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Vagus Nerve Stimulation and Right Median Nerve Stimulation in the Treatment of Coma: A Review of Previous Studies, Mechanisms of Action, and Future Potentials

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Abstract

Disorders of consciousness affect a large percentage of patients with brain trauma, and diagnosed patients face a high mortality rate. Recently though, two types of nerve stimulation have proved promising effects: vagus and right median nerve stimulation. Because of their extensive projections throughout the regions of the brain responsible for consciousness, the vagus and right median nerves have been targeted for studies of nerve stimulation in the treatment of coma and have proven effective in improving the states of consciousness in comatose patients. Although complete mechanisms are still unknown, many studies have corroborated the idea that delivering electrical pulses through such stimulation can elevate levels of brain activity in the stagnant coma-state brain, especially in sleep-wake cycle related brain regions such as the reticular activating system, locus coeruleus, parietal cortex, and thalamus. By activating the neurons in these parts of the brain, neural pathways — noradrenergic, cholinergic, GABAergic, dopaminergic, and orexin pathways — are enhanced. These pathways have shown to interact with each other in a complex manner still not yet thoroughly explored, but have proven to collectively increase arousal in coma patients. Furthermore, nerve stimulation seems to have positive effects on the physiological healing of the brain from traumatic brain injury, one of the root causes of coma, through increasing cerebral blood flow. Taken together, these studies point towards right median and vagus nerve stimulation as a promising treatment that can help better the outcome of coma.

Keywords: Coma, Nerve Stimulation, Vagus Nerve, Right Median Nerve, Cctivation, Reawakening

1. Introduction

A disorder of consciousness is defined as a deviation from the normal state of consciousness, typically caused by any form of damage to the brain. There are three major states of consciousness– coma, persistent vegetative state, or minimally conscious state. Firstly, the medical dictionary defines the coma state as "state of extreme unresponsiveness, in which an individual exhibits no voluntary movement or behavior"(Miller-Keane, 2003). If the patient has not regained consciousness after 2-4 weeks, the disorder may either progress into a persistent vegetative state (PVS) or minimally conscious state (MCS), or remain in a coma state. In PVS, a patient is awake but unaware of their personal state or surroundings; in MCS, a patient is awake and shows inconsistent but clear signs of being aware.

There are multiple ways to measure one's level of consciousness through assessing physical signs of wakefulness. In order to quantify these signs and symptoms, researchers use the Glasgow Coma Scale (GCS). This scale was developed by Professors Graham Teasdale and Bryan Jennette in 1974, and

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has since been the most popular method of quantifying coma severity. The GCS tests eye opening on a scale of 1-4 points, verbal responses on a scale of 1-5 points, and motor responses on a scale of 1-6 points. An overall GCS of 8 or less is classified as severe coma state, 9-12 as moderate, and 13-15 as mild (Magee, 2021). GCS is used in a clinical setting to diagnose patients as well as used in multiple studies of coma treatment to effectively quantify improvement in consciousness following nerve stimulation.

Another means of quantifying consciousness is through the JFK Coma Recovery Scale-Revised (CRS-R), initially discovered by Giacino in 1991 (Giacino and Kalmar, 2006). This scale also assesses auditory, oromotor, communication (including visually or aurally based forms), and arousal functions in addition to the responses already monitored by the GCS (Giacino and Kalmar 2004). CRS-R is more commonly used in traumatic brain injury and such related studies, as it provides a more comprehensive view of consciousness and the improvement thereof (Giacino and Kalmar, 2006).

One of the most common causes of coma is traumatic brain injury (TBI), which is an injury to the brain caused by external forces. TBI can result in brain lesions, hemorrhage, compression and depression that may cause damage to the consciousness-related brain regions, namely the reticular activating system (RAS), locus coeruleus (LC), thalamus, and the multiple regions of the cortex. Damage to these regions may disturb the pathways which regulate wakefulness, potentially leading to brain-wide malfunctioning in the form of a coma. Speculation about motivating brain activity in these areas to restore original function are used as a basis for coma treatment studies.

The prognosis of coma largely depends on the length of coma as well as the depth of consciousness as measured by state of consciousness (PVS or MCS) and the GCS and/or CRS. The longer time in the coma state and the deeper the coma, the less likely a full recovery will be made (Faugeras, 2018). 1 out of 8 traumatic brain injury patients fall into a coma, and face a fatality rate of 30-90% depending on the presence of accompanying signs (Firsching, 2017; Lombardi, et al., 2002). And only 13% of TBI patients with a GCS of 3 or less achieved a good functional outcome after six months (Chamoun, et al., 2009). Given the slim chances of awakening and full recovery, and the number of people with disorders of consciousness, searching for effective and safe treatment options is crucial.

2. Nerve Stimulation

Nerve stimulation has been used for hundreds of years to treat various mental disorders including depression, seizures, and now potentially, disorders of consciousness. This involves the stimulation of specific nerves to activate widespread neuron firing within the target region and its surrounding areas. When an individual is in a coma, the brain is functioning at its lowest stage of alertness, so the goal of nerve stimulation is to increase brain functioning by activating neural activity to regain consciousness (Universitat Pompeu Fabra, 2019). However, in order to ensure efficacy of nerve stimulation, specific nerves chosen for the stimulation process need to be extensive, but also selectively targeted towards the specific wakefulness-promoting regions of the brain. In addition, many studies utilize functional magnetic resonance imaging (fMRI), positron emission tomography (PET) scans, and monitoring of cerebral blood flow (CBF) as means to measure and track these changes in neural activity in different regions of the brain in order to determine improvement in nerve-stimulated consciousness.

