

Silencing the Brain May be Better than Stimulating it. The GABA Effect

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Abstract: Cases of recovery from vegetative and minimally conscious state after the administration of various pharmacological agents have been recently reported. These agents include CNS depressants (zolpidem, baclofen, lamotrigine) and CNS stimulants (tricyclic antidepressants, selective serotonin reuptake inhibitors, dopaminergic agents, methylphenidate). The action of CNS depressants as awakening agents sounds paradoxical, as they are commonly prescribed to slow down brain activity in the management of anxiety, muscle tension, pain, insomnia and seizures. How these drugs may improve the level of consciousness in some brain-injured patients is the subject of intense debate. Here we hypothesize that CNS depressants may promote consciousness recovery by reversing a condition of GABA impairment in the injured brain, restoring the normal ratio between synaptic excitation and inhibition, which is the prerequisite for any transition from a resting state to goal-oriented activities (GABA impairment hypothesis). Alternative or complementary mechanisms underlying the improvement of consciousness may include the reversal of a neurodormant state within areas affected by diaschisis (diaschisis hypothesis) and the modulation of an informative overload to the cortex as a consequence of filter failure in the injured brain (informative overload hypothesis). A better understanding of how single agents act on neural networks, whose functioning is critical for recovery, may help to advance a tailored pharmacological approach in the treatment of severely brain injured patients.

Keywords: Disorders of consciousness, vegetative state, minimally conscious state, GABA.

1. INTRODUCTION

The growing population of adults who sustain traumatic brain injury, stroke, and other disabling diseases, combined with advances in emergency treatments, have led to an increasing number of patients with disorders of consciousness (DOCs) or severe disability. Recovery of consciousness occurs along a clinical continuum that covers a wide range of disturbances including coma, vegetative state (VS) and minimally conscious state (MCS) up to full consciousness restoration [1-2]. The continuum can also proceed in an unfavorable way with deterioration leading from coma to brain death [1]. Indeed, recovery of consciousness does not necessarily correspond with a regaining of functional independence as a variable degree of cognitive or motor disability may persist indefinitely.

2. FROM SEVERE ACQUIRED BRAIN INJURIES TO SYNDROMIC DISEASES

Traditionally, consciousness has been considered as the result of the combination of wakefulness and awareness [1,2]. Wakefulness is an independent, autonomic-vegetative brain function, subserved by ascending stimuli from the pontine tegmentum, posterior hypothalamus, and thalamus. Awareness is subserved by cerebral cortical neurons and their reciprocal projections to and from the major subcortical nuclei. According to traditional conceptualizations, consciousness requires wakefulness while wakefulness can be present without consciousness [1,2]. However, more recent evidence suggests that the above statement might be questionable, that consciousness may be independent from wakefulness and, as such, that it may reveal itself even when wakefulness is minimal or absent. Conditions in which consciousness and wakefulness are dissociated include both physiological and pathological states; dreaming is a form of conscious experience in the absence of wakefulness, while in VS wakefulness is present but consciousness is not. Therefore it would be more correct to consider consciousness as modulated by the level of vigilance rather than by wakefulness [3]. Another issue to be debated is whether consciousness should be

considered as a gradual phenomenon which can be present to a range of degrees, from complete absence to full-fledged consciousness or as a discrete, all-or-none phenomenon [3]. The issue is controversial because to an external observer consciousness may appear to be present to a variable extent depending on the apparent level of vigilance and of cognitive engagement. In reality, from a 'first-person perspective' one is either fully aware of something or not; there is no subjective experience of intermediate degrees of consciousness [3]. What is varied is the quantity of information which vigilance makes available for consciousness [3,4].

Definitions of consciousness aside, according to the current taxonomy DOCs include coma, VS, and MCS: patients in coma show a condition of unarousability with a complete absence of sleep-wake cycles and of awareness; patients in VS are awake but not aware and patients in an MCS show minimal but definite behavioral evidence of self- and environmental awareness [1,2,5,6]. Unconsciousness implies global or total unawareness and is characteristic of both coma and VS. Patients in coma are unconscious because they lack both wakefulness and awareness. Patients in VS are unconscious because although they are wakeful they lack awareness. Comatose patients usually regain eye-opening and circadian rhythms within four weeks after injury. If the recovery of brain-stem-dependent bodily functions is not associated with a recovery of consciousness, patients move from coma to VS, which in turn has a variable duration ranging from weeks to years. Patients emerging from VS may pass into a MCS or a fully consciousness state with a variable degree of residual disability and cognitive impairment. However, if in the future the prevailing concept is of consciousness as an all-or-none phenomenon under the influence of vigilance, DOCs might be considered as belonging to a clinical continuum where consciousness is either present or absent without intermediate states, while the level of vigilance and cognitive recruitment are variable and fluctuating as a consequence of the loss of physical integrity in the brain.

2.1. Coma

Coma results from diffuse bilateral hemispheric lesions or selective damage to the ascending reticular activating system (ARAS) relayed to the cerebral cortex via the intralaminar thalamic nuclei

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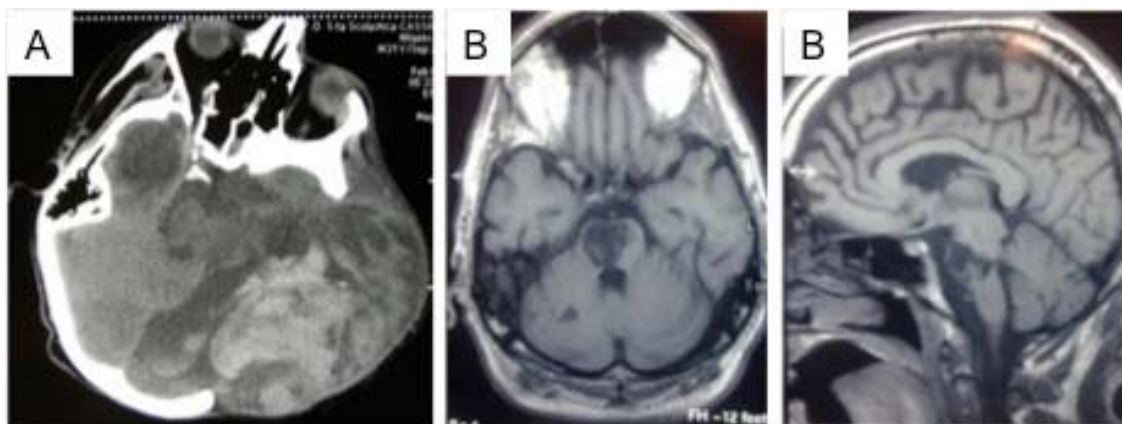


Fig. (1). Coma resulting from a wide supratentorial traumatic injury, with midline brain shift and bihemispheric damage (A) and from a selective damage to the Ascending Reticular Activating System (B).

[7]. The terms used to distinguish these two conditions are supratentorial and brainstem coma (Figs. 1a and 1b).

