Neuroscience of Near-Death

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Near-Death Experiences (NDEs) pose numerous unanswered questions within the realms of medicine and basic science. NDEs are experiences of someone who is dying or in the process of dying. During these encounters, The brain enters a hypoxic state affecting numerous neuronal pathways and brain connectivities.Studying and concluding NDE research has been challenging because most of it has been retrospective, raising the question of the reliability of the experiencer's memories (Greyson, 2013). This review article delves into recent advances in NDE research, focusing on molecular mechanisms related to hypoxia, neural circuits affected by NDEs, and potential treatments. It also explores the role of hypoxia-inducible factors (HIFs) in brain development and their potential connection to NDEs. Additionally, the article discusses the influence of brain networks and neurotransmitters on NDEs and raises intriguing questions about the relationship between NDEs and drug-induced experiences.

Near-death experiences (NDEs) have long captivated the human imagination, offering glimpses into the realm beyond mortality. While these ethereal encounters are often perceived as spiritual phenomena, the scientific community has delved into understanding the underlying mechanisms behind these extraordinary events (Nelson, 2015) For example, American physician, philosopher, and psychologist William James, in his seminal work, "The Varieties of Religious Experience," connected NDEs to his exploration of spiritual encounters (Nelson, 2015)

A unique aspect of NDEs is the occurrence of out-of-body experiences (OBEs). Roughly 45% of people who experience NDEs report OBEs. OBEs are not exclusive to near-death situations but are very frequent and considered a distinct phenomenon. OBEs are thought of as an illusion, emerging from the brain's temporoparietal region (Blanke, 2004). Research demonstrates that a small electrical current applied to the temporoparietal cortex can induce an OBE and potentially disrupt the integration of visual, proprioceptive, and motion senses, leading to the perception of an externalized self (Nelson, 2015).

To make sense of the intricacies of NDEs and their connection to the human brain, we must dive into the crucial role of cerebral blood flow. The brain's survival and optimal functioning depend on a constant supply of oxygen and glucose through aerobic metabolism. The control of cerebral blood flow is primarily regulated by the arterial baroreflex, which pivots on the interplay between cholinergic and adrenergic neurons in the peripheral and central nervous systems. (Watts et al., 2018) When cerebral blood flow diminishes, signaling a crisis, the brain orchestrates a cascade of survival responses, reminiscent of the fight-or-flight mechanism that ensured our ancestors' survival for millions of years (Nelson, 2015).

During the initial seconds of waning cerebral blood flow and fading consciousness, the brain's reactions are indistinguishable between uncomplicated syncope (fainting) and cardiac dysrhythmia (Nelson, 2015). The border between consciousness and unconsciousness becomes blurred, leading to a transitional state known as the borderland of consciousness. In this borderland, awareness can fluctuate as blood flow changes, even when the eyes remain open during fainting (Rothkirch et al., 2018). Surprisingly, individuals in this state may exhibit heightened awareness and vivid recall later on, challenging conventional notions of unconsciousness or death. Brain electrical activity can persist even in deep coma or seemingly flat electroencephalogram (EEG) readings (Kroeger et al., 2013).

Critics argue that selective, suggestible, reconstructed, and imperfect memory can contribute to the purported unexplained nature of NDEs (Nelson, 2015). Pinpointing the precise timing of these experiences becomes challenging, further complicating the quest for scientific explanations. However, no objective evidence supports the notion that consciousness can exist without a living brain. Plausible neuroscience explanations have been put forth, addressing previously "unexplained" cases and emphasizing the limitations of relying solely on subjective experiences (Nelson, 2015).

During NDEs, the brain becomes a hypoxic environment, meaning that cells and tissues receive little to no oxygen, causing severe symptoms such as: change in skin color, cough, fast heart rate, rapid breathing, sweating, and wheezing (Bhutta et al., 2023). When hypoxia occurs in mammals, specifically humans, we will initiate a series of downstream pathways: hypoxia-inducible factor (HIF), autophagy, energy metabolic pathways, and cell stress pathways (Lou1 et al., 2022). HIF transcription factors sense the hypoxic environment in the cells and react by inducing metabolic changes, regulating cell proliferation, controlling inflammatory response, etc. The HIF pathway explains how oxygen is sensed by cells, how they control downstream signal transduction, and how they offer potential therapeutic options for a variety of human disorders (Masoud & Li, 2015).

