Analysis of awareness and vigilance as main components of consciousness in selected brain disorders

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ANALYSIS OF AWARENESS AND VIGILANCE AS MAIN COMPONENTS OF CONSCIOUSNESS IN SELECTED BRAIN DISORDERS

GRADUATE THESIS

Zagreb, 2018.

This graduate thesis paper was made at the Department of Neuroscience, Croatian Institute for Brain Research under the mentoring role of Prof.dr.sc. Goran Šimić, MD, PhD

Thesis paper "Analysis of awareness and vigilance as main components of consciousness in selected brain disorders" was submitted for evaluation in the academic year 2017/2018.

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ABBREVIATIONS

ARAS – Ascending Reticular Activating System

BCC - Behaviour Correlates of Consciousness

BOLD – Blood Oxygen Level Dependent

DMN - Default Mode Network

DOC - Disorders of Consciousness

EEG - Electroencephalography

EMG - Electromyography

fMRI - Functional Magnetic Resonance Imaging

ICU - Intensive Care Unit

LIS - Locked-in Syndrome

LRP - Lateralized Readiness Potential

LZc - Lempel-Ziv complexity

MCS - Minimally Conscious State

NCC - Neural Correlates of Consciousness

NREM - Non-Rapid Eye Movement

PET - Positron Emission Tomography

PCC - Posterior Cingulate Cortex

PCI - Perturbational Complexity Index

PVS - Persistent Vegetative State

rCBF - Regional Cerebral Blood Flow

rCMRGlu - Regional Cerebral Glucose Metabolism

REM - Rapid Eye Movement

TMS – Transcranial Magnetic Stimulation

UWS - Unresponsive Wakefulness Syndrome

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ABSTRACT

Title: Analysis of awareness and vigilance as main components of consciousness in selected brain disorders

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Consciousness is a state in which we are able to interact with our external environment. Each person has their own way of interpreting and processing their surrounding environment and will have their own unique responses. The two major components that make up our conscious mind are awareness and vigilance. When one of these is compromised it generally leads to decreased cognitive processing of the external environment which in turn leads to the different disorders of consciousness. The inner workings of consciousness still remain a mystery. However, research is still ongoing into understanding the different correlates, behavioral and neural, that may be involved. In addition, further sleep studies may help bridge the gap between wakefulness and non-wakefulness and thus shed light on altering levels of consciousness. Furthermore, classifying the different types of disorders without any doubt still remains problematic due to the fact that the gold standard for diagnosis is still at bedside. Approximately 40% of patients are misdiagnosed due to the lack of proper imaging techniques. Research into more advanced imaging can open the window to better patient prognosis. It is imperative that these patients are diagnosed correctly as early as possible in order to receive the appropriate care.

Keywords: Consciousness, Awareness, Vigilance, Disorders of Consciousness, Coma, Unresponsive Wakefulness Syndrome, Minimally Conscious State, Locked-In Syndrome, Diagnostics

SAŽETAK

Naslov: Analiza pozornosti i stupnja budnosti kao glavnih sastavnih dijelova svjesnosti u odabranim bolestima mozga.

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Svjesnost je stanje u kojem smo u mogućnosti komunicirati sa svojom vanjskom okolinom. Svaka osoba ima svoj način interpretacije i procesiranja svoje okolinete će imat svoje jedinstvene odgovore. Dva sastavna dijela koja tvore naš svjestan um su svjesnost i budnost. Kada je jedan od njih ugrožen, to obično dovodi do smanjenja kognitivne obrade vanjskog okruženja što rezultira različitim poremećajima svijesti. Unutarnji rad svijesti još uvijek ostaje misterij. Međutim, istraživanje je još u tijeku kako bismo razumijeli različite korelacije, ponašanje i neuronske veze, koje mogu biti uključene. Također, daljnje studije spavanja mogu pomoći premostiti razmak između budnosti i ne-budnosti i tako rasvijetliti različite stupnjeve svijesti. Štoviše,razvrstavanje različitih vrsta poremećaja bez ikakve sumnje još uvijek je problematično zbog činjenice da je zlatni standard za dijagnozu još uvijek klinička procjena. Oko 40% pacijenata je pogrešno dijagnosticirano zbog nedostatka odgovarajućih tehnika snimanja. Istraživanje naprednijih tehnika snimanja može otvoriti prozor boljoj prognozi za pacijenta. Imperativ je rana točna dijagnoza pacijenata kako bi u najkraćem mogućem roku dobili odgovarajuću njegu.