The role of the ARAS in activating the cerebral cortex to maintain wakefulness is supported by two historic experiments [8-10]. In the early 20th century, Bremer showed that in lightly anaesthetized cats, the transection of the brainstem at the pontomesencephalic level caused coma, whereas a transection at the level of the spinomedullary junction did not [8]. In another pioneer experiment, Moruzzi and Magoun showed that the electrical stimulation of the brainstem reticular formation of lightly anaesthetized cats resulted in a high frequency/low amplitude (so-called desynchronized) EEG, an electrophysiological correlate of wakefulness, whereas lesions of the same region of the reticular formation caused coma with a low frequency/high amplitude (so-called synchronized) EEG [9,10]. Subsequent clinical observations showed that lesions in the upper brainstem reticular formation are a major cause of coma [11-14]. The brainstem structures whose damage is more likely to lead to coma belong to the pontomesencephalic tegmentum with lesions affecting either the midbrain and pontine tegmentum in combination or the upper pontine tegmentum alone [11]. Moreover, the duration of coma depends on the localization of lesions: longer duration of coma is associated with bilateral lesions and shorter duration is associated with unilateral lesions. On the other hand, lesions clustered in the anterior portion of the brainstem, regardless of their rostrocaudal level, do not cause loss of consciousness: these lesions spare the tegmentum but involve structures such as the cerebral peduncles, the pontine nuclei of the basis pontis or the pyramidal tracts, causing severe motor impairment without persistent loss of consciousness as in the locked-in syndrome [11].

2.2. Vegetative State

VS is characterized by preserved wakefulness despite a complete absence of awareness. Awareness seems to result from the activity of a frontoparietal network functionally connected with the thalamic structures [15]. VS is the consequence of a severe and widespread brain injury and can be regarded as a disconnection syndrome of different cortical networks rather than as a dysfunction of a single area or as the consequence of a global reduction in cortical metabolism. [15] Specifically, VS is considered as the result of the disconnection of long-range cortico-cortical pathways (between latero-frontal and midline-posterior areas) and cortico-thalamo-cortical pathways (between non-specific thalamic nuclei and lateral and medial frontal cortices) [15].

VS may be caused by conditions of traumatic brain injury, anoxic encephalopathy and stroke. Anoxic encephalopathy is responsible for a high proportion of cases of VS. This is in accordance

with the pathophysiology of anoxic-ischemic brain damage. When anoxic damage occurs, the cerebral cortex is the most severely damaged structure, as it is more vulnerable to diffuse ischemic injury than white matter. The thalamus and the large cell layers of the neocortex, hippocampus, Purkinje cells, putamen and caudate are the most vulnerable areas [16]. This vulnerability is the result of specific autoregulatory responses and the presence of receptors for excitatory aminoacids (e.g. glutamate) which contribute to neuronal necrosis [16]. White matter injury is commonly delayed: it is the result of wallerian degeneration and results in a symmetric periventricular leukoencephalopathy. As a consequence of the preferential involvement of the cerebral cortex after global anoxia, brainstem structures usually remain intact, allowing patients to resume wakefulness and other brainstem autonomic functions after the acute phase. However, despite the regaining of normal brainstem functions, global cerebral ischemia causes widespread telencephalic damage which favors a disconnection syndrome within the cortico-cortical and cortico-thalamo-cortical pathways responsible for awareness.

VS can be diagnosed according to the following criteria, as established by the Multi-Society Task Force on PVS: (1) no evidence of awareness of self or environment and an inability to interact with others; (2) no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; (3) no evidence of language comprehension or expression; (4) intermittent wakefulness manifested by the presence of sleep-wake cycles; (5) sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care; (6) bowel and bladder incontinence; and (7) variably preserved cranial-nerve reflexes (pupillary, oculocephalic, corneal, vestibulo-ocular, and gag) and spinal reflexes [2,6]. The regaining of normal circadian rhythms, denoting the transition from coma to VS, usually occurs within four weeks after the injury responsible for the impairment of consciousness: sleep-wake cycles, although present, are commonly irregular and are associated with electrophysiological patterns that are widely different from those recognized in healthy individuals [17-19]. Indeed, vigilance often fluctuates especially in the first phases. Patients are usually not immobile. They may move the trunk or limbs in meaningless ways, but usually they are progressively imprisoned by the development of hypertonus due to loss of physiological inhibition mechanisms between the cortex and the spine. As a result of the relative preservation of brainstem functions, most patients in VS retain good to normal reflexive regulation of vision and eye movement. Moreover, they may show automatic behaviors including smiling and crying and produce moans or screams. In most patients the gag, cough,

sucking, and swallowing reflexes are preserved. The presence of these movements may be ambiguous and give false impressions about consciousness to family members.

VS can last for a variable time interval ranging from weeks to years. It is considered persistent when remaining over time, with a duration of at least one month after the primitive injury. However, the term "persistent" does not imply a condition of irreversibility, as wrongly suggested on some occasions. VS may be defined persistent in the same way as rain when persisting over days: persistent VS may progress to a minimally conscious or a fully consciousness state exactly as prolonged rainfall may suddenly stop. On the other hand, the adjective "permanent" implies a condition of irreversibility, which is mainly deduced by instrumental findings. In fact, although ethical caution suggests avoiding terms referring to irreversibility, sometimes clinical, neuroradiological and neurophysiological findings are so dramatic that there are sufficient data to ascertain that the chances of recovery, if any, are exceedingly small. To avoid confusion between the condition of 'persistence' and 'permanence' the Royal College of Physicians in the United Kingdom suggested to replace the term 'persistent VS' with 'continuous VS' [20]. The generally accepted deadline for a prognosis is 12 months for post-traumatic and 3 months for non-traumatic VS. Nevertheless, several belated recoveries are described in the scientific literature [21-23]. Commonly, patients in VS as a consequence of an anoxic encephalopathy are less likely to recover awareness and have a worse long-term prognosis.

Neurophysiological exams may support the formulation of a prognosis in patients in VS: although VS is not characterized by specific EEG features, the presence of a persistent diffuse generalized polymorphic delta/theta activity, which is not modified by sensory stimulation, or the detection of very-low-voltage EEG activity, suggest a bad prognosis [24-26]. Moreover, in patients with an anoxic encephalopathy, EEG patterns are commonly classified, according to the Hockaday classification, into five grades ranging from normal to extremely abnormal [27]. The degree of EEG abnormality usually reflects the severity of brain damage: grade I predicts an excellent prognosis for recovery of consciousness whereas grades IV and V are usually associated with a permanent VS or death. Similarly, a bilateral absence of somatosensory evoked cortical responses (N20) [28], as well as breakdown of EEG functional connectivity [29] are highly predictive of failure to regain consciousness and suggest a condition of permanent unconsciousness. [28,29].

We recently proposed a novel neurophysiological approach to help in establishing prognosis in patients in VS. This approach moves from the assumption that consciousness depends on the normal activity of wide neural networks, which can be regarded as complex systems whose outputs show nonlinear behavior. Nonlinear analysis applied to electroencephalographic (EEG) and electrocardiographic (ECG) signals allows to explore the complexity of residual neural networks in patients in VS and to predict their outcome [30-32].

With respect to neuroimaging exams, there are no established correlations between their findings and the development of the VS or the potential for recovery, probably due to the extreme heterogeneity of brain damage accompanying the impairment of consciousness. Consequently, their predictive value remains controversial. However, special interest has recently arisen from the application of functional Magnetic Resonance Imaging in patients with DOCs. These techniques investigate the activation of specific cerebral areas in response to the setting of particular cognitive tasks. For example, while asking the patient to imagine playing tennis or moving around the rooms of his house, an evaluation can be made of whether the activation pattern of specific cerebral areas resembles that previously identified in healthy subjects [33]. In the case of an overlap of these patterns, it can be hypothesized that some behav-

iorally unresponsive patients are, in reality, conscious [33]. In fact, by means of this technique, recent studies reported to have recognized signs of hidden consciousness in subgroups of patients with a diagnosis of VS. Moreover, with respect to prognosis, a recent meta-analysis is of particular interest [34]. This study compares the results of all the studies based on the use of fMRI, and suggests that 'higher order' associative cortical activation in VS heralds the recovery of consciousness in the following months. These results are both evocative and highly controversial, but they have certainly paved the way for future multi-center cohort studies aimed at recognizing the neuroimaging correlates of consciousness in behaviorally unresponsive patients in order to reduce the rate of misdiagnosis and to better predict prognosis [34].

