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Review article

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A neuroscientific model of near-death experiences

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Abstract

Near-death experiences (NDEs) are episodes of disconnected consciousness that typically occur in situations that involve an actual or potential physical threat or are perceived as such, and the experiences are characterized by a rich content with prototypical mystical features. Several explanatory theories for NDEs have been proposed, ranging from psychological or neurophysiological to evolutionary models. However, these concepts were often formulated independently, and, owing to the fragmented nature of research in this domain, integration of these ideas has been limited. Lines of empirical evidence from different areas of neuroscience, including non-human studies, studies investigating psychedelic-induced mystical experiences in humans, and research on the dying brain, are now converging to provide a comprehensive explanation for NDEs. In this Review, we discuss processes that might underlie the rich conscious experience in NDEs, mostly focusing on prototypical examples and addressing both the potential psychological mechanisms and neurophysiological changes, including cellular and electrophysiological brain network modifications and alterations in neurotransmitter release. On the basis of this discussion, we propose a model for NDEs that encompasses a cascade of concomitant psychological and neurophysiological processes within an evolutionary framework. We also consider how NDE research can inform the debate on the emergence of consciousness in near-death conditions that arise before brain death.

Sections

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Key points

- The emergence of a rich phenomenology in near-death experiences (NDEs) during acute physiological crises might be attributed to a cascade of concomitant neurophysiological and psychological processes, including phylogenetically preserved threat responses.
- From a neurophysiological perspective, NDEs can result from impaired cerebral blood flow causing systemic hypotension, hypoxia and hypercapnia resulting in acidosis, and from increased neuronal excitability causing dysregulation of key neurotransmitter systems.
- From a psychological perspective, NDEs might be partially shaped by top–down processes and facilitated by non-pathological cognitive traits such as dissociation propensity.
- The evolutionary roots of NDEs are thought to be linked to survival and coping mechanisms, with serotonin probably mediating calming effects through 5-HT_{1A} receptors and contributing to hallucinogenic aspects through 5-HT_{2A} receptor hyperactivation.
- Understanding the slow recovery of brain activity after resuscitation might provide a valuable opportunity to explore the neural correlates of NDEs.

Introduction

Near-death experiences (NDEs) have long fascinated scientists, philosophers and the general public. First documented by Heim[1] in 1892, the phenomenon gained increased attention in 1975 with Moody[2] providing a definition based on the prototypical features reported by over 150 intensive care unit (ICU) survivors, including seeing a bright light, entering a tunnel, feeling deep peace, and out-of-body experiences (OBEs). Subsequent prospective studies have attempted to identify the most common aetiologies associated with the occurrence of NDEs, reporting a prevalence of 3% after traumatic brain injury[3], 15% after a prolonged ICU stay[4], and 10–23% after cardiac arrest[4–10]. However, NDEs can occur in various other critical situations, such as near-drowning, electrocution or childbirth complications, and research into NDEs is mostly retrospective owing to their unpredictability; only the aforementioned eight studies[3–10], along with another study on patients undergoing aortic surgery[11], have explored this phenomenon prospectively.

Subjective experiences closely resembling NDEs have also been observed in various non-life-threatening contexts. Historically, a distinction has been made between 'classic' NDEs that occur in situations considered life-threatening (for example, cardiac arrest or traumatic injury) and those that occur in contexts without apparent physical danger, such as syncope, a near-miss traffic accident or drug use[12,13]. These 'near-death-like experiences' (NDEs-like) seem to be as common as classic NDEs[14]. This traditional distinction is becoming outdated, however, and the differentiation between actual and potential life-threatening events lacks objectivity. Rather than relying solely on the external context, one should consider the perception and response of the brain to potential threats as a probable key factor in generating NDEs. The brain can activate a series of defence mechanisms when it detects a threat, even if not perceived as life-threatening by an external observer, triggering physiological reflexes that can lead to intense subjective experiences such as NDEs. Therefore, NDEs might be better understood on a multidimensional continuum that varies according to factors including the triggering context, perceived level of threat, and physiological and psychological responses. Given their occurrence across various situations, NDEs-like represent a heterogeneous group of states with varying levels of wakefulness and connectedness (that is, connection to the external world)[15], offering valuable research insights. For example, dissociative or psychedelic substances such as ketamine and *N*,*N*-dimethyltryptamine (DMT) are increasingly recognized for their potential to model NDEs in laboratory settings[16–18].

Various theories have been proposed to explain NDEs from psychological[19–22], neurophysiological[23–26] and evolutionary perspectives[27] (Box 1). These theories have often been formulated independently (Fig. 1), and establishment of a unified framework has been hampered by the fragmented nature of the research, coupled with aetiological heterogeneity. In the past, controversial dualistic theories[28–30] have dominated the debate owing to the seemingly paradoxical nature of generating a rich conscious experience during acute physiological crises. However, empirical data from different areas of neuroscience, including non-human studies, human studies involving psychedelics, and studies on the agonal brain, coupled with advances in technology that have facilitated in vivo investigations, are providing potential explanations for NDEs. These phenomena probably emerge from a combination of mechanisms, and a holistic approach integrating psychological, evolutionary and neurophysiological theories is now within reach.

In this Review, we provide an update on current knowledge of NDEs and suggest a unified, evidence-based model detailing the potential neurophysiological mechanisms in combination with psychological processes. By unravelling the intricate neurophysiochemical underpinnings, including insights from animal studies investigating the dying process[31], we aim to shed light on how NDEs occur. We also consider how the study of NDEs might influence the public understanding of brain death determination. We have excluded dualistic theories from our discussion owing to the lack of empirical neuroscientific evidence and the fact that a fundamental tenet of neuroscience asserts that human experience arises from the brain[32–35].