2.1 Vagus Nerve Stimulation

Vagus nerve stimulation has been used as a reliable and tested means to treat epilepsy since its FDA approval in 1997; recent studies, however, have revealed the vagus nerve as a promising site to deliver nerve stimulation to comatose patients. The vagus nerve is the longest of the 12 cranial nerves of the body, extending from the medulla oblongata of the brainstem to the colon. The vagus nerve is also connected to many organs in the body, and is important in carrying sensory information from these organs to the brain. In order to carry out this important function, the vagus nerve has extensive

projections from the medulla oblongata in the hindbrain to consciousness- regulating brain regions in the mid and forebrain areas. This makes the vagus nerve a strong candidate as stimulation of this nerve may activate multiple cortices of the brain that help to contribute towards increased arousal.

Vagus nerve stimulation is usually initiated via a minimally invasive procedure to implant a device. Firstly, a small incision is made on the left side of the chest for the pulse generator and on the collarbone where the thin wires and electrodes are placed to connect the generator to the vagus nerve, thus allowing for electrical impulses to be sent to the nerve. Nerve stimulation intensity and intervals are determined by the programming of the pulse generator, and are usually determined by doctors monitoring the patient.

In the first reported case study of vagus nerve stimulation, a 73 year old female patient remained in a VS for 50 days following respiratory and cardiac arrest and unsuccessful cardiopulmonary resuscitation. Three doctors who were not a part of the study assessed the patient using the CRS-R and the average of the two closest scores were taken to determine the starting level of consciousness. VNS was then implemented twice per day, lasting 20 minutes each session, for a total duration of one month. fMRI revealed activation of the thalamus and posterior cingulate precuneus, brain structures responsible for memory and visuospatial processing, following vagus nerve stimulation. Increased connectivity between the aforementioned regions and the ventral medial prefrontal cortex and superior temporal gyrus was also observed post-VNS, which may indicate increased cognitive and auditory processing, respectively. At the end of the treatment, although complete consciousness was not restored, the patient showed promising signs of increased wakefulness, including a diagnosis from vegetative to the minimally conscious state and an increase from 6 to 13 on the CRS-R (Yu, et al., 2017).

The results of this case study are supported by another study conducted on in vivo mouse models. This study used calcium imaging to measure the activity of neurons across the cortex of the brain following vagus nerve stimulation. Stimulation of the vagus nerve caused widespread activation of neurons in visuospatial processing regions like the medial to lateral somatosensory, motor and retrosplenial cortical regions (Collins, et al., 2021). Responses in these regions of the brain were found to be positively correlated with signs of wakefulness, such as whisker movement. Taken together, these results suggest that vagus nerve stimulation can be used to increase brain activity in the sensorimotor cortices of the brain, as well as improve both clinical and physical signs of arousal in coma patients. Further studies corroborate these findings, and even suggest that vagus nerve stimulation can also facilitate healing from traumatic brain injury (Shi, et al., 2013).

In a more recent study, patients above 17 years old diagnosed with severe TBI were given VNS up to 0.5 mA for an eight week period for up to 4 hours daily to increase wakefulness. 60% of the patients in the study exhibited over a 3 point improvement in the CRS-R score. As seen in past studies, there were no adverse side effects present in any of the patients, other than mild skin irritation of the stimulation spot. (Hakon, et al., 2020; Kreuzer, et al., 2012) Preclinical trials have assessed and confirmed cardiac safety when performing nerve stimulation (Kreuzer, et al., 2012), and multiple studies also support the safety of VNS usage (Redgrave, et al., 2018). With that being said, the efficacy of VNS in treating comatose patients are still being tested today in hopes of its implementation into coma treatment (Vitello, et al., 2023; Noe, et al., 2019).

2.2 Right Median Nerve Stimulation

The right median nerve is yet another potential target for stimulation in the treatment of coma. This nerve is both a sensory and motor nerve which stems from the lateral and medial cords of the brachial plexus, a network of nerves in the neck, and runs through the upper and lower spinal cord before finishing at the hands and fingers (Cleveland Clinic, 2021). Stimulation typically occurs via the placement of electrodes in the forearm. These electrodes are then controlled by a device which sends electrical pulses of different amplitudes and intensities through the electrodes to stimulate right median nerve connected structures (Lei, et al., 2015).