In the light of the above observations, it is clear that establishing a prognosis in patients in VS, especially after a global cerebral ischemia, is very hard. Forming a prognosis requires a combined analysis of clinical, neurophysiological, and neuroradiological findings. Prudence suggests forgoing conclusions exclusively based on isolated impressions since a shock phase may occur early after the insult from which the brain can partly recover, as occurring in patients with a minimal recovery despite negative early neurophysiological findings [35]. Consequently, considerations regarding neurological outcomes, especially after an anoxic encephalopathy, should be postponed as much as possible as should irrevocable decisions about the limitation of treatments for patients.

Finally, an important question that remains largely unanswered concerns the capacity of patients in VS to experience pain and, when it seems so, whether their responses to pain should be considered as purely reflexive or at least partly cognitively mediated. Major doubts and ambiguities about this issue arise from the term 'pain' itself, which usually refers both to physical pain and inner suffering. It is evident that these two dimensions of pain have to be distinguished in patients in VS if we admit, by definition, that they completely lost any self- and environmental awareness. Nevertheless, especially when patients show grimace-like behavior or what seems like crying, doubts about pain perception and its essence still remain. To date, there is a general trend to consider the nature of pain in these patients as reflexive: pain might be experienced as a merely sensory experience which is associated with actual or potential tissue damage in the absence of any mental suffering. However, this assumption is often met with doubts and controversy, suggesting the need for further systematic investigation. Doubts are further endorsed by the controversial results of neuroimaging studies which, in response to the administration of nociceptive stimuli in unconscious patients, reported either the isolated activation of the primary cortex without the involvement of higher-order associative cortices [36] or the contextual activation of the primary somatosensory cortex in the postcentral gyrus, the secondary somatosensory cortex in the posterior insula and the cingulate cortex [37]. Even more interestingly, a recent fMRI study discovered signs of residual affective consciousness in patients in VS, by identifying a specific brain activation pattern within the so-called pain matrix in response to others' pain cries [38]. Further evidence concerning this topic also comes from neurophysiological studies which point out how signs of residual cerebral perception in VS enable the prediction of the recovery of consciousness and the neurological outcome of patients in VS [39,40]. Moreover, a recent study, which investigated laser evoked responses in VS, recognized residual pain processing especially in response to high intensity stimuli, thus suggesting that the salience of the stimulus is able to influence its perception in unconscious patients [41]. In conclusion, the available evidence suggests that the possibility of residual perception of pain in VS cannot be excluded. It has therefore been recommended to carefully investigate any source and perception of pain through a combined clinical and instrumental assessment and to start analgesic treatments whenever necessary [2, 6, 20, 42].

2.3. Minimally Conscious State

MCS is characterized by minimal but definite behavioral evidence of preserved self- or environmental awareness [5]. Patients in MCS demonstrate discernible behavioral evidence of consciousness but remain unable to reproduce this behavior consistently. The diagnosis of MCS requires the repetition of neurological assessments along a prolonged follow-up period. A number of authors have dwelled upon the difficulties involved in assessing this group of patients, pointing out cases of misdiagnosis which highlight this difficulty [35,43,44]. To avoid such misdiagnoses, it has been indicated that VS and MCS diagnoses may only be formed by means of repeated specific neurological examinations of the patient in an optimal position and at an optimal time of day by means of the CRS-R [45-47]. Establishing whether a patient is in VS or MCS entails demonstrating his or her meaningful behavior over time. Clinical signs that denote the presence of an MCS include cognitively mediated behaviors, which, even if they occur inconsistently, are reproducible, or sustained for long enough to be differentiated from reflexive ones. The presence of behaviors whose properties are clearly cognitively mediated such as purposeful motor performances, gestural or verbal yes/no responses and intelligible verbalization, immediately suggest the diagnosis of MCS, but it is not the same for less complex tasks such as visual pursuit and object manipulation. For these behaviors, a prolonged follow-up based on repeated neurological examinations is of the essence to assess whether a response is merely reflexive or cognitively triggered. For example, in order to be considered in an MCS, a patient who follows basic motor instructions is required to show this behavior more frequently and consistently than a patient who verbalizes. In fact, misdiagnosis in this extremely challenging group of patients is mainly due to fluctuations in their clinical status and to the intra-rater and inter-rater variability when using clinical assessment tools, including the CRS-R [45]. Consequently, no diagnosis should be inferred from an isolated assessment or the impression of one examiner: reasonably stable scores over repeated measurements should be achieved.

Patients in an MCS may remain stable or further progress toward a fully conscious state: in the latter case, we talk about emergence from an MCS. There are specific behaviors whose appearance strongly suggests the emergence from a MCS [5,45]. These behaviors include the functional use of objects that are commonly used in basic daily activities and/or the functional interactive communication. Nevertheless, even in this case, misinterpretations may occur. Sensory deficits, motor dysfunction, or diminished drive in these patients may lead to an underestimation of these signs: for instance, a coexistent tetraplegia might avoid to explore the presence of a functional object use. Similarly, a patient with aphasia may be precluded from revealing the quality of his consciousness through verbal outputs. This suggests that a neurobehavioral view may not be enough, in some patients, to establish their real level of consciousness and that it is important to investigate the possibility that concomitant neurological impairments, rather than a diminished level of consciousness, are the reason for behavioral unresponsiveness.

2.4. Locked-in Syndrome

Locked-in syndrome (LIS) is a condition of severe neurological impairment characterized by the presence of quadriplegia or quadriparesis, anarthria, lower cranial nerve paralysis and preservation of vertical eye movements [48,49]. Despite their extreme degree of motor imprisonment, patients with LIS are fully conscious and cognitively intact: they are able to interact with the environment solely through eye-coded communication based on eyelid blinking and vertical eye movements. A locked-in patient was brilliantly depicted by Alexandre Dumas in 'The Count of Monte Cristo' as a corpse with living eyes and by Emile Zola in 'Therese Raquin' as a paralyzed corpse with language only in the eyes [50,51].

The clinical picture is the consequence of the complete interruption of corticospinal and corticobulbar pathways, which occurs at the pontine level. The interruption of central motor pathways may be detected through MRI tractography as shown in (Fig. 2). LIS can be subdivided into different clinical classifications depending on the severity of motor de-efferentation: 1) the classic form, characterized by the complete loss of any motor output with the exception of vertical eye movements and blinking; 2) the incomplete form, characterized by the sparing of any voluntary motion other than eye movements; 3) the total form, characterized by complete motor impairment also including ocular movements [52]. The crucial factor that makes the above forms of LIS different from each other is the degree of residual ability to communicate by means of preserved functions [52].



Fig. (2). MRI tractography showing a unilateral pontine lesion in a patient with an incomplete LIS.