Phenomenology of NDEs

The prototypical features of NDEs can be divided into two categories: perception-related features, such as hearing voices, experiencing unusual sensations and having a feeling of peace or fear, and interpretive features, such as coming close to a border or point of no return and precognition. The Near-Death Experience Content (NDE-C) scale[36], which consists of 20 items with a cut-off score of 27/80 for an NDE, is currently the most robust standardized scale to identify and quantify NDE phenomenology. The model that we present below effectively addresses the perception-related features that can be linked to one or more neurotransmitter systems or neurophysiological processes. However, the interpretive features tend to involve additional processes, such as psychological processes that occur in a physiological — that is, non-life-threatening — state when the patient has recovered from their critical event, as well as pre-event, personal, social and cultural influences. This distinction between NDE features appearing in the critical context and those resulting from the interpretation of an individual could constitute a framework to guide future NDE research. Another unresolved question concerns the duration of certain features, such as euphoric sensations: do these sensations persist only during the hallucinatory phase, or do they endure beyond it, potentially contributing to the acute or long-term consequences of NDEs?

Neurobiological processes in NDEs

In this section, we begin by reviewing the changes in brain blood gas levels, cerebral perfusion and neuronal function that might arise in the prototypical NDE context[5,7–10] — namely, cardiac arrest — although other contexts are considered where relevant. We then review the modifications in neurotransmitter release and electrophysiology that have been linked to NDEs.

Cerebral blood flow, blood gases and neuronal function

NDE phenomenology can occur at various levels of hypoxia or ischaemia, including rapid acceleration during airline pilot training[37], prolonged apnoea[38] and syncope[39–41]. However, the highest incidence and prevalence of NDEs has been reported in association with cardiac arrest, which represents the most severe form of altered blood flow[5,7–9].

Just before and during cardiopulmonary arrest, cerebral blood flow is compromised, resulting in a swift decline in oxygen and glucose supplies and an accumulation of CO_2. Oxygen deprivation (hypoxia) impairs cellular respiration and ATP production, thereby disrupting energy-dependent cellular processes. This deprivation also affects the function of enzymes such as monoamine oxidase[42] (MAO), which is responsible for degrading monoamine neurotransmitters, including serotonin, dopamine, noradrenaline and histamine. In addition, elevated CO_2 levels (hypercapnia) contribute to acid–base imbalance. CO_2 combines with water to form carbonic acid (H_2CO_3), which dissociates into H^+ and HCO_3^- ions. During hypercapnia, the buffering capacity of HCO_3^- is exceeded by an overabundance of H^+, leading to decreased pH[43], disrupted ATP production, and cerebral acidosis. Reductions in brain pH activate acid-sensing ion channels (ASICs), leading to an influx of Na^+ ions, which further contributes to neuronal depolarization and the triggering of action potentials.

Impaired cerebral blood flow restricts glucose delivery to neurons, thereby compounding the energy crisis. Because glucose is the primary substrate for ATP production through glycolysis and oxidative phosphorylation, its depletion further exacerbates ATP deficits. ATP is crucial for maintaining neuronal electrochemical gradients and supporting synaptic transmission. ATP depletion leads to dysfunction of the Na^+–K^+ ATPase pump, resulting in membrane depolarization, increased intracellular calcium levels, and heightened neuronal excitability[44]. Elevated intracellular calcium also triggers the fusion of synaptic vesicles with the presynaptic membrane, thereby inducing neurotransmitter release, which might have an important role in triggering NDE phenomenology.

Neurochemistry

Heightened neuronal excitability has various effects depending on the involved neurotransmitter systems, which can include — but are

Box 1 | Theories to explain near-death experiences

Most of the current theories regarding near-death experiences (NDEs) are not mutually exclusive and can coexist, with the exception of the dualistic theories, which often conflict with neurophysiological explanations.

Neurophysiological theories

Neurophysiological theories offer explanations for the prototypical features (phenomenology) of NDEs, based on changes in the physiological state of the brain. They encompass three main categories of events that can arise concomitantly or successively: alterations in blood gas levels or cerebral blood flow (ischaemia)[6,33,40], fluctuations in neurotransmitter activity[17,18,109,176], and more general or focal neurophysiological modifications at the brain level[14,25,26,65,124,125,177,178].

Evolutionary theory

Peinkhofer and colleagues[27] have proposed that NDEs and thanatosis (death-feigning behaviour) share a common biological purpose, namely, survival. This theory suggests that thanatosis is the evolutionary precursor of NDEs. As the brain evolved and language developed, humans were able to record and communicate their experiences, transforming this survival behaviour into a rich experience that we now call an NDE[27]. Of note, however, the benefits and biological purpose of such experiences might be less obvious now that humans encounter different selection pressures with changes in natural enemies and the nature of life-threatening situations (discussed in ref. 27).

Psychological theories

Psychological theories focus on two main areas: identifying cognitive or personality traits that might increase the likelihood of experiencing NDEs, such as dissociation or fantasy proneness[4,20], and attempting to relate NDEs to psychological processes that occur near death, such as an acute dissociative state triggered by a perceived threat[153,154].

Dualistic theory

The dualistic theory posits that the mind (or soul) can detach from the physical body, allowing mental functions to persist even when the brain is seemingly inactive or impaired, or when an individual is near death[28,179–181]. From this theoretical perspective, NDEs represent a specific state of transcendental consciousness in which cognition, emotions and the self operate independently of the brain[181,182].

