The altered state of consciousness: clinical assessment and monitoring

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Abstract

Aim of this work is to provide an overview on the main clinical issues concerning disorder of consciousness (DOC). After a briefly description of the debate on clinical differences in states of altered consciousness, we report the description of clinical features of the three different levels of DOC: coma, vegetative state, and minimally conscious state, according to the Multi Society Task Force for Persistent Vegetative State (1994) and the Aspen Work Group (Giacino et al., 2002). We will then describe an observation procedure, stated by Whyte and coworkers in 1999, based upon a single-case methodology aimed to assess responsiveness and its variations. At least, we will give a description of the evidences on stimulation treatment efficacy, as we collected in occasion of the last Consensus Conference in Neuropsychological Rehabilitation held in Siena (Italy) in 2010. Our conclusions confirm the lack of evidences concerning the efficacy of treatment for recovery of consciousness in agreement with other authors and we will finally provide suggestions for future research.

Keywords: DOCs; Coma; Vegetative state; Minimally conscious state; Assessment

1. Introduction

In recent years, several authors from various disciplines (philosophy, ethics, psychology, neuroscience, medicine, theology, law, etc.), tried to define consciousness and a great amount of definition is now available. In everyone of

them a variable number of aspects of "being conscious" are highlighted and all of them provide us a complex image of consciousness. In this work we want to emphasize the definition provided by Cohadon in his work published in 2003. This definition seems to be more functional in defining the criteria for determining when a patient is "not aware", when it is in an intermediate stage of transition between being not aware and conscious, or when at least he or she is fully conscious. Cohadon claims that consciousness could be explained as being aware of oneself, others, the surrounding environment, and being present to oneself and for others, in responding to stimuli. Consciousness is related to both the subjective quality of experience (not directly accessible to observation) and the awareness of self and environment. The interaction between these two last points (awareness of self and environment) generates behaviors and behaviors can be considered an implicit index of presence of consciousness (Chalmers, 1996). Consequently, the experience of being conscious requires two components: the waking state and the contents, which represent two distinct brain functions and depend on different systems and structures. Wakefulness or arousal is a brain independent function that involves the brainstem reticular system, the autonomic nervous system and the endocrine system, whose populations of neurons project directly, or via non-specific thalamic nuclei, to the cortex neurons. On the other hand, the content depends on the functional integrity of the cerebral cortex and subcortical connections (Jennett, 2002; Laureys et al., 2004).

The maintenance of consciousness depends on: the normal functioning of pons, the midbrain and diencephalon; the connection of projection network of reticulo-talamo-cortical system; a normal functioning cortical mantle; and adequate memory circuits. Brain lesions that involve one of these four structures may determine a consciousness deficit. The reticular formation is a compact structure, and a small injury can be enough to cause serious impairments of consciousness. On the contrary, the paths of the reticulo-thalamo-cortical projections and the cortical mantle are more extended and the consciousness is damaged only when they are involved in a widespread manner. Eye opening and brain stem reflexes determine the base to evaluate the functional integrity of the vigilance. The content requires a waking state to be active, unlike the waking state may be present in the absence of content (The Multi-Society Task Force on PVS, 1994; Laureys, 2005; Zeman, 2001). The content is identified with the higher processes: intelligence, language, memory, emotions, etc., and requires the waking state to be functional.

Some patients with altered state of consciousness show a quickly improvement; for others the recovery is very slowly, and still other patients show a stable level of responsiveness. For the latter in particular seems to

be necessary establishing criteria for defining whether there is possibility of improvement. In recent years, a great number of works (see as an example the document Scientific-Technical Commission of the Italian Ministry of Health, 2005) tried to establish the upper limit of the retrieval of people who might emerge from a vegetative state. The Commission in its final document concludes that, even considering extensive evidence of delayed recovery after the first year (Andrews, 1996), it is not possible to determine a precise temporal limit over which a patient is in a no further condition of improvement. So, establishing reliable criteria for the classification of the state in which these patients are, may provide more appropriate treatment and rehabilitation.