Additional clinical manifestations recognized as "non-motor symptoms" may be observed in patients with LIS. These symptoms include pathologic laughter and crying, motor imagery defects and impaired conscious recognition of negative facial expressions [53-56].

Most cases of LIS are caused by a ventral pontine lesion following an ischemic (Fig. 3) or hemorrhagic stroke. Trauma, amyotrophic lateral sclerosis, severe demyelinating processes, infective diseases and muscular disorders account for the remainder of cases.

The recovery of motor functions is minimal and patients remain severely dependent in all daily living basic activities. Nevertheless, the perception of these patients about their own personal health and life satisfaction often seem discordant with their objective health status and disability: in fact, despite their extreme degree of disability, it has been reported that chronic LIS survivors show a surprisingly high self-scored quality of life and that requests of treatment withdrawal or euthanasia are infrequent [57,58]. Depression and anxiety-related symptoms are apparently lacking if a pure ventral pontine lesion is responsible for the syndrome [57,59]. Nowadays, the quality of life of LIS patients can also be partly improved by training them to use brain computer interfaces: thanks to these systems, patients can be enabled to communicate via spelling systems

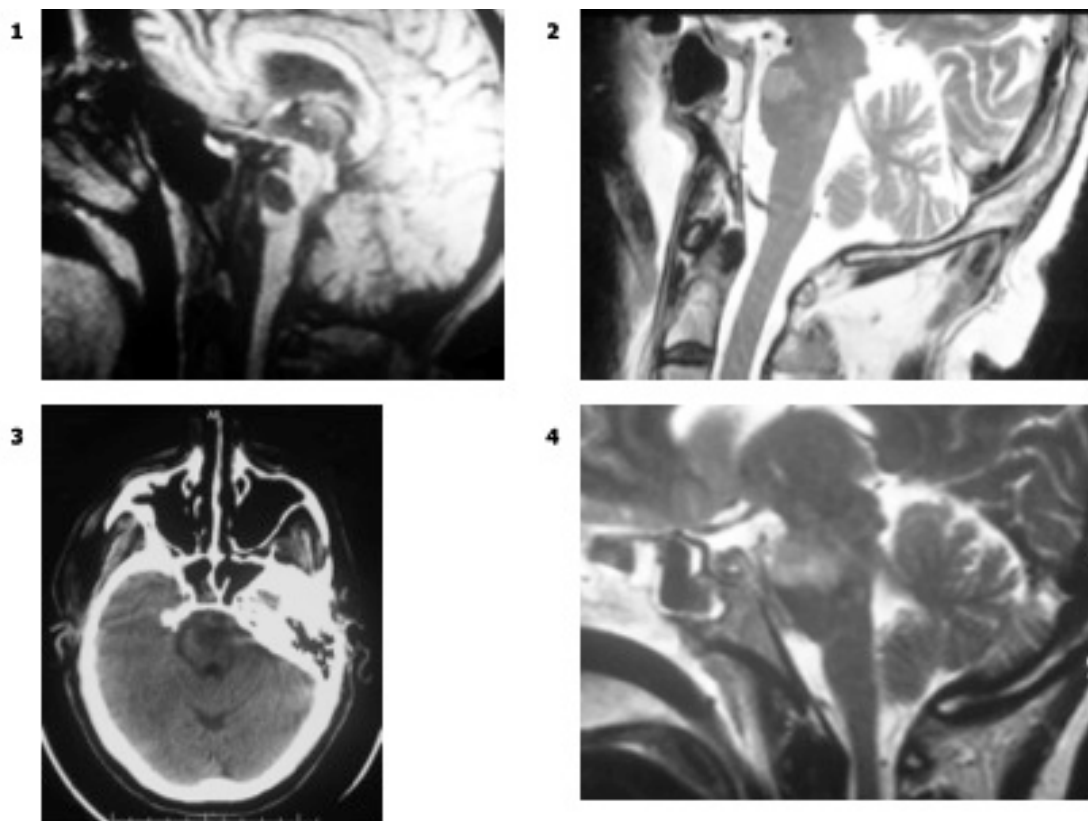


Fig. (3). Brain magnetic resonance (1,2,4) and computed tomography (3), all showing a ventral pontine ischemic lesion (reproduced with permission from Arch Phys Med Rehabil 2008; 89: 775-778).

on a computer (which can be coupled with a text to speech synthesizer) and therefore to have some control over their environment [60].

The diagnosis of LIS can be difficult especially in the acute phase: much evidence suggests that a high proportion of patients with LIS are erroneously diagnosed as being in a VS or MCS [61-62]. Great interest was aroused recently by the story of a man who spent 23 years lying motionless in bed, suffering from LIS, which had been misdiagnosed as a VS until functional neuroimaging techniques revealed that he was in fact fully conscious. In the light of this, it has been suggested that late recoveries of consciousness, even after twenty years, might hide misdiagnoses which are not corrected over a long period of time. The employment of behavioral assessment strategies alone in patients with an extremely restricted motor repertoire, as occurs in patients with LIS, seems to be the major factor responsible for diagnostic confusion. In fact, the high proportion of misdiagnoses is mainly due to the extreme difficulties that physicians experience in establishing a communication code with these patients. This is even more challenging when physicians are faced with patients showing a total LIS or suffering from eye movement disorders. We recently reported on the presence of an opsoclonus-myoclonus syndrome in some patients with LIS: opsoclonus-myoclonus symptoms represent an additional impediment to communication and may be partly responsible for misdiagnoses [59,63]. Experience with these patients prompts reflections about the difficulties we may encounter in distinguishing patients with a persistent consciousness disorder from those with an extreme degree of output impairment. Although VS, MCS and LIS are considered as well recognized and distinct conditions, cases with unusual features may put physicians at risk of underestimating the consciousness level of some patients, with all the ensuing ethical and scientific consequences: patients with LIS may be wrongly diag-

nosed as vegetative when ocular disturbances or cognitive deficits prevent them from revealing their true state.

2.5. Severe Cognitive Impairment

Cognitive impairment is a common sequela of acquired brain injury. It is characterized by a general slowing in cognitive performances with effects particularly prominent in terms of information processing speed, attention, memory, executive functioning, and cognitive flexibility [64,65]. Since cognitive functions which contribute to mental performances are distinct but heavily intermingled, most patients who survive acquired brain injury show multifaceted cognitive dysfunctions which rarely imply the loss of a single function. However, rare cases do occur of damage to higher cognitive functions, resulting for example in aphasia, hemi-inattention or sensory deficits.

Widespread damage or strategic lesions, either traumatic or vascular, may interfere with the process of memory formation. This process commonly proceeds through three general stages: the acquisition (learning) which involves the initial perception of a new experience, the formation of a short-term memory of the newly acquired experience and finally its consolidation into a more durable long-term memory [66]. Any stage of memory formation can be hindered by brain injury. Patients with sensory deficits as a result of acquired cerebral injury may not be able to store new information through common perception channels. Conversely, patients with hippocampal lesions, despite regular perception mechanisms, are not able to efficiently store short-term memories as the memory traces they form are too transient and labile to be converted into long-term memories. Patients with widespread cortical-subcortical damage often show a memory impairment as a consequence of inadequate initial learning or difficulties in retrieving data they have previously stored in long-term memory [66]. On the other hand,

some patients with dysfunctions in frontosubcortical pathways seem to persistently re-experience past traumatic events (as occurs in post-traumatic stress disorder). The psychobiological mechanisms underlying this re-experiencing involve brain circuits such as the limbic system, hippocampus and prefrontal cortex, which modulates explicit memory [67]. It has recently been observed that patients who have suffered a stroke are more likely to experience such intrusive symptoms if basal ganglia are involved, confirming that the phenomenon of re-experiencing may be modulated by thalamo-subcortical pathways [67].

