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Emerging from an unresponsive wakefulness syndrome: Brain plasticity has to cross a threshold level

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Abstract

Unresponsive wakefulness syndrome (UWS, previously known as vegetative state) occurs after patients survive a severe brain injury. Patients suffering from UWS have lost awareness of themselves and of the external environment and do not retain any trace of their subjective experience. Current data demonstrate that neuronal functions subtending consciousness are not completely reset in UWS; however, they are reduced below the threshold required to experience consciousness. The critical factor that determines whether patients will recover consciousness is the distance of their neuronal functions from this threshold level. Recovery of consciousness occurs through functional and/or structural changes in the brain, i.e., through neuronal plasticity. Although some of these changes may occur spontaneously, a growing body of evidence indicates that rehabilitative interventions can improve functional outcome by promoting adaptive functional and structural plasticity in the brain, especially if evidence from a comprehensive neurophysiological theory of consciousness is followed. In this review we will focus on the pathophysiological mechanisms involved in UWS and on the plastic changes operating on the recovery of consciousness.

Key words: vegetative state; minimally conscious state; consciousness; awareness; rehabilitation; recovery; cortex; thalamus; thalamocortical projections; brain hypoxia; traumatic brain injuries (TBI); EEG.

Contents

1. Overview

Just think for a moment of two people: the first one has suddenly lost the ability to experience thoughts and memories, and the second one looks at the first without knowing if or when he/she will recover consciousness. The first person is a patient in a vegetative state (VS) following an acute brain injury; the second one is his/her doctor. The VS is a condition still described mainly in clinical terms rather than according to its pathophysiological mechanisms. It begins when the coma phase ends, which is, by convention, when patients open their eyes spontaneously. Patients breathe spontaneously, their vital functions usually are not mechanically supported, and they may have sleep-wake cycles near normality, but they do not retain any trace of their subjective experience. In other words, the VS may be described as an "unresponsive wakefulness syndrome" (UWS) (Laureys et al., 2010). This definition will be used throughout this paper because it is more respectful of patients than that of VS (Machado et al., 2012), and it better reflects the pathophysiology of this condition.

UWS is the effect of a sudden injury that quickly resets the higher functions of the human brain, such as the ability to create thoughts and reasoning, to experience sensations and emotions or to recall past events. Traumatic brain injuries (TBI), cerebrovascular diseases, and cerebral hypoxia are the most common causes of UWS. Additionally, UWS can be the final stage of chronic neuronal degeneration in diseases such as Alzheimer’s disease. This last condition, in which the loss of cognitive function occurs slowly and progressively and is dependent on neuronal degeneration, will not be dealt with in the present review.

An interesting feature of UWS following an acute brain injury is that cognitive functions are often not definitively impaired and, thus, may be recovered after several weeks, months or even

years (in some anecdotal cases) of unconsciousness. The first stage of recovery from UWS is the minimally conscious state (MCS). Transition into a MCS starts when patients' spontaneous eye movements display focusing, when patients show eye tracking, or when they become able to follow reproducible simple commands (Giacino et al., 2002). Because the mechanisms underlying the recovery from UWS are largely unknown, its prognosis is particularly challenging, which is frustrating for physicians and shocking for patients' relatives.

The recovery of consciousness is a dynamic process that involves many plastic changes in several brain areas. If this reorganization crosses the threshold of the *minimal neuronal mechanisms that are jointly sufficient for any one specific conscious percept* (Tononi and Koch, 2007), the patient will regain consciousness. Otherwise, he/she will remain indefinitely unresponsive. In this sense, consciousness is a discrete (all-or-none) phenomenon rather than a sliding scale (Fingelkurts et al., 2012a). What is varied and presents itself in a gradual manner is the amount of content (information) available for conscious awareness (Rusalova, 2005; Overgaard, 2009; Overgaard and Overgaard, 2011; Fingelkurts et al., 2012a).

In this review we will focus on the pathophysiological mechanisms involved in UWS and on the plastic changes that operate in the recovery of consciousness. Finally, we propose that rehabilitative interventions, specifically oriented for the recovery of consciousness in patients with UWS, should be developed based either on knowledge of neurophysiological mechanisms of consciousness impairment or neuroplasticity tenets.

2. Brain areas or brain functions to explain consciousness impairment in UWS?

The human brain contains more than 100 trillion (10^{14}) synaptic connections that form all of its neural circuits (Eroglu and Barres, 2010). This extremely complex and dynamic neural network, organized as a nested hierarchy, is the basis of all brain activities and is involved in every brain function, including those related to normal expressions of consciousness (Fingelkurts et al., 2010). In a nested hierarchy, all the elements comprising the lower levels of the hierarchy are physically combined or nested within higher levels to create increasingly complex wholes (Feinberg, 2000 and 2011). Although it is beyond the aim of this paper to define in detail the hallmarks of consciousness (for reviews see: Zeman, 2001; Cavanna et al., 2011), from a neurophysiological perspective it may be concisely characterized in terms of awareness, which is related (though indirectly) to arousal. The term arousal refers to the degree of vigilance and alertness during wakefulness (de Lecea et al., 2012). Wakefulness is a conscious state in which a person can perceive and interact with his/her environment. Arousal pathways, originating in the brainstem, activate awareness networks in the cerebral cortex via synapses in the thalamus and basal forebrain (McCormick 1992; Jones, 2004;

Parvizi and Damasio, 2001) or, alternatively, via direct innervation of the cortex itself (McCormick 1992; Parvizi and Damasio, 2001) (Figure 1). In some pathological conditions, awareness is not achievable without arousal, as has been evidenced in comatose patients with brainstem lesions but an anatomically intact cerebral cortex (Parvizi and Damasio, 2003; Laureys, 2005). At the same time, there are many states in which subjective experiences are present, while arousal is absent, for example, dreaming during sleep or subjective awareness during ketamine anesthesia (Hudetz, 2010).

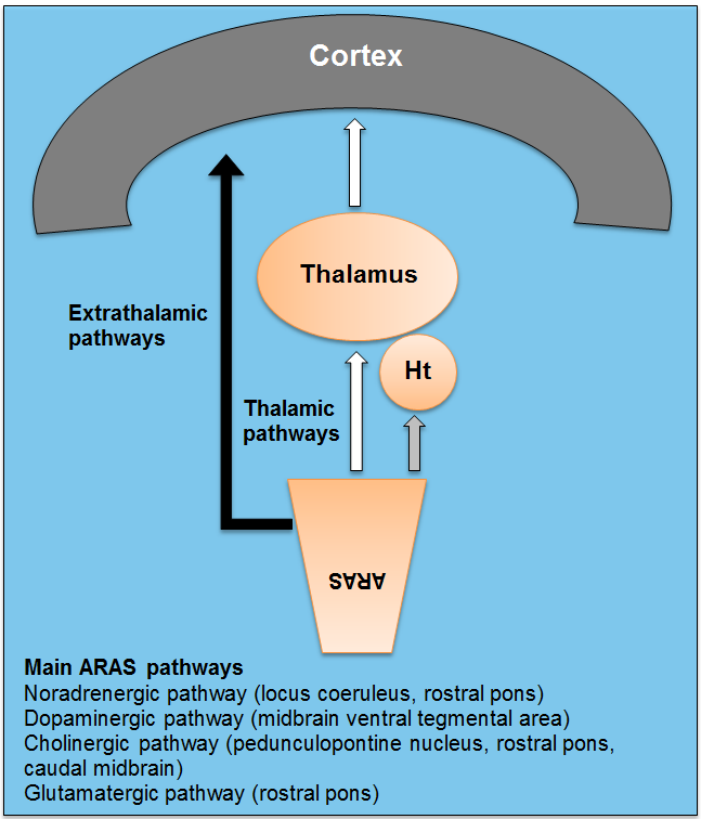

Figure 1. **Simplified representation of arousal control system.** The ascending reticular activating system (ARAS) is composed of a complex and diffuse network of neurons projecting from multiple brainstem nuclei (in brackets) to the cortex, via thalamic (white arrow) and extrathalamic (black arrow) pathways. The different pathways are typically identified depending on specific neurotransmitters (noradrenalin, dopamine, acetylcholine, and glutamate). In particular, ARAS brainstem nuclei project to the intralaminar nuclei in the thalamus, which project diffusely to the cerebral cortex in order to activate it (Edlow et al., 2012). Arousal is further mediated by ARAS connectivity with the hypothalamus (Ht) (gray arrow), which participates in the regulation of autonomic function and circadian sleep-wake cycles, and with the basal forebrain (not shown in figure), which participates in cortical activation and autonomic integration. This multiplicity and redundancy of the ascending wakefulness control system suggests an adaptive mechanism for the recovery of consciousness when some components, but not the entire system, are clinically disrupted.