The primary mediators of downstream gene expression in response to hypoxic stress are the HIFs. The HIF family comprises two distinct subunits, HIF-1 and HIF-2 (Majmundar et al., 2010). Within this family, there is a singular protein, HIF-3, which encompasses HIF-1, HIF-2, and HIF-3. In hypoxic conditions, the enzymatic activity of Prolyl Hydroxylase (PHD) is inhibited, preventing HIF hydroxylation and subsequent ubiquitin-mediated proteasome degradation. Following interaction with HIF-1 to form a transcriptional complex through dimerization, the HIF subunit translocates to the nucleus and associates with hypoxia-responsive elements (HREs), initiating the expression of numerous downstream genes (Majmundar et al., 2010). HIF-3 plays a distinct role in regulating hypoxia-related genes and can also inhibit angiogenesis and control cell division. Multiple signaling pathways are involved in HIF transcription, thereby impacting the

regulatory process in addition to protein-level regulation. Importantly, the upregulation of PI3K-mTOR signaling has been shown to increase HIF mRNA expression, indicating its role upstream of HIF. Elevated PI3K-mTOR signaling in cancer cells can enhance HIF activity, leading to the production of angiogenic factors (Porta et al., 2014).

HIFs take role in a variety of biological activities, including metastasis, immunological response, glycolysis, cell growth and survival, metabolism, and proliferation. This translates into effects on multiple organ systems and cells including: the brain, stem cells, tumors, and endothelial networks (Luo et al., 2022).

As hypoxia is an emerging area of research in science, specifically in Neurology, there are important roles of HIFs that remain overlooked. One role may consist of the maintenance of neural stem cells (NSCs), which are stem cells that specifically differentiate into various brain cells (neurons, glial cells, etc.) (De Filippis & Delia, 2011). HIFs help in preserving the pool of NSCs and regulating their proliferation, which is essential for the proper development of the brain. Proper HIF regulation ensures that the right balance of neurons is generated, contributing to the formation of functional brain circuits. Moreover, the expression and activity of HIFs are tightly regulated by oxygen levels (Imanirad & Dzierzak, 2013). Under normoxic conditions (normal oxygen levels), HIFs are rapidly degraded. However, during hypoxic conditions (low oxygen levels), HIFs are stabilized and translocated to the nucleus, where they initiate the expression of target genes involved in various aspects of brain development. So, in all, HIFs are crucial to the smooth working of the brain. Additionally, recent research has extended fascination with HIFs to the intriguing phenomenon of near-death experiences (NDEs) (Long, 2014). Exploring the potential role of HIFs and hypoxia in near-death experiences offers a fascinating avenue for unraveling the neurobiological underpinnings of these extraordinary occurrences.

Amidst their critical roles in brain development, HIFs and their association with hypoxia have piqued the curiosity of researchers, extending their investigation into the enigmatic realm of near-death experiences (NDEs). There is a growing body of research suggesting that near-death experiences might be linked to the brain's response to hypoxia, the condition of reduced oxygen supply to tissues (Luo et al., 2022). During situations of oxygen deprivation, such as cardiac arrest or other life-threatening events, the brain can experience significant changes in its functioning (Bhutta et al., 2023). One area of functioning it affects is the hippocampus, where the hippocampus is a sensitive area to hypoxia; This could potentially aid in and contribute to the experiences and symptoms reported in NDE’s. However, even though there is research in the effect of hypoxia towards NDE, the role of HIFs is less understood and in the early stages of research (Anand & Dhikav, 2012). It has been hypothesized, though, that HIF’s might be involved in the neurobiological mechanism underlying NDEs. (Bao et al., 2021)

