findings are consistent with those reported in these studies attesting improvements on the degree of arousal, the interaction with the environment, the psychomotor initiative or the level of consciousness. To some extent, another comparison could be made with the study of Lanz et al. (Lanz, Moret, Rouiller, & Loquet, 2013) regarding multisensory integration. In their study, non-human primates were engaged in a detection sensory-motor task where visual and auditory stimuli were displayed individually or simultaneously. Mainly, they demonstrated a multisensory advantage increasing speed of stimulus detection and improving

performance accuracy: motor responses were better and faster when subjects were exposed to multimodal sensory stimulation.

Furthermore, the significant improvements demonstrated in seven items of our behavioral grid concern four of the main modalities assessed by the CRS-R, which is the validated and recommended scale for use in individuals with disorders of consciousness (American Congress of Rehabilitation Medicine et al., 2010). One interesting point is that six of these items involve signs of volitional top-down cognition implying that the patient understood the verbal command and willfully responded, therefore attesting her or his level of conscious awareness. First, this endorses the initial assumption made on the MBT assessment, identifying these patients as presenting subtle motor behaviors consistent with residual cognition. Besides, nine CMD patients behaviorally demonstrated consciousness recovery at discharge, as assessed by the CRS-R scoring signs qualifying emergence, hence supporting the correlation between the presence of residual cognition at an early stage and subsequent consciousness recovery (Pignat et al., 2016); (Pincherle, 2018). Second, this finding is in line to a certain extent with those reported in studies exploring the detection of covert awareness in patients with DOC by means of complementary neuroimaging approaches. Indeed, signs of such covert cognition can be detected in roughly 20% of patients in a behavioral state of UWS with functional MRI and EEG command-following paradigms (e.g. (Monti et al., 2010); (Cruse et al., 2011); (Edlow et al., 2017). Recently, Curley et al. (Curley, Forgacs, Voss, Conte, & Schiff, 2018) even demonstrated a higher rate of responders to command (13/20 patients with severe DOC studied) describing a new approach at the bedside using repetitive testing with EEG command-following protocols.

Another point of interest in the study of Curley et al. concerns the physiological explanation they provided to characterize cognitive motor dissociation, in terms of globally preserved cerebral metabolism associated with severely impaired motor outflow. According to this view, preserved cognitive networks allowing motor imagery and enabling goal-directed attention are expected in patients presenting with CMD. FDG-PET data of CMD patients from an ongoing study in our group are coherent with this view, as they demonstrated a globally normalized uptake in cortico-thalamic networks (Allenbach, 2018. *Unpublished data*) i.e. their lack of overt goal-oriented behaviors could not be explained by an extensive cortico-thalamo-cortical connectivity failure.

In this context, motivational drive mechanisms could easily be considered to explain the increase in the frequency of volitional behaviors observed in the present study. Motivation impacts behavior and has received much concern in the literature, yet the exact mechanisms underlying its neurophysiology remain unclear. In case of the most severe disorder of motivation, i.e. akinetic mutism syndrome (AM), characterized by profound apathy and a lack of verbal and motor output for action, despite preserved alertness and the intention to speak, meaningful responses can be occasionally elicited when acting on mesocortical dopamine pathways (Spiegel, Casella, Callender, & Dhadwal, 2008). In the so-called « telephone effect », patients with AM appear to speak better whilst on the phone; a phenomenon explained by a temporary reversal in the severe decrease in drive by a release of dopamine which activates the damaged motivational circuit and results in brief verbalizations (Yarns & Quinn, 2013). The clinical presentation of the patients in our study resemble those of AM in a less severe intensity, therefore it is conceivable that the relevance brought by an outdoor

environment may modulate and increase the activation of such dopaminergic circuits and improve the realization of the action itself.

This hypothesis also finds support in the approach developed by Bosch-Bouju et al. (Bosch-Bouju, Hyland, & Parr-Brownlie, 2013) who emphasize the role of multiple driver or driver-like inputs in motor control, including a strong influence of motivational mechanisms. They proposed that, in order to evoke an optimal movement, the motor thalamus acts more than a simple relay structure, but as a « super-integrator » of information from the prefrontal cortex (initiating the motor program), the basal ganglia (processing motivational information) and the cerebellum (processing complex proprioceptive information), which then sends all super-integrated signals back to the cortex. According to this view, we can speculate that promoting motivational stimulation and increasing sensory inputs may modulate neural activity of the loop, resulting in a better generation of motor programs. This interpretation is supported by the fact that any measured behaviors were higher in the indoor condition considered as less motivational and with lower multisensory stimulation.