Disturbances of attention are also frequent in patients with severe brain injury, particularly in situations that require the division of attention [64,66]. The dysregulation of a cholinergic axis underlying attentive processes make mental performances more vulnerable to distractors, as a consequence of inadequate activation of top-down mechanisms [66]. Neglect may also be considered an attention disorder, characterized by a disruption in the spatially directed aspects of selective attention. This is commonly observed in patients with a variety of dorsal lesions within the right hemisphere.

Executive functioning and cognitive flexibility are frequently impaired when the prefrontal cortex is damaged. The prefrontal cortex is functionally divided into ventro-medial and dorsolateral sections. Lesion and functional imaging studies have shown that different prefrontal circuits, along with their respective cortical and subcortical connections, are implicated in specific cognitive abilities [68]. The most common deficit associated with the ventromedial region of the prefrontal cortex is impaired social function, as epitomized by the famous case of Phineas Gage, who after a freak accident that damaged his frontal lobe, exhibited what is now recognized as the typical frontal syndrome: inappropriate social behaviors, lack of moral judgment, few social inhibitions, few abstract thought processes, an inability to plan for the future, and/or difficulties in maintaining a plan of action [68]. On the other hand, damage to the dorsolateral prefrontal cortex mainly results in disturbances of the working memory, directed attention and temporal integration processes, which are all prerequisites for cognitive flexibility, abstract thinking and strategic planning [68]. A frontal lobe injury may also lead to a specific syndrome which is called 'akinetic mutism' [69]. Patients presenting with this syndrome neither move nor speak due to a motivational impairment which is the consequence of frontal lobe damage. Patients with akinetic mutism might sometimes be thought to have a DOC or LIS, as the immediate impression can be very similar and they can be equally behaviorally unresponsive. However, it has to be stressed that these are completely different syndromes. Patients with akinetic mutism show a disorder of diminished motivation; patients with VS or MCS show a condition of impaired consciousness; patients with LIS suffer from a severe motor imprisonment which prevents them from moving and speaking despite their preserved consciousness and motivation [70,71].

Finally, it should be highlighted that cognitive dysfunctions in the early months after injury represents a risk factor for future disability, interfering with independent living, return to work, social relationships, and quality of life.

3. PHARMACOLOGIC DOMAINS AND INTERVENTIONS

Recently there have been descriptions in the scientific literature of sporadic cases of recovery from VS and MCS after the administration of various pharmacological agents [72]. These agents include drugs of various classes, which can be grouped in two general categories: CNS depressants (zolpidem, baclofen, lamotrigine) and CNS stimulants (tricyclic antidepressants, selective serotonin reuptake inhibitors, dopaminergic agents, methylphenidate) [72].

The above drugs have different pharmacodynamic profiles: i) zolpidem seems to exert prompt but transitory effects in terms of improved consciousness. Some patients treated with zolpidem are described as awakening and remaining awake for as long as the

drug maintains its pharmacological effect [73-76]. The maximum arousal is observed one hour after the start of treatment and arousal progressively declines within four hours, as the effect of the drug subsides; ii) baclofen, especially in its intrathecal form, may favor a recovery of consciousness which is more delayed in time but more lasting than that observed with zolpidem [77,78]. Some patients may show an improvement in the level of consciousness and functional autonomy several weeks after the administration of intrathecal baclofen. In some patients, this improvement remains stable over time and independently of the pharmacokinetic profile of the drug; iii) lamotrigine has also been found to have beneficial effects which emerge several weeks after the start of treatment and remain stable over time, although these effects have been described more rarely [79]; iiiii) tricyclic antidepressants, selective serotonin reuptake inhibitors, dopaminergic agents and methylphenidate can all have similar advantageous effects [80-84]. Whether these drugs favor a recovery of consciousness or encourage functional recovery in patients who are spontaneously emerging from an MCS is still the subject of debate. In our opinion, they are more likely to promote a functional recovery when pyramidal or extrapyramidal sub-syndromes variably contribute to the behavioral unresponsiveness of the patients [72,85]. In this respect, we recently suggested that the behavioral unresponsiveness of patients may be the consequence of the variable combination of the following subsyndromes: i) pyramidal syndrome; ii) extrapyramidal syndrome; iii) cortical syndrome; IV) disconnection of associative areas; V) brainstem dysfunction (Fig. 4) [85]. Therefore, disparate treatments may seldom restore consciousness by improving one or other of the sub-syndromes [85].

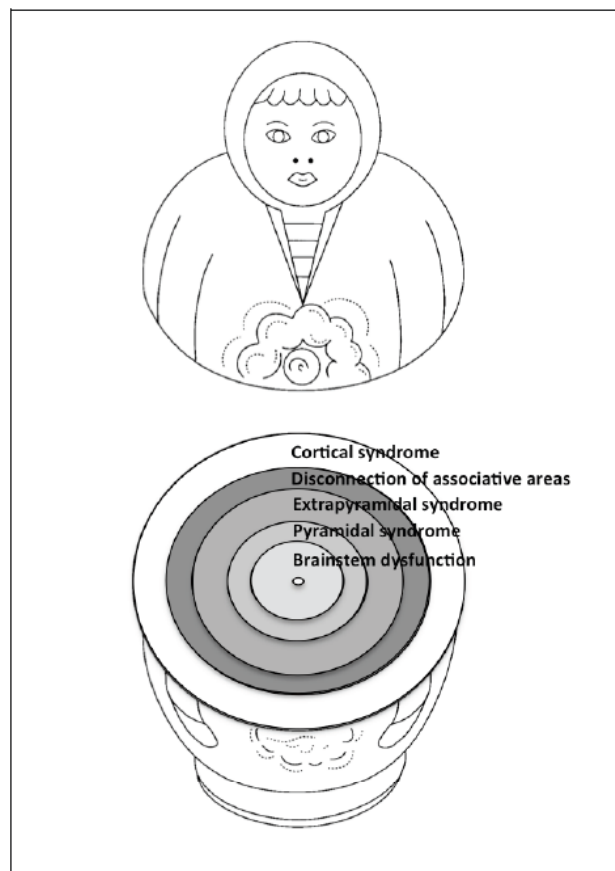


Fig. (4). Possible combination of subsyndromes within vegetative and minimally conscious states (modified from Sandea Vandermerwe, 1993. The metaphor and design are used with permission). Reproduced from [85] with permission.