Empirical evaluation

Empirical testing of these theories poses various challenges and follow different timelines, influenced by the speed and sophistication of technological development. Some psychological hypotheses have already been explored using subjective measures such as self-report scales, whereas dualistic theories lack robust tools for empirical validation, and the few empirical studies that have attempted to test them were not able to exclude alternative non-dualistic hypotheses[122,183,184]. Evolutionary theories are also difficult to test, although advances in phylogenetics and phylogeny might provide supporting scientific evidence. Despite their complexity and diversity, neurophysiological theories could be tested further using a range of techniques, including EEG and physiological monitoring of blood gas and cerebral perfusion.

probably not limited to – serotonergic, glutamatergic, noradrenergic, cholinergic, endorphinergic, dopaminergic and γ-aminobutyric acid (GABA)ergic systems (Fig. 2).

The serotonergic system. Serotonin (also known as 5-hydroxytryptamine or 5-HT) is a monoamine neurotransmitter found across the animal and plant kingdoms[45–47]. In animals, serotonin is most abundant in the gastrointestinal tract, but its presence in the CNS has been highly preserved throughout evolution. Here, we present evidence that a surge in serotonin release and an impaired serotonin cycle participate in NDE phenomenology through the overactivation of two main types of serotonin receptor.

In rats undergoing asphyxia[31], a dramatic initial surge in brain serotonin levels was observed – up to 100–200 times higher than baseline – alongside decreasing levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA). Under normal conditions, after release in the synaptic cleft, serotonin is internalized back into the presynaptic neuron through the 5-HT transporter (5-HTT) and is then either recycled in synaptic vesicles or degraded into 5-HIAA by MAO. Both recycling and degradation of serotonin are ATP-dependent processes that might be compromised under low blood flow or hypoxic conditions, leading to increased extracellular 5-HT availability and subsequent increased and/or prolonged activation of postsynaptic serotonin receptors, which could explain both the increased serotonin and the decreased 5-HIAA levels observed in asphyxiated rats[31].

Two serotonin receptor subtypes, the inhibitory 5-HT_{1A} receptor and the excitatory 5-HT_{2A} receptor[48–50], show dense and widespread expression in key brain regions potentially involved in NDE. 5-HT_{1A} receptors are highly expressed in the midbrain, limbic and cortical regions[51] and are particularly abundant in the raphe nuclei – the primary serotonin-producing sites. These receptors function as presynaptic autoreceptors that regulate serotonin release to the forebrain. Postsynaptic 5-HT_{1A} receptors are involved in moderating anxiety and stress, promoting patience and enhancing (especially passive) coping mechanisms[52,53], which are of particular interest from an evolutionary perspective in the context of NDEs.

By contrast, 5-HT_{2A} receptors are the most abundant receptors in the cerebral cortex[51,54]. They modulate neuronal activity by facilitating depolarization of their host neuron, with excitatory and inhibitory effects on glutamatergic and GABAergic neurons, respectively. These receptors are highly concentrated in high-level associative cortices, such as regions belonging to the default-mode network (DMN)[51], and in visual areas[55–57], which might account for aspects of NDE phenomenology such as encountering entities. Studies have demonstrated that 5-HT_{2A} receptor activation and altered density in the visual cortex can trigger visual hallucinations[58,59], occasionally exhibiting mystical dimensions, as shown by research into the effects of lysergic acid diethylamide (LSD), psilocybin and mescaline[60,61].

In addition, 5-HT_{2A} receptor activation can affect DMN regions that are responsible for processing self-representation[62,63], including the temporoparietal junction (TPJ). As shown in pioneering studies, TPJ activation through electrical stimulation can produce effects that resemble the early stages of OBEs[64,65], as well as illusions of experiencing the presence of another person that can be likened to encounters with entities typically reported in NDEs[66], as discussed further in the section 'Whole-brain and regional brain contributions' below.

Only one placebo-controlled study has prospectively explored the potential of a typical (that is, acting on 5-HT_{2A} receptors) psychedelic drug, DMT, to model an NDE[18]. This study has revealed a substantial phenomenological overlap between NDEs and the effects of DMT. This similarity in phenomenology was actually noted decades ago, leading to the controversial suggestion that endogenous DMT could be released during dying, potentially leading to an NDE[67] (Box 2). More generally, the study of serotonergic substances that generate striking phenomenological similarities with NDEs, such as 5-methoxy-DMT (5-MeO-DMT)[68], is of particular interest for NDE research.

Consistent with a hypothesis formulated by Peinkhofer et al.[27] (Box 1), we suggest that NDEs and thanatosis, a form of passive coping behaviour, could share a common evolutionary origin, at least partly underpinned by serotonergic mechanisms. Through its 5-HT_{1A} receptor-mediated activity, serotonin is known to participate in thanatosis. This activity is also associated with calming and anxiolytic effects, which could contribute to the state of contentment and peacefulness that is often reported in NDEs. We also propose that the hallucinogenic features of NDEs might be induced by hyperactivation of 5-HT_{2A} receptors, which could be an evolutionary by-product rather than an anti-predator adaptation.

Our evolutionary hypothesis is based on several observations. First, the amino acid composition of 5-HT_{1A} receptors (or their equivalents) is largely preserved across species, from invertebrates to mammals. The expectation value (*E* value) indicates the likelihood of the

