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Review

A Behavioral Approach to Treatment and Assessment of People with Disorders of Consciousness: The Response-contingent Stimulation Strategy

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Abstract

Response-contingent stimulation is a behavioral strategy used to improve the situation of patients with disorders of consciousness. Such strategy involves the presentation of brief periods (e.g., 10 to 15 s) of stimulation considered preferred by the patients, contingent on (immediately after) the emission of specific patients' responses. The aim is to help the patients learn the link between their responding and the preferred stimulation and thus learn to use their responding to access the stimulation in a self-determined/independent manner. Achieving these goals is considered important for the patients' recovery process and thus the response-contingent stimulation strategy that promotes such an achievement can be considered a valuable treatment approach. The same strategy combined with the use of periods of non-contingent stimulation (i.e., stimulation delivered independent of responding) may also serve as an assessment supplement with patients with apparent unresponsive wakefulness. The patients' increase in responding during the response-contingent stimulation and decline in responding during the non-contingent stimulation could be taken as a sign of discrimination between conditions, and possibly a sign of awareness of the immediate environmental situation, compatible with a diagnosis of minimally conscious state. This paper analyzes a number of studies aimed at using the response-contingent stimulation as a treatment strategy and a number of studies aimed at combining response-contingent stimulation with non-contingent stimulation for treatment and assessment purposes. The results of the studies are discussed in terms of the effectiveness, accessibility and affordability of the strategy. The need for new research (i.e., replication studies) is also pointed out.

Keywords: disorders of consciousness; response-contingent stimulation; treatment; assessment; learning; technology

1. Introduction

People with disorders of consciousness may be characterized by a comatose state, a vegetative state (VS) (now frequently indicated as unresponsive wakefulness syndrome; UWS), or a minimally conscious state (MCS) [1–6]. People in a comatose state are considered to be not arousable or difficult to arouse and are typically viewed as being unaware of themselves and the surrounding environment [6–8]. People in a VS (or unresponsive wakefulness) are typically awake and may also display a number of basic/simple head and limb movements as well as reflex responses such as grinding teeth and yawning [6,9,10]. In spite of their wakefulness and movements, these people seem to be unaware of and unresponsive to the environment [11–14]. People in a MCS typically display fluctuating signs of awareness, which may also involve the ability to follow some simple verbal commands and to utter comprehensible words [4,6,10,15].

Efforts to improve the situation of people with disorders of consciousness (e.g., to help them increase their arousal and responsiveness and foster their recovery process) can be based on behavioral and non-behavioral intervention strategies [16–18]. The most common non-behavioral intervention strategies include among others the use of pharmacological agents (e.g., amantadine [19,20]) and the application of transcranial stimulation, that is, transcranial direct current stimulation [21,22], and repetitive transcranial magnetic stimulation [23,24].

The main behavioral intervention strategies include the use of music stimulation, verbal stories/messages, multisensory stimulation, and response-contingent stimulation [15,25–29]. The extensive literature on music stimulation has reported (a) different ways of presenting music (e.g., recorded music delivered through different types of elec-

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tronic devices and music presented/improvised live by a music therapist), (b) different types of music (e.g., patient's preferred music, classical music, and folk music), and (c) different presentation lengths (e.g., from less than 1 min to about 30 min). Music is thought to affect neural networks, improve brain plasticity, and prevent sensory deprivation [30,31]. Moreover, the emotional content of salient music can activate limbic and paralimbic structures with important implications for the participants' functioning and well-being [32–34].

Verbal stories/messages mainly involve the narration/recalling of meaningful events the patient had previously experienced and/or the description of the current situation with a positive perspective for recovery and future [28,35,36]. The use of such an intervention strategy is supported by the view that (a) the emotional content of the stories/messages can activate limbic and paralimbic structures of the brain (see above) [37–39], (b) the calling of the patient's name can promote forms of behavioral or non-behavioral (physiological) responses of alertness and attention [31,40], and (c) the overall narration can constitute a useful form of auditory stimulation, that is, beneficial input for a sensory channel, which is generally well preserved in this population [26,41].

