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The form of consciousness in brain & pathology and treatment of UWS

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Abstract. The study of consciousness, a fundamental aspect of human existence, spans neurobiology, brain science, and psychology. In nested hierarchies in the brain, consciousness is a confluence of wakefulness, arousal, and awareness. Disorders of consciousness, such as the Unresponsive Wakefulness Syndrome (UWS), present profound challenges in the medical domain. UWS patients experience severe disturbances in awareness and reactivity, often due to traumatic or non-traumatic brain injuries. Central to the debate on consciousness is the thalamus, a neural relay pivotal to cognitive function. Recent research emphasizes the thalamus's role in disorders like UWS, particularly when stemming from thalamic injuries. Novel thalamic interventions, like Deep Brain Stimulation (DBS) and Stereotactic Thalamotomy, have been explored for therapeutic potential, showing varying outcomes. The transition towards targeted thalamic treatments, underscored by advanced imaging insights, marks a shift in UWS therapeutic strategies. However, the intricacies of the thalamus and the heterogeneity of UWS necessitate a comprehensive and individualized approach. As researchers delve deeper, the thalamus stands central to potential breakthroughs in restoring consciousness in UWS patients.

Keywords: Araosal, Unresponsive Wakefulness Syndrome, Thalamic Damage, UWS Pathologies

1. Introduction

The study of consciousness primarily falls within the domains of neurobiology, brain science, and psychology. All the neurons and synapses in the brain build a nested hierarchy. This means every single electrical signal will gradually lie up, from a lower level to a higher level, to a more complex image [1,2]. Brain scientists, or neuroscientists, believe that consciousness is a "conscious subjective experience... A subjective awareness and experience, whether it is the sensory experience of the internal or external environment, or the subjective experience of feelings and thoughts, or simply the awareness of our being and of this being in the world."[3]. The broad concept of consciousness refers to the brain's response to the objective world, which shows a special academic phenomenon of psychology derived from philosophy, while the narrow concept of consciousness refers to people's awareness and attention to the outside world and themselves [4]. This literature review aims to delve deeper into the field of neurobiology and brain science to investigate the role of the posterior cortex in the formation and sustenance of consciousness. Consciousness is fundamental to human existence, as it underlies our perception and understanding of the world. It can be defined by two key features: wakefulness and arousal. Without wakefulness, consciousness cannot be achieved, as a clear and alert mind is necessary

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for the formation of awareness. These three concepts, Wakefulness, Arousal, and Consciousness, are considered independent, while awareness is above the other two and has a closer meaning to Consciousness. That is, if a person shows the presence of wakefulness or arousal, it does not necessarily prove that the individual has an awareness of the situation or condition externally [5]. In other words, consciousness does not necessarily occur when awakened, and it is not possible to be conscious without wakefulness.

2. Introducing Unresponsive Wakefulness Syndrome (UWS)

One common disorder of consciousness is unresponsive wakefulness syndrome (UWS), previously referred to as a vegetative state. UWS is the disease of rapid injury that resets the complex information processing capacity and reasoning ability of the human brain, such as the ability to form thoughts and conclusions, experience feelings and emotions, or recall memories from the past. Traumatic brain injury (TBI), cerebrovascular disease, and cerebral hypoxia are the most common causes of UWS [6]. In UWS, patients experience severe brain injury which results in a complete loss of subjective awareness and an inability to react to external stimuli. The central region of the thalamus plays a crucial role in stimulating wakefulness, while the posterior cortical thermal region, including the sensory region, is responsible for neurological awareness. This paper aims to explore the role of the posterior cortex and hypothalamus in the formation of consciousness, as well as the pathology and treatment of UWS.

2.1. ARAS System

To understand the function of arousal *further* more, *the* ascending reticular activating system (ARAS) is introduced into the theory. It is a functional component of a complex neural network in the reticular structure of the upper brainstem [7]. 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, all of which are the main ARAS nuclei involved in arousal [7]. Two major axes of the ARAS have taken over the function of activating the cortex to stimulate arousal: the thalamic pathway and the extrathalamic *pathway*. Activation of thalamic pathways promotes cortical arousal by facilitating transthalamic transmission of sensory information to the cerebral cortex [8]. Extrathalamic pathways activate the cortex through a series of direct inputs originating in the brainstem and basal forebrain, which together exert a major influence on arousal [8]. The reticular nucleus is a narrow, shell-like nucleus that surrounds the lateral border of the thalamus and extends from the rostral pole to the medulla and lateral geniculate nucleus. The TRN can receive input from the reticular formation and in turn projects to other thalamic nuclei. Since it can modulate the flow of information through the thalamus [9]. This section is considered to have *an* important role in all types of states of consciousness [10]. Since that's exactly needed in the formation of attention and consciousness, thalamus reticular nucleus leision might cause disturbance of consciousness of UWS patient.