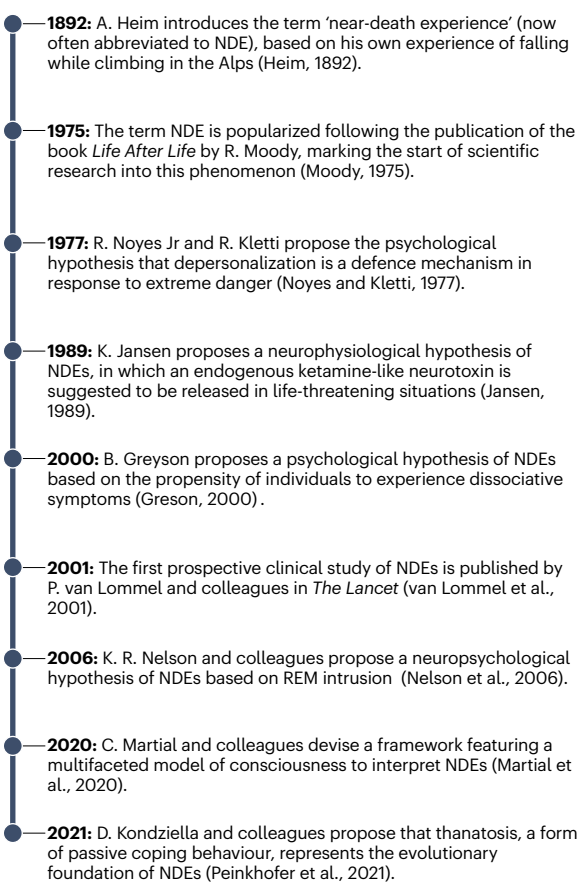


Fig. 1 | Timeline of key events and theories in the near-death experience research field. A chronological overview of some major events and theoretical developments in the field of near-death experience research[1,2,9,15,19,25,27,83,155].

alignment occurring by chance, with lower values indicating more significant matches. The amino acid sequence similarity between human 5-HT_{1A} and hexapod 5-HT_{X1} receptors is 40% (E value = 4×10^{-97}), whereas the similarity between human 5-HT_{2A} and hexapod 5-$HT_{2A\text{-like}}$ receptors is only 27% (E value = 1×10^{-79}), indicating that 5-HT_{1A} receptors are more evolutionarily conserved than 5-HT_{2A} receptors[69]. Second, the divergence of the 5-HT_2 subtypes occurred 500–550 million years ago, following the split between vertebrates and invertebrates[69]. This timeline makes it improbable that invertebrates display analogues of the 5-HT_2 receptor subtype[69] and probably explains why 5-HT_{1A} and 5-HT_{2A} receptors share only 31% of their amino acid structures[70], reflecting their distinct evolutionary paths and functional differences. Last, the striking structural differences between 5-HT_{1A} and 5-HT_{2A} receptors, in addition to their diverse distributions among brain structures, could explain how they developed opposing effects (inhibitory versus excitatory, respectively) and different functions, whereby 5-HT_{1A} mediates relaxing, calming effects and 5-HT_{2A} mediates perceptive and hallucinogenic features. Future investigations should further explore evolutionary hypotheses, which will be crucial for understanding distressing NDEs among other phenomena (Box 3), and should also examine whether the massive release of serotonin during the dying process serves a neuroprotective function[71,72].

The glutamatergic system. Since the late 1970s, glutamate has been recognized as the primary excitatory neurotransmitter in the vertebrate nervous system[73]. Glutamate receptors encompass both metabotropic and ionotropic receptors. Given the diverse effects of metabotropic receptors and our lack of knowledge about the ionotropic kainate receptors, especially under anoxic conditions, we will focus on the best-known glutamate receptors in humans, namely, AMPA receptors (AMPARs) and NMDA receptors (NMDARs).

AMPARs mediate the most rapid synaptic transmission in the CNS, with very fast activation times, ranging from 0.2 to 8.0 ms (ref. 74), and a remarkably rapid recovery time (150 ms (ref. 75)). These properties allow repeated activation of AMPARs, resulting in neuronal depolarization[76]. AMPARs are abundant in pyramidal neurons and are responsible for fast synaptic transmission in associative cortical regions. The involvement of AMPARs in the fast synaptic processes that are characteristic of associative regions and their potential for repeated activation might contribute to the experience of altered self-perception and sensory processing associated with NDEs.

By contrast, NMDARs activate more slowly[74] and act as coincidence detectors, requiring both presynaptic glutamate release and postsynaptic membrane depolarization to activate[77]. This dual requirement allows them to regulate synaptic strength and synchronize neural activity on the basis of input timing[78], which is crucial for long-term potentiation (LTP). LTP has an essential role in the formation of memory traces and is particularly prominent in the hippocampus, which exhibits a high density of NMDARs[79,80]. Memory is essential to NDEs, as their existence depends on the recollection of the experience.