Arousal is a function of the ascending reticular activating system (ARAS), a functional component of the complex neuronal network within the reticular formation of the upper brainstem (Edlow et al., 2012). The main ARAS nuclei involved in arousal are as follows: the cuneiform/subcuneiform nucleus, the pontis oralis, the median and dorsal raphe, the locus coeruleus, the pedunculopontine nucleus, the parabrachial complex (i.e., the combined medial and lateral parabrachial nuclei), and the ventral tegmental area (Edlow et al., 2012). The ARAS contains two major axes, the thalamic pathway and extrathalamic pathways. Activation of the thalamic pathway promotes cortical arousal by facilitating the transthalamic passage of sensory information towards the cerebral cortex (Mesulam, 2000). The intralaminar and reticular nuclei are the thalamic components most associated with this pathway of the ARAS (Benarroch et al., 2008). Extrathalamic pathways activate the cortex via a series of direct inputs originating in the brainstem and basal forebrain and collectively exert a large influence on arousal (Mesulam, 2000). Moreover, ARAS connectivity with the suprachiasmatic nucleus of the hypothalamus, which is the master circadian pacemaker of the brain, comprises the neuroanatomical connection that joins arousal with circadian rhythms (Aston-Jones et al., 2001; Krout et al., 2002).

Awareness refers to the subjective experience of conscious mental contents. The content of an individual's subjective experience is comprised of his/her sensations, thoughts, emotions, memories, imagination, and other major psychological processes. These contents of consciousness may be associated either with activity in specific cortical areas (Cavanna et al., 2011) or with a nested functional hierarchy of dynamic and ever increasing complex spatial-temporal structures of synchronized neuronal assemblies (Fingelkurts et al., 2013a).

The distinctive feature of UWS is the dissociation between arousal and awareness: patients in UWS seem to be awake but lack any sign of awareness of themselves or of their environment (Royal College of Physicians, 2003). Although the exact amount of impairment of arousal is questionable in UWS, awareness cannot be detected. In other words, during UWS as a result of a brain injury, the functions of the neural net subtending consciousness (awareness) are reduced in both hemispheres below the threshold level required for minimal consciousness expression. Yet, not all brain areas are equally involved in such consciousness loss, and it is speculated that there are some critical junctions in the brain networks (Blumenfeld, 2010). It is very difficult to clearly identify the brain areas mainly involved in the maintenance of normal consciousness, both in its daily fluctuations – such as the sleep-wake cycle – or in its loss in different pathological conditions, such as epilepsy, coma, UWS, and MCS. As a consequence, this intriguing issue of the modern neurosciences has not been exhaustively studied. Different methodological approaches have been used in the last years in order to discover the brain areas, processes and cerebral functions primarily

involved in the loss of consciousness in patients with UWS. In the following sections of this review, we will briefly discuss findings from neuropathological, neurophysiological, and neuroimaging methodologies.

2.1 Evidence from neuropathology

Neuropathological studies in patients with UWS have been carried out both for traumatic and non-traumatic etiologies (Graham et al., 1983, 2005a,b; Adams et al., 1999, 2000, 2011; Jennett et al., 2001). This distinction is essential for clinical purposes: indeed, patients with UWS caused by a TBI have better outcomes in terms of recovery of independence (24% versus 4%) and consciousness (52% versus 13%) than those with non-traumatic injuries (due to cerebral anoxia or stroke) (Monti et al., 2010; Royal College of Physicians, 2003; The Multi-Society Task Force on PVS, 1994a,b). Therefore, it may be deduced that different mechanisms of lesions affect the brain areas involved in consciousness impairment differently. For TBI cases, the most recent studies have been carried out on the same population of 35 patients (Graham et al., 2005a,b; Adams et al., 1999, 2000, 2011; Jennett et al., 2001). The most common abnormalities in these patients were thalamic damage (80% of patients), lesions in the neocortex (80%), and diffuse axonal injury (DAI) (71%) (Adams et al., 1999, 2000, 2011; Jennett et al., 2001; Graham et al., 2005a,b).

Thalamic damage is very common in patients with UWS. The thalamus is the main brain structure involved in sensory processing and integration of information, with prominent feedback loops throughout the cerebral cortex. Because of its extremely complex interconnections between the subcortical (i.e.: arousal control) and cortical (i.e.: awareness) areas, the thalamus is considered a central region for the integration of sensory and cognitive processes required for full consciousness (Vakalopoulos, 2005; Min, 2010; Ward, 2011). Small lesions either within the thalamus or within its complex network of afferent-efferent connections with the cerebral cortex may result in major impairments in cognitive functioning (Tatemichi et al., 1992; Kalashnikova et al., 1999; Hermann et al., 2008). The deep, central location of the thalamus in the brain provides it some protection from direct impact in TBI. Thus, diffuse thalamic damage, the most common form of thalamic damage in patients with UWS following a TBI, may reflect: (I) a retrograde thalamic degeneration that occurs as a result of widespread axonal damage or (II) a diffuse thalamic neuronal loss as a result of hypoxia (Adams et al., 1999, 2000; Bigler and Maxwell, 2011). Regarding specific thalamic nuclei involvement, some studies suggest different rates of loss of neurons among the different nuclei after TBI. In particular, a study showed a selective neuronal loss in the reticular nucleus in patients with severe head injuries (Ross et al., 1993). The thalamic reticular nucleus is a pure gamma-aminobutyric acid (GABA) population of neurons that do not send axons to the

cerebral cortex but send projections exclusively to other thalamic nuclei (Jones, 1975). The GABA-ergic cells of the thalamic reticular nucleus receive collateral inputs from both thalamocortical and corticothalamic fibers and are modulated by cholinergic projections from the brainstem and basal forebrain (McAlonan and Brown, 2002). As the thalamic reticular nucleus is believed to be an essential component of the circuitry mediating the focusing of sensory transmission between the thalamus and cortex, which is required in attention and conscious awareness (McAlonan and Brown, 2002; McAlonan et al., 2006; Min, 2010), lesions of the thalamic reticular nucleus might contribute to consciousness impairment in patients with UWS (Ross et al., 1993). More recently, neuronal loss in the ventral posterior thalamic nucleus (VPN) has been described in 10 patients with UWS (Maxwell et al., 2004). The VPN is both the major site of termination for afferent fibers forming the dorsal column/medial lemniscus pathway and spino-thalamic tract and the origin of fibers to the primary somatic sensory areas of the cerebral cortex (Jones, 2007). The observed neuronal loss in the VPN in patients with UWS may reflect impairment in responses to sensory stimuli, but, as this neuronal loss was also described in severely disabled patients without consciousness loss (Maxwell et al., 2004), it is difficult to justify a correlation with the severe consciousness impairment affecting UWS.

Lesions in the neocortex are very common after a TBI and they are reported in approximately 80% of patients with UWS, both in the form of cerebral contusions and ischemia (Adams et al., 2000). The frontal and temporal lobe regions of the brain have a higher vulnerability to mechanical damage as a consequence of a head trauma. The main reason for this selective susceptibility is due to the anatomical site where the frontal and temporal regions are located in the anterior and middle cranial fossa of the skull; this localization creates areas of contact between the brain and the skull as a consequence of a cranial trauma (Bigler, 2007). However, in the above-mentioned population of 35 patients with UWS following TBI, in no cases using a quantitative method of evaluation (total contusion index) were the contusions classified as severe (Adams et al., 2000). Ischemic damages, described in patients with UWS after TBI, may be diffuse, multifocal, localized on the arterial boundary zones of the cerebral hemispheres or affect specific arterial territories (Adams et al., 2000, 2011). Ischemic damage was classified as moderate or severe in only 45% of the cases in the referenced study. These data suggest that massive neocortical lesions may be described by means of neuropathological studies in only a minority of patients with UWS. Moreover, although the neocortex is the site of the highest cognitive functions, no specific cortical lesions have specifically been described as related to UWS (Adams et al., 1999, 2000, 2011; Jennett et al., 2001; Graham et al., 2005a,b).

DAI is the most frequently described abnormality in patients with UWS following a TBI (Adams et al., 2000; Graham et al., 2005a,b). The principal mechanical force associated with induction of DAI is a rotational acceleration of the brain resulting from the head movement that occurs instantaneously after the injury (Smith et al., 2003; Wang and Ma, 2010). DAI may be classified in three grades, according to its extension: in grade 1, histological evidence of axonal injury in the white matter of the cerebral hemispheres has been found; in grade 2, a focal lesion in the corpus callosum has been documented; in grade 3, an additional focal lesion in the rostral brainstem has been shown (Adams et al., 1989). In patients with UWS, degree 2 and 3 DAI were found in 71% of the cases, and this percentage increases to 80% if degree 1 is included (Adams et al., 2000; Graham et al., 2005a,b). The presence of a severe DAI may deeply affect intracortical, cortico-subcortical and inter-hemispheric connections, affecting the long-term outcome after a TBI evaluated by means of the Glasgow Outcome Scale-Extended (Skandsen et al., 2010). However, DAI cannot be the only pathophysiological mechanism operating in UWS, as demonstrated by the 20% of patients without any evidence of DAI.