2. Definition of various states of disorder of consciousness

The recovery of consciousness can be identified in three main levels: Coma, vegetative state and minimally conscious state.

(i) Coma, as defined by Jennet and Teasdale (1981), is a clinical condition characterized by absence of eye opening, no comprehensible speech output, lack of response to command. Coma is the contrary of consciousness (Plum et al., 1982), and it is a condition in which both components of consciousness, awake and content, are lost: the patient in a state of coma never open his or her eyes, even if intensely stimulated; he or she also has no content of consciousness, even basically, and therefore does not emit sounds understandable, does not execute simple orders neither voluntary movements.

(ii) Vegetative State (VS): many efforts have been made over the years to find a common terminology, however, many important elements remain unclear and this determine extreme confusion in the definition of this state.

In 1961 Arnaud and collaborators used for the first time the French term *vie vegetative*. Jennet and Plum (1972) introduced the concept of "persistent vegetative state" to describe individuals who had emerged from a coma and was in a state of "wakefulness without awareness". They noted that "sometimes, fragments of coordinated movements may be seen such as scratching, or even movement of the hands towards a noxious stimulus". They recognize the lack of criteria to determine the irreversibility of the condition, therefore, they point out that the use of "persistent" is more conservative than "permanent" or "irreversible", but do not judge as clear enough the adjective "extended".

According to the authors, the essential component of this syndrome is the absence of any adaptive response to the external environment, the absence of any evidence of a functioning mind which is either receiving or giving information, in a patient who has long periods of wakefulness. They recognized that the ability to diagnose this condition was severely limited by the accuracy of the overt behavior assessment. In their article alternated the use of "persistent vegetative state" with a "vegetative state", without clarifying the difference between the two definitions.

After this work other definitions have been proposed such as "prolonged post-traumatic unawareness", "post-coma unawareness", "post-coma unresponsiveness". Before an agreement on the diagnostic criteria, there were many definitions of vegetative state, not always coherent among them. One of the first words used to describe patients who awoke from a coma with no apparent awareness of self and environment, was "apallic syndrome". This term coined by Kretschmer in 1940 emphasized the pathologic lesion on the base of clinical observation: loss of the "pallium", i.e. the cortical gray matter that covers the brain. This definition is considered inappropriate if we consider functional brain imaging data that show a huge variety of situations compared to the damage of the cortex in vegetative state patients. Along the years, many inadequate terms have been created to describe conditions in which the patient is in a state of unawareness of self and environment, such as decortication, decerebration rigidity, state of decerebration. The term "cortical death" should be discouraged, as it seems even more confusing in terms of bioethics; this may lead to a dismissive therapeutic attitude and threatening.

Similarly, the term "awake coma" implies a semantic paradox: if it is a documented state of vigilance, the definition of coma is nonsense. Similarly, it is considered inappropriate the use of other terminologies like coma, stupor, prolonged coma, protracted coma, post-comatose hyperton to refer to VS patients.

VS generally follows a coma, the latter usually caused by a severe traumatic or anoxic brain lesion. After a period of 6-8 weeks with coma, the sleep-wake rhythms are restored in survived patients, and in fact they recover the opening of the eyes without showing signs of awareness. In 1994, The Multy-Society Task Force on the vegetative state suggests the behavioral parameters that define the SV: this is a clinical condition of recovery of consciousness (eye opening) without the ability to interact with the surrounding environment, characterized by: no evidence of consciousness of oneself or environment-awareness and inability to interact with others; no evidence of sustained response, reproducible, voluntary in response to visual, auditory, tactile or nociceptive stimuli; no evidence of language comprehension

and verbal production; intermittent wakefulness manifested by sleep-wake cycles; sufficient autonomic vegetative system and hypothalamic functions which allows life in the presence of appropriate medical and nursing care; urinary and fecal incontinence; preservation of the variable spinal reflexes and cranial nerve (pupillary, oculocefalic, corneal, vestibular, ocular reflexes); no evidence of major cognitive functions.