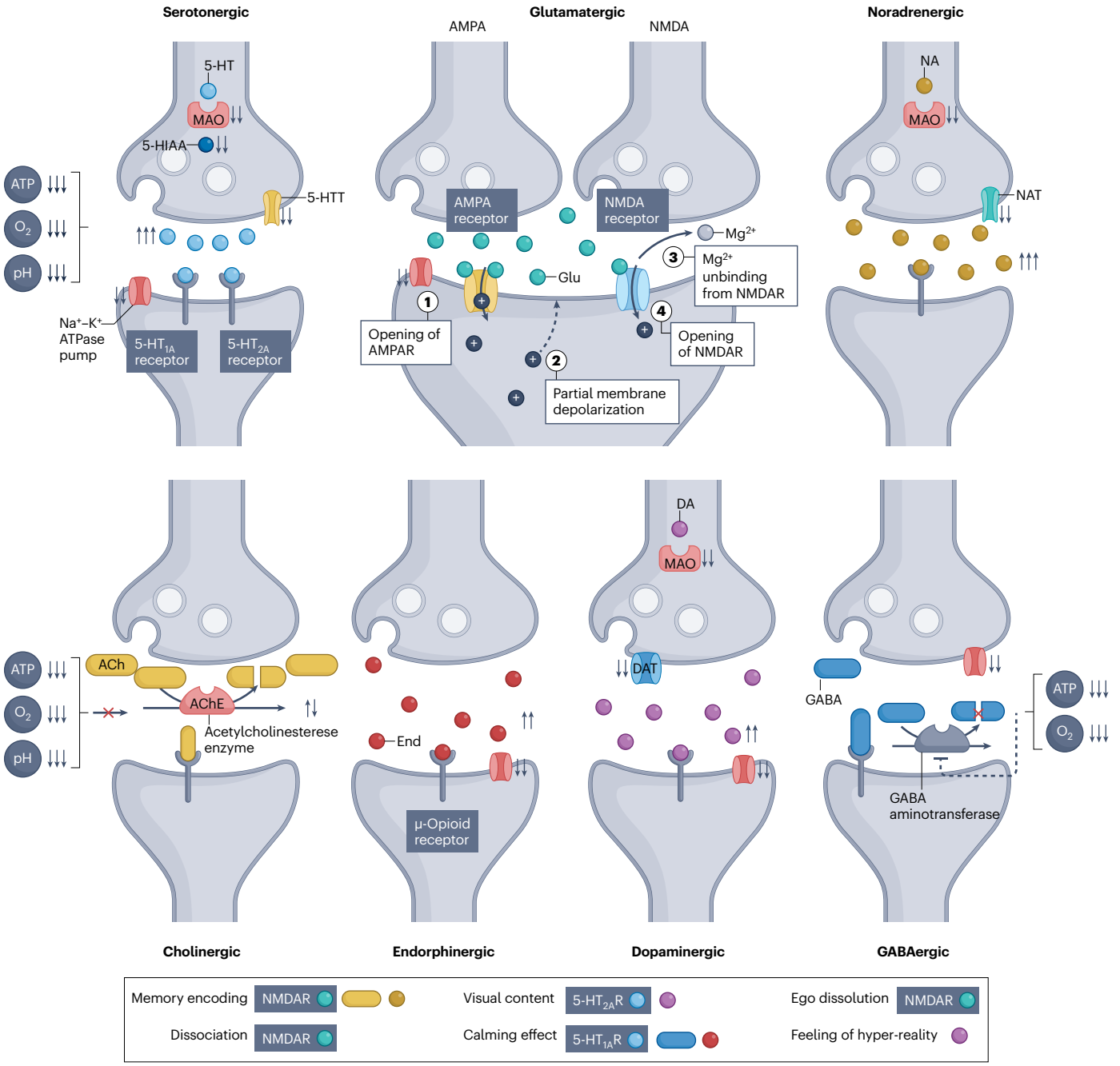
As well as NMDA signalling, NMDAR antagonism has been implicated in NDEs owing to their phenomenological similarities with ketamine-induced experiences[17,81,82]. Ketamine, a potent NMDAR antagonist, was linked to NDEs by Jansen in the 1990s[83]. Although Jansen recognized that NMDAR overactivation occurred during acute hypoxia, he hypothesized that in life-threatening situations, an endogenous ketamine-like neurotoxin might be released. To date, however, no empirical evidence has been found to support the existence of such a molecule. In addition, NMDAR antagonism is reported to provoke LTP disruption, thereby adversely affecting learning and memory encoding[75,84], which is incompatible with the inherent recallability of NDEs. Moreover, the vividness and detailed nature of NDEs are difficult to reconcile with NMDAR antagonism.

Jansen's model was largely based on shared phenomenological features – an idea that was supported by a study of 165 psychoactive substances, in which high semantic similarity was observed between reports of ketamine experiences and NDEs[17]. However, the effects of serotonergic psychedelics such as LSD, 5-MeO-DMT, psilocybin and DMT also rank highly in similarity to NDEs, suggesting that NDE phenomenology is not solely linked to NMDAR antagonism. As Jansen acknowledges, his NMDAR antagonism hypothesis is not intended to apply to all NDEs[83].

If no substance acts as a ketamine-like neurotoxin, how can the shared phenomenologies of NDEs and ketamine experiences, especially regarding dissociation, hallucinations and ego dissolution, be explained? Under physiological circumstances, a balance exists between excitatory and inhibitory inputs. The inhibitory inputs are primarily mediated by GABAergic interneurons, the activation of which is regulated by NMDARs, among other receptors. NMDAR activation leads to depolarization of interneurons, resulting in inhibition of pyramidal neurons, which are mostly glutamatergic and are crucial for sensory and associative processing[85]. Through its action as an NMDAR antagonist, ketamine decreases the inhibition of pyramidal neurons, thereby increasing neuronal excitability in sensory and associative regions and potentially leading to altered perceptions (including self-perceptions) and visual hallucinations. This hypothesis is supported by schizophrenia research, in which ketamine serves as a model owing to the observed NMDAR dysfunction in this condition[86,87]. Similarly, in hypoxic conditions, the increased release of glutamate overwhelms interneuron-mediated inhibitory mechanisms, leading to neuronal hyperexcitability and altered perceptions, analogous to the effects of ketamine[88,89]. Furthermore, although ego dissolution is frequent after taking ketamine, it is not exclusive to NMDAR antagonism: serotoninergic drugs such LSD can also induce ego dissolution, suggesting that the anti-NMDAR activity of ketamine is not specific to this phenomenon or its neurophysiological substrate. Rather than focusing on the involvement of hypothetical endogenous NMDAR antagonists with neuroprotective properties, investigating the relationship between NDEs and glutamate signalling, particularly through NMDARs, might be a more fruitful approach.

The noradrenergic system. Noradrenaline, another key monoamine neurotransmitter, is known to be released in response to stress, such as during fight-or-flight situations, and under hypoxic conditions[90]. Once in the synaptic cleft, noradrenaline is recaptured by the noradrenaline transporter, which is similar to 5-HTT in that it needs ATP to function and to internalize noradrenaline. Low blood flow or hypoxic conditions lead to increased extracellular noradrenaline availability and subsequent increased and/or prolonged activation of postsynaptic noradrenaline receptors.