The features of neuropathological damage change in patients in UWS after hypoxic damage. Only 14 hypoxic patients have been described (Adams at al., 2000): the most commonly reported abnormality was a diffuse neuronal loss in the thalamus and hippocampus (100% of the patients), followed by damage in the basal ganglia (globus pallidus, 86%; putamen, 79%; caudate nucleus, 71%) and by diffuse damage in the neocortex (64%), in form of laminar necrosis increasing in intensity from the frontal to the occipital poles (Adams at al., 2000). Although the number of patients is rather small, the involvement of the thalamus has been documented in all cases.

2.2 Evidence from neuroimaging

A large number of neuroimaging studies on UWS have been conducted in recent years (for a recent comprehensive review see Laureys and Schiff, 2012). The first studies were performed with conventional magnetic resonance imaging (MRI) and showed that DAI (particularly if involving the corpus callosum and dorsolateral brainstem) is the typical feature of post-traumatic UWS: this type of DAI may be predictive of a poor outcome (Kampfl et al., 1998a,b). More recently, structural MRI studies have been refined by means of diffusion tensor imaging, permitting the quantitative evaluation of lesions in the brain's white matter tracts often invisible to conventional radiological approaches (Newcombe et al., 2010). These data have confirmed "in vivo" and in a larger number of patients the results previously described in neuropathological studies. Additionally, the merit of the modern neuroimaging techniques is to analyze not only the lesions but also the residual functions in the brain of patients with UWS. The introduction of $H_2{}^{15}O$ positron emission

tomography (PET) and functional MRI (fMRI) paradigms have enabled the evaluation of residual neuronal functions. Resting state fMRI studies have shown that the midline frontoparietal connectivity of the "default mode network", believed to reflect internal self-related awareness (i.e., spontaneous thoughts, inner speech, and mind wandering), is decreased in patients with UWS (Cauda et al., 2009; Vanhaudenhuyse et al., 2010; Soddu et al., 2011). Moreover, activation PET and fMRI studies allow the identification of blood flow increases in response to passive external stimulation. Actually, a low level of cortical activations in the auditory, visual, and somatosensory areas has been documented in patients with UWS (Boly et al., 2004; Coleman 2007; Di et al., 2007; Heelmann et al., 2010). While neuroimaging studies have remarkably contributed to our understanding of the disorders of consciousness, they still have some limitations regarding their extensive clinical use mainly related to cost, patient safety, data acquisition, analysis, and interpretation (for a comprehensive review, see Harrison and Connolly, 2013).

2.3 Evidence from neurophysiology

Neurophysiological studies have been performed in patients with UWS mainly by means of evoked potentials (EPs) and electroencephalogram (EEG) recordings. EPs enable the evaluation of the integrity of neurological pathways (somatosensory, acoustic, visual, and motor EPs) or responses related to voluntary or involuntary cognitive processing mechanisms (event-related potentials). Among the EPs related to specific neurological pathways, somatosensory evoked potentials (SEPs) have shown a better correlation with the outcome of comatose patients (Amantini et al., 2011). In the brain, SEPs assess the integrity of the medial lemniscus system through the thalamus as far as the somatosensory cortex. By stimulating the median nerve, the bilateral absence of a cortical N20 response after anoxic coma has always been associated with death or UWS, and no sufficiently documented counterexample to this rule has been found (Cruccu et al., 2008). Similarly, the absence of a cortical N20 response has been associated with a poor outcome in patients with UWS due to hypoxic etiology (Estraneo et al., 2013). The bilateral absence of cortical SEPs often indicates a poor outcome (90 to 95% of non-awakening) in post-traumatic coma patients; moreover, the favorable prognostic significance of bilaterally normal cortical SEPs has also been highlighted (over 90% of awakening) (Robinson et al., 2003; Amantini et al., 2011). In summary, studies with SEPs seem to indicate that UWS may be the result of: (I) severe lesions in the neocortex (hypoxic etiology) or (II) interruption between subcortical-cortical pathways (traumatic etiologies).

Dealing with event-related potentials, the presence of mismatch negativity has been associated with subsequent recovery of responsiveness in patients with UWS in different studies

(Kotchoubey et al., 2005; Wijnen et al., 2007; Qin et al., 2008; Fischer et al., 2010). Mismatch negativity is generated by the brain's automatic response to physical stimulus deviation from the preceding stimulus in repetitive auditory input, revealing that physical features of auditory stimuli are fully processed regardless of whether they are attended to or not (Näätänen et al., 1993). Mismatch negativity generators are localized in the superior temporal gyri, especially in Heschl's gyrus (Ha et al., 2003), and it may be speculated that their dysfunction is a marker of lesions in the more generalized network of neural connections subtending awareness.

In recent years, a growing body of data has documented EEG usefulness either in predicting the outcome or elucidating the pathophysiology of UWS (Harrison and Connolly, 2013). Actually, it has been shown, by means of qualitative scales, that even the simple description of standard EEG patterns may correlate both with the level of consciousness impairment (UWS or MCS) and with the degree of short-term consciousness recovery (Bagnato et al., 2010; Boccagni et al., 2011). These studies suggest that the overall brain electrical activity is differentially impaired in patients with different disorders of consciousness and that it may be related to the degree of recovery at the group-analyses level.

Advanced quantitative EEG analyses have contributed in a much more specific way to the evolution from the neural *correlates* of consciousness to the neural *constituents* of consciousness; furthermore, advanced quantitative EEG analyses have improved the understanding of the neural constituents of consciousness' impairment from the level of a *site in the brain* to the level of a *degree of operational architectonics dysfunction* within the brain. According to traditional views, brain function is primarily described on the basis of functional anatomy. Anatomical and functional connectivity can be considered the spatial or geometrical dimension of the mind; however, for a more comprehensive understanding, an additional dimension must be considered: time (Fingelkurts et al., 2010). The brain generates its own temporal structure within a nested hierarchy, which is largely organized by multiple oscillations (Buzsaki and Draguhn, 2004). EEG provides a direct measure of brain functions, reflecting the operations of large-scale cortical networks (neuronal assemblies), which are temporally and spatially organized and remarkably correlated with behavior, cognition (John, 2002; Kaplan et al., 2005), and consciousness (Fingelkurts et al., 2012a). Studies on EEG oscillatory microstates suggest that patients with UWS have a considerably reduced repertoire of local EEG oscillatory microstates available to the cortex than those in a MCS or in a full conscious state (Fingelkurts et al., 2012a). Unawareness in patients with UWS is associated with the lack of diversity in EEG alpha-rhythmic oscillations and with occurrence of delta-, theta- and slow-alpha-rhythmic oscillations, whereas the probability of occurrence and duration of fast-alpha-rhythmic oscillations is associated with full consciousness (Fingelkurts et al., 2012a). These

data are particularly noticeable in the light of the concept that alpha-band oscillations reflect the temporal structure of "knowledge-based consciousness", which mediates the access to any type of knowledge, including procedural, implicit and perceptual knowledge (i.e.: awareness) (Palva and Palva, 2001; Klimesch, 2012). The main idea of this theory is that consciousness is integrated knowledge and that its quality is determined by informational relationships that are mediated by alpha-band oscillations (Tononi, 2004 and 2008; Palva and Palva, 2007 and 2011). In agreement with these concepts, it has been reported that the degree of reduction in the dynamic correlates of the neuronal networks' complexity may be useful to distinguish patients with different levels of consciousness impairment or as a prognostic measure (Fingelkurts et al., 2011, 2013b; Sarà et al., 2011; Lehembre et al., 2012) (Figure 2).

In addition, the modern techniques of EEG analysis, utilizing principles of the theory of operational architectonics of brain-mind functioning (Fingelkurts et al., 2010, 2013a), allow the evaluation of the spatio-temporal patterns of operationally connected neuronal assemblies (operational modules) and their dynamics (Fingelkurts and Fingelkurts, 2001, 2008).[1] It has been proposed that such nested spatio-temporal organization could constitute the neurophysiological basis of the mind architecture (Feinberg, 2000; Fingelkurts et al., 2010, 2012b, 2013c). In the context of this theoretical approach, it has been demonstrated that neuronal assemblies become smaller, their life spans are shortened, and they became highly unstable and functionally disconnected (desynchronized) in patients with UWS (Fingelkurts et al., 2012b) (Figure 2). At the same time, fluctuating (minimal) awareness in patients in a MCS is paralleled by a partial

[1] In a series of publications, Fingelkurts and Fingelkurts (Fingelkurts and Fingelkurts 2001, 2004, 2005, 2006; Fingelkurts et al., 2010, 2013a) established the basis for, and developed the general theory of, *brain operational architectonic* according to which the simplest mental/cognitive operations (i.e., those responsible for qualia or simple computations) are manifested in the brain in the form of *local 3D fields* produced by *transient functional neuronal assemblies*, while complex operations (i.e., those responsible for complex objects, images or thoughts) are brought into existence by *joint simple operations* (i.e., the temporal coupling of local 3D fields through operational synchrony) in the form of so-called operational modules (OM) of varied complexity. Therefore, brain operational architectonics are manifested a highly structured and dynamic extracellular electric field nested in the spatial and temporal domains (John 2002; McFadden 2002) and over a range of frequencies (Basar et al., 2001) and thus form a particular operational space–time (OST) (Fingelkurts et al., 2010). This OST exists within brain's internal physical space–time and is best captured by the EEG measurements (Freeman, 2007). Notably, the operational architectonics theory is neutral about any concrete anatomical structures; it does not attach itself to a specific neural location or locations. Instead, operational architectonics theory considers the overall dynamic or "functional" properties of the electromagnetic field of the brain. The nested hierarchical and dynamical architecture of such 3D electromagnetic brain fields corresponds to the structure and dynamics of phenomenal consciousness as experienced from the first-person perspective (Fingelkurts et al., 2013c).