The use of multisensory stimulation is typically justified by the notion that a complex stimulation approach involving the presence of various multimodal stimuli (possibly meaningful/relevant for the person receiving them) is more likely to be effective in promoting brain activation and overall responding than the use of simple and repetitive stimuli [42–44]. Based on this notion, a number of studies were carried out to assess the impact of multisensory stimulation with patients in a comatose state, in a vegetative state, and in a minimally conscious state [8,45,46]. The length of the stimulation sessions and the types of stimuli used within the sessions varied across studies. The various combinations of stimuli aimed at the different sensory channels could also involve (a) familiar objects to be manipulated, (b) physical contact with therapists or family members, and (c) the presence of (contact with) animals [47,48].

Response-contingent stimulation is a strategy that involves the presentation of brief periods (e.g., 10 to 15 s) of stimulation considered to be preferred by the patients (thus allegedly motivating for them) contingent on specific responses performed by the patients [15,49,50]. In essence, the brief stimulation periods are delivered immediately after the emission of those specific responses. The responses targeted for stimulation delivery are typically selected based on the fact that (a) they are already present in the patients' repertoire but have a low frequency of occurrence (so such frequency could be increased by a successful stimulation process; see below), and (b) they can be recorded in a reliable manner [51–55].

2. Similarities and Differences between the Response-Contingent Stimulation Strategy and the Other Strategies

The most obvious and relevant similarity consists in the fact that the response-contingent stimulation strategy uses stimulation events comparable to those that are employed by the other strategies. Specifically, response-contingent stimulation may involve the use of music, such as songs and instrumental pieces, voices of loved ones addressing the patients, as well as multimodal stimulation events (e.g., visual and auditory stimuli that may be delivered alternatively or in combination). Another general similarity between the response-contingent stimulation and the other strategies is that the type of stimulation presented to the patients is considered to be relevant/meaningful and pleasant for them [15,25,28,50,55].

Next to the aforementioned similarities, clear differences also exist between the response-contingent stimulation strategy and the other three strategies. One major difference is that the response-contingent strategy presents the stimulation events immediately after the patients' emission of a specific behavioral response while the other strategies present the stimulation independent of any form of response (behavior) by the patients. A second difference concerns the length of the stimulation delivered to the patients. The response-contingent stimulation strategy typically uses brief stimulation events (e.g., 10- or 15-s events) after each response occurrence. The other strategies generally rely on longer periods of stimulation delivery [15,55].

A third difference is that the implementation of the response-contingent stimulation strategy relies on the availability of a technology system that monitors through small sensors the patients' responses (even minimal responses such as eye blinking and head or finger movements) and automatically delivers the stimulation right after the emission of those responses [55]. The implementation of the other strategies may be based (a) on simple technology devices that, once switched on, present the stimulation as scheduled, independent of the patients' behavior or (b) on therapists, caregivers, or family members that can introduce variations in the types of stimulation scheduled and/or add forms of interaction with the patients [39,56,57].

A fourth difference is that response-contingent stimulation (contrary to the other strategies) is not really applicable with patients in a comatose state, that is, patients who apparently have no observable responses to monitor and target with stimulation events. A fifth difference concerns the goal of the stimulation process. In the response-contingent stimulation strategy, the stimulation events are used not simply as means to foster arousal and brain activation (as it typically occurs in the other strategies), but also as a way to motivate/reinforce specific behavioral responses of the patient (i.e., the responses that are followed by those events) with the view of increasing and strengthening the patient's performance of those responses [15,50,53,58,59].

3. Application of Response-Contingent Stimulation as a Treatment Strategy for MCS Patients

3.1 Background

The application of this strategy with MCS patients, as stated above, is directed at promoting their performance of specific responses and associating those responses with the preferred environmental stimulation following them [59]. Indeed, MCS patients are considered to be capable of associating (learning the link between) their responding and the environmental stimulation contingent on such responding [55,60–64]. Learning such a link enables them to acquire a level of self-determination, an active role within their own context, and thus ensure that they can be in charge of their stimulation input rather than being simple recipients of externally determined stimulation deliveries [15,55,58,65]. The acquisition of such an active role and the underlying learning process may be viewed as highly valuable phenomena/experiences with relevant therapeutic implications for the advancement of the patients' recovery process [15,50,51,53,55,66–68]. The application of this strategy in the treatment of MCS patients has been reported in 14 studies including a total of 64 patients [50–54,64,69–76]. Some of those studies are summarized below as a way to clarify how the strategy is set up and how it can work with the patients.