Physiologically, noradrenaline release can be triggered by several mechanisms. First, in CO_2-asphyxiated rats, elevated CO_2 levels produce a sixfold-to-eightfold increase in noradrenaline within 30–75 s (ref. 91). Second, reduced oxygen and pH levels[91] activate highly sensitive glomus cell chemoreceptors in the aortic and carotid bodies, leading to sympathetic activation and rapid noradrenaline release[31]. Last, decreased blood flow, as observed in hypotension, reduces the activity of the baroreceptors in the carotid sinus, leading to activation of the locus coeruleus to counterbalance the hypotension.



The locus coeruleus is located in the rostral pons and is the primary source of noradrenaline, containing over 50% of all noradrenergic neurons. This structure has a crucial role in regulating various physiological and behavioural processes, including arousal, stress responses and mood, and is strongly suppressed during REM states[92]. Moreover, in primates, locus coeruleus discharge patterns seem to anticipate behaviours that are necessary for responding to crisis situations[93,94]. The locus coeruleus also has extensive connections with brain regions involved in emotion and memory, including the amygdala and the hippocampus. The hippocampus has a high density of noradrenergic terminals, suggesting a role for noradrenergic signalling in learning and memory[95]. In fact, noradrenaline has repeatedly been shown to enhance memory encoding[96,97], potentially by influencing LTP[98–100]. Noradrenaline might also aid memory consolidation through its effects on the amygdala[101]. Therefore, the ability of humans to recall vivid memories even on the verge of death could be explained by high noradrenaline levels during asphyxia[102,103]. In addition, the frequent medical use of adrenaline or noradrenaline during cardiac arrest could account for the frequent recall of an NDE, which is reported in up to 20% of survivors[5,7–9].

The cholinergic system. Acetylcholine in the CNS is well known for its crucial role in learning processes: it enhances memory formation by

Fig. 2 | Neurotransmitter systems involved in the generation of near-death experience features. Following cardiac arrest, alterations in cerebral blood flow lead to ATP depletion, reduced oxygen (O_2) supply and decreased pH (acidosis) (strength of effects represented by number of arrows). These changes cause disruptions across multiple neurotransmitter systems, primarily through enzymatic dysfunction. ATP depletion inactivates the Na^+–K^+ ATPase pump, which increases postsynaptic excitability. In the serotonergic system, dysfunction of the serotonin (5-HT) transporter (5-HTT) results in increased synaptic serotonin availability. In addition, monoamine oxidase (MAO) dysfunction reduces serotonin degradation, as indicated by decreased 5-hydroxyindoleacetic acid (5-HIAA) levels. In the glutamatergic system, Na^+–K^+ ATPase dysfunction leads to postsynaptic depolarization, which increases excitability and enhances AMPA receptor (AMPAR)-mediated transmission, contributing to an overall amplification of synaptic responses. Depolarization also reduces the magnesium (Mg^{2+}) block of NMDA receptors (NMDARs), facilitating their activation. NMDARs, which require both presynaptic glutamate release and postsynaptic membrane depolarization for activation, have a crucial role in long-term potentiation (LTP). In the noradrenergic system, noradrenaline (NA) transporter (NAT) dysfunction leads to increased NA availability in the synaptic cleft. In addition, MAO dysfunction prevents the degradation of presynaptic NA. The cholinergic system is relatively independent of ATP, as indicated by the red 'X'. Because acetylcholinesterase (AChE), which degrades acetylcholine (ACh), does not require ATP, the cholinergic system is less affected by ATP depletion (as indicated by the bidirectional arrow), allowing it to continue to play an important part, especially in LTP. Among endogenous opioids, endorphins (End) have the highest affinity for μ-opioid receptors. In the dopaminergic system, dysfunction of the dopamine (DA) transporter (DAT) leads to increased synaptic availability of DA. Moreover, presynaptic dopamine degradation is hindered owing to MAO dysfunction. In the GABAergic system, an increase in GABA in the synaptic cleft occurs owing to the slowing or cessation of its degradation by GABA aminotransferase (dashed line), an enzyme that depends on O_2. We propose that specific neurotransmitter systems might be associated with the emergence of distinct features of near-death experiences. Glu, glutamate.

strengthening synaptic connections through LTP[104]. Acetylcholine is primarily produced in the basal forebrain, including the Meynert nucleus, and in the brainstem from structures such as the pedunculopontine and lateral dorsal tegmental nuclei[105–108]. Although cholinergic neurons are excitatory, acetylcholine acts primarily as a neuromodulator, influencing the release of various neurotransmitters, including dopamine, noradrenaline, glutamate and GABA, as well as acetylcholine itself.

When cholinergic neurons are activated, they release acetylcholine into the synaptic cleft, wherein it binds to postsynaptic acetylcholine receptors, generating an excitatory postsynaptic potential. This acetylcholine is rapidly hydrolysed by acetylcholinesterase into choline and acetate — a process that uses the energy from hydrolysis itself and requires no external energy. This ATP-independent breakdown ensures that acetylcholine levels are tightly regulated, preventing excess accumulation and allowing the system to function efficiently even under low-energy conditions, such as low blood flow or hypoxia. The rapid ATP-independent degradation of acetylcholine aligns with Li et al.'s observation of a more modest increase in levels of acetylcholine compared with monoamine neurotransmitters in asphyxiated rats[31]. These mechanisms could help to explain how vivid memories are recalled in near-death situations, despite the challenges posed by limited energy supply.

The endorphinergic system. Endorphins, a subgroup of endogenous opioids, act as neurotransmitters that are released in response to pain and stress, including intense physical exercise. Their primary role is to counteract stress and maintain balance by modulating the activity of neurotransmitters such as noradrenaline and dopamine. Although effective at maintaining this balance under normal stress levels, the capacity of the endorphinergic system can be overwhelmed in extreme situations, such as severe pain or excessive neurotransmitter release.