The first study utilizing the right median nerve to

hasten awakening from coma was conducted by researcher J. Bryan Cooper of the East Carolina University School of Medicine in 1998. The right median nerve was targeted because of clinical observations of increased alertness and increased activity in the Broca's area (an area important for speech production) following right median nerve stimulation. A group of 6 patients, each having been in a coma for at least 3 months due to traumatic brain injury, were admitted to the study. Patients were stabilized, and given a score of 4-8 on the Glasgow Coma Scale prior to right median nerve stimulation. Patients were then randomly assigned to either control or treatment group; the procedure was double blind in order to minimize bias. Rubber electrodes were then placed on the experimental patients' right distal forearm as a direct pathway to the brain via the right median nerve. 8 or 12 hours of stimulation was implemented daily for 2 weeks. At the end of the stimulation period, measurement of consciousness was quantified by two major factors: GCS scores and days spent in the intensive care unit (ICU). Patients who received right median stimulation had an average GCS improvement of 4.0 while patients who did not receive right median stimulation had an average of 0.7, indicating a significant difference and providing evidence of right median nerve stimulation's effect in increasing arousal. ICU results further confirmed the conclusions from the GSC scores; patients who received stimulation treatment stayed in the ICU on average 10 days less than patients in the control group (Cooper, et al., 1999).

Much like the vagus nerve, the right median nerve shows connectivity with the reticular activating system (a sleep-wake regulating structure in the brain), and therefore may be an effective target for nerve stimulation to hasten awakening from coma (Peri, et al., 2001).

More comprehensive studies have started looking into the means behind right median nerve stimulation's effectiveness. A concept of measuring cerebral blood flow (CBF), which indicates potential enhancement of metabolism and brain activity throughout the brain, was applied to and measured in right median nerve stimulation patients before, throughout and after stimulation. It was seen that in patients who received right median nerve stimulation, there was a significant increase in CBF compared to patients in the control group (Liu, et al., 2003), suggesting right median nerve stimulation's overall effectiveness in increasing brain activity.

Another study provided evidence of which specific regions were activated by such stimulation. In the study, 10 healthy male patients underwent right median nerve stimulation at multiple frequencies, ranging from 0.2 to 20 Hz. PET scans were taken every 10 minutes to monitor CBF as a metric for changes in neural activity in different regions of the brain. It was found that there was a significant increase in CBF in the sensorimotor and parietal cortices at a frequency of 4 Hz. Nearby sulci and gyri, namely the central sulcus (a brain structure important in transporting blood the lateral brain that allows it to function) and the sylvian fissure also saw an increase in CBF (Ibanez, et al., 1995; Griffiths, et al., 2010). These results are significant because they identify regions of the brain activated by stimulation, help researchers form hypotheses of the mechanisms behind stimulation, and suggest potential pathways to target in the treatment of coma.

Throughout multiple studies, traumatic brain injury patients in the comatose state have responded positively to right median nerve stimulation with increase in Glasgow Coma and JFK-CRS-R scores, (Lei, et al., 2015; Sharma, et al., 2015; Straughn and Denais, 2019), physical signs of arousal (Liu, et al., 2003), and in some cases even the regaining consciousness (Liu, et al., 2003; Lei, et al., 2015). A more recent study examined the effect of right median nerve stimulation on comatose patients suffering from heavy TBI. These patients received two weeks of nerve stimulation along with standard treatment which resulted in increased brain functioning and early awakening in these patients (Jia, et al., 2022).

3. Mechanisms of Action

As both vagus nerve and right median nerve stimulation target similar areas of the brainstem and forebrain such as the reticular activating system, locus coeruleus, thalamus, and cortex; both use and produce similar effects at a neural activity level. Many of these different neurotransmitter pathways

overlap with one another (due to their proximity within the aforementioned target regions) in a complex manner that is still not completely understood today. However, studies have slowly begun to reveal the potential mechanisms of action with how these pathways work to regulate consciousness, and the effects of nerve stimulation in modulating these pathways.

3.1 Norepinephrine

Norepinephrine has long been associated with increased wakefulness and attention (Larner, 2002). Therefore, both vagus and right median nerve stimulation are able to regulate and increase consciousness by producing an acute increase in norepinephrine levels in the cortical and hippocampal regions of the brain (Follesa, et al., 2007; Lei, et al., 2015; Kayama and Koyama, 1998). This response may be explained by the vagus nerve's projections to the nucleus tractus solitarii (NTS) in the medulla, which then projects to other areas including the locus coeruleus, the main production center of norepinephrine (Cooper, et al., 1999; Berger, et al., 2021). Once the locus coeruleus is activated by nerve stimulation, norepinephrine is released from this small but extensive brain structure to the rest of the brain and spinal cord, thus helping to increase overall wakefulness (Schwarz and Luo, 2015).

3.2 Acetylcholine

Additional studies show how exactly this happens via interactions between norepinephrine and acetylcholine: norepinephrine from the locus coeruleus is released through its projections and onto the basal forebrain. As norepinephrine is released, it binds to the adrenergic receptors on the cholinergic neurons and activates them. Activation of these cholinergic neurons occurs when the locus coeruleus neurons are active in order to activate cholinergic cells, which occurs during periods of waking (Jones, 2004). So when these norepinephrine-activated cholinergic cells then rapidly fire, they release acetylcholine from the basal forebrain. This release allows for information exchange between the thalamus and the cortex, and induces widespread cortical activity to increase wakefulness (Vazquez and Baghdoyan, 2001; Cooper, et al.,1999). Note that both of these studies demonstrate right median nerve stimulated increase in activity within the thalamocortical regions of the brain which have been correlated with increased consciousness (Steriade, 1981), while inactivation in these corresponding areas has promoted the onset of sleep (Magnin, et al., 2010). Right median and vagus nerve stimulation induces a norepinephrine-modulated acetylcholine release from the reticular activating system, which may play a key role in regulation of activity in the thalamus and its projections into the cortical regions, promoting overall wakefulness and sensorimotor processing.