Ključne riječi: Svijest, Budnost, Poremećaji Svijesti, Koma, Vegetativno Stanje, Minimalno Svjesno Stanje, Locked-In Syndrom, Dijagnostika

1.0 INTRODUCTION TO THE CONSCIOUS EXPERIENCE

Our bodies have the incredible ability to take information from the outside world and interpret it into an experience. However, perception of the environment around us varies amongst individuals and thus quantifying experiences for the purposes of exact standardization poses a significant challenge (24). We are able to only approximate how specific environmental factors may be interpreted by others. How one's healthy conscious mind interprets and responds to these experiences is of great interest in the field of neuroscience. Two types of experiences, critical in pursuit of this information, are classified as subjective and objective (24). For instance, one of the most common causes of traumatic brain injuries are car accidents. We can recognize how someone only witnessing the accident would have a different perception than the person directly involved. However, it is also important to understand that if there were multiple parties directly involved, each person may have a completely singular view on how the accident felt to them. Some individuals may walk away from such a stressful event and move on with their lives while others may never want to enter another vehicle again. Therefore, if a patient were to survive, regardless if they sustained any major brain damage or not, they could potentially be at a higher risk for developing post-traumatic stress disorder just based on how they may have perceived the event. PTSD is a psychiatrically based brain disorder that is driven by an individual's experience or witnessing of a traumatic event (20). Knowing which individuals will develop PTSD is not an exact science and so it is difficult to predict. Nonetheless, there has been some exploration on the possible personality traits that may lead to an increased risk in PTSD in certain individuals (20). Research has found high risk identifiers based on inherited personality traits which may attribute potentially ‘negative’ or ‘protective’ components for the development of PTSD (58). Other potential attributes such as neuroticism is claimed to be a negative factor for dealing with traumatic experiences while extroversion is looked upon as being a protective element in the risk for developing PTSD (58). As we can see, when someone has an experience, there are an infinite number of factors to consider when thinking about how a particular event may affect them. However, further discussion is beyond the scope of this article.

2.0 COMPONENTS OF CONSCIOUSNESS: AWARENESS

Consciousness sets us aside from most animals. When we receive information from our environment, we do not have an entirely primal response. We also possess the advanced ability to understand the world around us and to contemplate solutions to most problems we face. The ability to express compassion and empathy is something that is unique to humans in comparison to other species. Therefore, in order to know when to express and feel these emotions, along with many others, depends on our conscious mind being able to perceive a situation in a certain way. The term awareness and consciousness are often used interchangeably, however, as ongoing research is discovering, awareness is just one component. Since awareness is essentially the perception of our external environment, in other words, the content of consciousness (8), we can ask how would consciousness change if this component was altered. For instance, when we consider brain injuries, we are able to determine that a patient may not be capable of communicating the same way as before. An intact awareness would suggest that the patient perceived a certain stimulus and therefore was able to generate an appropriate and purposeful response (16). The absence of this, as we will discuss shortly, could indicate issues with awareness and thus help classify many disorders of consciousness. Communication is not the only indicator of a lowered level of awareness. Patients with brain injuries often have a distorted sense of self. For example, they may not be familiar with their identity or what their name is. They may even have a complete distortion of their own personal beliefs, personality traits, or any aspect that makes one unique. These patients have some level of vigilance in regards to their environment, but their self-awareness is compromised.

3.0 COMPONENTS OF CONSCIOUSNESS: VIGILANCE

In comparison, vigilance is one's level of wakefulness, or level of consciousness (8). For example, travelers should always remain *watchful* when exploring areas they are unfamiliar with. This statement explains how we as humans, as well as most other living creatures, have the innate ability to keep a close eye on our surroundings in order to react to particular threats we might encounter. Another common example would be how parents remain *alert* when taking their young children to the park. In this case they keep a "watchful eye" on their children to prevent them from wandering off, getting physically injured and most importantly engaging with potential predators.

Vigilance is an important component of consciousness because it allows us to appreciate the need to act in order to protect ourselves. In other words, it allows us the ability respond to our immediate environment after registering potential threats. Therefore, when comparing the two components of consciousness we can state that awareness provides us with the ability to perceive and understand our external environment, while vigilance helps us maintain a level of wakefulness and arousal for response. Both components have shown to be essential for the proper diagnoses of DOC's. The reason for this is that certain disorders of consciousness may only have an altered vigilance, awareness, or even both as in comatose patients which will be discussed later. It is not to say that awareness and vigilance are the only two factors contributing to consciousness, but for the purposes of this review article we will only focus on these two components and their relation to brain disorders.

4.0 SLEEP AND VIGILANCE

Although sleep is not a DOC, there is ample value in understanding how consciousness is altered during this natural state. The time we spend awake is a time during which we are constantly taking in external stimuli via our senses. Our brains then appropriately process this information for us to be able to complete specific tasks. We thus consider ourselves to be conscious as we are able to interact and understand the environment around us. However, what happens to our brains when we are sleeping? Are we then in a state of unconsciousness? How is it that we are able to sense our external environment at certain points during sleep? For the most part, many of these questions remain a mystery as ongoing research continues to uncover what happens to our brains while sleeping. What we can say is that there is a loss of behavioral responsiveness when someone is sleeping but not a complete environmental disconnect (4). Currently, we can detect different sleep stages using an EEG and in turn analyze the different patterns to get a better grasp on what happens to our brains. The two broad categories of sleep are non-rapid eye movement (NREM) and rapid eye movement (REM). NREM is characterized by spontaneous K-complexes or sleep spindles without arousal (4). A k-complex is detected on EEG as a slow oscillating waveform (4). Although they are not completely understood, k-complexes help provide some information into the inner workings of the brain particularly during NREM sleep. In some instances, they have been related to neuronal silencing while in other circumstances are related to potential arousal in sleeping patients (4). This phenomenon can be classified as *neuronal bistability* (4). It is thought that perhaps this type of system allows for blockage of certain stimuli at the thalamic level as well as hindering cortical processing (4).