The hypothalamus releases endorphins in response to cortisol, which is released following adrenocorticotropic hormone (ACTH) secretion. ACTH secretion is triggered by a corticotropin-releasing hormone, which is itself released by the hypothalamus in response to depolarization of neurons in the amygdala that are highly sensitive to changes in pH owing to their expression of ASIC1a channels[108]. The release of endorphins is intimately linked to stress factors, as demonstrated in an animal study[109] that found elevated blood and cerebrospinal fluid levels of endorphins in dogs undergoing sudden death through potassium chloride injection, provided that they were not anaesthetized beforehand. This stress-linked endorphin release could explain why a disproportionately high number of NDEs are reported after high-stress events, such as near-drowning incidents[110,111], which have been identified as the second most frequent cause of NDEs[14].

Endorphins primarily activate μ-opioid receptors, contributing to stress regulation, feelings of well-being, and pain relief. Therefore, endorphin release could explain the euphoric or peaceful sensations often reported during NDEs — a notion previously suggested by Blackmore[112].

The dopaminergic system. Dopamine has a crucial role in reward, pleasure and emotional responses. Like noradrenaline, dopamine is rapidly released during asphyxia, with studies showing a more than sevenfold increase in levels within 1 min in asphyxiated rats[31]. Once released into the synaptic cleft, dopamine is re-internalized by the dopamine transporter (DAT), which acts as a cotransporter for Na^+ ions and dopamine molecules, exploiting the physiological Na^+ gradient between the extracellular and intracellular spaces. However, under anoxic conditions, this gradient is disrupted, impairing DAT function and leading to elevated dopamine levels. Dopamine breakdown by MAO is also hindered under these conditions.

Besides its well-known involvement in movement regulation (via the nigrostriatal pathways), dopamine has a prominent role in cognition and reward processes (via the mesocorticolimbic pathways) and contributes to psychological well-being[31,113–115]. Furthermore, dopamine and dopaminergic receptors seem to contribute to hallucinations, although they are not solely responsible, as discussed above in the section 'The serotonergic system'. This phenomenon has been studied extensively in Parkinson disease and schizophrenia, both of which involve dopaminergic dysfunction. Schizophrenia, like most forms of psychosis, is often marked by impaired source monitoring, that is, the meta-cognitive ability that allows the origins of internally and externally generated events to be inferred. Of note, Martial et al.[116] found that coma survivors who reported NDEs exhibited suboptimal source monitoring and an increased tendency to illusory recollection, compared with those without NDEs. These observations might help to explain why NDE experiencers often have the strong conviction that their NDE was a real-life-based event[103].

The aberrant salience hypothesis, originally proposed to explain the positive symptoms of schizophrenia, suggests that abnormal dopamine

Box 2 | The endogenous DMT controversy

N,*N*-Dimethyltryptamine (DMT), a structural analogue of serotonin that shares the same precursor molecule (tyrosine), is best known as a potent hallucinogenic drug that activates 5-HT_{2A} serotonin receptors. For decades, however, some people have speculated that DMT is also produced endogenously in mammals, possibly — but not necessarily exclusively — originating from the pineal gland[185–190]. DMT was proposed to be released during the dying process[67], potentially contributing to NDEs. However, this claim has faced several criticisms, in particular, the observation that although DMT has been repeatedly observed in mammals, only trace amounts have been measured[191]. It was argued that the quantities of endogenous DMT do not tend to be sufficient to generate psychoactive effects, even if the pineal gland can release a substantial quantity of DMT on the verge of death. Another criticism was the fact that these measurements were mainly done in non-human brains. Technical limitations could have also been a factor: ultra-sensitive and reliable methods are now available, and Glynos and colleagues[192] were able to detect endogenous DMT in comparable concentrations to those of endogenously produced dopamine and serotonin in the medial prefrontal cortex and somatosensory cortex. Considering the accumulating evidence for similarities between NDEs and exogenous DMT-induced psychedelic experiences[17,18], the potential role of endogenous DMT in the generation of NDEs warrants further investigation.

release causes individuals to attribute excessive importance to otherwise trivial stimuli[117]. This misattribution of meaning can lead to unconventional or disturbing experiences. This hypothesis could provide a compelling framework for NDEs, whereby vivid and profound encounters, such as feelings of detachment from the body, encounters with very bright lights, or an intense sensation of peace, could be driven by a surge in dopamine activity, causing the brain to give exceptional importance to otherwise normal or ambiguous sensory input. However, dopamine might not be the only mechanism involved, and the role of 5-HT_{2A} receptors should also be considered, as they seem to contribute to the dysfunctional personal relevance attribution in schizophrenia, causing individuals to ascribe meaning to otherwise meaningless stimuli[118]. Nevertheless, this process could indirectly affect dopamine, as serotoninergic substances such as LSD have been found to stimulate dopamine receptors[119,120].

Overall, these insights provide a neurobiological framework for understanding the profound feelings of hyper-reality and transformative experiences in people who undergo NDEs.

The GABAergic system. GABA is the main inhibitory neurotransmitter in the vertebrate brain and is found in 20%–40% of CNS neurons[121]. GABA is synthesized from glutamate in a single enzymatic step that does not require oxygen; however, its degradation is oxygen-dependent, so the levels rise under hypoxic conditions[121]. This increase can have several notable behavioural consequences, including loss of consciousness, relaxation and anti-anxiety effects, similar to those produced by GABA-enhancing drugs such as benzodiazepines and barbiturates. In the context of NDEs, elevated GABA levels might contribute to the profound peaceful experience, as well as to reductions in neural activity and metabolism, triggering deep relaxation and a sense of serenity.