Operational connectivity (i.e., operational synchrony) refers to a specific type of functional connectivity, namely the temporal coupling of discrete operations that is produced by spatially distributed neuronal assemblies (i.e., OM) (Fingelkurts and Fingelkurts, 2001, 2008). Operational connectivity is measured by estimating the temporal synchronization of the quasi-stationary EEG segments obtained from different cortical locations. Notably, such coincidences of the beginnings and ends of the quasi-stationary EEGs segments are related to a specific type of signal coupling (the synchronization of discrete events), and the levels of continuous signal synchronization in the intervals (segments) between the coinciding boundaries are completely ignored. This is a principle difference between operational synchrony and other methods to assess functional connectivity such as coherence, phase synchrony, and others (Fingelkurts et al., 2005).

restoration of EEG operational architecture, approaching the level found in healthy fully conscious participants (Fingelkurts et al., 2012b) (Figure 2). Specifically, it has been found that the operational synchrony among frontal and posterior operational modules (chosen to fit with those of DMN) is smallest or even absent in patients with UWS, intermediate in patients in a MCS and highest in healthy fully self-conscious subjects (Fingelkurts et al., 2012c) (Figure 2). Moreover, frontal EEG operational modules demonstrate the strongest decrease in operational synchrony strength as a function of self-consciousness loss, when compared with the DMN's posterior modules (Fingelkurts et al., 2012c). These studies lead us to conclude that consciousness is likely to vanish in the presence of many *small*, *short-lived*, and highly *unstable* neuronal assemblies that perform their operations totally independent of one another (*functional disconnection*) and, thus, are not capable of supporting any content to be experienced subjectively. Importantly, it has been documented that observed impairment in the brain operational architectonics is independent from brain damage etiology and, thus, reflects functional (and potentially reversible) damage, as opposed to irreversible structural neuronal loss (Fingelkurts et al., 2013c). This fact brings hope that rehabilitation strategies and/or drug treatments specifically targeting the brain operational architectonics might be especially effective in reversing the consciousness loss in patients with UWS or improving the consciousness lack in patients in a MCS.

In summary, data obtained with different methodologies converge on the idea that the brain systems subtending consciousness are widely distributed, dynamic and involve both hemispheres and cortical and subcortical areas (Dehaene and Changeux, 2011). The presence of widespread and redundant circuits of neuronal assemblies is in agreement with the evidence that UWS occurs only after a *large brain damage*. Some considerations seem to be specifically relevant to patients with UWS. Firstly, the sites of neuronal impairment vary depending on the etiology. Secondly, a wide range of neuronal dysfunctions may occur in the brain of patients suffering from UWS. Thirdly, despite the same clinical presentation, the degree of these dysfunctions may vary in a significant way, conditioning patients who will recover consciousness or will not. Fourthly, it seems that some characteristics of impairment in the brain operational architectonics in patients with UWS are similar, despite different etiologies of brain damage. In future years, a more specific characterization of the neuropathological, neuroimaging and neurophysiological markers of the neuronal impairment in patients with UWS will have remarkable neuroscientific, therapeutic and ethical implications.

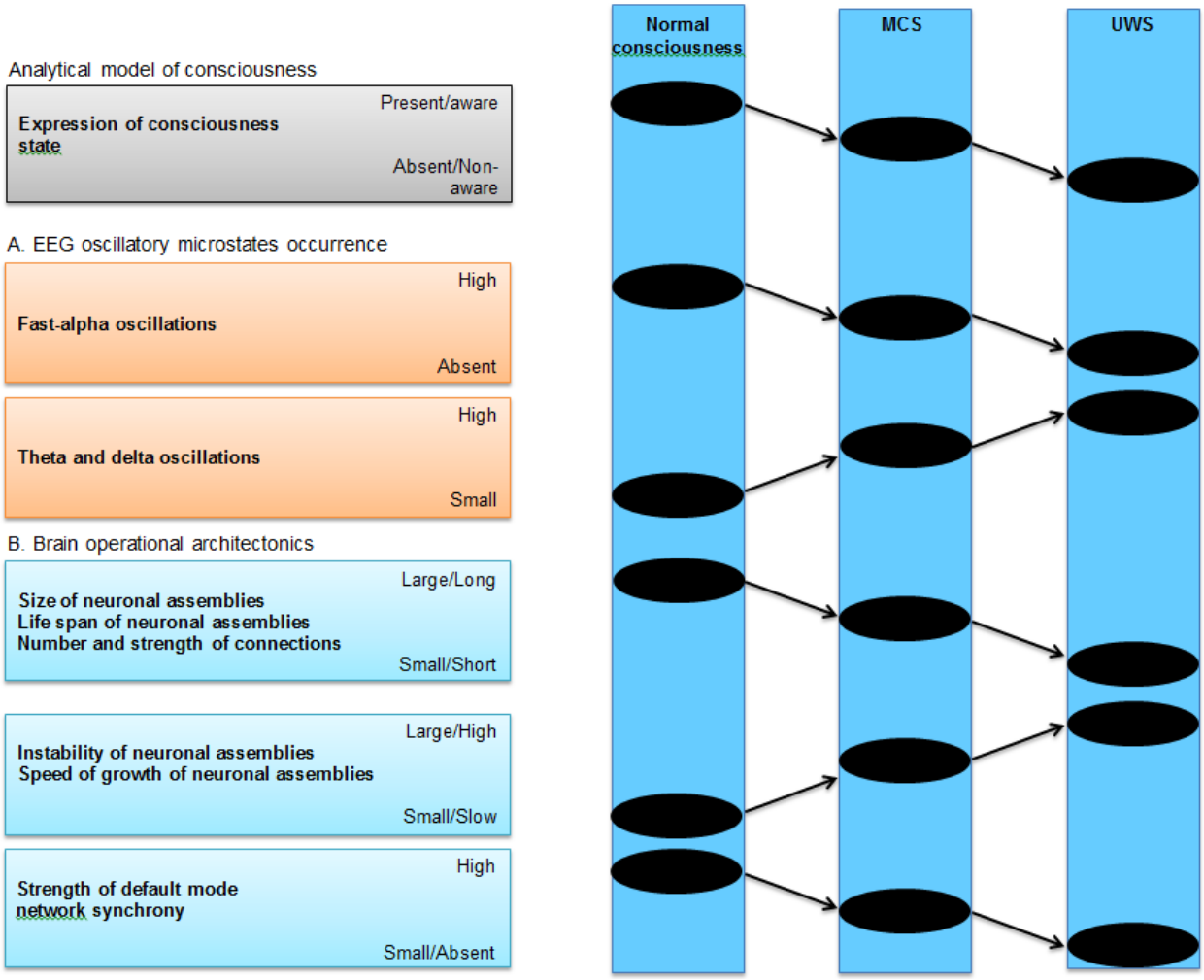

Figure 2. Relation of analytical model of consciousness to: (A) EEG oscillatory microstate occurrence and (B) brain operational architectonics. The level of consciousness (normal consciousness, MCS, UWS) is dependent on neuronal functions, which may be related to EEG findings. Notably, fast-alpha oscillations are absent in UWS, while the probability of occurrence of theta and delta oscillation is lower in normal consciousness, intermediate in patients in a MCS and higher in patients with UWS (panel A). Similar considerations are applicable for various brain operational architectonics constituents (panel B). The figure summarizes the results of group-level analyses; for details see also Fingelkurts et al., 2012a, 2012b, 2012c, 2013b, 2013c. Modified from Fingelkurts et al., 2013c. MCS, minimally conscious state; UWS, unresponsive wakefulness syndrome.