Stimuli with emotional salience also provide a reliable motivational resource. Emotional stimuli capture attention (Phelps, 2006), are prioritized in cognitive system, or intensify sensory integration (Vuilleumier, 2005). Although emotional stimuli were not directly provided here, a significant effect was found when addressing the patient with her or his own name. This finding is consistent with those reported in several studies with DOC patients that use the patient's name as an effective stimulus. For instance, name sequences containing the patient's own name or other names were presented to 8 UWS and 14 MCS in passive and active (instructed to count their own name) conditions of an evoked-related potentials paradigm (Schnakers et al., 2008). Results demonstrated that MCS patients, like controls, presented a greater P3 (the

third positive wave of event-related potentials) to their own name in both conditions. Further research must be conducted to reach more concrete conclusions regarding the benefits of emotional salience on increasing volitional behaviors in patients presenting with CMD.

5. Limitations

The present study only provides preliminary findings and might be considered as a pilot trial; more patients are needed in order to overcome statistical limitations, and confirm the beneficial effect of a neurosensory stimulation program applied outdoors on the increment of volitional behaviors in acute patients presenting with an inability to communicate behaviorally their conscious awareness.

The lack of heterogeneity regarding the clinical impression according to the MBT-r (all but one of the patients were classified as presenting with CMD) was challenging to avoid here. Non-CMD patients, i.e. real DOC, are more subjected to therapeutic decisions, including withdrawal or limitation of life-sustaining treatments when in the ICU, in view of poorer outcome and lower rehabilitation potential. Among the total of 124 patients admitted to the NRA unit from November 2011 and July 2017, 14% were classified as real DOC. Multicenter studies involving different countries with different regulations are needed to compare the efficacy of a neurosensory approach applied outdoor with a wider range of patients presenting disorders of consciousness.

Another limitation of our study concerns the absence of randomization, due to obvious ethical considerations, as well as the difficulty to ascertain the degree to which the benefits of the study interventions are independent from the effect of the individualized rehabilitation program followed by each patient. However, the overall amount and intensity of rehabilitative therapies were controlled and did not differ significantly

between patients (patients whose clinical conditions require a less intensive rehabilitation program were not included in the study). Further studies may use additional measurements to evaluate more specifically motivational aspects such as participation performances or reactions to specific emotionally salient stimuli. In addition, physiological measurements such as salivary cortisol to evaluate the effect of natural settings on the stress level of patients with severe brain injuries would be valuable.

6. Conclusions

Our findings suggest that outdoor therapy provides a beneficial complementary rehabilitative treatment for patients in the early phases following a severe brain injury. Although preliminary, this study shows reliable evidence supporting the effectiveness and appropriateness of an outdoor neurosensory intervention in patients presenting with CMD, in improving their adaptive goal-oriented behaviors hence helping to restore a functional interactive communication. Notwithstanding the small sample size, the results are promising and demonstrate their applicability even with a heterogeneous etiology, as well as their easiness to apply to any health-care setting that has access to outdoors facilities. Finally, in a more global perspective, they advocate for the restorative benefits of natural settings as a relevant resource for public health.

Conflict of interest

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article. This study was partially supported by a grant from The Gianni Biaggi de Blasys Foundation.

Acknowledgments

The authors would like to thank the families of the patients for giving their consent to our study. Thanks to the therapists for performing the therapeutic interventions, to Veronique de Goumoëns for her investment and senior advice, to H  l  ne Brioschi Levi for her support and to Melanie Hirt for English-language editing and proofreading the manuscript.

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Table 1. Clinical and demographic characteristics of patients

| | <i>Age</i> | <i>Sex</i> | <i>Injury etiology</i> | <i>Time since injury (days)</i> | <i>Initial clinical diagnosis per CRS-R</i> | <i>MBT-r classification</i> | <i>mRS at admission</i> | <i>mRS at discharge</i> | <i>RoC (CRS-R)</i> |
|------------|------------|------------|-------------------------------|---------------------------------|---|-----------------------------|-------------------------|-------------------------|--------------------|
| P1 | 51 | F | IS | 19 | MCS | CMD | 5 | 4 | Yes |
| P2 | 53 | F | Metabolic encephalopathy | 49 | UWS | CMD | 5 | 4 | Yes |
| P3 | 61 | M | IH | 15 | COMA | CMD | 5 | 4 | No |
| P4 | 60 | M | IH | 26 | COMA | CMD | 5 | 4 | Yes |
| P5 | 78 | M | Infectious encephalopathy | 48 | COMA | CMD | 5 | 4 | No |
| P6 | 43 | M | TBI | 19 | COMA | CMD | 5 | 3 | Yes |
| P7 | 60 | F | SAH | 19 | COMA | CMD | 5 | 5 | No |
| P8 | 68 | F | Multifactorial encephalopathy | 36 | MCS | CMD | 5 | 5 | No |
| P9 | 53 | F | TBI | 21 | COMA | NON CMD/DOC | 5 | 5 | No |
| P10 | 50 | M | Anoxic encephalopathy | 22 | MCS | CMD | 5 | 3 | Yes |
| P11 | 59 | F | IH | 26 | MCS | CMD | 5 | 4 | Yes |
| P12 | 78 | F | SAH | 26 | MCS | CMD | 5 | 5 | No |
| P13 | 27 | M | TBI | 18 | UWS | CMD | 5 | 2 | Yes |
| P14 | 25 | F | TBI | 22 | UWS | CMD | 5 | 4 | Yes |
| P15 | 23 | M | TBI | 12 | COMA | CMD | 5 | 3 | Yes |

IS = Ischemic stroke; IH = Intraparenchymal hemorrhage; SAH = subarachnoid hemorrhage; TBI = Traumatic brain injury; CRS-R = Coma Recovery Scale-Revised; MCS = minimally conscious state; UWS = unresponsive wakefulness syndrome; CMD = Cognitive-motor dissociation; mRS = Modified Rankin Scale; RoC = Recovery of consciousness.