3.2 Illustrative Studies (with One Response Targeted)

Most of the studies carried out have focused on one response per patient. The response was selected based on the patient's abilities and represented a behavior that had low frequency and could be reliably monitored through basic sensors (e.g., optic, touch, or tilt sensors). That response was then followed by preferred stimulation (i.e., stimulus events that were considered preferred/pleasant for the patient) during treatment. For example, Lancioni *et al*. [52] carried out a study involving five MCS patients (aged 37–78 years) with Coma Recovery Scale-Revised [CRS-R] scores of 8–13. All patients also presented with extensive motor impairment with lack of body and head control and absence of speech or any other communication means. For three patients, the response selected was a protracted eyelid closure. For the fourth patient, the response was finger movement. For the fifth patient, the response was a movement of the big toe. An optic sensor was used to detect the protracted eyelid response, a pressure sensor fixed inside the hand was used to detect finger movement, and a combination of two tilt sensors served to detect the movement of the big toe. The sensors were connected to a computer system that regulated the presentation of the stimulation events contingent on the selected responses during 5-min sessions. The stimulation events lasted 10 or 15 s and involved songs and instrumental music, which could be combined with familiar voices or videos. The study was conducted according to an ABAB design (i.e., a design in which A-baseline phases without stimulation were alternated with B-treatment phases, in which the emission of the aforementioned responses was followed by stimulation events) for each patient. Data showed that during the first treatment (B) phase, the response frequencies approximately doubled the values of the first baseline. Those frequencies showed a clear decline during the second baseline and increased again during the second treatment phase (i.e., exceeding the levels of the first treatment phase).

Lancioni *et al*. [70] completed a study with 11 MCS patients aged 38 to 81 years whose CRS-R scores varied between 7 and 16. The responses targeted for stimulation included protracted eyelid closure, repeated eyelid closure, hand closure, eyebrow upward movement, lateral head movement, and lips/mouth movement. Those responses (one per patient) were detected through optic sensors and touch and pressure sensors, which were linked to a computer system. Each patient was exposed to an ABAB design, which involved sessions lasting 5 min. During the B-treatment phases, the responses were followed by 10-s stimulation events, which included video clips of singing, praying, or eating and dancing, and audio-recordings of songs, comedy, and loved ones speaking to the patients. During the treatment phases, the patients' mean frequencies of responses showed a two- or three-fold increase compared to the baseline values.

Lancioni *et al*. [71] carried out a replication of the studies described above with a group of 10 MCS patients (aged 25 to 81 years) who had CRS-R scores of 10 to 14. The responses selected as stimulation targets included protracted or repeated eyelid closures and head, hand/finger, foot or lip movements. Optic, touch or pressure sensors were used to detect the responses and to trigger a computer system that would provide 10-s stimulation events contingent on the occurrence of the responses. The stimuli included audio-visual clips of events such as singing, praying, and loved ones speaking to the patients. The results showed that during the intervention phases the mean response frequencies had a three-fold increase compared to the baseline levels.

Eight of the aforementioned 10 patients were also involved in a second investigation in which three stimulation conditions were rotated [71]. One was the response-contingent stimulation to which the patients were used. The second consisted of stimulation presented uninterruptedly for the 5-min sessions. The third involved the research assistant guiding the patients in the manipulation of common daily objects and talking about those objects and their use. Two measures were recorded during the sessions. One measure concerned the patient's eyes (i.e., whether they were open or closed). The other measure concerned small body movements (other than the response used for activating the sensor available) that could suggest patient's alertness and participation. Data showed that in the response-contingent condition, the presence of eyes closed was significantly lower than in one or both the other conditions for four patients, and the presence of movements was significantly higher than in the other conditions for six patients.