The characteristic feature of the VS is the presence of irregular sleep-wake rhythms in the absence of awareness of self or environment, or substantial evidence of attention or significant or learned behavior. Patients in VS may show dysfunctional movements of the trunk or limbs, which include reflex reactions and facial expressions but not intentional, such as the smile or the tears (Jennett, 2002). As a result of the relative preservation of the functions of the brain stem, many patients in VS maintain a normal reflexive control of eye movements; although the spontaneous eye movements are still possible, there is an inability to follow the gaze stimulus with a deviation of at least 45° (The Multi-Society Task Force on PVS, 1994; Royal College of Physicians Working Group, 2003). The Royal College of Physicians in 2003 ranks among the clinical features compatible with a diagnosis of SV: sphincter incontinence; conservation of blink responses and pupillary and corneal; no intentional setting of the eyes, as well as tracking the movement of moving objects in the visual field of view of the potential patient does not blink response to threat; there may be occasional movements of the head and eyes toward the sound sources or moving objects, there may be a generalized muscular reaction of alarm, such as startle reflex; there may be facial expressions that simulate a smile or a grimace of pain; there can be erratic eye movements. Especially these behaviors can be misinterpreted by family members and no expert-staff, as signs of intentionality; it is therefore necessary to instruct all the people who work with the patient in VS about the behavioral repertoire compatible with that state clarifying that it is not a deliberate behavior. The opinion of the experts of The Multi-Society Task Force on PVS is that the term "persistent" refers only to a "condition of past and continuing disability with an uncertain future" and does not imply the "irreversibility". So "persistent vegetative state" is a diagnosis; "permanent vegetative" state is a prognosis. It is therefore advisable not to use the term permanent, as proposed in a document of American neurologists (ANA Report, 1993) when the VS is going on for at least a month. The reason is that the term seems to convey an implicit prognostic evaluation of non-reversibility of the neurological condition. It is therefore recommended to use the only term VS, as pure diagnostic label, along with the date of its occurrence and its cause. Many patients remain in VS for a very long time, even years, next to family members who range from anxiety, denial and res-

ignation because their management reduce energy, destroys families, defies reason and the ethical questions (Cohadon, 2003).

(iii) Minimally Conscious State (MCS): the nosographic category of MCS was coined by the Aspen Consensus Group (Giacino et al., 2002) in an attempt to introduce and define a single diagnostic term for a medical conditions subsequent to the VS. This is characterized by severe impairment of consciousness with the presence of small, but definite, behavioral manifestation of relationship with the environment. The patient is also able to execute simple commands inconsistently and fluctuating. The same group has considered confusing, the use of other terminology such as "minimally responsive state" or "poor state of consciousness". The MCS is a condition of severe impairment of consciousness in which behaviors that express awareness of oneself and environment are documented, although inconsistently (*ibid.*). The determination of the presence of consciousness is based on one or more of the following signs: response to simple commands; verbal or gestural responses (independent on the accuracy of the response); understanding verbalization; specific behaviors that occur in response to environmental stimuli relevant; appropriate smiles and tears; vocalizations or gestures meaningful in direct response to verbal stimuli or questions; achievement of objects with power adequate to the size and shape of the object; tracking eye movements or fixation supported in direct response to salient stimuli or movements in the surrounding. The term MCS should be reserved for patients demonstrating unequivocally intentional behavioral responses, even inconsistently (Giacino, 1997).

MCS patients typically have their eyes open or open when stimulated; they can sometimes follow a visual stimulus with their eyes; they can make finalistic movements in relation to their neuromotor deficits; they can give intentional responses after a verbal command (e.g. close eyes, move fingers). In the first observations this could be occasional, but more constant and significant over time; he or she maintains or recover in time the ability to swallow. They generally do not speak, and nor give full meaning of words; moreover it should be noted that the ability to verbalization qualifies in itself the patient as MCS even in the absence of any other voluntary activities. The Consensus Conference in Aspen (Giacino et al., 1997) identifies the probable existence of a "border zone" between SV and MCS in which the first signs of an emergency from VS is the presence of eye movement tracking. The transition from coma to the VS is often easily identified by the opening of the eyes. Much more difficulties are found in the differential diagnosis between states of altered consciousness; however, it is crucial to identify any signal indicative of responsiveness; this is the difficult task of the examiner,

since there is no sign without someone who interprets it and gives it a meaning (Cohadon, 2003).