REM sleep presents with theta oscillations, reduced muscle tone, rapid-eye movements, saw-tooth waves, and an absence of sleep spindles or alpha oscillations (4). In regards to recognizing vigilance, it is usually characterized by some form of arousal such as body movements and EMG activation (4). The question here remains to what extent our brains "shut-off" when we are sleeping (4)? There must be some connectivity to the outside environment since we are able to jolt out of sleep from a bad dream, or even just a loud noise produced by our environment (4). Is there perhaps some basic "stand-by" mechanism our brains innately have (4)? Certain studies have indicated the conservation of cognitive function during sleep (4) and that, what are referred to as K-complexes, may be linked to our arousal systems (46). These k-complexes have been classified as possibly safeguarding sleepers against external environmental stimuli (57,5) via large-scale neuronal suppression (56). Therefore, these systems may just be the windows of vigilance to those that are asleep (14). LRPs or lateralized readiness potentials are recorded on EEG as electrical activity produced by the brain (4). These reflect the appropriate motor preparation responses that are elicited via external stimuli (27,48). During sleep, if there is an LRP recorded, this can be a feature which would help indicate the conservation of intricately dispersed processes (4).

The Lempel-Ziv complexity (LZc) is an algorithm which is showing great promise in helping understand the differences between sleep stages. Although the details about this parameter are beyond the scope of this article, it is still worth mentioning. LZc works by following the level of consciousness in healthy patients, those that are anesthetized with no ailments, and patients that are asleep (8,1,42). It is a mathematical measurement of a signals complexity by assessing its compressibility (61). Therefore, with this in mind, we can suggest that a high LZc value would be due to a signal with minimal compressibility, such as a signal that is not predictable (4). For instance, the LZc value may differ among the varying stages of sleep. In deep NREM sleep, the EEG signal is usually a high-amplitude synchronous slow wave (4). This would then suggest that the signal is predictable and the LZc value would decrease in comparison to other stages (4). During vigilance however, the EEG signal is unpredictable which indicates an ultimately complex signal (4). REM sleep as well as light NREM have moderate LZc values, however, REM is the closest in value to vigilance (4). Therefore, we can conclude that perhaps there is some level of consciousness still in effect while we are asleep. Further research may help uncover these levels of consciousness and their relation to different correlates of consciousness. These correlates will be discussed in the next section.

5.0 CORRELATES OF CONSCIOUSNESS

Interactions between several cerebral networks are speculated to be involved when trying to understand how consciousness works (24). There are several theories about which pathways contribute such as neuronal specificity (8). Here the belief is that there are unique and complex organizations of neural cells that essentially supply the basis for consciousness (8). Another theory holds a more holistic view of the matter (8). In this case it is hypothesized that all neurons are united and form neural correlates of consciousness (24). A third theory is the information integration theory of consciousness (IITC) (28,53). This states that the brain is capable of consolidating multiple different patterns of internal communication and thus comprising our consciousness (28,53). At this time, there is not enough research solely supporting one theory over another and therefore we cannot say which theory carries the most weight. What we can claim is that the current method for diagnosing patients with disorders of consciousness for the most part is behavioral in the clinical setting (16). This has thus far been the most consistent method for diagnosis since other more quantitative diagnostic methods are still being developed. We refer to these criteria as behavioral correlates of consciousness and the details about how they relate to DOCs will be discussed in the next section.

5.1 BEHAVIOURAL CORRELATES OF CONSCIOUSNESS

It is important to be able to distinguish between purposeful and reflexive behaviors when dealing with a patient with an altered state of consciousness. In the clinical setting this is generally done visually. For example, the physician may ask the patient to lift their finger. If this results in a positive response from the patient, then the action can be classified as an intentional behavioral response (24). Generally, patients that are in a minimally conscious state have relatively clear behavioral responses that are not considered reflexive (24). This is how in recent years minimally conscious state (MCS) has been distinguished from unresponsive wakefulness syndrome (UWS), which consists of reflexive behaviors (24).