The connection of NDE's reaches far through our brain also affects many neural pathways and brain connectivities. Hypoxia can lead to the alteration of patterns of activity in different brain regions which might be related to the odd sensations and experiences of near death

The brain is a complex organ which performs various functions.The organ includes different patterns of structural connections that support cognition and a variety of behaviors; these patterns are called brain networks. (Bassett & Gazzaniga, 2011) The brain network system includes many different cell types but the most prominent are neurons and nerve cells which aid our body in transmitting and processing information. (Bassett & Gazzaniga, 2011) However, when it comes to NDEs and their effect on neural networks, there is very little research as it is a complex and evolving area, but there are a few perspectives.

There are many brain networks, some of which include the limbic system, visual system, sensorimotor system, and the central executive network. They help our body by performing their own specialized functions, (Pessoa, 2014) For example, NDEs deeply affect the visual system; individuals often report experiencing vivid visual phenomena, such as seeing a bright light, encountering deceased loved ones, or viewing scenes from their lives. These visual perceptions can sometimes be experienced with heightened clarity and detail. (Pessoa, 2014) It's possible that the brain's processing of visual information is altered during NDEs, leading to these unique and intense visual experiences. (Vicente et al., 2022) However, when regarding NDEs and the limbic system, it is a disease in the limbic system that causes NDEs: limbic lobe dysfunction. NDEs are signs of limbic lobe dysfunction because they share many characteristics with cases of limbic lobe neuron activation. Neurons in the limbic lobe may become hyperactive for a variety of reasons, including iatrogenic causes like electrical brain stimulation or spontaneous causes like temporal lobe epilepsy (Vicente et al., 2022).

NDEs are seen not just in brain networks themselves but the parts made up of them specifically as well, such as neurotransmitters. Neurotransmitters are essential chemical messengers that your body needs to function. They are responsible for transporting chemical "messages" from one neuron (nerve cell) to the subsequent target cell. Releases of specific neurotransmitters and neurochemicals, including serotonin, have been linked to NDEs (Wutzler et al., 2011).

In conclusion, the connection between brain networks and NDEs presents a fascinating area for investigation within the disciplines of neuroscience, psychology, and consciousness research. The reported intense visual sensations, intense emotional experiences, and altered states of consciousness during NDEs pose fascinating concerns about how these experiences may be closely related to the functional connections of the brain. The intense visual phenomena

experienced during NDEs, which are intertwined with emotional and sensory components, point to a complex interaction between the brain areas in charge of memory, emotion, and vision. Neurotransmitters like endorphins, dopamine, and serotonin are also involved in this relationship, which adds a complex layer to it. These chemicals have an impact on emotions and perceptions and may even be a factor in the increased emotional and sensory experiences. As brain networks adapt in response to factors such as oxygen scarcity or heightened stress, alterations in connectivity may underlie the NDE phenomenon.

Near Death is a vague topic, regarding the amount of research in neurology. There are still too many questions yet to be answered. First reports of NDE go back to ancient times, but the first medical description of near-death came from a French Physician, Pierre-Jean du Monchaux, in 1740. He discovered that excessive blood flow to the brain could account for the mystical sensations people describe experiencing when they regain consciousness. NDEs continue to happen often today, and while there isn't a known cure for them, it's more crucial to research how to recognize and diagnose them in the first place. The "near-death" phenomena was recognised by psychiatrists while they also contributed to the topic's popularization and subsequent investigation. A doctor, Russell Noyes, published journal articles on the topic even before Raymond Moody, a young psychiatrist, coined the term "near-death experience" (NDE) in his book Life after Life. As NDE cases continue to grow, so does the corresponding research with them.