2.2. UWS Pathologies

There are a variety of pathologies that can lead to UWS. The following is an overview of different types of trauma that can lead to UWS. According to neuropathological studies performed in patients with UWS, there are both traumatic and non-traumatic etiologies. This distinction is of great importance to utilize in clinical application. Patients with UWS caused by a TBI have better outcomes in terms of regaining independence (24% vs. 4%) and consciousness (52% vs. 13%) than patients with nontraumatic injuries (due to cerebral anoxia or stroke) [11]. In the human brain, the neocortex occupies a large part of the brain, covering the two cerebral hemispheres. The neocortex is responsible for a variety of functions. Therefore, injury to this area often results in the loss of certain cognitive abilities [12]. Neocortex lesions are very common after TBI. Approximate statistics show that 80% of UWS patients suffer this type of injury, which takes the form of cerebral contusions and ischemia [13]. Diffuse axonal injury is the most common abnormality in patients with UWS after TBI. It usually results from extreme acceleration and deceleration and causes mild to severe damage to axons at the border between gray and white matter in the brain [14]. Patients with severe DAI usually suffer from persistent loss of consciousness and exhibit the features of UWS. Few severe DAI patients heal and regain consciousness within the first year after injury. Hypoxic brain damage is caused by global cerebral ischemia due to cardiac arrest. It also has other reasons like near drowning, hanging, strangulation or poisoning with carbon monoxide. Clinical studies showed that 27% of patients with coma after hypoxia regained consciousness within 28 days, 9% remained in coma or unresponsive arousal syndrome, and 64% died [15]. And only 14 hypoxia patients had features of neuropathological damage. All patients had diffuse neuronal loss in the thalamus and hippocampus, and 71% to 86% had damage to the basal ganglia (caudate nucleus, putamen, globus pallidus), and 64% had diffuse damage in the neocortex. Although only a few patients were involved, it can be demonstrated that the thalamus was involved in all cases, highlighting the importance of the thalamus in consciousness formation.

2.3. Possible Treatments Existed

Unresponsive Wakefulness Syndrome (UWS), formerly known as a vegetative state, represents one of the most intricate challenges in modern neurology. This condition is characterized by a patient having intact wakeful periods but lacking any signs of awareness or purposeful interaction with their environment [16]. The profound disturbance in consciousness makes UWS a formidable therapeutic challenge, particularly when it stems from underlying thalamic injuries. The significance of the thalamus in cognitive function cannot be understated. It serves as a central relay for most sensory impulses, modulating and relaying them to appropriate cortical regions for further processing [17]. Furthermore, recent studies have highlighted the thalamus's role in maintaining and modulating consciousness, making it a critical area of interest for disorders like UWS [16,17].

The thalamus's relevance is further emphasized in cases where UWS is attributed to thalamic damage. Injuries to the thalamus, whether due to trauma, infarction, or other causes, can profoundly impact consciousness, even if other brain regions remain relatively.

The mesocircuit model, as proposed by Schiff [17], elucidates how disruptions in this region, particularly the central thalamus, can lead to profound consciousness disorders. Given the foundational role the thalamus plays in cognitive processes and its evident involvement in UWS cases arising from thalamic injuries, there's a compelling rationale to focus on thalamic interventions for treating UWS. Stereotactic thalamotomy [18], represents one of the potential therapeutic avenues. Similarly, other neuromodulatory techniques, such as deep brain stimulation, targeting the thalamus and its connecting pathways, may hold promise in restoring some level of awareness in UWS patients [19].

However, this focus on the thalamus is not without challenges. Given the thalamus's central role in processing a plethora of sensory inputs, interventions targeting this region must be precise to avoid unintended side effects [16]. The integration of advanced neuroimaging, as highlighted in the aforementioned studies, with therapeutic modalities is paramount to ensure targeted and effective treatment. In conclusion, Unresponsive Wakefulness Syndrome presents a formidable challenge for clinicians and researchers alike. The emerging understanding of the thalamus's role in consciousness and its disruption in UWS, especially in cases stemming from thalamic injuries, offers a new frontier in the quest for effective treatments. Leveraging insights from foundational works may pave the way for novel, effective interventions that can bring about meaningful improvements in the lives of UWS patients.

2.4. Pharmacological Interventions and Rehabilitative Therapies

Existing treatment methodologies for UWS span a range, from pharmacological interventions to rehabilitative therapies. However, the central role of the thalamus in mediating consciousness has prompted researchers to explore thalamic-centric interventions [17].