4. DIVERGING RESULTS FROM CLINICAL TRIALS: INEFFECTIVE DRUGS OR THE WRONG PATIENTS?

Only a minority of patients benefits from the above reported treatments and no single treatment is right for everyone. It is extremely difficult to understand how drugs which have opposite pharmacological profiles can exert similar effects on the above patients, in some cases helping their recovery [72]. This makes the pharmacological management of patients with DOC one of the most disputed issues. In our opinion, the extreme variability of responses to specific treatments depends on the heterogeneity of the patients included in the different studies; although usually grouped in rigid categories (coma, VS and MCS), patients often show characteristics which are overlapping between one group and another [72]. Further confusion stems from the erroneous inclusion in studies of patients with locked-in syndrome. Their inclusion arises because of their similarities, on the level of behavioral unresponsiveness, to patients with disorders of consciousness (VS, MCS). Indeed these are two completely different categories of patients: in VS consciousness is compromised while spontaneous motility can be preserved, whereas LIS is a condition of extreme motor entrapment which sometimes precludes the revealing of a state of consciousness which remains absolutely unharmed. Moreover, the frequent overlapping between these groups is not only the result of possible misdiagnoses caused by a phenotypic similarity obscuring a difference in the underlying neuropathological nature of the conditions; there is also the possibility of a neuropathological overlap between the two groups [61,62,86]. In fact, it cannot be excluded that patients in a VS may also incorporate a locked-in component, especially when the primitive neurological damage has produced coupled lesions both at the level of the structures underlying consciousness and also at the level of motor pathways necessary to reveal it [86]. Therefore, from a purely phenomenological perspective it may be difficult to distinguish which of the behaviorally unresponsive states are the result of a loss of awareness and which are not. Ascertaining whether behavioral unresponsiveness in these patients is the consequence of damaged consciousness or is the result of an injury involving the centers and pathways necessary to express consciousness is not an easy task and may sometimes be impossible. Matters are further complicated by the recent introduction of the new diagnostic category known as functional locked-in state. This term refers to behaviorally unresponsive patients with evidence of consciousness revealed only through paraclinical tests such as functional magnetic resonance imaging, positron emission tomography, electroencephalography, or evoked potentials [87]. According to current knowledge, functionally locked-in patients are in a situation of extreme behavioral motor dysfunction together with preserved higher cognitive functions [87]. In the light of this definition, it has recently been suggested that a subgroup of patients with a diagnosis of VS may in fact be functionally locked-in rather than unconscious.

The consequence of the above reported issues is that little and confused evidence-based medicine is available to help physicians who care for these patients and that some patients are at risk of being erroneously included or excluded from drug trials. There is an urgent need, therefore, to revise the taxonomy of patients with disorders of consciousness in order to develop diagnostic criteria which more accurately reflect the peculiar traits of each subgroup of patients [88]. The new classification should accommodate developments as they emerge and should avoid the risk of different subgroups of patients being interchangeable. This is the prerequisite for planning robust studies, based on rigorous clinical research design, and advancing a tailored pharmacological approach in the treatment of severely brain injured patients.

5. THE GABA EFFECT

The available studies suggest that CNS depressants are often more effective than stimulants in speeding the recovery of patients with disorders of consciousness [72]. On the other hand, CNS

stimulants seem to play a relevant role in improving cognitive functions in patients who have already shown a spontaneous recovery of consciousness [72]. To date, the mechanisms responsible for the improvement of consciousness after the administration of CNS depressants can only be hypothesized.

5.1. GABA Impairment Hypothesis

There is a general consensus that wide cortical-subcortical neural networks give rise to consciousness, but no full agreement exists regarding which areas and networks are specifically involved [15]. In this respect, we recently suggested the use of the term 'ghost networks' when referring to the neural substrates of consciousness [31]. The neural networks underlying consciousness can be regarded as complex systems characterized by sufficient functional connectivity with good lines of communication within their parts [31]. As a product of complex systems, consciousness can be considered an emergent phenomenon. In other words, it is a new event which emerges from the interaction of two or more other events, but is entirely different from and cannot be reduced to its initiating events [89]. Other examples of nonlinear emergent phenomena include the flame of a candle and the flocking of birds. The appearance of consciousness, as an emergent phenomenon, strictly depends on the synchronized behavior of neuronal assemblies (located in different brain areas) that participate in the same functional act as a group [90]. Fingelkurts and Fingelkurts recently proposed a model of brain operational architectonics, which brilliantly describes the mechanisms of transient functional neuronal assemblies during cognitive operations of varied complexity [91,92].

What is certain is that coherent synchronization within the whole system is crucial to push in the direction of specific outputs (emergence of consciousness or goal-oriented activities) [93-96]. In the absence of appropriate synchronization, specific behavioral outputs, including consciousness, may fail to emerge. In this respect, traffic flows through neural networks can be compared to the information transfer within the large networks of the web [97]. The web consists of about 120 million hosts, or endpoints, and more than 100,000 distinct networks, totaling millions of routers and links connecting the hosts to the routers and the routers to one another [97]. These links differ widely in speed as well as in technology. As a result of a strong interconnectivity within so complex data-delivery networks, each endpoint receives convergent information from the others, ultimately providing measurable responses to the users [97]. Such responses may be labeled as emergent phenomena and, like consciousness, rely on a balanced dialogue between the nodal points of the involved networks.

Severe brain injury causes a reduction in interconnectivity within consciousness-related networks, with crucial biological messages either becoming slow to transmit and receive or no longer able to reach their destination [31]. The reduced connectivity of these systems leads to a greater autonomy and isolation of their parts and interferes with the synchronization of the whole system. As a result, consciousness fails to re-emerge and patients remain in a condition of VS [98-100]. How might CNS depressants contribute to restoring the interconnectivity of neural networks and restituting consciousness? According to our hypothesis, CNS depressants might partially reverse a condition of impaired cortical GABA neurotransmission, which hinders functional synchronization in the injured brain. Many studies suggest that the organization of the functional networks of the brain in a resting state is different from their organization in conditions of cerebral computation [101,102]. When the brain is in a condition of wakeful rest, the so-called default mode network (DMN) or task-negative network (TNN) is active. This network includes medial parietal and frontal brain regions such as the posterior cingulate cortex and the ventral anterior cingulate cortex. During goal-oriented activities, the DMN undergoes specific deactivation through the action of the GABAergic system. This deactivation reflects an interruption of previous intro-

spective processes to engage in attention-demanding actions [101]. Examples of task dependent deactivation also include the deactivation of auditory areas during visual imagery tasks and the deactivation of the extrastriate visual cortex during auditory stimulation [103]. This confirms that the execution of goal-oriented activities requires both the activation of specialized areas and the concurrent deactivation of specific interconnected regions, the latter being the result of an active suppression process.

The deactivation of the DMN during goal-oriented activities has been recently investigated through fMRI both in healthy subjects and patients [101,102]. These studies show that such deactivation is completely absent in patients in VS and only partially preserved in patients in MCS [101]. Impairment in the GABAergic system, through an increased ratio of synaptic excitation to synaptic inhibition, may be responsible for the lack of deactivation of the DMN and the failure in the emergence of goal-oriented activities in these patients. It can be hypothesized, therefore, that patients with DOC show impaired GABA modulation and that CNS depressants may facilitate an improvement in the level of consciousness by restoring the brain interconnectivity and a balanced level of inhibition during transition from rest to computational states. This hypothesis is also in line with the findings of a double-blind, randomized, placebo-controlled, cross-over study showing, in healthy subjects, an increase of functional connectivity in the human cortex following the administration of lorazepam, a benzodiazepine hypnotic drug that binds to the GABA_A receptors [104]. This additional evidence confirms that GABA-induced inhibition is an active process which, through interaction with specific synaptic and diffuse extrasynaptic GABA receptors, may enhance brain synchronization [104]. The above study reported that an increase in the number of operationally synchronized cortical areas, together with an increase in the strength of long-range and interhemispheric connections, may be considered a specific "signature" of the influence of lorazepam on the cortex and may be used as a functional marker for future studies evaluating the effects of GABA agonists in patients with DOCs.