Aware of these difficulties, the work group in Aspen (Giacino et al., 2002) has developed recommendations for an accurate diagnosis: (1) incentives to ensure the highest level of arousal should be adequately given; (2) factors that may interfere with the responsiveness should be controlled (such as sedatives, epilepsy, infections, malnutrition, pain, disvegetative crisis etc.); (3) attempts to elicit voluntary responses through verbal instruction should not involve behaviors that frequently occur on a reflex; (4) tests to assess the ability to execute command should include only requirements that consider the motor ability of the patient; (5) the patients should be evaluated for their response to the greater range of stimuli as possible; (6) assessment procedures should be conducted in a quite environment, free from noise and distractions; (7) revaluations should be performed with serial and systematic observations and reliable measurements to confirm the validity of the initial assessment. It is recommended to use specific tools and procedures appropriate for the quantitative assessment; (8) the observations of family should be considered in the evaluation procedures, and operators of the rehabilitation team involved in daily care as well.

The condition of MCS has a more positive trend compared to VS. Conscious behaviors are limited and fragile, therefore it is necessary to accurately analyze and remove the possible confounding factors when the examiner has to judge the presence of responses indicative of the level of responsiveness achieved: pain, presence of undercurrent infections, lack of adequate sleep, fatigue to participate in physiotherapy sessions, excessive environmental noise affecting the reception of stimuli and exhausts the limited attentional resources available, etc. The period of "unresponsiveness" or the time between the onset and the date on which the first signs of conscious behavior appear documented, it is an important prognostic index, so a proper and timely differential diagnosis between VS and MCS is considerable important. Furthermore, when the patient is able to interact with the environment, it is necessary to vary rehabilitation project with richer and more complex stimuli to provide better opportunities for recovery. The assessment of the condition of VS and MCS can be defined based solely on clinical criteria. No instrument can substitute for systematic observation of the patient's behavior (Jennet, 2002); MCS is distinguished from SV for the presence of behaviors that are expressions of conscious purpose. MCS in these behaviors occur inconsistently, but they are reproducible and sufficiently lasting to distinguish them from reflex activity; moreover MCS may require repeated observations to decide whether a simple response (e.g. "move a finger") even not consistent, is intentional or accidental.

Despite the recommendations proposed by the Aspen Workgroup and the application of more accurate clinical criteria for diagnostic classification, assessing the level of responsiveness of serious brain damage is still problematic as evidenced by studies on large samples of patients. Nancy Childs and coworkers (1993) published a series of not totally adequate observations on patients with a diagnosis of persistent vegetative state at a rehabilitation hospital in Texas, USA in which 37% of VS diagnosed patients were not actually in this state. They tried to assess whether the patients were able to perform movements on command (opening and closing the hand), if they had eye-movement tracking, if they answered yes or no with eyes and/or mouth, and finally questions whether he or she was able to laugh after telling a joke. More recently Keith Andrews (1996) in Great Britain shows the same situation in 15 out of 16 patients admitted with a diagnosis (wrong) in a persistent vegetative state (15). Most of these patients were labeled as vegetative for months or even years (6-82 months). Other authors have reported varying percentages of errors in the classifications of consciousness (15%, Tresh et al., 1991; 45%, Gill-Thwaites & Munday, 2004), with severe negative consequences on the decisions taken with respect to their level of care disbursed.

The difficulties is detecting the presence of intentional behavior arising from possible factors that hinder the patient to detect and understand the demands and to prepare/execute appropriate responses: sensory deficits, motor deficits, cognitive deficits, drug use, environmental conditions (excessive noise), the general state of health, in particular the presence of pain, fatigue or lack of adequate rest can influence the behavior in itself. The evolution between SV and MCS is never sudden, but falls along a continuum and is characterized by rare and infrequent moments at first, then more and more close and prolonged in time in which you can detect behaviors conscious and aware.