3.3 Orexin

Another neural pathway involves orexin and orexin-producing neurons located in the lateral hypothalamic area, which interact with monoamine pathways present in regions of the brain activated via nerve stimulation where important sleep-wake cycle regulating regions reside (Sakurai, 2007).

More specifically, there are two types of orexin neuropeptides, orexin-A and orexin-B, both of which are released in the lateral hypothalamus and once bind to their receptors, orexin receptor 1 / oxrein receptor 2 (OXR1/2), promotes wakefulness possibly by its connections to monoaminergic systems as previously mentioned. Because the vagus nerve connects indirectly to the lateral hypothalamus via the nucleus tractus solitarii and parabrachial nucleus (Barry and Eleni, 2022), studies have hypothesized and shown that stimulation of the vagus nerve would cause an upregulation of orexin-A to bind to OXR1 within those parts of the brain to promote wakefulness (Wang, et al., 2018; Dong and Feng, 2018; Dong and Papa, 2018). More comprehensive results show that 1) when OXR1 receptors are blocked with an antagonist, rats tend to wake up less from comas despite vagus nerve stimulation, and 2) orexin-A is upregulated immediately following traumatic brain injury and loss of consciousness (Wang, et al., 2018).

Further research demonstrates how right median nerve / median nerve stimulation promotes arousal from coma by these same orexin mechanisms (Chen, et al., 2018), potentially through stimulation of regions of the brain namely the reticular activating system and intralaminar nuclei of the thalamus (Zhong, et al., 2015; Feng and Du, 2016). These findings indicate the importance of the orexin-A and OXR1 in the brain's natural attempts at reawakening, and nerve stimulation's role in upregulation of these neuropeptides. There have been additional studies that have shown, however, that OXR2 and dual orexin receptor antagonists, and not only OXR1 antagonists alone, inhibit wakefulness; this suggests the importance of both neuropeptides and their receptors in increasing consciousness (Kalogiannis, et al., 2011**).**

Some combination of OX1R and OX2R mRNA, which codes for the different orexin receptors, were expressed in cholinergic, noradrenergic, GABAgernic and serotonergic neurons, indicating orexin importance in regulation of these monoamine neural activity (Mieda, et al., 2011), and suggesting the possibility of maintaining consciousness through modulation of orexin expression/orexin release to regulate wakefulness related monoaminergic/ cholinergic pathways (Mieda, et al., 2004).

3.4 GABAergic Pathways

There has also been speculation regarding the interconnectivity between cholinergic and GABAergic neurons in the basal forebrain in which both are located near each other and stimulation of cholinergic neurons also caused firing of GABAergic neurons (Yang, et al., 2014). Some studies hypothesize that cholinergic and related monoamine pathways inhibit GABAergic neurons to promote wakefulness (Jones, 2004). Still, more recent studies corroborate the opposite, that these cholinergic and noradrenergic pathways increase GABA function to produce the same effects (Zank, et al., 2016); although both studies seem contradictory, their results do suggest the same hypothesis that GABA neurons play a more extensive role in regulating consciousness than previously thought to have played, debunking the idea that its only function is the inhibition of all other neural activity. However, a more recent study may suggest a way to corroborate both these findings: depending on where GABAergic neurons are active, this may either promote or inhibit wakefulness. Through a combination of viral tracing, circuit mapping, electrophysical recordings, and optogenetics in mice, researchers found that GABAergic neurons in the lateral hypothalamus selectively inhibit certain GABAergic neurons whilst allowing a large portion of the uninhibited neurons in the dorsal raphe nucleus fire, thereby promoting arousal (Gazea, et al., 2021; Cai, et al., 2022). The opposite is also true: an inhibition of GABAergic neurons in the hypothalamus would result in its inability to interact with GABAergic neurons in the dorsal raphe nucleus and a reduction in wakefulness (Huang, et al., 2020).

3.5 Dopamine and Serotonin Parallel Functioning

Additionally, another neurotransmitter known as dopamine functions similarly to norepinephrine in maintaining wakefulness, arousal, and attention. Consistent overlaps in the two neural pathways have led researchers to hypothesize the parallel functioning between the two neurotransmitters, as dopamine is also released from the locus coeruleus as a cotransmitter to norepinephrine (Slamloo and Fazlali, 2020). Further research has correlated right median nerve stimulation with increased levels of dopamine that contribute to an increase in arousal in comatose patients (Jia, et al., 2022).

In another study, serotonin is demonstrated to work in opposition with dopamine and norepinephrine functions. Mutant mice that don't express the serotonin gene for the serotonin receptor (meaning serotonin responses were inhibited) were demonstrated to have a greater amount of REM sleep and decreased slow wave sleep. These signs of increased consciousness and decreased serotonin release may be related to increased release of norepinephrine and dopamine (Monti, 2010). Additional electrophysiological data show that serotonin can exert inhibitory effects on dopamine – parallel to increased levels of dopamine that coupled

with a decreased serotonin response – both directly and potentially indirectly through modification of GABAergic signals (Giovanni, et al., 2008). Again, these are loosely related observations that suggest a potential in targeting different neurotransmitters through drug therapy in treatment of coma.