Another interesting phenomenon is known as *blindsight* (24). This suggests that patients who are cortically blind are still able to produce strong responses in correlation to visual stimuli (24). This is generally seen experimentally where the patient is meant to choose between one of two options (24). An example for these options can be "yes" or "no" in response to specific questions (24), or even classifying colors such as "red" or "blue". These patients are expected to commit to one of two options and therefore contrasts free-choice procedures. However, this does not suggest actual awareness of the stimulus since many other neurological factors can play a role in getting to the correct response such as memory or just purely guessing. To help combat this dilemma, a perceptual awareness scale was introduced (41). In this method patients are offered the ability to give more description of the type of stimulus they perceived (41). For example, how clear was the image and how confident they were with their answers (24).

As we can see a purely behavioral correlate of consciousness approach holds great limitations when making the decision to utilize them for diagnostic purposes. Thus, scientists have been making progress in the actual neural correlates of consciousness to get a better visual understanding of the neuroanatomical pathways involved. With this breakthrough, neuroimaging techniques may provide an even greater window to properly diagnosing patients with disorders of consciousness.

5.2 NEURAL CORRELATES OF CONSCIOUSNESS

Neural Correlates in contrast involve the most minute neuronal system that is collectively responsible for one single percept of consciousness. We can subcategorize these correlates into content-specific NCCs or full NCCs (24).

Content-specific neural correlates propose that single neuronal systems are involved in the make-up of NCCs (24). An example of this would be seeing a hand and the neural systems involved in allowing the brain to process what kind of object it is (24). During the absence of a hand, these mechanisms should be reticent. However, we are able to activate these processes artificially in which the patient would be able to see a hand (24). Transcranial magnetic stimulation (TMS) should allow the patient to observe a hand even if it is absent (24). However, full neural correlates can be understood as the unity of multiple content-specific neuronal correlates that comprise an entire conscious experience (24).

An important factor to consider for the proper functioning of correlates is proper oxygen and glucose levels in the body (24). Glucose and oxygen do not specifically supply the content of consciousness however, they are key factors that could potentially lead to altered states of consciousness if not controlled (24). Delirium for instance is a disorder of consciousness and could be a result of low glucose levels, which could be corrected. This DOC is generally of rapid onset and does subside after some time (37). Any factor that alters the normal function of the brain, such as inflammation, urine retention, or constipation may potentially lead to a state of delirium, the latter being one of the most common causes of delirium in elderly patients. Hence, proper care in retirement homes and hospitals, especially in the ICU, is of the utmost importance in order to avoid misdiagnosis of a more irreversible DOC.

Neuroanatomy plays an important role in discerning which NCCs are responsible for the conscious experience. To name just a few regions which may have particular significance, the Thalamus, Ascending Reticular Activating System, and the Cingulate Cortex (8). The thalamus and its close network to the cerebral cortex helps secure the preservation of consciousness as well as the inflection of arousal (8). Any damage to this area could potentially lead to disorders of consciousness, such as minimally conscious state or even unresponsive wakefulness syndrome (8). The ARAS on the other hand is important in the control of the level of consciousness and its fluctuations (8). Damage to it could lead to coma and other less severe forms of DOC (8). The Cingulate cortex is composed of a posterior and anterior portion (8). Like the thalamus, it is important in maintenance of consciousness, but also contributes to the default mode network which will be discussed shortly (8). Lesions here, especially the anterior cingulate cortex region could lead to states like unresponsive wakefulness syndrome. (8).

In addition to the neuroanatomy correlates we should also discuss the potential neurophysiology that is involved as well. Consciousness is expected to be achievable only when a 40Hz electrical hum is uninterrupted amid brain circuitries (8). While in a state of deep sleep, intralaminar thalamic nuclei are dormant and therefore no 40Hz oscillations exist (8). This evidence could provide a potential window into how consciousness really works since we know from the previous discussion in that the thalamus is responsible for maintaining a level of consciousness (8). In contrast however, certain gamma frequency (24) has been shown to be present in both wakefulness as well as REM sleep (8). Furthermore, it is important to be aware that considerable changes in neurophysiology does not only change consciousness levels but also a persons' vigilance which is reliant on arousal-promoting neuromodulators (19). Some research has indicated that in NREM and REM, the neural correlates of consciousness remain localized to a temporo-parieto-occipital region (46). This region is thought to be associated with perceptual experiences (46). On the other hand, NCCs for thought-like processes seem to be localized to a more frontal region (46). With just this minimal yet insightful information, we can state that consciousness works across a multitude of different levels and disciplines.

5.3 DEFAULT MODE NETWORK

The default mode network is another important component of consciousness research. It is defined by a system within the brain consisting of multiple regions that are operating even when the awake patient is at rest (16). In other words, when we are not focused on any particular task, our brains would in theory resort to this network and increase its activity (16). What we can appreciate from this is that the DMN may allow for thought processes that are not directly linked with the current outside environment such as daydreaming or revisiting memories (16). However, this thought is not the universal theory in what exactly these DMN activations mean. Many psychological disorders such as Alzheimer's Disease, show alterations in this network (10). Perhaps discovering more about the DMN could lead to a better understanding of not just DOCs but also many other debilitating neurological illnesses.