3. Where and how do plastic changes operate in order to recover consciousness?

To determine where and how the surviving neurons in patients with UWS rewire the brain circuits in order to restore consciousness has an obvious therapeutic relevance, although our knowledge in this field is still very poor. This lack of understanding is the consequence of several factors, involving both pathophysiological and methodological aspects. Firstly, the neural systems underlying consciousness are much less well characterized than other systems involving both

cortical and subcortical areas (i.e.: the motor system). Although some brain areas are believed to be more specifically involved in consciousness (Blumenfeld, 2010), we still scarcely know about their reciprocal interactions in normal and pathological conditions. We may speculate only that the sites of lesions and the types of neural dysfunctions operating in patients with UWS are remarkably heterogeneous: so, as a consequence, plastic restorative mechanisms necessarily work in several areas and with different modalities. Secondly, because animal models for UWS are not available, data are currently drawn only from neuroimaging and neurophysiological studies carried out on humans. Despite these limitations, in the following sections we will try to identify some targets for specific plasticity mechanisms allegedly involved in the recovery of consciousness. Thus, this discussion should be viewed with caution, as the mechanisms discussed here are currently only hypotheses requiring validation.

3.1 Plasticity in cortical areas

The neocortex is the site of the main cognitive functions expressed in a full awareness state, and neurophysiological studies have shown that the degree of cortical dysfunction reflects the level of consciousness impairment (Bagnato et al., 2010; Boccagni et al., 2011; Sarà et al., 2011; Rosanova et al., 2012; Fingelkurts et al., 2012a, 2012b, 2012c, 2013b, 2013c). As a consequence, consciousness recovery necessarily involves various cortical plasticity mechanisms.

In general, brain remodeling after an injury occurs through: (I) spontaneous reorganization and/or (II) training-induced recovery. Experimental models show that the brain injury itself induces plastic changes in different ways. In vitro studies have demonstrated that oxygen and glucose deprivation (*in vitro* ischemia) exerts long-term effects on the efficacy of synaptic transmission via the induction of a post-ischemic long-term potentiation (i-LTP) (Crepel et al., 1993). Post-ischemic long-term potentiation may deeply influence the plastic reorganization following a brain injury; thus, the most intriguing question with regards to i-LTP concerns the potential detrimental or beneficial nature of i-LTP. In particular, it has been hypothesized that i-LTP may represent the electrophysiological correlate of the delayed, apoptosis-like, neuronal death process that occurs in the areas near an ischemic infarct (Calabresi et al., 2003). From an opposite point of view, it can be speculated that the final effect of ischemia-induced neuroplasticity is to permit the reorganization of cortical circuits by which some individuals achieve return of function after a brain injury (Di Filippo et al., 2008). Interestingly, i-LTP and physiological, activity dependent LTP are dependent on the activation of N-Methyl-D-Aspartate (NMDA) glutamate receptors and require a rise in intracellular calcium (Crepel et al., 1993; Crepel and Ben-Ari, 1996). Several other similarities have been demonstrated between i-LTP and activity dependent LTP. Nitric oxide (NO) signaling is

deeply modulated by ischemia and is required for the generation of i-LTP (Huang and Hsu, 1997). Interestingly, long-term depression (LTD) and LTP are highly regulated by NO in the striatum and hippocampus (Hopper and Garthwaite, 2006; Calabresi et al., 2007), suggesting that events (i.e., hypoxia) leading to an increase in NO via neuronal NO synthase expression may trigger both LTD and LTP.

Another mechanism of spontaneous recovery may be mediated by the production of specific neurotrophins. After a brain injury, brain-derived neurotrophic factor (BDNF) production is up-regulated (Kokaia et al., 1998). Brain-derived neurotrophic factor is a neurotrophin that performs a critical function in the modulation of synaptic efficacy (i.e.: LTP) involved in learning, memory and adaptive behavior (Kleim et al., 2006; Tyler et al., 2002). Current knowledge concerning BDNF function shows that it is involved in mechanisms underlying LTP induction and maintenance by activating latent synapses (Shen et al., 2006) and modulating cytoskeletal functions (Rex et al., 2007). A brain injury triggers BDNF expression (Kokaia et al., 1998), which seems to be associated with enhanced neurogenesis and sensori-motor recovery (Schabitz et al., 2007; Keiner et al., 2009). A recent study has evaluated the role of the Val66Met BDNF polymorphism in patients suffering from post-traumatic UWS (Bagnato et al., 2012). This polymorphism is present in about a third of the normal subjects and, although it does not affect transcription and translation processes necessary for mature BDNF protein function, it has been shown to dramatically alter the intracellular trafficking and packaging of pro-BDNF and, thus, the regulated secretion of the mature peptide (Chen et al., 2004). Surprisingly, no differences in the recovery of consciousness after 12 months have been found between patients who were Val66Met BDNF polymorphism carriers and those who were not carriers (Bagnato et al., 2012).

Apart from plastic changes induced by the brain injury itself, recovery may also occur as a consequence of an experience-induced plasticity. It is well known that an important feature of plasticity is its regulation by activity and sensory experience (Trachtenberg et al., 2002). In animal models, these effects can be studied with protocols of environmental enrichment. Several studies show that major correlates of environmental enrichment are the birth and maturation of new neurons into functional circuits (Kempermann et al., 2002; Bruel-Jungerman et al., 2005), synapse remodeling, including synapse formation and destabilization (Bednarek and Caroni, 2011), and enhancement in the expression of molecules involved in neuronal signaling (Zhu et al., 2006). Under in vivo conditions, training in motor skill learning tasks results in a rapid rewiring through the formation and elimination of dendritic spines in the primary motor cortex, affecting different sets of synapses for different motor skills (Xu et al., 2009). In animal models of traumatic brain injury, environmental enrichment leads to an improvement of several cognitive functions

(Passineau et al., 2001; Maegele et al., 2005), which seems to increase if combined with multimodal sensory and motor stimulation (Maegele et al., 2005). The presence of social interactions positively affects histological features and behavioral outcomes following cerebral ischemia (Craft et al., 2005; Karelina et al., 2009). Notably, early enrichment increases the dendritic branching of layer V cortical neurons, whereas enrichment delayed until 30 days following brain injury (stroke) has no effect (Biernaskie et al., 2004). These results provide strong evidence for a critical period after brain injury, during which the brain is most receptive to modification by rehabilitative experience, and suggest that earlier and intensive therapy leads to a better and faster recovery.

It is becoming increasingly evident that inhibitory circuits play key roles in experience-dependent plasticity as well as neurological diseases. Reduced inhibition augments plasticity under a number of different conditions, including environmental enrichment and fluoxetine treatment (Sale et al., 2007; Maya Vetencourt et al., 2008). Animal models of traumatic brain injury show a dramatic shift in excitatory/inhibitory dynamics, suggesting a long-term hyperexcitability of the cortical circuits, after an initial suppression, that could be linked to the disruption of one or more inhibitory mechanisms of the thalamocortical circuit (Ding et al., 2011). Following a brain injury, NMDA glutamate receptors are up-regulated, whereas $GABA_A$ receptors are down-regulated, in both the ipsilesional and contralesional hemisphere (Nudo, 2007). Similarly, changes in the balance between excitatory and inhibitory circuits have been described in humans after stroke both in the affected and non-affected hemisphere, leading to changes that allegedly influence the recovery of functions (Huynh et al., 2013). On these bases, it has been proposed that an inhibitory transmission reduction could facilitate restructuring of circuits impaired by damage, allowing activity-dependent plastic changes (Pistoia et al., 2010; Chen et al., 2011). In accordance with these data, recent studies have reported impairments in the cortical inhibitory mechanisms mediated by GABA-ergic (Bagnato et al., 2012) and cholinergic circuits (Lapitskaya et al., 2013) in patients suffering from UWS. In this context, the observed inhibitory transmission reduction may represent an attempt to prepare more favorable conditions to develop restorative plastic changes.