3. Individualized quantitative evaluation

Aware of the difficulties related to the recognition of signs of intentional behavior, Whyte (1999) proposes a different approach to evaluate the responsiveness of patients. He asserts that the difficulty in determining accurately the state of consciousness is often caused by unpredictable fluctuations in the performance of the patient and the difficulty in distinguishing voluntary behavior, issued following a specific request by the spontaneous and reflex movements that the patient performs random. As an example, it is important to determine whether the repeated beating of the eyelids is an attempt

to establish a code for communication or is it just a random movement. Traditional methods of assessment of cognitive functions are based on the cooperation of the patient; it is assumed that the performance exam is representative of its actual cognitive abilities. However, patients with severe brain injury have large fluctuations from one moment to another or from one day to another, and also their potential collaboration is inconstant. It is easy, in the case of an individual assessment, seriously underestimate or overestimate the real ability of the patient and diagnose a patient able to provide answers as VS. The examiners often disagree about the nature of the behavior observed in patients, whether it is a voluntary act or a spontaneous movement aimless or a simple reflex response. In addition to the clinical variability of the patient, when the state of unresponsiveness is prolonged in time, for months, the results of evaluations conducted by examiners who turn-over, can be contradictory and in the end one cannot get a unanimous opinion. Traces may be lost in the various medical records, and each operator tends to recall the information that confirms their opinions rather than the more objective response.

In order to provide an accurate assessment of the cognitive status of these patients appropriate diagnostic tools that can take into account these barriers and ensure a more accurate assessment are needed. Available standardized tools developed specifically for the evaluation of patients with severe impairment are very limited and mostly relatively insensitive to minor changes in level of consciousness, also they do not consider the obstacles that may affect the detection of responses to the presence of motor, sensory or cognitive deficits (Inzaghi et al., in press) increasing the risk of mistakenly attributing the patient to a state of unresponsiveness or not to highlight improvements. It can be crucial to detect changes in the frequency with which one can get a certain response from the patient, even if it is not expected in a rating scale, but that is the only way to show intentionality between low possible motor responses.

Whyte (2003) tried to overcome these difficulties by using the model of the single-subject experimental design and applying it to specific clinical questions raised by each patient. In the individual assessment, when the examiner wants to check whether a specific behavior (e.g. "moving arm") is really intentional, even if it occurs inconsistently, can set up specific protocols to verify the hypothesis. It is necessary to find a command B (e.g. "close your eyes"), compatible with the patient residual motor abilities. Three conditions occur: command A that should lead to the behavior A, command B that should not be followed by the behavior A and an observation phase in which the examiner is limited to looking at the patient without asking any request, also in this condition behavior A should not be present.

The correct answers are behavior A after the execution of command A and the non-execution of A after the command B or during the observation.

All wrong answers, that is the execution of A behavior after B command or after an observation phase, must be recorded as well.

The basic hypothesis is that if there is really a response to intentional behavior this will be more likely to occur following a request from A, less likely to occur after the command or in the B phase of observation.

When the answer A is also present in the observation phase, probably it is a spontaneous behavior, and for this reason cannot be interpreted as intentional.

However, if the answer after the command B is still A behavior, this could be interpreted as a non-specific motor response or, on the other hand, this could be due to the patient inability to distinguish between two alternative commands because of deficits in verbal comprehension.

The analysis of the lesion site could lead to hypothesis the presence of an aphasia, in this case it becomes necessary to proceed with another assessment protocol involving the use of gestural commands in order to overcome the obstacle impaired language. A protocol for administration of tests should be set up creating randomized blocks with the target behavior, the distractor and the lack of demand. It is necessary to specify the posture in which to place the patient during the assessment, to facilitate the elicitation of the response, and making sure that status is restored at the beginning of each test block and after each behavioral response.