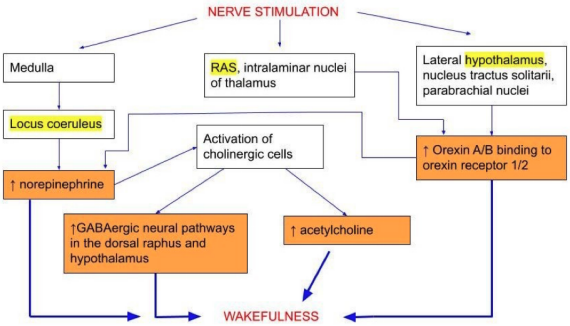

Figure 1. A physical representation of the multiple pathways activated by nerve stimulatin that lead to wakefulness. Highlighted are brain regions crucial in the regulation of consciousness, and the orange boxes are the distinct pathways aforementioned.

4. Physiological Responses to Nerve Stimulation

Nerve stimulation also facilitates physiological responses which aid the physical healing of the brain from traumatic brain injury, the root cause of coma and disorders of consciousness. Some studies suggest that this healing is due to increases in cerebral blood flow immediately following vagus / right median nerve stimulation to different areas of the brain (Ibanez, et al., 1995; Liu, et al., 2003; Cooper, et al., 1999; Schiff, 2008; Henry, et al., 1998). As the blood delivers glucose to the brain, that glucose is metabolized by neurons for energy and used to send neural impulses, which may aid increased wakefulness and eventual recovery from coma. One such neural pathway activated by increased cerebral blood flow is the initiation of release of acetylcholine via vagus nerve stimulation, which inhibits an inflammatory response in the brain and promotes arousal from coma (Shi, et al., 2013; Collins, et al., 2021). This anti-inflammatory effect of vagus nerve stimulation as shown in multiple studies (Neren, et al., 2015; Bonaz, et al., 2013; Liu, et al., 2020) has been used in treatment of traumatic brain injury, which makes using it in the treatment of coma the logical subsequent step. Lowering swelling in the brain via nerve stimulation would allow for the brain to heal and regain functioning consciousness.

5. Discussion

Disorders of consciousness are highly common and devastating conditions for both the patients and their families. However, at the moment, there is still no approved definitive treatment for a comatose patient; the general protocol is to try to reverse the coma and reawaken the patient using the help of medication (MayoClinic 2020). Recent studies have shown potential, however, in the treatment of coma via nerve stimulation to deliver pulses to activate regions of the brain connected to the selectively targeted right median and vagal nerves. Mechanisms include general increased brain metabolism, connectivity and functioning via neural pathways (mainly noradrenergic and cholinergic pathways), all of which interconnect with each other, though exact interactions between these mechanisms and how they work together to promote consciousness are still unclear.

With nerve stimulation's potential, also comes more factors that should be thoroughly tested and resolved before its approval in a clinical setting. The first factor being the actual efficacy in its treatment of all comas; the longer a patient is in a coma, generally the more severe the coma is and therefore harder it is to stimulate reawakening (Sherer, et al., 2008). In many of these studies, patients have been in comas for at least several months and although subjects have demonstrated signs of increased consciousness and brain activity, a percentage of coma patients within these studies still have yet to make a complete recovery in regaining consciousness. This suggests the potential in longer stimulation periods to aide in the full recovery of coma; however, that in and of itself also entails complications; long term nerve stimulation, especially in vagus nerve stimulation where the stimulator is installed surgically, causes side effects including nerve damage, cognitive side effects, paresthesias, etc. (Ben-Menachem, 2001). Furthermore, although nerve stimulation may help trigger signs of consciousness with TBI-induced

comas, it has not proved as effective when treating coma caused by other factors such as hypoxia (Liu, et al., 2003). However, these side effects are rare and only present in extreme cases. When used in the short term, multiple studies have come to the consensus that vagus and right median nerve stimulation are safe, low-cost, and an effective means to increase wakefulness in comatose patients (Straughn and Denais, 2019; Hakon, et al., 2020)

Researchers continue to explore the safety and efficacy of right median and vagus nerve stimulation for recovery of consciousness on a wider level. One of which the ACES Trial studying right median nerve stimulation in which 360 patients from the neurocenters of China, India, Nepal and Kazakhstan will undergo nerve stimulation treatment. Results have still yet to be published, but if successful will provide the evidence needed to implement its widespread usage in hospitals across Asia and potentially across the globe (ACES, 2016). Similar trials on a smaller scale are being conducted for vagus nerve stimulation (Vitello, et al., 2023; Noe, et al., 2019). Studies exploring the potential of nerve stimulation as a whole in the treatment of coma have continued, including other stimulation types such as spinal cord stimulation and deep brain stimulation (Bai, et al., 2017; Rezaei Haddad, et al., 2019). nerve stimulation has the potential to activate or inhibit these complex systems in order to promote arousal and even reawakening from coma.

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References

American Association of Neurological Surgeons. (n.d.). Vagus nerve stimulation. https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Vagus-Nerve-Stimulation

Asia Coma Electrical Stimulation (the ACES Trial) (ACES). (2016, January 1). NIH U.S. National lIbrary of Medicine — ClinicalTrials.gov. Retrieved December 18, 2022, from https://clinicaltrials.gov/ct2/show/study/NCT02645578.