3.2 Plasticity in thalamocortical and corticothalamic projections

As previously described, structural and or functional abnormalities in the thalamocortical projections are frequently described in patients with UWS. The thalamocortical projections represent a crucial integration node among the different pathways that receive sensory inputs and the cortical mechanisms that shape the external world structure through them. In other words, the thalamocortical projections have been proposed to be a part of the processes leading to awareness of the external environment (Tononi, 2004, 2008). Projections from the thalamus to the cortex play a

key role in the "mesocircuit" model that was proposed to elucidate impairment of consciousness and provide a rational for therapeutic interventions in UWS (Schiff, 2008, 2010). This circuit has its main stations in the central thalamus (i.e., the intralaminar nuclei and the related paralaminar nuclei), striatum (i.e., medium spiny neurons) and the anterior forebrain. Located at the center of this mesocircuit model, central thalamic neurons receive projections from ARAS nuclei and cholinergic neurons of the basal forebrain (Schiff, 2008). The central thalamus, in turn, projects widely throughout the frontal lobe, including the supplementary motor, anterior cingular, premotor and prefrontal cortices (Morel et al., 2005). Another key element in this model is constituted by the medium spiny neurons in the striatum that, through their inhibitory projections to the globus pallidus interna, inhibit the central thalamus (Goldberg and Fee, 2012). Virtually, all the elements in these circuits are vulnerable to deafferentation following severe brain injuries that may deeply affect anterior forebrain function through abnormal outflows of the thalamocortical projections arising from central thalamus (Schiff, 2010). In addition, recent studies have demonstrated that the thalamocortical projections have a strong impact on the cortical states (Hirata and Castro-Alamancos, 2010; Poulet et al., 2012) that regulate many aspects of behavior, from perception, learning and cognition to consciousness (Buzsáki and Draguhn, 2004; Haider and McCormick, 2009). Notably, the ability of thalamocortical projections to drive excitation within the cortex has been reported to be stronger than that of the cortico-cortical projections (Rigas and Castro-Alamancos, 2007). Consequently, down-regulation of the thalamic output may lead to broad effects on behavioral aspects depending on the cortical states of patients. Due to these assumptions, the role of the thalamocortical projections in patients suffering from disorders of consciousness received considerable interest when a behavioral improvement following bilateral deep brain stimulation of the central thalamus was described in a patient in a MCS (Schiff et al., 2007). Thus, it can be expected that plastic changes aimed at restoring the thalamocortical connections may play a part in the processes that lead to the recovery of consciousness in patients with UWS.

Thalamocortical plasticity may occur through different mechanisms. Animal models show that sensory experience or deprivation may deeply affect thalamocortical arborization and dendritic spine density (i.e.: plasticity) in adulthood, in visual and somatosensory systems (Montey and Quinlan 2011; Oberlaender et al., 2012). Changes in the environment (enrichment or sensory deprivation) up- or down-regulate synaptic strength and plasticity of the thalamocortical pathways associated with specific changes in glutamatergic and GABAergic neurotransmission (Kuo and Dringenberg, 2009; Mainardi et al., 2010; Cooke and Bear, 2010). The presence of synaptic plasticity in the thalamocortical projections has also been described beyond the sensory cortices. For example, plastic changes have been supposed or described in the connections among different

thalamic nuclei (i.e.: intralaminar, reuniens, rhomboid, and mediodorsal nuclei) and the prefrontal cortex and/or hippocampus (Loper et al., 2009; Loureiro et al., 2012; Bueno-Junior et al., 2012), which are involved in several cognitive functions (Antoniadis and McDonald, 2006; Izquierdo et al., 2010; Padilla-Coreano et al., 2012; Watanabe and Funahashi 2012). After the formation of cortical lesions, the unmasking of existing thalamocortical connections may restore connectivity and functions (Padberg et al., 2010). Processes such as the unmasking of connections may operate in post-traumatic conditions to restore some pathways destroyed by DAI, but they probably have a minor role in the recovery of connectivity in other conditions associated with UWS, such as massive hypoxic brain injury. This difference may affect the dissimilar outcome between traumatic and hypoxic UWS.

The relationship between the thalamus and cortex is bidirectional, as the cortex receives thalamocortical fibers and itself projects to the thalamus via corticothalamic fibers (Jones, 2009). An increasing number of studies of different sensory systems and species has revealed that the thalamus is not just a simple relay center; rather, it performs complex information processing and integration that underlies different mammalian behaviors through of corticothalamic feedback input (Briggs and Usrey, 2008). Corticothalamic projections comprise nearly 50% of the synaptic input into thalamic sensory neurons, outnumber the corresponding thalamocortical projections, and regulate sensory information processing at the level of the thalamus (Jones, 2002). The massive reciprocal feedback from the cortex to the thalamus (Deschenes et al. 1998; Winer et al. 2001; Rouiller and Durif 2004) suggests that the central processing of sensory information is far more intricate than the traditional notion of feed-forward processing. During brain development, corticothalamic and thalamocortical projections guide each other to reach their specific targets (Grant et al., 2012; Deck et al., 2013), and the cerebral cortex provides feedback to the thalamus via the projections of two distinct classes of pyramidal cells located in different layers. The majority of cells projecting to a particular thalamic nucleus are located in layer VI of the cortical area receiving input from that nucleus. A smaller number of cells are found in layer V of the same area and project mainly to different, although functionally related, thalamic nuclei (Steriade et al., 1997; Jones, 2007). Corticothalamic projections may both shape thalamic receptive fields and enhance the transmission of sensory information from the thalamus to the cortex (Briggs and Usrey, 2008). Moreover, corticothalamic projections contribute to the neuronal circuitry involved in adjusting the activity patterns of thalamic neurons during sleep and wakefulness (Destexhe et al., 2007). Recent studies suggest that plastic changes in the thalamus may occur through corticothalamic projections in the visual, auditory or other sensory systems (Augustinaite et al., 2011; Tang et al., 2012; Zembrzycki et al., 2013). Corticothalamic synapses display both short- and long-term forms of use-

dependent synaptic plasticity (Castro-Alamancos and Calcagnotto, 1999; Sun and Beierlein, 2011). Also the strength of the cortical input to thalamic neurons is selectively subjected to plastic use-dependent modifications, which could be a mechanism for regulation of thalamocortical–corticothalamic interactions and their underlying processing (Miyata and Imoto, 2009; Hsu et al., 2010). In summary, thalamocortical and corticothalamic projections mediate a complex pattern of reciprocal interactions between the thalamus and the cortex that is involved not only in any sensory processing but also in cognitive functions and the regulation of sleep and arousal.

Taken together, experimental data show that a wide range of plastic changes may occur in different brain areas and circuits after a severe brain injury. Nevertheless, most of these data have been achieved from models of focal brain injury, while UWS is the result of *massive brain damage*. Therefore, in the future we will need to refine this knowledge in experimental models reproducing the extensive brain injuries that cause UWS in humans.

4. Current difficulties and strategies in the rehabilitation of patients with UWS

The rehabilitation of patients with UWS is a complex and challenging task, and specific standards of care do not currently exist (Laureys et al., 2006). However, the available data allow us to propose some general considerations. First, the starting point of any rehabilitative intervention is a careful assessment of patients that is able to define all the rehabilitative needs of each person with UWS. From this point of view, the same diagnosis of UWS raises serious problems. Clinicians should be aware that current diagnostic standards, which are based on behavioral evaluations (Royal College of Physicians, 2003), only enable us to suppose unconsciousness in patients with UWS. In the UWS acronym, the letter "U" stands for "unresponsive", which is not equivalent to "unconscious" (i.e., we cannot be absolutely sure of the real absence of awareness in the patient). Indeed, an alarming high misdiagnosis rate of patients with UWS and in MCS has been reported (Schnakers et al., 2009). Moreover, when advanced fMRI or EEG protocols have been applied, awareness was detected in patients previously believed to have an UWS (Owen et al., 2006; Monti et al., 2010; Cruse et al., 2011). Errors in the diagnosis of UWS may arise from the difficulty of assessing low levels of responsiveness (because conscious behavior may be highly variable, especially in the first phases of emersion from UWS) or because sensory (e.g., blindness), motor (e.g., paralysis), or cognitive deficits (e.g., aphasia, apraxia) prevent the patient from demonstrating consciousness in specific assessment tasks (Giacino et al., 2013). To reduce these high misdiagnosis rates, the use of specific tools in the neurobehavioral assessment of patients with disorders of consciousness is recommended. Specifically, the Coma Recovery Scale Revised (Giacino et al.,

2004) has been identified as the better tool for the assessment of patients with disorders of consciousness (UWS, MCS, emergence from MCS) in both clinical practice and research (Seel et al., 2010). Moreover, the World Health Organization's *International Classification of Functioning, Disability and Health* (ICF) (WHO, 2006) may be useful for the careful assessment of functioning and disability in patients with UWS. The ICF biopsychosocial model enables us to obtain specific profiles of functioning and disability for each patient with UWS, and it may be used to plan rehabilitative interventions (Leonardi et al., 2009, 2012; Seel et al., 2013).

Further, some reports suggest that targeted rehabilitative treatments performed in specific departments for patients with disorders of consciousness produce better results (Dolce et al., 2012; Seel et al., 2013); these are probably due to several factors that mainly involve the refinement of internal care protocols and the availability of specialized personnel and equipment, which are essential for the management of patients with severe disorders of consciousness.