6.0 BRAIN DISORDERS

Based on the input of sensory stimuli, our brains formulate individual perceptions of the world around us. Disruption of this system, whether from trauma, stroke, or degenerative diseases, can lead to various impairments, thus gaining the classification of a brain disorder. What we perceive as a “normal”, functioning brain, in regard to societal constructs, is often debatable. As many people are able to achieve an excellent quality of life with minor impairments, we can discern that there are varying levels to which our brains are affected. In most cases, we could say that consciousness remains reasonably, if not fully, preserved. However, in a variety of other cases which will be discussed here, consciousness is disrupted. Therefore, extensive brain damage leads to disorders of consciousness which encompass a deep disruption of awareness (14) in association with vigilance. Some of these alterations of consciousness include Minimally Conscious State (MCS), Unresponsive Wakefulness Syndrome (UWS) or Vegetative State, and Coma. In order to differentiate between these disorders properly, it is critical to understand their clinical presentations. Misdiagnoses remain alarmingly high when comparing DOCs to one another as well as other disorders that may present in a similar manner such as Locked-In Syndrome. Therefore, further research into neuroimaging techniques, and alternate quantifying methods is imperative. Accurately diagnosing such patients with such limited understanding into the inner workings of the conscious mind becomes incredibly challenging and therefore a thorough workup is crucial.

TABLE 1. Diagnostic criteria for patients with severe acquired brain injuries (Modified from: Gosseries et al.2014.)

CLINICAL ENTITIES	DOC	DEFINITION
Coma (Plum and Posner,1983.)	+	No wakefulness
		No awareness of environment or self
Vegetative state/ Unresponsive wakefulness syndrome (Laureys et al.,2010.;Multi-Society Task Force on PVS, 1994.)	+	Wakefulness
		No awareness of environment or self
		No language comprehension or expression
		No sustained, reproducible, purposeful behavioral responses to external stimuli
		Relatively preserved hypothalamic and brain stem autonomic responses
		Variably preserved cranial nerve and spinal reflexes
		Bladder and Bowel incontinence
Minimaly conscious state (Bruno et al. 2011.; Giacino et al. 2002.)	+	Wakefulness
		Fluctuating awareness with reproducible, purposeful behavioral responses to external stimuli
Emergence from minimally conscious state (Giacino et al., 2002.)	-	Functional object use
		Functional communication
Locked-in syndrome (American Association of Rehabilitation Medicine,1995.)	-	Wakefulness
		Awareness
		Quadriplegia
		Aphonia
		Able to communicate via ocular movements
		Preserved cognition

6.1 COMA

Coma is a life-threatening complication of brain injury. Necessary precautions must be taken in order to minimize further brain damage as well as damage to other organs. In relation to consciousness, a patient that is considered to be comatose is also considered to have a disorder of consciousness. These patients do not exhibit signs of vigilance, a sense of self, or awareness of the environment surrounding them (35). In addition, these patients lack the ability to portray voluntary eye opening, whereas in other DOCs, patients reveal some visual clues (16). Additionally, comprehension of language or expression is inadequate and there seems to be no evidence of the sleep-wake cycle (16). Some patients are able to come out of a coma and into other forms of DOCs. Patients fortunate enough to progress to some level of vigilance while still lacking awareness are then classified as having unresponsive wakefulness syndrome or as it is more commonly referred to as vegetative state. (26).

The predictive parameters for which direction a patient in coma will go are not yet completely understood. Possible scenarios are progression to other disorders of consciousness such as UWS/VS or MCS, and brain death, which would eventually lead to clinical death.

6.2 UNRESPONSIVE WAKEFULNESS SYNDROME

Unresponsive wakefulness syndrome was once referred to as vegetative state. In contrast to coma, these patients seem to possess vigilance but express no indication of their awareness to the environment surrounding them (12). Patients can develop UWS via any form of traumatic brain injury or even stroke. In certain situations, patients that are comatose may progress to UWS and therefore be considered to have some conscious wakefulness. The extent of this vigilance is still unquantifiable and clinicians are unable to determine if these patients are even aware of it (16). Patients with UWS are unable to reproduce purposeful behaviors and therefore most of their responses are considered to be reflexive in regard to environmental stimuli (26). Most patients are incapable of understanding language and may present with both bladder and bowel incontinence (26). However, although these patients may seem unconscious, their sleep-wake cycle is well preserved (50). Some recent evidence in research has started to make breakthroughs in deciphering exactly what goes on in patients with UWS. Without observational motor responses to simple commands, the task of diagnosing a patient's level of awareness and vigilance is quite troublesome (12). Patients may in fact have a fully intact perception and understanding of these commands, but it is their peripheral motor function that is severely impaired.