Awareness. (2003). Retrieved April 28th, 2020, from https://medical-dictionary.thefreedictionary.com/awareness

Bai Y., et al. (2017, March) Spinal cord stimulation modulates frontal delta and gamma in patients of minimally consciousness state. Neuroscience. https://doi.org/10.1016/j.neuroscience.2017.01.036.

Ben-Menachem, E. (2001). Vagus nerve stimulation, side effects, and long term safety. PubMed. https://doi.org/10.1097/00004691-200109000-00005

Berger, A., et al. (2021, December 2). How is the norepinephrine system involved in the antiepileptic effects of vagus nerve stimulation? https://doi.org/10.3389/fnins.2021.790943

Bonaz, B., et al. (2013) Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway. *Neurogastroenterology & Motility, 25(3),* 208-221. https://doi.org/10.1111/nmo.12076

Cai, P., et al. (2022) Regulation of wakefulness by GABAergic dorsal raphe nucleus-ventral tegmental area pathway. *Sleep, 45,* 235. https://doi.org/10.1093/sleep/zsac235

Chamoun, R.B., Robertson, C.S., & Gopinath, S.P. (2009) Outcome in patients with blunt head trauma and a Glasgow Coma Scale score of 3 at presentation. J Neurosurg. https://doi.org/10.3171/2009.2.JNS08817

Chen, Y. H., et al. (2018) Median nerve stimulation induces analgesia via orexin-initiated endocannabinoid disinhibition in the periaqueductal gray. https://doi.org/10.1073/pnas.1807991115

Cleveland Clinic. (2021, September 24). Median nerve. Cleveland Clinic. https://my.clevelandclinic.org/health/body/21889-median-nerve

Collins, L., et al. (2021). Vagus nerve stimulation

induces widespread cortical and behavioral activation. Current Biology. https://doi.org/10.1016/j.cub.2021.02.049.

Coma. (2020, November 20). Retrieved April 22, 2022, from https://www.mayoclinic.org/diseases-conditions/coma/diagnosis-treatment/drc-20371103

Cooper, J. B., et al. (1999, April). Right median nerve electrical stimulation to hasten awakening from coma. PubMed. https://doi.org/10.1080/026990599121638

Dong, X. Y., et al. (2018). Vagus nerve stimulation causes wake-promotion by affecting neurotransmitters via orexins pathway in traumatic brain injury induced comatose rats. International Journal of Clinical and Experimental Medicine. https://e-century.us/files/ijcem/11/5/ijcem0067767.pdf

Dong, X.Y. & Feng Z. (2018, February) Wake-promoting effects of vagus nerve stimulation after traumatic brain injury: upregulation of orexin-A and orexin receptor type 1 expression in the prefrontal cortex. Neural Regen Res. https://doi.org/10.4103/1673-5374.226395.

Faugeras, F., et al. (2018) Survival and consciousness recovery are better in the mttpinimally conscious state than in the vegetative state, Brain Injury, 32:1, 72-77, https://doi.org/10.1080/02699052.2017.1364421

Feng, Z., & Du, Q. (2016, June). Mechanisms responsible for the effect of median nerve electrical stimulation in traumatic brain injury-induced coma: Orexin-A-mediated N-methyl-D-aspartate receptor subunit NR1 upregulation. PubMed. https://doi.org/10.4103%2F1673-5374.184494

Firsching, R. (2017, May 5). Coma after acute head injury. PubMed. https://doi.org/10.3238/arztebl.2017.0313

Follesa, P., et al. (2007). Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. PubMed. https://doi.org/10.1016/j.brainres.2007.08.045

Gazea, M., et al. (2021) Reciprocal Lateral Hypothalamic and Raphe GABAergic Projections Promote Wakefulness. *Journal of Neuroscience 2, 41(22),* 4840-4849. https://doi.org/10.1523/JNEUROSCI.2850-20.2021

Giacino, J & Kalmar, K. (2006). Introduction to the JFK Coma Recovery Scale-Revised (CRS-R). The Center for Outcome Measurement in Brain Injury. http://www.tbims.org/combi/crs

Giacino, J. T., & Kalmar, K. (2004). CRS-R coma recovery scale-revised - administration and scoring guidelines. SRALAB. https://www.sralab.org/sites/default/files/2017-06/coma%20recovery%20scale%20-%20revised%20%28crs-r%29.pdf

Giuseppe, G. D., et al. (2008) Serotonin-dopamine interaction: electrophysiological evidence. In Giuseppe, G. D., et al. (Eds.), Progress in Brain Research. (pp. 45-71). https://doi.org/10.1016/S0079-6123(08)00903-5.

Griffiths, P. D., et al. (2010) Section 1 - Surface Anatomy of the Brain. Atlas of Fetal and Postnatal Brain MR (Pages 7-34) https://doi.org/10.1016/B978-0-323-05296-2.50004-7.

Hakon, J., et al. (2020) Transcutaneous Vagus Nerve Stimulation in Patients With Severe Traumatic Brian Injury: A Feasibility Trial. *Neuromodulation: Technology at the Neural Interface, 23,* 721-892. https://doi.org/10.1111/ner.13148

Henry T. R., et al. (1998, September) Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: I. Acute effects at high and low levels of stimulation. Epilepsia. https://doi.org/10.1111/j.1528- 1157.1998.tb01448.x.