In a schematic way, the rehabilitative treatments in patients with UWS may be distinguished between interventions that are not specifically oriented toward the recovery of consciousness and interventions that are specifically oriented toward the recovery of consciousness. Interventions that are not specifically oriented toward the recovery of consciousness include interventions that aim to restore circadian rhythms and interventions that aim to treat or prevent neurological, medical and surgical complications. Contrary to previous assumptions, recent studies have reported sleep-wake cycle disruption in a high percentage of patients with UWS (Cologan et al., 2013; Cruse et al., 2013). The hypothalamic suprachiasmatic nucleus is thought to be the primary clock that maintains the timing of circadian rhythms (Morin, 2013). The most important afferent pathway to the hypothalamic suprachiasmatic nucleus is the retinohypothalamic projection, through which photic information accesses the clock (Muscat et al., 2003). Interventions that aim to restore circadian rhythms through the activation of this pathway, such as changes in illumination, are usually utilized in patients with UWS (Dolce et al., 2012). Moreover, other interventions that are assumed to be useful in circadian rhythm recovery, such as feeding and transfers from bed to wheelchair at regular times, are currently being proposed for patients with UWS (Dolce and Lucca, 2010; Dolce et al., 2012). Interventions to prevent or treat complications are an essential feature of the rehabilitation of patients with UWS. Currently, the core of rehabilitative treatments for patients with UWS is constituted by programs that aim to treat and prevent neurological, medical, and surgical complications and that expect to improve overall health, which might support spontaneous recovery (Giacino et al., 2013). Complications are extremely common during the inpatient rehabilitation of people with disorders of consciousness (Ganesh et al., 2013), and these complications affect the final outcomes and are responsible for maintaining the mortality rates during rehabilitation at 2.3%

for traumatic injury and 7.9% for anoxic injury (Avesani et al., 2013). In particular, spasticity and epileptic seizures are the most commonly reported neurological complications in patients with UWS (Ganesh et al., 2013). Spasticity affects 57% of patients with UWS and is associated with poor outcomes (Ganesh et al., 2013). Spasticity rehabilitative treatment includes non-pharmacological and pharmacological interventions. The non-pharmacological interventions involve assisted passive mobilization, postural positioning, and use of specific orthoses. Pharmacological intervention for the treatment of spasticity and the prevention of pathological posturing is needed in many cases. Oral or intrathecal baclofen and botulinum toxin are the most commonly administrated drugs. Baclofen is a $GABA_B$ agonist that is used to manage of patients with spasticity (Kheder and Nair, 2012); in addition to the effects on spasticity, it has been reported that intrathecal baclofen might have a positive effect on the level of consciousness in some patients with UWS (Sarà et al., 2009). Two different mechanisms have been proposed to explain this result: a functional restoration in the corticothalamocortical connections involved in the integration of arousal and awareness, and an activation of centripetal inputs from spinal neurons to the cortex (Sarà et al., 2009). More recently, it has been reported that repeated botulinum toxin injections are a safe and effective treatment for spasticity in patients with severe disorders of consciousness (Clemenzi et al., 2012).

Epileptic seizures are another common complication in patients with UWS, and they occur in 32% to 46% of cases (Bagnato et al., 2013a; Ganesh et al., 2013). Pharmacological interventions are adopted to prevent seizures recurrence, and current data interestingly suggest that antiepileptic drug therapy does not affect the recovery of consciousness in patients with UWS or in a MCS (Bagnato et al., 2013b). Finally, dystonia has been reported to affect 21% of patients with disorders of consciousness (i.e., UWS and MCS) in the early rehabilitation phase (Boccagni et al., in press). Dystonia has been found to be more frequent in patients suffering from severe disorders of consciousness caused by cerebral anoxia (32% of patients) than in patients with traumatic brain injury (24%) or with cerebrovascular diseases (10%). Generalized dystonia has been found to be prevalent in patients with cerebral anoxia, whereas focal dystonias (cervical dystonia, blepharospasm, oro-mandibular dystonia) have been reported to predominate in TBI (Boccagni et al., in press). Botulinum toxin injections are an effective treatment for focal dystonias, whereas generalized dystonia requires pharmacological interventions (e.g., anticholinergic drugs), which may potentially affect the recovery of cognitive functions.

Interventions to treat and prevent medical and surgical complications are an essential component of the programs carried out in units specialized for the rehabilitation of patients with UWS (Giacino et al., 2013; Seel et al., 2013). These interventions include protocols for ventilator

weaning with subsequent withdrawal of tracheal cannulas, and protocols to treat or prevent infections, deep vein thrombosis, pressure ulcers, heterotopic ossifications, dysautonomia, and hydrocephalus (Seel et al., 2013; White et al., 2013). Specific descriptions of these interventions are beyond the aims of this paper, but it must be emphasized that the early management of complications may substantially reduce disability and improve the patient's final outcome (Ganesh et al., 2013).

Specifically oriented interventions for the recovery of consciousness are based on programs of multisensory stimulation, i.e., combined auditory, visual, olfactory, gustatory and tactile stimulation. The assumptions of this approach lie in the concept that environmental changes after a severe brain injury realize a patient's virtual isolation (for example, during an intensive care unit stay) and have potentially detrimental effects on recovery (Lancioni et al., 2010). Although some encouraging results have been reported in unresponsive and minimally responsive patients (Canedo et al., 2002; Barreca et al., 2003; Oh and Seo, 2003), these studies lack in description of the patients and study design or assessment tools. Another strategy is based on attempts to restore social interactions with the family members closest to the patient or to evoke emotions with music (Machado et al., 2007; Riganello et al., 2010). As reported in the previous section, the role of social interactions in brain injury outcomes has been highlighted in animal models; moreover, studies on humans suggest that patients with high levels of social support exhibit better functional recoveries after strokes than socially isolated patients (Glass et al., 1993). However, currently, only effects on EEG or autonomic parameters have been reported (Machado et al., 2007; Riganello et al., 2010), and no prospective studies have been performed. More recently, new interventions based on learning principles and technological support have been developed. These procedures rely on hand-closure, eye-blinking responses and microswitch technology to detect reactions to stimuli or social interaction requests (Lancioni et al., 2009a,b). However, this targeted use of microswitch technology with the aim of detecting, inducing and improving learning has been successfully described only for a limited number of patients with UWS (Lancioni et al., 2009b).

In conclusion, most current rehabilitative treatments are not specifically oriented toward the recovery of consciousness, and they lack theoretical validity in terms of current concepts of unconsciousness pathophysiology and the ability to promote restorative plastic changes. Results regarding new technologies are promising, but, currently, only preliminary reports with small numbers of patients are available. In the following section, we will provide some general concepts to be taken into account in the design of successful new rehabilitative interventions that should be evaluated in clinical trials.

5. Developing a rehabilitation specific for UWS and based on a neurophysiological consciousness theory and on neuroplasticity tenets

In UWS, the loss of consciousness occurs abruptly as the result of an acute brain injury. Still, neurophysiological and neuroimaging studies have provided increasing evidence that neuronal functions subtending consciousness are not completely reset in UWS but are reduced below a minimal threshold level required for consciousness. The critical factor regulating the occurrence or absence of consciousness recovery, is the distance of these neuronal functions from this threshold level of “non-return”. In spite of some interesting findings reported in recent years by group-level analysis (see Section 2), currently physicians cannot obtain suitable clinical, neurophysiological or neuroimaging data to determine in a timely manner (early after brain injury) if the residual neuronal function of a particular patient is sufficient for recovery of consciousness. Thus, the major challenge for clinical neuroscience currently is how to characterize the minimum level of specific brain functions (reflected in a particular brain architecture) required for consciousness individually in each patient. In an empirical way, we may think about these residual neuronal functions as a potential "cognitive reserve" that should be enhanced through different stimulation strategies. Improvement occurs necessarily through functional and/or structural changes in the brain, i.e., through plasticity at different brain levels, at the micro-, meso- and macro-level (Schiff, 2012; Fingelkurts et al., 2010).

Although some of these changes may occur spontaneously, there is a growing body of evidence indicating that behavioral or instrumental interventions can increase functional outcome by promoting adaptive functional and structural plasticity in the central nervous system. In animal models, a commonly used behavioral intervention is the above-mentioned enriched environment housing, which constitutes a mixture of social, sensory, cognitive and motor experiences. In the future, we will need to develop and validate neurocognitive programs providing all essential interventions to support the recovery of inner and external environmental awareness. Our studies on the operational architectonics of brain-mind functioning (Fingelkurts et al., 2010, 2011, 2012a,b,c, 2013b,c) pointed to a hypothesis that rehabilitation strategies aiming to normalize the impaired operational architectonics in patients with UWS or in a MCS could result in consciousness recovery.

Data obtained from other neurological diseases suggest that rehabilitative treatments need to be early, specific and intensive in order to guarantee a better chance of recovery. Rehabilitative treatment timeliness allows patients to take advantage of the "critical period" of enhanced plasticity after brain injury, during which an up-regulation of genes promoting neuronal growth,

synaptogenesis, and proliferation of dendritic spines predominates (Carmichael et al., 2005; Murphy and Corbett, 2009). If treatment is given early, the implications for restoration of function are enormous; currently, delays in initiating rehabilitation after severe brain injuries vary considerably, and, in many patients, rehabilitative treatment might fall outside of this decisive time window. The usefulness of a specific training regimen has been described for the recovery of motor (Arya et al., 2012) and cognitive functions, including self-awareness (Doesborgh et al., 2004; Cheng and Man, 2006). Finally, principles translated from the tenets of the activity dependent plasticity in animal models suggest that the intensity of training has a critical role in recovery (Nudo et al., 2011), and current standard rehabilitative programs are probably under-dosed (Lang et al., 2009; Nudo et al., 2011). Although the definition of the exact amount of cognitive training for patients with UWS is still far from being identified, we may hypothesize that, as the dose of training affects the overall effects of activity dependent plasticity (Nudo et al., 2011), intensive neurocognitive programs may be much more advantageous in order to recover consciousness. In this context, we propose that specific cognitive stimulations, aimed to recover at least some constituents of awareness, should take into consideration the individual operational architectonics of the brain of each patient in order to be more specific and more effective for consciousness recovery.