The command is repeated up to three times, spaced apart by about 5 seconds and the response records obtained within 15 seconds of the command. The examination is conducted by trained-member of the clinical staff which in different moments of the same day and in the following days, pose questions and record the responses. It is possible to check the reliability of the response considering how many times the specific motor pattern has been properly issued after appropriate stimulation and when it was realized incorrectly, or after a different command was executed spontaneously, in the absence of requests. Conducting the review in the course of several sessions on different days and at different times of the day, it possible to overcome patient variability and to characterize the global cognitive abilities of the patient. Finally, using graphical and statistical methods to evaluate them over time, you can eliminate distortions in the clinical observations due to memory limitations and systematic errors in data collection.

This method of evaluation may also be useful when you are looking for a binary code, and can demonstrate the reliability of the patient to communicate intentionally with a yes and a no (Whyte, 2003).

The first step consists in identifying a behavior that the patient knows how to do intentionally. Then it sets up a protocol in which A is the command "show me a yes" and the command B require the execution of an order that involves a motor act.

When a reliable and consistent response is recorded, another motor behavior should be identified; in this case a new protocol is realized in which A corresponds to the command "show me a no". Only after verified total reliability in patient responses it is possible to find that the patient can use the binary code for communication aims.

With the help of family members biographical questions are realized alternated with others that require the analysis of the environmental context (is the light on?) or the examiner's behavior (am I touching my nose?).

Particular attention must be paid on the construction of the questions contained biographical notes: they should not be based on facts and events for which the recent retrograde amnesia may affect the potentiality to make a correct response. The protocol requires that half of the questions requiring yes and half no answer. Very often one can find a high percentage of errors even when patients have shown in the two previous stages, individual answers yes and no, a good accuracy. This is due to the increased difficulty in understanding and processing questions. Also in this last protocol often emerges perseveration tendency to respond with a single code with disproportionate share. Protocols can also be implemented to verify the effect of the drug, that is if drugs are considered stimulants an increase in accuracy of answers should be expected (Laborde et al., 1997). However, we recommended caution in interpreting the results because it is difficult to distinguish whether the changes is induced by the drug or is attributable to spontaneous recovery. The suspension of the drug and the detection of a concomitant deterioration in some cases may clarify its role. The advantage of the assessment modality proposed by Whyte is the enormous flexibility that allows to see every patient with respect to specific questions, this limit lies in the impossibility to perform comparisons between patients because it is not possible to generalize the obtained results. Since the range of behaviors and cognitive abilities of patients with severe impairment of consciousness is extremely limited, Whyte says that in many cases it is possible to adapt to new patients the evaluation protocols previously used, albeit with some adjustments, and provides examples of specific protocols (Whyte et al., 1999).

4. Stimulation, control or monitoring?

Many authors have argued the usefulness of rehabilitation programs of sensory stimulation designed to encourage the resumption of contact with the patient in coma or VS and several methods were proposed in last years. Intensive multi-sensory stimulation programs have been proposed by Doman et al.

(1993), administered for 15-20 minutes every hour, repeated for 12-14 hours a day, six days a week on the assumption that subjects in coma or in VS are growing under conditions of sensory deprivation. Non-intensive stimulation programs were then proposed (Mitchell et al., 1990; Wilson et al., 1993) as cycles of 10-60 minutes stimulation twice a day in a cycle of a single-mode and multi-modal stimulation. The neurophysiological basis of stimulation would be based on the demonstration that sensory deprivation in animals produces loss of neurological function, as the first authors claimed (Le Winn & Dimancescu, 1978). However it should be noted that, according to the theory of neuronal plasticity, not all sensory stimuli are by nature positive compared to the production of stable synaptic connections. There is a possibility that negative stimuli produce a phenomenon of synaptic depression and that can adversely affect learning (Holscher, 1999; Izquierdo, 1997). One of the criticisms of sensory stimulation programs, defined as administering intensive and simultaneous stimuli applied sequentially at maximum intensity on sensory receptors (Doman et al., 1993) is set on the risk of an indiscriminate and prolonged stimulation that can produce phenomena of "habituation" to background noise with a corresponding decline in the ability of information processing (Wood, 1991). Another approach is based on the total control of the environment, that is the patient is inserted in order to facilitate recovering and processing of environmental information, reducing the number and complexity of the stimuli to a level compatible with its limited ability to analyze them. Some studies have followed over time in favor of different approaches, however, the issue has remained controversial. A critical element in analyzing the results is the lack of uniform criteria for classifying patients: before the definitions proposed by the working group of Aspen, rating scales were not be able to highlight subtle changes in the framework of the transition between various states of altered consciousness. A systematic review of the works published from 1966 to 2002 on the effectiveness of sensory stimulation in patients in coma or SV was conducted for the Cochrane Library (Lombardi et al., 2002); the purpose of this work was to determine whether these programs were more effective in facilitating the recovery of responsiveness than standard rehabilitation treatments and whether those programs were more effective in the quality of functional recovery after the coma.