Huang, Y., Li, Y., Leng, Z. W. (2020) Melatonin inhibits GABAergic neurons in the hypothalamus consistent with a reduction in wakefulness. *NeuroReport, 31(2),* 92-98. https://doi.org/10.1097/WNR.0000000000001374

Ibáñez, V., et al. (1995, October) Effects of stimulus rate on regional cerebral blood flow after median nerve stimulation. Oxford Academics. https://doi.org/10.1093/brain/118.5.1339

Jia, Y., et al. (2022) MicroRNA alteration in cerebrospinal fluid from comatose patients with traumatic brain injury after right median nerve stimulation.
https://doi.org/10.1007/s00221-022-06414-7

Jones, B. E. (2004). Activity, modulation and role of basal forebrain cholinergic neurons innervating the cerebral cortex. In L. Descarries, K. Krnjevic, M. Steriade (Eds.), Acetylcholine in the Cerebral Cortex (pp. 157–169).
ScienceDirect.
https://doi.org/10.1016/s0079-6123(03)45011-5

Jones, B. E. (2004). Activity, modulation and role of basal forebrain cholinergic neurons innervating the cerebral cortex. PubMed.
https://doi.org/10.1016/S0079-6123(03)45011-5

Kalogiannis, M., et al. (2011, April 13). Cholinergic modulation of narcoleptic attacks in double orexin receptor knockout mice. PLOS One Journals.
https://doi.org/10.1371/journal.pone.0018697
Kayama, Y., & Koyama, Y. (1998). Brainstem Neural Mechanisms of Sleep and Wakefulness. Karger.
https://doi.org/10.1159/000052235

Komisaruk B. R., & Frangos E. (2022) Vagus nerve afferent stimulation: Projection into the brain, reflexive physiological, perceptual, and behavioral responses, and clinical relevance. Autonomic Neuroscience.
https://doi.org/10.1016/j.autneu.2021.102908.

Kreuzer, P. M., et al. (2012) Transcutaneous vagus nerve stimulation: retrospective assessment of cardiac safety in a pilot study.
https://doi.org/10.3389/fpsyt.2012.00070

Larner A. J. (2002, November) Neurochemistry of consciousness: Neurotransmitters in mind. (Brain, Volume 125, Issue 11, Pages 2581–2582).
https://doi.org/10.1093/brain/awf244

Lei, J., et al. (2015, October 15). Right median nerve electrical stimulation for acute traumatic coma patients. PubMed.
https://doi.org/10.1089/neu.2014.3768
https://pubmed.ncbi.nlm.nih.gov/25664378/

Levy, D. E. et al. (1981, March). Prognosis in nontraumatic coma. PubMed.
https://doi.org/10.7326/0003-4819-94- 3-293

Liu, C. H., et al. (2020) Neural networks and the anti-inflammatory effect of transcutaneous auricular vagus nerve stimulation in depression. *Journal of Neuroinflammation, 17,* 54.
https://doi.org/10.1186/s12974-020-01732-5

Liu, J. T., et al. (2003). Regaining consciousness for prolonged comatose patients with right median nerve stimulation. Neurosurgical Re-Engineering of the Damaged Brain and Spinal Cord.
https://doi.org/10.1007/978-3- 7091-6081-7_3

Lombardi, F., et al. (2002, April 22). Sensory stimulation for brain injured individuals in coma or vegetative state. PubMed.
https://doi.org/10.1002/14651858.cd001427

Magee, D. J. (n.d.). Head and face. In J. L. McDougal (Eds.), Orthopedic physical assessment (pp. 73-163).
ScienceDirect.
https://doi.org/10.1016/B978-0-323-05226-9.50011-6

Magnin M., et al. (2010, February) Thalamic deactivation at sleep onset precedes that of the cerebral cortex in humans. Proc Natl Acad Sci USA.
https://doi.org/10.1073/pnas.0909710107.

Mieda M., et al. (2004, March) Orexin peptides prevent cataplexy and improve wakefulness in an orexin neuron- ablated model of narcolepsy in mice. Proc Natl Acad Sci USA.
https://doi.org/10.1073/pnas.0400590101.

Mieda, M., et al. (2011, April 27). Differential roles of orexin receptor-1 and -2 in the regulation of non-REM and REM sleep. Journal of Neuroscience.
https://doi.org/10.1523/JNEUROSCI.6506-10.2011

Monti, J. M. (2010, October) The role of dorsal raphe nucleus serotonergic and non-serotonergic neurons, and of their receptors, in regulating waking and rapid eye movement (REM) sleep. ScienceDirect.
https://doi.org/10.1016/j.smrv.2009.10.003.