Table 2. Mean difference between the indoor and outdoor protocols regarding total number of behavioral responses.

| <i>Function sub-scales</i> | <i>Behavioral Responses</i> | <i>Mean</i> | <i>SD</i> | <i>Multiple correction p-value</i> |
|----------------------------|---|-------------|-----------|------------------------------------|
| <i>Auditory</i> | Reaction to a simple command | 2.13 | 4.18 | < 0.001*** |
| | Reaction to a semi-complex command | 0.08 | 0.51 | 1.711 |
| | Reaction to a complex command | 0.00 | 0.00 | 4.74 |
| | Head orients toward an auditory stimulus | 0.47 | 2.42 | 0.35 |
| | Eyes orient toward an auditory stimulus | 0.56 | 2.42 | < 0.005 ** |
| | Eyes opening in response to an auditory stimulus | 0.03 | 0.52 | 5.52 |
| | Eyes opening on command | 0.05 | 0.56 | 4.424 |
| | Reaction when addressed by own name | 0.34 | 1.28 | < 0.001 *** |
| <i>Visual</i> | Spontaneous exploration/fixation of an object | 0.44 | 3.25 | 2.304 |
| | Exploration/fixation of an object on command | 0.48 | 3.28 | 1.792 |
| | Visual pursuit of an object on command | 0.16 | 0.90 | 0.296 |
| | Spontaneous exploration/fixation of an individual (person) | 0.67 | 4.27 | 1.333 |
| | Exploration/fixation of an individual on command | 0.74 | 2.44 | < 0.001 *** |
| | Spontaneous visual pursuit of a moving object or individual | 1.01 | 5.94 | 0.594 |
| | Pursuit of an individual on command | 0.02 | 0.15 | 2.369 |
| | Spontaneous designation of an object | 0.00 | 0.00 | 4 |
| <i>Motor</i> | Designation of an object on command | 0.00 | 0.00 | 3 |
| | Choice of an object on command | 0.01 | 0.11 | 5.088 |
| | Spontaneous seizing of an object | 0.30 | 1.59 | 0.408 |
| | Seizing of an object on command | 0.29 | 1.68 | 0.992 |
| | Spontaneous movement related to an object/task/individual | 1.90 | 4.34 | < 0.001 *** |
| | Movement on command | 2.38 | 6.10 | < 0.001 *** |
| | Imitation of a movement | 0.20 | 1.44 | 2.052 |
| | Eyes open on tactile stimulus | 0.07 | 0.91 | 4.667 |
| <i>Oro-motor</i> | Teeth grinding | 0.01 | 0.08 | 3.135 |
| | Yawning | 0.26 | 1.27 | 0.324 |
| | Sighing | 0.37 | 2.77 | 2.225 |
| | Smiling/laughing | 0.13 | 0.83 | 1.333 |
| | Frowning/gesturing | 0.01 | 1.37 | 5.082 |
| | Spontaneous swallowing | 0.56 | 1.56 | < 0.001 *** |
| | Swallowing on command | 0.02 | 0.61 | 5.184 |
| <i>Communication</i> | Response following an established communication code | 0.26 | 2.11 | 2.331 |
| | Spontaneous audible vocalization | 0.05 | 0.67 | 5.088 |
| | Spontaneous audible production of a word | 0.17 | 1.36 | 2.369 |
| | Spontaneous audible production of a simple or complex sentence | 0.04 | 2.05 | 5.082 |
| | Audible vocalization on command | 0.12 | 1.32 | 4.641 |
| | Audible production of a word on command | 0.23 | 2.68 | 4.624 |
| | Audible production of a simple or complex sentence on command | 0.11 | 2.90 | 5.256 |
| | Non-audible diction | 0.23 | 2.10 | 3 |
| <i>Attention</i> | Raising the voice | 0.02 | 0.15 | 2.052 |
| | Attention on a stimulus held for 5 secs, at least 3x during the whole activity | 0.01 | 0.11 | 5.52 |
| | Distracting stimulus self-inhibited | 0.01 | 0.08 | 2 |
| | Distracting stimulus (max 10 secs) and resuming the task without external stimulation | 0.01 | 0.08 | 4.806 |
| | Distracting stimulus (max 10 secs) and resuming the task with external stimulation | 0.02 | 0.17 | 4.806 |

** significant at $p < 0.005$; *** significant at $p < 0.001$