Where standard clinical assessment lacks, there's been some new research that has begun to break the barriers for this diagnostic burden. One study helped to demonstrate that perhaps physical motor movements exhibited by the patient is not the only way to decipher the patient's effort to follow specific commands (12). In this case, fMRI was used to detect hemodynamic signals within the brain in response to simple commands such as the imagery of one playing a type of sport (12). As we know, different brain regions "light up" on imaging when activated by what we believe to be conscious thought perception and relative response. Activation of these specific areas depends on different variables such as types of thought and related emotion. When asked to imagine playing a sport like tennis, patients with UWS demonstrated brain region activations that were almost equivalent to those of healthy and cognizant individuals who imagined performing the same motions (12). Limitations still exist even with fMRI since there is no way of definitively concluding whether or not these patients are aware of the subjective thought of playing tennis. (12).

As with any other type of DOC, it is unknown how long a patient will remain in this state or whether they will ever regain full consciousness. Predicting which insults to the brain will result in a DOC is still not clearly understood. A deeper knowledge and understanding into the neural correlates of consciousness may provide such a window and thus earlier accurate diagnoses may be possible. However, still to date the most conclusive test for these patients, with all of its major limitations, is behavioral assessment. The rate for misdiagnosing a patient as UWS/VS is as high as 40% (16;21). This is why clinicians must remain rigorous in their examination of patients to avoid the imminent risk of misdiagnosis. What remains one of the most important factors for patients, with any form of DOC, is optimal care and patience. If properly cared for, these patients have the potential to advance to what is known as a minimally conscious state. As we will see in the next section, in contrast to UWS patients, here we see vigilance as well as awareness still intact, even on a behavioral level (18). This new classification has helped place patients in a more promising category for recovery in which hope is one of the driving factors for both physicians and family members to continue seeking signs of conscious activity. As we continue to see infinite differences in awareness and wakefulness from one DOC patient to the next, more subcategories will need to be created in order to provide proper therapies. However, due to the vast limitations in the diagnostics available for such patients, there is still much research to be done before modern medicine reaches a comfortable level for conclusive diagnosis. However, the gold standard of assessment for now is still behavioral at the level of the bedside for all DOCs including minimally conscious state which will be discussed next.

6.3 MINIMALLY CONSCIOUS STATE

Up until the year 2002, patients that presented with what we now know as a minimally conscious state were considered to be in a persistent vegetative state (18). PVS patients present with the inability to follow commands, they lack intelligible speech and are unable to track objects with their gaze (18). As we will see here, patients that are now considered to be MCS did not present in the same way as patients with PVS. Therefore, it was concluded that the former had some level of cognitive function still intact (18). Patients who present with oscillating signs of awareness as well as vigilance but are unable to communicate with their environment in a functional manner are considered to be in a minimally conscious state (7;15). Patients that are considered to be in a MCS also present with signs of reproducible, non-reflexive actions such as following straightforward commands (14). This suggests that the patient has some perception of the environment surrounding them or some intact sense of self. Reflexive responses are not considered part of the criteria for diagnosing MCS (16). This is because our bodies are capable of producing unconscious movements such as blinking in response to threats, flexion away from painful stimuli, oral reflexes (15) and finger twitching. Verbal and/or gestural yes or no response patterns are preserved for patients in MCS (16). These different types of responses in combination can help differentiate whether the patient is producing solely reflexive behaviors or if there is more deliberation involved. Patients that are able to follow an objects movement with their gaze denotes that they are aware of that particular object (18). In contrast, patients in a coma as was discussed previously, have the exact opposite response to moving objects. From an observational standpoint, in comatose patients it is as though the object itself does not exist.

Production of emotional responses, for example smiling, given the appropriate situation (18), is another valuable predictor that the patient is aware of his or her surroundings. However, communication that is purposeful remains impaired in some cases (15).

Furthermore, in an attempt to better differentiate between levels of consciousness, MCS can be sub-categorized as minimally conscious state minus and minimally conscious state plus (7;16). The former is characterized by the ability to physically reach for objects, engage in visual pursuit, and have effective behavioral interaction with the environment (16). The latter is thus defined by production of deliberate communication, comprehensible speech and the competence to follow commands (16).

Minimally conscious state is a difficult disorder of consciousness to diagnose and therefore it is imperative to take into consideration some elements that may mimic reduced responsiveness. In particular, physicians should pay attention to the type of sedatives administered and whether or not the patient has an ongoing infection (60). Other conditions that are noteworthy include aphasia, agnosia, and motor impairment (43). All of these situations can make the assessment process that much more complicated since DOCs are as of now mainly diagnosed at bedside. It is critical to remember to keep these patients well hydrated, nourished, and ventilated. In addition, medical professionals should take extra care in preventing these patients from getting any infections (18). If this is not controlled, then there could be complications that may lead to regression of the patient's current condition or decreased chances for recovery. With optimal care, patients that are in a minimally conscious state present with a higher probability of rehabilitation than those that are in UWS/VS (16).