3.3 Illustrative Studies (with Two Responses Targeted)

The studies summarized above focused their response-contingent stimulation treatment on a single response per patient. Studies were also conducted in which the treatment was extended to two different responses. For example, Lancioni *et al*. [75] worked with two MCS patients of 53 and 56 years of age whose CRS-R scores were 11 and 12. The responses targeted in the study were finger movements and minimal head-nodding movements for one patient and upward eyelid movements and hand stroking for the other patient. Treatment focused on one response at a time. Then, treatment sessions on one response were alternated with treatment sessions on the other response within or across days. All sessions lasted 5 min. The responses were monitored via optic, touch/pressure, or tilt sensors, which were linked to an electronic control system that would deliver 10 or 15 s of preferred stimulation in connection with each response occurrence. Different stimulation events (i.e., popular music and videos) were used for the two responses. Both participants showed large increases of each of the two responses during the treatment sessions thus enriching their stimulation input and increasing their control of it.

Lancioni *et al*. [76] taught two MCS patients aged 35 and 60 years two responses (i.e., two different arm/hand movements or a hand and a foot movement). One of the responses led to the automatic delivery of about 10 s of preferred stimulation (i.e., as in the study described above) while the other response resulted in a call to the caregiver who would then intervene and talk to the patient and show the patient pictures, video clips, and other relevant material for about 20 s. The results were highly satisfactory with both patients displaying large increases of the two responses and rotating those responses during the single treatment sessions.

4. Application of Response-Contingent Stimulation as a Treatment and Assessment Strategy for Non-MCS Patients

4.1 Background

Treatment programs based on response-contingent stimulation may also be set up for people whose disorders of consciousness are not clearly defined or for people who have a diagnosis of VS (i.e., people who are supposed to have a plausible behavioral response to be used as target for stimulation events). For all these people, the treatment program might be carried out as described for MCS patients and might also be extended for assessment/diagnostic purposes. The program extension may involve the addition of a treatment phase in which the stimulation is provided without any relation to the patients' responses (e.g., uninterruptedly throughout the session). The patients' performance during this phase as opposed to their performance during the response-contingent treatment phase might help one to gather relevant clues about their functioning (discrimination) skills and thus might serve as a supplement to other assessment (e.g., behavioral and neuroimaging) procedures used in the diagnostic process [77–83]. The addition of a new treatment phase would modify the experimental design used for the study from a possible ABAB (as described in the studies summarized above) to a possible ABACAB or variations thereof, in which the C stands for a response-unrelated stimulation phase [49,50,84–86].

The frequency of the patients' responding (i.e., the frequency of the response selected as the treatment target) would be typically expected to increase during the B-treatment phases due to the stimulation occurring contingent on the emission of the target response during those phases [58,59,87]. The nature of the patients' response increase during the B phases might be explained based on their responding during the C phase. If during the C phase, the patient shows a response increase comparable to that observed during the B phases, one might draw two inferences. First, the patient does not discriminate the two (B and C) conditions and does not perceive the link (or lack of link) between response and stimulation in those conditions [87]. Second, the response increases observed in each of the conditions may be representative of a general activation of the autonomic nervous system and subcortical structures responsible of general arousal [15,17,68,78,88–90]. If during the C phase, the patient shows a decline in responding as compared to the B phases, one might interpret such decline (i.e., response differentiation) as a sign of discrimination between B and C conditions and presumably a sign of awareness of the instrumental role or absence of role of responding for stimulation access in the two conditions [13,49,52,66–68,84,85,91–94]. In psychological terms, such discrimination and awareness could be taken to indicate a learning process and to suggest a patient's non-reflective (pre-reflective) state of basic consciousness or of minimal self-awareness (i.e., awareness of changes occurring in the immediate environment) [66,67,71,95–97]. In essence, patients able to successfully discriminate the C phase from the B phases and differentiate their behavior accordingly could be considered to be in a condition compatible with the minimally conscious state [49,50,91,98–101]. Conversely, persons unable to change their behavior across the C and B phases (i.e., unable to discriminate the C from the B phases) would be considered to be in a preconscious processing state [66,87,98,102].