Controlled randomized trials were considered comparing the effectiveness of various programs of sensory stimulation with traditional rehabilitation treatment as a treatment intended to reduce motor complications, cognitive and behavioral interventions using usual nursing, treatment of swallowing disorders, nutrition, of hydration, and physical therapy and neuropharmacologic treatments. Controlled trials with historical control group, case series

and case reports with no control group were not considered. Twenty-five studies were selected, in which were described the rehabilitation methods used and how to monitor its clinical efficacy. Of these studies, 22 were excluded from the review for various reasons: 14 were case series without a control group, 2 were case reports and 1 study was a CCT in the experimental group but considered other interventions in addition to stimulation. Only 3 studies (Johnson et al., 1993; Kater, 1989; Mitchell et al., 1990) met the inclusion criteria with a total of 68 patients. The authors emphasized that the overall methodological quality of these studies was poor and the studies widely differed in terms of outcome measures and the study design. For these reasons it was not possible to make any quantitative summary but only a review of studies from a qualitative point of view.

Here are the main constraints identified: (i) The only randomized controlled trials do not report the method of randomization, (ii) In the two CCTs there are missing information on methods for selecting groups, (iii) No study has evaluated outcomes in "blind"; (iv) Two studies have only used the GCS without functional indicators; (v) short follow-up were performed (only 1 study of more than 3 months); (vi) samples were small (14, 24, 30 patients); (vii) imprecision in the definition of coma and VS (Kater included patients with a GCS of 10 to 14); (viii) lack of precision in the definition of the experimental treatment (1 or 2 sessions per day, the role of family, etc.); (ix) lack of functional indicators in outcome measures, (x) inappropriate statistical analysis (e.g. the scale LCF considered as a continuous variable rather than a descriptive nominal). The review concludes that there is no reliable evidence to support efficacy of sensory stimulation programs for patients in a coma and VS and the effectiveness of sensory stimulation programs should be evaluated in randomized controlled trials (Lombardi, 2002). In a more recent review (Inzaghi et al., in press) we analyzed the literature on rehabilitation treatments aimed at achieving significant changes in level of consciousness compared to spontaneous recovery. The research was conducted from 2002 to 2010 because the previous works used classification modalities of patients not fully compatible with the criteria identified by Aspen Workgroups, so it was not possible to understand their results if there were significant steps in altered states of consciousness. Although we have found 270 articles, based on the analysis of the title and the contents were eliminated those works that were not relevant to our purpose. From this preliminary analysis only studies of type 2 RCTs (Randomized Clinical Trial) corresponded to the criteria established: Oh and Seo (2003) and Barreca and colleagues (2003), the level of evidence of both is class 3 (SPREAD, 2007). Oh and Seo used sensory stimulation treatment designed to promote contact with the environment in a sample of 7 patients. Following a death or a trans-