Deep Brain Stimulation (DBS) has emerged as a potential therapeutic modality, primarily due to its success in other neurological disorders like Parkinson's disease. By targeting the central thalamus, DBS aims to modulate neural circuits responsible for arousal and awareness. The underlying hypothesis, as proposed by Schiff [17], revolves around the mesocircuit model. This model underscores the critical role of the central thalamus in coordinating inputs and outputs vital for consciousness. Disruptions to this mesocircuit, through traumatic or non-traumatic brain injuries, can lead to disorders of consciousness like UWS.

Another intriguing intervention is Stereotactic Thalamotomy. Historically employed for pain control in thalamic syndrome patients, its potential applicability to UWS emerges from the fundamental idea of modulating thalamic activity [18]. By selectively ablating a portion of the thalamus, the procedure seeks to restore some of the lost functional connectivity associated with UWS.

While both DBS and Stereotactic Thalamotomy present promising avenues, patient outcomes vary. Some UWS patients undergoing DBS have shown signs of improved arousal and even sporadic responsive behaviors. However, the precise determinants of success remain elusive, and not all patients benefit uniformly [17].

Stereotactic Thalamotomy, on the other hand, remains in its nascent stages of application for UWS. Preliminary findings, extrapolated from its success in thalamic pain syndromes, hint at possible positive outcomes. Yet, a comprehensive understanding necessitates further rigorous clinical trials.

The focus on thalamic interventions in UWS treatment brings forth a paradigm shift from a more generalized approach to a targeted one. Laureys, Owen, and Schiff [16] emphasized the nuanced brain activities in UWS, particularly in the thalamus, as evidenced by advanced imaging. These findings bolster the rationale for thalamic-targeted therapies.

However, challenges persist. The heterogeneity of UWS causes, coupled with individualized brain injury patterns, means a one-size-fits-all approach is untenable. Furthermore, while our understanding of the thalamus has grown, it remains an intricate structure with functions yet to be fully unraveled.

The quest to restore consciousness in UWS patients is fraught with challenges but buoyed by relentless scientific endeavor. Thalamic interventions like DBS and Stereotactic Thalamotomy offer promising horizons, but their full potential and applicability are still under exploration. Guided by pioneering works such as those by Schiff [17] and Laureys et al. [16], the future holds promise, with the thalamus at the epicenter of this therapeutic revolution.

3. Conclusion

Understanding how the brain of patients with Unresponsive Wakefulness Syndrome (UWS) undergoes plastic changes to recover consciousness is crucial yet challenging due to our limited knowledge in this area. The brain regions responsible for consciousness are not as well-defined as those for other systems, like the motor system. Nevertheless, certain areas are believed to play specific roles in consciousness [20], but their interactions in both healthy and pathological states remain enigmatic.

The neocortex, responsible for critical cognitive functions in a fully aware state, is central to these discussions. The degree of cortical dysfunction can indicate the level of consciousness impairment [20-24]. Recovery of consciousness, hence, requires plastic changes in cortical areas. Two primary mechanisms for brain remodeling post-injury have been identified: spontaneous reorganization and training-induced recovery.

In vitro studies have shown that oxygen and glucose deprivation can induce a long-term enhancement in synaptic transmission, termed post-ischemic long-term potentiation (i-LTP) [25]. The possible beneficial or detrimental roles of i-LTP are still debated. Some believe i-LTP might be linked to delayed neuronal death near ischemic regions [26], while others suggest it aids cortical circuit reorganization, leading to functional recovery post-brain injury [27]. A notable player in spontaneous recovery is the brain-derived neurotrophic factor (BDNF). Following brain injuries, BDNF production increases, facilitating synaptic efficacy modulation pivotal for memory, learning, and adaptive behaviors [28,29]. Intriguingly, even with the apparent importance of BDNF, a study revealed that the Val66Met BDNF polymorphism did not significantly affect consciousness recovery 12 months post-injury [30].

Experience-induced plasticity is another avenue for recovery. Studies in animal models have shown that environmental enrichment can promote the formation and maturation of new neurons, synapse remodeling, and enhanced neuronal signaling [31-34]. Such enrichment, especially when initiated early post-injury, can significantly improve recovery outcomes [35].

Lastly, there’s a growing understanding of the role of inhibitory circuits in experience-dependent plasticity and recovery. For instance, after traumatic brain injuries, there’s a notable shift in excitatory/inhibitory dynamics [36]. Imbalances between excitatory and inhibitory circuits, as seen post-stroke, can influence recovery [37]. Reductions in inhibitory transmission might pave the way for beneficial plastic changes, aiding in recovery [38,39]

In summary, while our grasp on the mechanisms of plastic changes for consciousness recovery is still evolving, studies emphasize the neocortex’s role, the potential of i-LTP, the significance of BDNF, and the intricacies of excitatory and inhibitory circuit dynamics.

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