The GABA hypothesis awaits further confirmation in order to establish whether DMN deactivation through GABA mechanisms may represent a target for novel therapeutic strategies in this challenging group of patients. Future studies will investigate to what extent the depletion of GABA contributes to the behavioral unresponsiveness of these patients and how GABAergic drugs may encourage their recovery.

5.2. Diaschisis Hypothesis

The concept of *diaschisis* was first described by von Monakow in the early 20th century [105]. The term *diaschisis* denotes a sudden loss of function in brain areas which are distant from a damaged area but functionally connected to it. Diaschisis can occur within a working unit with parts that must cooperate to assure normal functioning. Within such working units, the damage to one part can have disruptive effects on other parts: negative repercussions which may later wear off and be associated with some recovery of function. In the brain, diaschisis is most likely to be triggered by sudden injuries such as traumatic brain injuries and strokes; it does not usually occur in the case of slowly growing lesions [105]. The development of a brain diaschisis is promoted by an 'abolition of excitability' or a 'functional standstill' of remote brain areas. A putative mechanism has been proposed which would explain the processes underlying the development of brain diaschisis [105]. Traumatic or anoxic cerebral injury results in altered dynamics of neurotransmission, either as a direct consequence of the initial injury or as part of the subsequent adaptation of the brain. In particular, two notable and co-occurring alterations have been reported: i) an increase in the release of glutamate, leading to excitotoxicity and augmented apoptosis; ii) a surplus of GABA and a lasting hypersensitivity of GABA_A receptors, with the inhibitory neurotransmitter binding to its ion channel receptors and a consequent reduction

of blood flow and cell metabolism in brain areas surrounding the damaged area [105,106]. This adaptation, which probably develops as a mechanism to contrast hypoxia, leads to a condition of cell dormancy or diaschisis in brain areas which are functionally connected with the damaged one [106]. The duration of diaschisis, before it eventually wears off, is variable and may be influenced by factors such as the brain areas involved, the patient's age and comorbidities. According to von Monakow's original theory, diaschisis may also persist indefinitely, without undergoing dissipation over time [105]. Diaschisis may be more persistent in the presence of interactive factors such as vascular disorders which can interfere with the recovery of distant brain areas. The concept of diaschisis may contribute to explaining why some brain injured patients show more severe and diffuse symptoms than is expected on the basis of the initial damage. Similarly, the wearing off of diaschisis may be a reasonable explanation for a delayed recovery of functions in the same patients.

Diaschisis may also be involved in the functional breakdown of interconnected areas which is associated with DOC. The phenomenon of diaschisis, through a splitting off of these previously interconnected units, may play a significant role in the pathological process leading to the breakdown of consciousness. In these circumstances, DOC may persist until diaschisis is reversed, or may last indefinitely if the interconnectivity is not restored. The diaschisis hypothesis allows us to speculate about the mechanisms by which zolpidem, a short acting nonbenzodiazepine hypnotic of the imidazopyridine class that binds to the GABA_A receptors, may exert its effects and enhance the level of consciousness in some brain injured patients with a diagnosis of VS. The action of zolpidem as an awakening agent in VS may sound paradoxical as it is commonly prescribed for the short-term treatment of insomnia. It can be hypothesized that zolpidem exerts its effects by binding to the modified GABA_A receptors of neurodormant cells within areas affected by diaschisis, thus promoting the reversal of metabolic inhibition [106].

5.3. Overflow Hypothesis

It can be hypothesized that in some injured brains there is a flooding of stimuli caused by damaged filtering, or 'gating' mechanisms [77]. This would lead to a sort of traffic jam, with excess outputs creating an overload of information to the cortex. In such cases CNS depressants may alleviate the problem by suppressing superfluous information circulating within the injured brain, helping to re-balance the exchange between nuclei. This could contribute to improving the effective interconnectivity within networks involved in consciousness [72].

This overload hypothesis has been proposed as a possible explanation for the beneficial effects of intrathecal baclofen (ITB), a derivative of GABA acting as an agonist for the GABA_B receptors, in patients with disorders of consciousness [77]. The underlying assumption is that ITB exerts a modulating action within spinal circuits, helping to counteract the gating deficits caused by the brain injury and thereby reducing the overload of sensory stimuli flooding to the cortex. Melzack's theories on gating and the neuromatrix suggest that perceptual stimuli modulated by gating mechanisms at the thalamic and spinal level may affect self-awareness, and the ability to distinguish self from non-self can be seen as an important component of healthy consciousness [107]. In a patient with VS where there is impairment of the gating mechanisms the resulting information overload might impede the restoration of the cortico-thalamo-cortical connections which are primarily responsible for the recovery of consciousness [77]. The putative mechanism by which a relative balance is restored is that ITB acts through inhibitory interneurons and presynaptic inhibition at the level of GABA-related gating systems within the spinal circuits, effectively modulating the quantity of impulses directed to the cortex. In particular, we would suggest that spasticity in these patients, combined with a

compromised gating system at the spinal level, might lead to a flooding of altered afferent proprioceptive impulses which would interfere with the patient's ability to maintain awareness [77]. There is evidence from experimental studies that tonic sensory and muscle spindle activity may play a role in modulating brain activity and wakefulness [108]. Spinal cord stimulation (SCS), sometimes used to control spasticity, has also been seen to improve consciousness in a number of cases of VS, and although the dynamics behind this remain unclear the observed clinical improvement lends further support to the overload hypothesis [109,110]. Perhaps SCS causes a release of GABA in the spinal dorsal horn, triggering the same beneficial process as is activated by ITB [110]. These treatments both intervene at the segmental spinal level and share a number of characteristics: they are both GABA receptor related, have an anti-spastic effect, suppress pain, and may have an observable effect on coma. It is reasonable to hypothesize that the improvement in consciousness which sometimes follows one or other of these therapies is in both cases due to their action in improving filtering mechanisms within spinal circuits [77].

A similar hypothesis has recently been suggested as a possible explanation for autism [111]. According to this hypothesis, autism might result not from poor cognitive functioning but from an excess of cognitive activity due to excessive excitation or reduced inhibi-

tion. Specifically, the neurophysiological substrate of autism might be excessive neuronal information processing and storage in local circuits of the brain, which would cause a hyper-functioning of affected brain regions [111]. Such hyper-functioning in different brain regions might cause hyper-perception, hyper-attention and hyper-memory, which could be responsible for the full spectrum of symptoms. Autism could then be considered an Intense World Syndrome [111]. This hypothesis is consistent with data suggesting a reduced long-distance functional connectivity in affected children. In fact, it may be argued that hyperactive microcircuits are likely to become autonomously active and functionally isolated from the others, as they are more difficult to coordinate and engage within the wide neural networks responsible for cognition [111].

Specific experimental studies should be planned to test the overload hypothesis both in vegetative state and autism. If this hypothesis is confirmed, we will be able to conclude that vegetative as well as autistic patients need treatments that reduce rather than increase the activity of the neural networks supporting cognition.

5.4. The Mesocircuit Hypothesis

Functional alterations within the anterior forebrain mesocircuit may contribute to triggering and maintaining a condition of consciousness impairment after severe brain injury (Fig. 5) [112,113].