Improvement from minimally conscious state, whether MCS plus or MCS minus, to a condition where the patient has regained control of fundamental abilities such as functional communication and object use, is referred to as the *emergence from a minimally conscious state* (33). In turn, patients with emergence from MCS are no longer considered to have a disorder of consciousness in contrast to other patients that are still in a minimally conscious state. Just how some patients are able to recover this way still remains unclear. Further studies into the neural correlates of consciousness may help unveil potential clues into the inner workings of the human consciousness. Some headway has already been made, particularly with regards to which potential neurophysiological components offer information on the differences between emergence from MCS patients and MCS. A patient diagnosed with emergence from MCS may have a PET scan which proposes that both positive and negative DMNs are conserved metabolically (14). According to the discussion by (14), negative DMNs may play a much more important role than positive DMNs in detecting levels of consciousness in patients that have emerged from MCS. A study claims that there are anti-correlates of consciousness in healthy participants as well as those that emerged from MCS (14). However, these anti-correlations lacked in patients that have DOCs (13). This information suggested that in order for conscious brain function, there should be some level of network switching. The exact mechanism is not clearly understood since consciousness itself still remains a mystery, however, we can appreciate any minor breakthrough in unraveling this enigma.

Another area of intrigue are the differences observed within the posterior cingulate cortex (8). Here it was observed that the PCC was not metabolically preserved in patients that had disorders of consciousness (14). However, in patients that were able to emerge from a minimally conscious state, the metabolic function of their PCC was spared (14). Studies claim that the posterior cingulate cortex may play a major function in producing the NDMN connection and therefore be a significant center for consciousness (14).

Not all conditions which present similarly to the disorders of consciousness discussed above actually qualify as being a DOC. In the next section, we will take a look at Locked-in Syndrome and the reasons it is not classified as fitting the criteria for a disorder of consciousness.

6.4 LOCKED-IN SYNDROME

Locked-in syndrome, in contrast to the aforementioned DOCs, presents as severe motor impairment while preserving awareness in the patient (33). Regardless of sustained awareness in these patients, they are often misdiagnosed as DOC due to paralysis of all voluntary muscles and limitations in diagnostic testing (6). Although there is significant efferent pathway impairment, most patients maintain the ability to communicate via ocular cues such as vertical eye movements and blinking (6). Cognitive function is generally well preserved in these patients suggesting that the cortical and subcortical framework is still majorly intact (6). What seems to be the main issue in LIS patients is the lesion in the pontine region. How this may in turn end up affecting the previously mentioned cortical regions down the line remains unknown (33). Since the gold standard is still behavioral assessment at the bedside for patients in these situations, the risk for misdiagnoses remains high (33). What we now know is that patients who may appear to be in a completely unconscious state could potentially have some level of remaining awareness and vigilance, as is the case with LIS. It is important to develop more sophisticated diagnostic methods in order to provide proper rehabilitative therapies as soon as possible for optimal recovery potential (editorial or something). To date, there are some neuroimaging techniques that have shed light on proper patient analysis when dealing with multiple types of brain injuries.

7.0 DIAGNOSTICS

As we have discussed previously clinical examination at the bedside remains the gold standard for diagnosis patients with altered states of consciousness (8). However, these methods have huge limitations and expose the patient to a higher risk for being misdiagnosed. Other imaging techniques are undoubtedly of heavy importance in adjunct to the bedside assessment. Some of these diagnostic methods are discussed in the following sections.

Positron Emission Tomography is a very hypersensitive method that measures physiological and biochemical processes within an organ. In the case for brain activity it has the ability to localize cerebral activity distributions into an objective quantification. What is quantifiable in this case is the utilization of oxygen and rCMRGlu (regional cerebral glucose metabolism), as well as rCBF (regional cerebral blood flow) (47). As previously mentioned, glucose and oxygen levels play an important role in the brain's ability for conscious experiences. Any alterations in these parameters when comparing the different DOCs could lead to valuable evidence into the inner workings of consciousness and the evolution of probable new theories.

The fMRI scan, in contrast to PET but in comparison to EEG, quantifies specific oscillations at a specific point in time (16). These oscillations are reflective arrangements in the blood oxygen level dependent (BOLD) fMRI signal (8,16). This analysis is based on deoxyhemoglobin and its paramagnetic properties (8). Neuronal activity is connected to the fluctuation in blood flow and oxygenation of brain tissue (8). A recent study has demonstrated some peculiar yet extremely compelling new insight into the inner workings of consciousness. On fMRI imaging, it was noted that a patient with UWS was able to analyze specific environmental stimuli in respective regions such as frontal, parietal, auditory and visual cortices of the brain as a healthy subject (8). However, in order to gain any more conclusive data, further studies must be performed.