4.2 Illustrative Studies (with VS Patients)

Eight studies including a total of 18 patients have been carried out in which response-contingent stimulation was used as treatment and assessment strategy [49,69,84–86,103–105]. Those studies used an extended experimental design that allowed one to compare the response-contingent

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stimulation with baseline conditions as well as with a control condition in which stimulation was provided independent of the patient's responding. For example, Lancioni *et al*. [84] worked with three patients aged 17, 36 and 68 years, who had a diagnosis of VS and CRS-R scores of 4, 5, and 6. The responses consisted of protracted or simple eyelid closure, and a slight hand closure. The study was carried out according to an ABABCB design, in which A represented baseline phases with no stimulation; B treatment phases with stimulation contingent on the occurrence of the aforementioned eyelid- or hand-closure responses; and C a control phase with stimulation presented in a non-contingent manner (i.e., independent of the target response). Each phase included multiple 5-min sessions. The stimulation, which was deemed to be pleasant for the patients, included a variety of songs and music pieces and video clips.

During the first B phase, the patients had a (near) two-fold or a four-fold increase in responding compared to the first baseline. Responding declined during the second baseline to increase again during the second B phase and remain high during the last B phase. In the C phase, two patients had either a very large or a moderate but still visible response decline (both declines were statistically significant $p < 0.01$). The third patient had virtually no decline. In essence, the B phases were an effective treatment to increase responding for all patients. The B and C phases showed that one patient had strong discrimination between conditions. A second patient also showed discrimination (albeit not as strong and consistent as the first). Their discrimination performances were viewed as suggestive of possibly different levels within a non-reflective minimal consciousness state. The third patient showed responding with no discrimination and this was thought to be suggestive of a preconscious processing state with clear sensory-motor activation (i.e., a state that is between a subliminal processing state where no response to external stimuli is present and a non-reflective minimal consciousness state [67,86,98,102]).

Kim *et al*. [103] worked with a 65-year old VS patient who had a CRS-R score of 4. The response selected for the delivery of contingent stimulation was eye blinking. This response was detected through an optic sensor linked to an electronic control device. The study was carried out according to an ABABCB design comparable with that described in the previous study. Stimulation consisted of brief presentations of preferred pictures, voices, and hymns, which occurred contingent on eye blinking responses (during B phases) and independent of eye blinking responses (during the C phase). Data showed that the patient's mean frequency of responses had a strong increase during the B phases and a large decline during the C phase. The difference between the B and C frequencies was taken as a sign of discrimination learning and suggestive of a state of non-reflective minimal consciousness.

Lancioni *et al*. [49] carried out a study with seven patients of 27 to 82 years of age. At the start of the study four patients had a diagnosis of MCS (with CRS-R scores of 7 to 12) and three a diagnosis of VS (with CRS-R scores of 5 to 7). The study included an ABACB sequence, in which A, B and C represented baseline, treatment and control phases. During the B phases, each response occurrence was followed by 10 s of preferred audio-visual stimulation (e.g., video clips of singing, comedy and family events). During the C phase, the same stimuli were available continuously during the sessions. Data showed that the patients' response frequencies during the B phases were two- to three-fold their A-baseline levels. During the C phase, all patients had response frequencies comparable to those observed during the A phases. These findings showed that all patients (a) benefited from the B (treatment) phases, and (b) had clear discrimination between the B and C conditions. This discrimination confirmed the diagnosis of MCS for the four patients with such a diagnosis at the start of the study and suggested a similar diagnosis also for the three who had been reported to be in a VS.

5. Discussion

5.1 Effectiveness of the Response-Contingent Stimulation Strategy

The data reported by the studies using response-contingent stimulation as a treatment strategy seem to be highly encouraging as to the effectiveness of this strategy to help MCS patients to increase their responding and learn to use such responding to control environmental stimulation. It may be interesting to note that these data are in line with data reported by studies involving people with extensive intellectual and multiple disabilities (i.e., people sharing a variety of behavioral and functional characteristics with MCS patients) [93,106–110]. Working to allow the patient to control environmental stimulation may be more beneficial than making the patient rely on others for stimulation. In the first case (i.e., with the use of response-contingent stimulation), the patient is encouraged and enabled to develop initiative and self-determination, that is, to acquire two behavioral skills that may be relevant in fostering the interaction with the environment and the recovery process. In the other cases (i.e., with the use of the other strategies available) the patient remains largely dependent on external agents without any specific development in terms of responses and initiative [15]. Obviously, the response-contingent stimulation strategy can achieve the successful results reported above only through the support of specific technology systems including sensors and electronic control (computer) devices. The technology is set up to monitor the responses selected and ensure that the occurrence of such responses is met with stimulation in a consistent and reliable manner.