National Health Services. (2018, August 6). Overview disorders of consciousness. NHS UK.
https://www.nhs.uk/conditions/disorders-of-consciousness/

Neren, D., et al. (2015) Vagus nerve stimulation and other neuromodulation methods for treatment of traumatic brain injury. *Neurocritical Care, 24,* 308-319. https://doi.org/10.1007/s12028-015-0203-0

Noe, E., et al. (2019) Feasibility, safety and efficacy of transauricular vagus nerve stimulation in a cohort of patients with disorders of consciousness. *Brain Stimulation, 13,* 277-522. https://doi.org/10.1016/j.brs.2019.12.005

Peri C. V., et al. (2001, October) Pilot study of electrical stimulation on median nerve in comatose severe brain injured patients: 3-month outcome. Brain Inj. https://doi.org/10.1080/02699050110065709.

Redgrave, J., et al. (2018) Safety and tolerability of Transcutanous Vagus Nerve stimulation in humans; a systematic review. *Brain Stimulation, 11,* 1225-1238. https://doi.org/10.1016/j.brs.2018.08.010

Rezaei Haddad, A., Lythe V., & Green A. L. (2019, June) Deep Brain Stimulation for Recovery of Consciousness in Minimally Conscious Patients After Traumatic Brain Injury: A Systematic Review. Neuromodulation. https://doi.org/10.1111/ner.12944

Sakurai T. (2007, March) The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nat Rev Neurosci. https://doi.org/10.1038/nrn2092.

Schiff N. D. (2008) Central thalamic contributions to arousal regulation and neurological disorders of consciousness. Ann NY Acad Sci. https://doi.org/10.1196/annals.1417.029.

Schwarz, L. A., & Luo, L. (2015, November 2). Organization of the locus coeruleus-norepinephrine system. Current Biology. https://doi.org/10.1016/j.cub.2015.09.039

Sharma, V., Kaur, H., & Gupta, D. (2015). Right median nerve stimulation for improving consciousness: A case series. https://doi.org/10.1055/s-0035-1569473

Sherer M., et al. (2008, June) Comparison of indices of traumatic brain injury severity: Glasgow Coma Scale, length of coma and post-traumatic amnesia. J Neurol Neurosurg Psychiatry. https://doi.org/10.1136/jnnp.2006.111187

Shi, C., Flanagan, S. R., & Samandani, U. (2013, November 12). Vagus nerve stimulation to augment recovery from severe traumatic brain injury impeding consciousness: A prospective pilot clinical trial. Neurological Research. https://doi.org/10.1179/1743132813Y.000000016

Slamloo, Y. R., & Fazlali, Z. (2020, January 21). Dopamine and noradrenaline in the brain; Overlapping or dissociate functions? Frontiersin. https://doi.org/10.3389/fnmol.2019.00334

Steriade, M. (2010, February 4). EEG desynchronization is associated with cellular events that are prerequisites for active behavioral states. Cambridge University Press. https://doi.org/10.1017/S0140525X00010037

Straughn, J., & Denais, Z. (2019, October 1). Application of right median nerve stimulation in an inpatient rehabilitation setting for disorders of consciousness. Archives of physical medicine and rehabilitation. https://doi.org/10.1016/j.apmr.2019.08.115

Universitat Pompeu Fabra - Barcelona. (2019) Consciousness rests on the brain's ability to sustain rich dynamics of neural activity. ScienceDaily. www.sciencedaily.com/releases/2019/02/190212104217.htm.

University of Glasgow. (2014, July 14). 40 years of the glasgow coma scale. Gla.ac.uk. https://www.gla.ac.uk/news/archiveofnews/2014/july/headline_346523_en.html

Vazquez J., & Baghdoyan H. A. (2001, February) Basal forebrain acetylcholine release during REM sleep is significantly greater than during waking. American Journal of Physiology. https://doi.org/10.1152/ajpregu.2001.280.2.R598

Vitello, M. M., et al. (2023) Transcutaneous vagal nerve stimulation to treat disorders of consciousness: Protocol for a double-blind randomized controlled trial. *International Journal of Clincial and Health Psychology, 23,* 100360. https://doi.org/10.1016/j.ijchp.2022.100360

Wang, C., et al. (2018, June 28). The orexin/receptor system: Molecular mechanism and therapeutic potential for neurological diseases. Frontiersin. https://doi.org/10.3389/fnmol.2018.00220

Wu, X., et al. (2017, July 10). Right median nerve electrical stimulation for acute traumatic coma (the asia coma electrical stimulation trial): Study protocol for randomised controlled trial. PubMed.

https://doi.org/10.1186%2Fs13063-017-2045-x

Yang, C., et al. (2014, February 19). Cholinergic neurons excite cortically projecting basal forebrain gabaergic neurons. The Journal of Neuroscience. https://doi.org/10.1523/JNEUROSCI.3235-13.2014

Yu, Y.T., et al. (2017) Transcutaneous auricular vagus nerve stimulation in disorders of consciousness monitored by fMRI: The first case report. Brain Stimul. https://doi.org/10.1016/j.brs.2016.12.004.

Zank, J. C., et al. (2016, February 10). Cholinergic neurons in the basal forebrain promote wakefulness by actions on neighboring non-cholinergic neurons: An opto-dialysis study. The Journal of Neuroscience. https://doi.org/10.1523%2FJNEUROSCI.3318-15.2016

Zhong, Y. J., et al. (2015). Wake-promoting actions of median nerve stimulation in TBI-induced coma: An investigation of orexin-A and orexin receptor 1 in the hypothalamic region. Molecular Medicine Reports. https://doi.org/10.3892/mmr.2015.3898