In an article whose purpose was to investigate whether cultural and socio-demographic factors may be involved in why some patients report NDE after surviving, also further explains the thought process behind why NDEs might occur and an explanation for them. The article mentioned a 30-year-old woman who was sent to emergency with a significant head injury and a Glasgow Coma Scale score of E1 V1 M2. The Glasgow Coma Scale is used to score how much a patient is “conscious” based on three aspects; eye-opening, motor, and verbal responses. She underwent surgery for a left-side acute subdural hematoma. She remained unconscious for around two months and on a ventilator for eight days. She gradually recovered over the next year after this. She claimed that she floated while in a brilliant light during this moment of unconsciousness. She then traveled to "heaven," where a hierarchy of Gods was present. Another patient, A 22-year-old graduate student who had peritonitis, as described in the article, experienced an allergic reaction that lasted for about 10 minutes and resulted in cardiac arrest. He emerged from his period of unconsciousness, and in about 3 weeks, he recovered from sepsis. He described moving quickly through a white light tunnel while he was in an unconscious state. Throughout the arrest, he had complete calm and serenity. He also had an out-of-body experience (OBE) as he detachedly watched as medical personnel rushed to revive him. After a few months, he could only remember the light in terms of the specifics (Purkayastha & Mukherjee, 2012). These two patients' accounts of facing NDEs provide intriguing insights into the phenomenon. NDE, according to this article, is reported to be a non-pathological experience

that involves the psychological processes of dissociation as a response to trauma, despite the existence of neuropsychological, neurochemical, or neurohumoral ideas concerning it. (Purkayastha & Mukherjee, 2012) Trauma and other related factors could help in diagnosing NDEs and preventing them as well.

NDEs are naturally explained and thought of as sharp and vivid recollections with physical experiences that strongly resemble reality. NDEs have been cited by many as proof of heaven, life after death, and the existence of god. However, such similarity raises the possibility that NDEs derive from something more fundamental than cultural or religious expectations; presumably, NDEs are a reflection of changes in the brain's physiological makeup as we go closer to death. In a 2019 study, scientists compared the stories of 625 individuals who had near-death experiences (NDEs) with those of over 15,000 people who had used various psychoactive drugs. Similarities in the way these experiences were described were discovered, especially among those who had used a specific class of drugs. Ketamine, in particular, seemed to produce experiences closely resembling NDEs. This suggests that NDEs might involve changes in the brain's chemical system targeted by drugs like ketamine. The stories concerning hallucinogens and psychedelics had the most parallels to NDEs when memories of drug effects were compared with NDEs, and the hallucinogen ketamine scored the highest similarity to NDEs. The word "reality," was most frequently used to describe both NDEs and ketamine experiences. (Martial et al., 2019). Nonetheless, this study has its weaknesses, some of them more significant than others. The study is based solely on subjective accounts, some of which were collected decades after the fact. It is intriguing but far from conclusive to say that ketamine usage and near-death experiences are caused by the same chemical processes in the brain. It would be difficult technically and morally to conduct the kinds of investigations required to support this concept, such as monitoring neurochemical alterations in severely ill patients. The authors, instead, advocate for a more realistic and practical proposal, which was to use Ketamine, therapeutically, inducing an NDE-like state in terminally ill patients as a preview to alleviate their death-related anxieties.

The research on NDEs promises exciting avenues for exploration. First, further investigations into the role of HIFs in brain development and their potential involvement in NDEs could shed light on the neurobiological underpinnings of these experiences. Understanding how HIFs regulate neural stem cells and brain development in response to hypoxia may unlock valuable insights. Second, delving deeper into the impact of NDEs on brain networks, such as the limbic system and visual system, offers an intriguing path of research. These networks are central to emotional and sensory experiences during NDEs, and uncovering how they adapt and interact during such events could provide valuable context. Lastly, investigating the chemical processes in the brain associated with NDEs and their resemblance to drug-induced experiences could open up innovative avenues for managing NDE-related distress. Further

research into this might not only enhance our understanding of NDEs but also reveal novel approaches to treating the suffering brought on by NDEs.

In conclusion, NDE research continues to offer a captivating and medically relevant frontier. By delving into the molecular, neural, and experiential aspects of NDEs, we have the opportunity to shed light on profound mysteries surrounding these unique phenomena. This exploration may not only provide solace to those who have encountered NDEs but also advance our understanding of the human brain, consciousness, and the intricate interplay between physiology and subjective experiences.

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