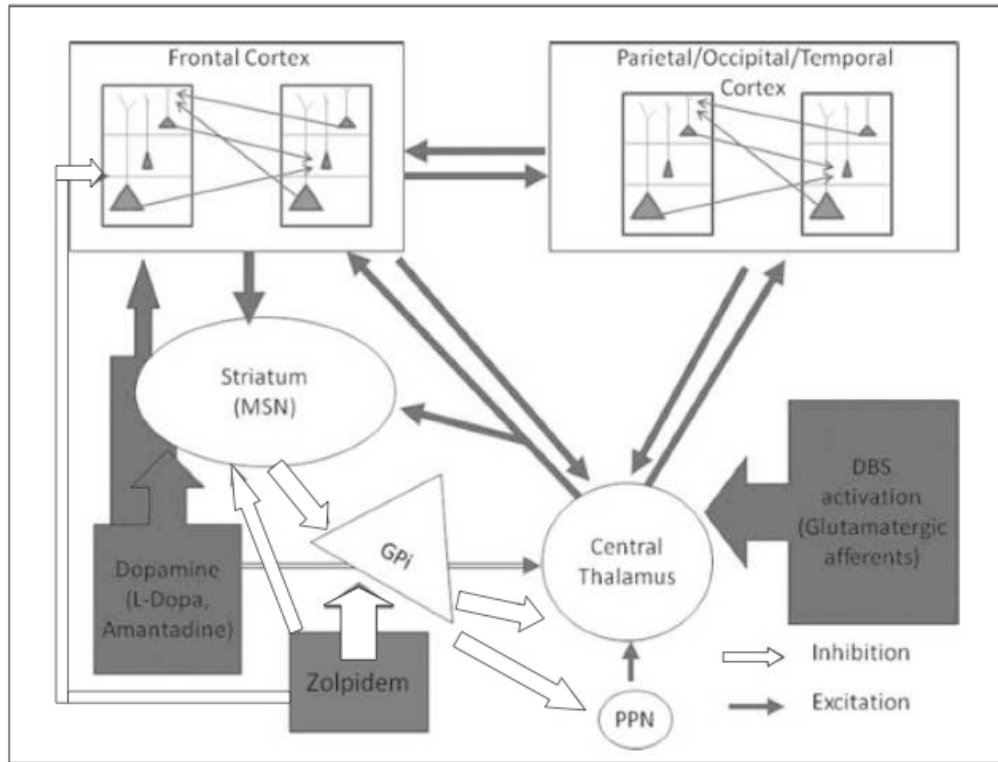


Fig. (5). Mesocircuit model placing central DBS (CT/DBS) in the context of mechanisms underlying spontaneous and medication induced recovery of consciousness. A mesocircuit model organizing mechanisms underlying recovery of consciousness after severe brain injury [113]. Diffuse disfacilitation [114] across frontal cortical, central thalamic, and striatal neurons arises from severe structural brain injuries. In particular, reduction of thalamocortical and thalamostriatal outflow following deafferentation and loss of neurons in central thalamus [115] withdraws important afferent drive to the medium spiny neurons (MSNs) of striatum that may then fail to reach firing threshold because of their requirement for high levels of synaptic background activity [116]. Loss of active inhibition from the striatum allows neurons of the globus pallidus interna (GPI) to tonically fire and provide an active inhibition to their synaptic targets including relay neurons of the already strongly disfacilitated central thalamus and possibly also the projection neurons of the pedunculopontine nucleus [117]. Amantadine [82], L-DOPA [118-119] and zolpidem [120] may reverse these conditions of marked down-regulation of anterior forebrain activity across frontal cortices, striatum, and central thalamus acting at different locations with the mesocircuit [113]. Collectively, restoration of thalamocortical and thalamostriatal outflow will depolarize neocortical neurons and facilitate long-range cortico-cortical, corticothalamic, and corticostriatal outflow. CT/DBS can be considered as a final common pathway aggregating these effects and partially remediating the effects of strong deafferentation of these neurons in severe brain injuries. Reproduced with permission from Shiff [112].

Strategic lesions within this circuit may cause deafferentation [114] and subsequent disfacilitation of the thalamus, which, in physiological conditions, is tonically facilitated by the nucleus cuneiformis and the central tegmental field of the mesencephalic reticular formation. As a result of the above deafferentation, a broad withdrawal of excitatory inputs through thalamocortical projections occurs. Moreover, the activity of the output cells of the striatum may be down-regulated as a result of the reduced thalamostriatal inputs [115,116]. The decreased activity of the striatum may prevent the inhibition of the internal globus pallidus which, in turn, provides an active inhibition of the already strongly disfacilitated central thalamus, thus triggering a vicious inhibitory circle. The cumulative result of such functional alterations within the corticostriatopallidal-thalamocortical loop is the down-regulation of anterior forebrain activity across the frontal cortices, striatum, and central thalamus, with a decrease in arousal, vigilance and responsiveness [112]. CNS depressants and CNS stimulants, as well as central thalamic deep brain stimulation (CT/DBS), may act at different sites of the mesocircuit and contribute to restoring the balance between excitatory and inhibitory components and to improving consciousness [117]. Amantadine might facilitate the outflow of the striatum and the cortical activation [82]. Similarly, L-Dopa and dopamine agonists [118,119] might contribute to restoring the activity of the striatum and the frontal cortex, but it also has a direct effect on the central thalamus. Zolpidem might exert its effects by returning the internal globus pallidus to a condition of tonic inhibition and interrupting the vicious inhibitory circle within the corticostriatopallidal-thalamocortical loop, thus contributing to the restoring of original thalamocortical activity [120]. The therapeutic role of central thalamic deep brain stimulation, in turn, may be one of synchronisation, bringing together these restored functions within the mesocircuit and channeling them to facilitate the emergence of consciousness [113,114,121], much as a conductor might bring together the sounds emitted from re-tuned instruments, enabling a symphony.

5.5. The Role of Transcranial Magnetic Stimulation

Treatments, which have been recognized useful in the management of DOC, also include Transcranial Magnetic Stimulation (TMS) [122]. We recently reported that the combination of single pulse TMS with visual facilitation might contribute to unmask signs of preserved consciousness and latent capacities for further recovery in a subgroup of behaviorally unresponsive patients [123]. The action of TMS might have promoted the recovery of purposeful motor behaviors in patients in VS by encouraging the development of transient functional neuronal assemblies as prerequisite for the emergence of goal-oriented activities [123]. Contextually, visual facilitation might have contributed to the reported recovery by encouraging the transformation of perceived actions into motor images and performances, due to the mirroring properties of motor neurons [123].

6. CONCLUSIONS AND FUTURE DIRECTIONS

The injured brain in patients with DOC shows specific neuropathological and neurophysiological alterations, which may hide the re-emergence of consciousness. These alterations, including the depletion of GABA, the presence of diaschisis and the possibility of overflow phenomena, may be coinciding or overlapping and may represent the target for novel therapeutic interventions. However, ascertaining to what extent each single alteration contributes to the functional breakdown underlying the persistent loss of consciousness is not easy. It may be expected that patients with DOC are extremely different each other with respect to brain lesions and involved neural networks and neurotransmitter systems. The consequence is that pharmacological treatments may be successful only if tailored to the individual characteristics of the patients and to their chances for recovery. The causal relationship between the start of specific treatments and putative improvements should be carefully

investigated through rigorous controlled trials. Moreover, when analyzing findings from clinical trials, case reports and case series, particular attention has to be made to fluctuating behaviors of patients with DOC. In fact, we have to remember that even a broken clock is right twice a day.

Similarly, even an injured brain may be considered to work or be correct some of the time.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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