fer, the study participants were reduced to 5: all male, aged between 39 and 60 years with a GCS from 3 to 7. The experimental design was provided in the study with repeated measurements of single-subject ABA (A = treatment, B = no treatment) in blind (examiner different from the operator dedicated to the treatment). The first operation was carried out twice a day for five days a week, each day has been rated the level of consciousness by GCS. The duration of treatment was two to four weeks each, separated by a resting phase of four weeks. The stimulation protocol included the presentation of sensory stimuli, visual, auditory, olfactory and tactile. During recovery, the patient underwent to medical care and nursing. The authors apply a mathematical model for the comparison between the data obtained and the prediction of the effect of intervention in order to determine the significance of the results (Yaffe & McGee, 2000). An analysis of the average obtained from patients with GCS during the study shows that the most evident effects occur within 4 months after cessation of the second phase of treatment. The effects of the first treatment tend to be gradual, but to disappear within two weeks after its suspension. The second treatment shows its effect after two weeks and, according to the authors, these effects are permanent and not temporary as in the first case, as you keep within four months (however, data not shown). After both first and second treatment, the authors did not detect statistically significant results. Authors' hypothesis is that changes in the levels of awareness of the program following the application of sensory stimulation are more than offset the trend of spontaneous recovery but they recognize that, as the smallness of the sample, the results of this study can not be generalized.

In the study by Barreca et al. (2003) a treatment aimed to elicit consistent yes/no responses and a more classical approach defined has been compared. The experimental condition included, besides conventional speech therapy sessions, a training of structured responses to familiar stimuli with visual and auditory, closed questions relating to his own autobiography, a rich hospital environment, and classical music four hours per day. The control treatment consisted of sessions of speech therapy, sensory stimulation with general yes/no questions. The sample consisted of 13 subjects evaluated as well as through the LCF via Western Neuro Sensory Profile (WNSSP), the Clinical Outcomes Variable Scale (COVS) and the Western Aphasia Battery (WAB), the sub-tests of the yes/no answers to 20 specific questions and abstract. The experimental design used in this study is a crossover with a single subject, each patient was randomly assigned to treatment sequence ABAB or BABA. In phase A, which lasted 8 weeks, the patient was subjected to the experimental training. The assessment by the ANOVA shows no effects of ordering in the sequence ABAB BABA and the (AB vs. BA $F = 0.29$, $p = 0.60$). Assessments made on each individual subject

showed an improvement only in four participants who had scored highest on admission to WNSSP. There was no significant change in score (WAB subtest answers yes/no) at the beginning of the research and obtained within six months ($p \geq 0.05$). One limitation of this research is the brevity of the treatment due to the temporary admission of patients into the hospital. The authors also point out one of the difficulties encountered in the study that may have a negative impact on the results: the insufficient knowledge of the protocols used by staff who worked on weekends. Therefore it was not always possible to control the number and quality of the responses to each condition.

There are still few scientific evidences that can demonstrate the effectiveness of specific rehabilitation interventions and comparison of different approaches, able to demonstrate the advantages of one method over another, and did not lead to shared conclusions. The work that we found, both published in 2003, although subsequent to the Aspen Workgroup, presented a set of data collected and processed with scales that provide wide intervals (GCS), or global scores (WNSSP) and this may not reveal subtle changes in the state of altered consciousness. Improvements in the altered state of consciousness should be demonstrated both in the modification of the waking state than in content, with the processes identified above. Therefore, studies should also provide indicators of improvement in both the state of activation and of cognitive processes,

At present, therefore, it is difficult to find evidences in the literature to support rehabilitation programs that can raise awareness and accelerate the transition between various states if compared to the evolution of spontaneous recovery. The works have also highlighted methodological limitations that should be considered in future work; more specifically they should recruit patients in stable clinical condition, since 50% of patients spontaneously recover within one month after onset (Grosswasser et al., 1990), and also when it is still in ICU, the patient is often sedated, so the assessment of the state of consciousness may be impaired and its participation in a specific program may be partial. A larger samples possibly through multicenter studies should also be recruited; then it is recommended the use of assessment tools that help to identify the critical steps along the continuum of consciousness from coma to full responsiveness and allow to detect even small changes in behavior. It is necessary to ensure the homogeneity of the groups controlling variables such as age, diagnosis, severity of brain injury, time interval from the event; moreover consider the effect of potential interfering cognitive deficits in setting of the intervention protocols and use in a blinded evaluation procedures. At least they should provide follow-up at a distance to control the maintenance of the results.

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