The recovery promoted by cognitive rehabilitation may be reinforced by means of pharmacological or neurostimulatory approaches. Two recent studies involving a large number of patients suggested a role for some drugs. A placebo-controlled trial has shown a favorable effect of amantadine on recovery of patients with UWS and in a MCS (Giacino et al., 2012a). Amantadine, facilitating dopamine presynaptic release and blocking its reuptake, may promote dopaminergic neurotransmission in the nigrostriatal, mesolimbic, and frontostriatal circuits, which are involved in arousal and attentional functions (Giacino et al., 2012a). Another study reported an increase in cerebral flow perfusion after zolpidem administration in patients with UWS without brainstem involvement (Du et al., 2013). Zolpidem is a non-benzodiazepine hypnotic drug that potentiates $GABA_A$ transmission, which is supposed to be reduced in patients with UWS (Bagnato et al., 2012). Nonetheless, favorable behavioral responses to zolpidem medication occur only in a minority of patients suffering from severe disorders of consciousness (Whyte and Myers, 2009). Also neurostimulation seems to be effective in some patients affected by UWS or who are in a MCS, either using epidural spinal cord stimulation (dorsal columns at cervical level) (Kanno et al., 2009) or central thalamus deep brain stimulation (Schiff et al., 2007; Yamamoto et al., 2010). The proposed mechanisms for neurostimulation include activation of thalamocortical and thalamostriatal pathways and changes in neocortical microcircuits (Giacino et al., 2012b). Despite some promising

results, pharmacological and neurostimulation interventions for UWS still have a low level of evidence (Oliveira and Fregni, 2011). Moreover, they may operate in a too widespread or selective manner: actually drugs act, in addition to their intended functions, outside the circuits involved into consciousness recovery with potential adverse effects, while neurostimulation cannot activate all circuits encompassing it.

In conclusion, a rehabilitative treatment specific for consciousness recovery needs to use every possible strategy (behavioral, cognitive, pharmacological, and neurostimulation interventions) in order to promote: (i) neuroplasticity in the brain areas/systems (micro-level) and (ii) restoration of operational architectonics of brain functioning (meso- and macro-levels) involved in consciousness expression (Figure 3). Currently, virtually every modern therapeutic approach in post-injury rehabilitation should rely on the fundamental principles of neuroplasticity for its theoretical validity (Nudo and McNeal, 2013). If the assumptions of this paper are correct, i.e., if recovery from an UWS necessarily occurs through plastic changes, current rehabilitative standards, which are mainly based on non-specific interventions, may have limited ability to promote specific plastic changes and thus cannot be considered adequate.

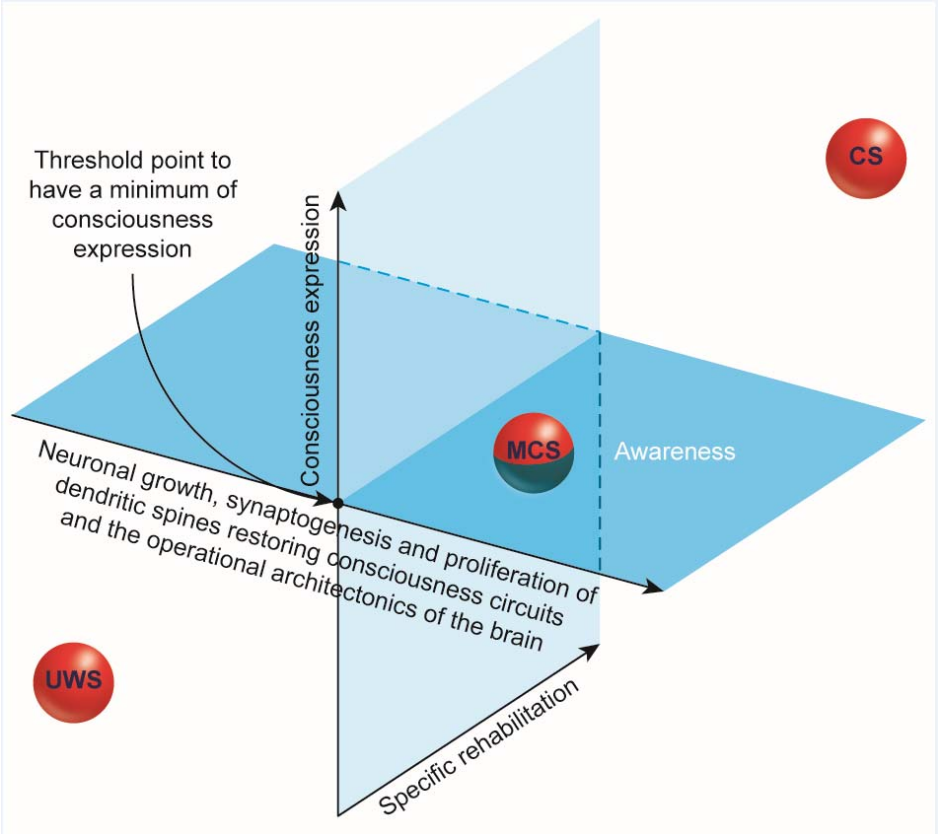

Figure 3. Proposed relationship among rehabilitative treatment, brain plasticity, and level of consciousness. A critical point for the recovery of consciousness is how far neuronal functions are from the threshold level required to experience awareness. This mainly depends on brain injury

severity. In the next years, new rehabilitative treatments that are based on the tenets of neuroplasticity should be developed to induce several plastic changes that may promote progressive recoveries of consciousness. Moreover, in future studies we will need to characterize in each patient the residual neuronal functions, to see if they are susceptible to improvement by means of plastic changes. This will orient the rehabilitative treatments in a more specific way. CS, conscious state; MCS, minimally conscious state; UWS, unresponsive wakefulness syndrome.

Future clinical trials to test the efficacy of specific rehabilitative interventions (i.e., protocols of cognitive stimulation, neuromodulation, etc.) should take into account the above-mentioned principles of neuroplasticity (especially, the specificity, intensity and timeliness with which treatment is initiated). Current data suggest impairments in neuronal function at an overall thalamocortical level; therefore, rehabilitative treatments based on sensory stimulation (visual, auditory, tactile, proprioceptive, olfactory, and gustatory stimulation, alone or in combination) that are able to gain access to the cortex through the thalamus should be explored in new clinical trials that employ the higher modern standards of behavioral, neurophysiological and functional neuroimaging assessments. Removal of confounding stimulations (e.g., the causes of pain) may allow better results to be obtained from the rehabilitative treatment. Indeed, recent studies suggest that cortical activations occur during the experience of one's own or other people's pain (de Tommaso et al., 2013; Yu et al., 2013). However, consciousness is much more than just sensory processing, so other methods should also be explored. Data from animal models suggest that approaches based on environmental enrichment (e.g., to promote interactions with the patient's family members, and to introduce psychological interventions targeted toward biographic information or cognitive stimulation with multimedia support) have adequate scientific bases that justify testing in patients with UWS. Yet, these principles should be integrated with the increasing knowledge about the neurophysiology of consciousness. Therefore, rehabilitative interventions should specifically aim to normalize the impairment in the characteristics of brain operational architectonics using known principles of neuroplasticity in order to reach the critical level of "non-return" at which awareness of the environment and of the self can be reliably supported and self-regulated by the brain. An essential aspect of any rehabilitative intervention is that the efficacy of that intervention should be assessable. Current clinical evaluation standards cannot be considered satisfactory because of the high rate of misdiagnosis (Schnakers et al., 2009). The development of new technologies may help to detect and monitor conscious behaviors in the early phase of recovery (Lancioni et al., 2009; Riganello et al., 2010; Pignolo et al., 2013), and the use of these new technologies with current clinical evaluation standards should be tested in clinical trials. Finally, it is likely that neuroimaging and neurophysiological techniques will be validated in the next years

not only to reduce the rate of misdiagnosis, but also to assess the efficacy of rehabilitative interventions via quantifiable correlates of the neuronal functions related to consciousness in each patient. Much work is still to be done, but we now have the theoretical and instrumental tools to plan future clinical trials that, by joining the tenets of neuroplasticity, neurophysiological knowledge and new technical equipment, will strongly impact the recovery of consciousness in patients with UWS.

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