8.0 MEASURING CONSCIOUSNESS: ZAP-ZIP MODEL

A recent study in 2016 used a model that is referred to as Zap and Zip. In this study, the subject's brains were zapped by transcranial magnetic stimulation (TMS) and then using EEG, brain activity was identified (23). This activity was then evaluated using a data-compressing algorithm, which lead to the term Zip (23). The perturbational complexity index, or PCI number, with a value of 0.31 was calculated from the collective EEGs (23). This then became the threshold to help determine potential consciousness in patients with different disorders of consciousness (23). If the subject scored below 0.31 on TMS, then they were considered to be in an unconscious state (23). If the subject scored above, then there was some potential consciousness present (23). This PCI number indicates the minimal amount of complex activity residing in the brain needed to reinforce consciousness (23). This study shows great promise is helping decrease the rate of misdiagnoses. Alarmingly, since some patients that were considered unconscious with severe DOC at the bedside scored above the threshold number. These patients could therefore indeed have some, regardless of how minimal, connection to their surrounding environment than initially thought (23).

9.0 DISCUSSION

Consciousness consists of two major components known as awareness and vigilance. Awareness focuses on one's perception of their external environment whereas vigilance focuses more on wakefulness. While awake the way one individual interprets and responds to a specific environmental stimulus varies in comparison to another. However, not all experiences occur during the time we are awake. Some research has been done in order to uncover the underlying mechanisms of consciousness in its relation to sleep. Through the different sleep stages, our consciousness fluctuates. The exact level to which consciousness is altered during sleep remains unknown. However, recent EEG findings have provided some insight in potentially uncovering similarities in certain neuronal networks that function while both asleep and awake.

Brain disorders in which consciousness is impaired present with great diagnostic issues. Since diagnosing one DOC from the next is majorly done at bedside, the room for misdiagnosis remains remarkably high. For example, a patient that presents with impaired awareness and vigilance is classified as being comatose. However, the grey area is when there is impairment of only one of these two components or the extent of this impairment is difficult to pinpoint. UWS patients have some level of vigilance but lack awareness of self or their environment. MCS patients retain wakefulness as well as some fluctuating awareness. Some patients may slip in and out of varying states and thus it may be difficult to notice. Extensive inspection and even multiple examinations done throughout the day are important in order to observe any fluctuating levels of consciousness and potential emergence from states such as MCS.

It is also important to exclude Locked-in Syndrome as a diagnosis since here patients have spared consciousness but are paralyzed to the point where their only form of communication is ocular, as previously described. Sedating medications and/or infections should also be ruled out when dealing with patients with an impaired conscious state.

Furthermore, proper nutrition for patients with disorders of consciousness is imperative for optimum recovery potential. Continuous research into advanced imaging techniques is important for more accurate and earlier diagnoses. This could be the window in helping more patients emerge from these debilitating states and return home to their families. The Zap and Zip model shows great promise in gaining access to this diagnostic problem by giving clinicians a numerically standardized scale in order to aid them in coming up with the correct diagnosis. Also, uncovering the true neural correlates of consciousness can also provide us with a deeper understanding of the conscious or unconscious mind. Both, NCC and advanced imaging techniques, are of vital importance to accurate diagnosis in patients with altered states of consciousness.

10.0 ACKNOWLEDGEMENTS

I would like to thank my mentor Prof.dr.sc. Goran Šimic, MD, PhD, for his supervision, enthusiastic support, and patience during the writing of this thesis. I am truly thankful to him for opening up my eyes to new areas in research within the field of neuroscience and the limitless opportunities he has extended. In addition, I would like to thank the rest of the committee members, Professor Mario Vukšić as well as Professor Zdravko Petanjek. I would also like to thank my mother, Ankica Salamunec, for being my rock in the roughest of waters and for reminding me "hard work giving result". Without her love and support, I would not be where I am today. Thank you also to my father, Franjo Salamunec and my sister Natalie Salamunec for always being there for me and providing love and support whenever needed. I would like to thank my extended family as well for supporting me. Most recently, I would like to thank my fiancé and future husband, Zvonimir Horvatic, for providing me with love, support and that extra boost in confidence whenever I needed it.

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12.0 BIOGRAPHY

This graduate thesis in the form of a review paper, is written by Stefanie Angela Salamunec. Stefanie was born on August 15, 1990 in Windsor, Ontario, Canada. She completed two years of Biochemistry as a major and Psychology as a minor at the University of Windsor before moving to Zagreb, Croatia to further her education at the University of Zagreb School of Medicine. In December of 2012, while in her second year of medicine, Stefanie was studying for a physiology exam when she came across something called “Cushing’s Disease”. She recognized many of those symptoms relating to her and immediately called her clinician in Canada to run some tests when she returned home. The results came back positive and she underwent surgery in February of 2013. For years prior to her discovery of Cushing’s Disease, her symptoms got progressively worse and she blamed it all on being in such a stressful career path. It was at this point, after everything Stefanie had been through, she realized her love for medicine and her eagerness to help others like herself; those that have been overlooked. She vowed to always listen to her patients and never stop questioning what if. In addition, Stefanie has always had a passion for Neurology and Neuroscience even at a young age and hopes to pursue further research in this field along with clinical duties. She hopes to combine and utilize what she has learned from her own experiences as a patient and a medical student in her future career as a medical doctor.