The use of the response-contingent stimulation strategy in combination with non-contingent stimulation for assessment purposes may be considered fairly effective and promising on at least two counts. First, its use provides evidence that a number of patients who receive a diagnosis of unresponsive wakefulness via behavioral scales (e.g., CRS-R) may show signs of learning (i.e., the ability to discriminate two different situations and to adjust their behavior to those situations). Such evidence may help modify their diagnosis and recovery/rehabilitation perspectives [49,103,111,112]. Second, the assessment component of the strategy (a) may be viewed as part of the general treatment program more than as a separate/independent procedure [26,112–114] and thus (b) might be taken to represent a moderate extra cost of the treatment process.

5.2 Accessibility and Affordability of the Strategy

With regard to the issue of accessibility, the most immediate question is whether the technology used for the response-contingent treatment strategy can be readily and directly set up by different professionals within different contexts. The answer to this question is twofold. First, while some of the sensors employed in the studies reported (i.e., optic and touch sensors) were specifically arranged for the purpose of the investigations, those sensors can now be largely replaced by commercial technology that can be easily available. This makes the basic (technological) component of the strategy accessible to a vast number of professionals or caregivers interested in applying it.

Second, setting up the technology is only one part of the preparatory work for a successful implementation of the strategy. The other part, which would also be considered fairly accessible to professionals and caregivers, involves the selection of (a) the response(s) that should be followed by stimulation, (b) the types of stimulation to use contingent on the response(s), and (c) the duration of the stimulation events set to follow the single emissions of the response(s). With regard to the responses, one would need to ensure that they are already present in the patient's repertoire but at low frequency (so it would be possible for those responses to grow in frequency/strength and show the strategy's impact level). The stimuli should be relevant/meaningful and also include variations so as to remain effective/motivating over time [87]. The duration of the single stimulation events following the single response occurrences could be relatively short (e.g., 10–15 s) as indicated by a number of studies with people with disorders of consciousness and people with intellectual and multiple disabilities [15,107,115,116].

With regard to the issue of affordability, the basic question concerns the amount of staff or caregiver's time needed for the implementation of the strategy. Two considerations may be relevant here. First, the implementation of the strategy is based on the use of technology that serves to monitor responding and deliver stimulation. This makes the strategy's demand on staff or caregiver's time relatively light and thus reasonably compatible with other duties and commitments these personnel have during the day. Second, the use of new (advanced) technology in substitution of the sensors employed in the studies reported so far (a) can further simplify the implementation of the strategy (minimizing the need for staff supervision/intervention) and thus (b) can facilitate an extension of the strategy's use across various periods of the day, that is, periods in which patients show a condition of wakefulness.

6. Conclusion and Future Research

In light of the studies reviewed and of the issues discussed above, one could argue that the response-contingent stimulation strategy appears to be a useful treatment and assessment resource for professionals working with MCS or VS patients. It may also be added that the applicability of the strategy would at present be enhanced by the availability and continuous upgrading of a number of commercial technology devices and software applications that are easily accessible and readily usable within a variety of daily contexts. New research will need to extend the evidence so far available with regard to the strategy through systematic replication studies entailing new patients and new technology as well as the direct involvement of new research groups [117,118]. Positive outcomes of the studies and involvement of different groups of researchers (professionals) in carrying out the studies would be critical (a) to further substantiate the strategy's impact and refine its setup and implementation process, and (b) to help the strategy become a practical tool within rehabilitation and care contexts where the need for supplementary treatment and assessment means is still apparently high [111,114,119–122].

Author Contributions

GEL was responsible for conceiving the article, collecting the material, and writing and editing the manuscript. MOB collaborated in setting up the article, and writing, reviewing and editing the manuscript. NNS, MOR, JS, GA and LD collaborated in writing, reviewing and editing the manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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