The increase in GABA levels during oxygen deprivation could have evolved as a protective mechanism to reduce metabolism and neural activity, potentially contributing to the death-feigning behaviour described in the specific context of thanatosis, as discussed above. Overall, through its role in modulating neural activity and consciousness during hypoxia, GABA might influence both the occurrence and the nature of NDEs.

Whole-brain and regional brain contributions

In recent years, research efforts have reflected a growing interest in the brain conditions that lead to NDEs, including a study from 2023 on patients who experienced in-hospital cardiopulmonary resuscitation[10]. However, methodological limitations[122], such as overly simplistic analytical techniques, inconsistent or ambiguous use of terminology, and inaccuracies in interpretation of the results, have rendered the findings inconclusive. Even if these limitations can be overcome, the exact timing of NDE occurrence — before, during and/or after (that is, during recovery from) the cardiac arrest — remains open to debate. Anecdotal accounts of perceptions during NDEs are available[9,123], but no empirical research to date has used sufficiently rigorous methodology to objectively verify whether these perceptions corresponded to actual external stimuli. Although no biological signature for NDEs has been identified, evidence from both animal and human studies might help us to formulate strong hypotheses.

Under certain conditions, humans can experience bursts of electrical activity that disrupt normal brain activity patterns, sometimes producing features similar to those seen in NDEs. For instance, mesiotemporal lobe epilepsies can be associated with specific types of focal seizure accompanied by an aura resembling an NDE[124–127], involving intense pleasure, euphoria or the sensation of presence, known as ecstatic seizures[128,129]. In addition to the mesiotemporal lobe, this type of epileptic syndrome, and its associated symptoms, probably involves the insular cortex[124,125]. Interestingly, Britton and Bootzin[130] demonstrated that NDE experiencers tend to have more temporal lobe epileptiform EEG activity and more temporal lobe epileptic symptoms than matched controls who never had an NDE. In parallel, pioneering studies have implicated the TPJs of both hemispheres in specific NDE features: intracranial stimulation of the right junction seems to elicit disembodiment resembling an OBE[61], whereas electrical stimulation of the left junction can trigger an own-body illusion of another person in the extrapersonal space, resembling the encounter of entities reported in NDEs[66]. This phenomenology does not precisely match what is recalled during NDEs, possibly because the electrical stimulation used in these studies was highly localized to the TPJ. Therefore, this stimulation model is devoid of the multiple influences of activation of other brain areas or bulk neurotransmission, including serotonin and dopamine release, that could modulate the perception of an OBE in the context of an NDE. Bodily dissociation experiences occur on a spectrum, ranging from the sensation of splitting of one's body to more complex or intense perceptions such as the feeling of observing one's own body from a completely detached perspective, and to date, no study has been able to fully replicate the intricate OBE phenomenon commonly reported by NDE experiencers. In the context of NDEs, sensory deafferentation and the subsequent hallucinations might function as an adaptive compensatory mechanism, helping to maintain mental coherence in response to the sudden loss of sensory input.

Another major advance in the NDE field was the proposal of the REM intrusion hypothesis. REM sleep is a physiological sleep stage that has been evolutionarily conserved across mammalian species[131–133], and

it is characterized by a waking-like EEG activity, vivid dreams and loss of muscle tone. REM sleep-like bursts of activity, known as REM intrusions, can occur in the normal awake state[134]. This phenomenon, which commonly occurs during consciousness state transitions such as awakening from REM sleep, affects around 25% of the general population at some point in their lives[14,25,135]. Importantly, three studies[25,26,136] have shown that NDE experiencers are strongly predisposed to REM intrusion, possibly mediated by a pontine REM 'flip-flop' switch in the arousal system that is responsible for shifting consciousness between waking and REM states[137]. This idea is consistent with the existence of a cohesive physiological system that integrates regional brain function with the potential to contribute to NDEs. Under cerebral hypoxic–ischaemic conditions, the physiological boundary between conscious states might be disrupted by the brainstem arousal system that controls the transition between conscious states, thereby blending wakefulness with elements of REM consciousness into a hybrid state of REM intrusion (Supplementary Box 1). Although many questions regarding the underlying mechanisms of REM intrusion remain, including the context of its inhibition and specific triggers, it has the potential to contribute key NDE features, including unusual light perception, atonia, euphoria and out-of-body sensations[138,139], probably through selective temporoparietal inactivation accompanying the REM state[140,141]. Among these features, atonia is of particular interest from an evolutionary perspective. Atonia almost always occurs at the onset of cerebral hypoperfusion that leads to impaired consciousness[39,40]. With physical collapse, increased blood return might increase cardiac output and cerebral blood flow at times when perfusion is most needed. Furthermore, an animal experiencing profound hypotension from severe blood loss will lie still[142], perhaps evading detection by predators.

Evidence indicates that NDEs resemble experiences induced by some typical or atypical psychedelic drugs[16], suggesting that the psychedelic literature could aid the formulation of hypotheses about NDEs. A study published in 2020 (ref. 143), which investigated the effects of different doses of ketamine (up to 24 mg/kg) in sheep, has identified alternating bursts of slow (theta) and rapid (gamma) oscillations in the brain, which were suggested to underlie the dissociative effects of the drug. This idea aligns with other studies that revealed a prominent role for slow waves, such as delta and theta activity, in conscious mental states[144,145]. Timmermann and colleagues[146] observed an emergent theta and delta rhythmicity during DMT-induced psychedelic experiences and an increase in theta and delta power in ketamine-anaesthetized people has also been observed in several studies[147–150]. Interestingly, a 2024 study has shown that in healthy volunteers, a dream-like experience resembling NDE during vasovagal syncope episodes was strongly associated with a similar delta and theta rhythmicity[41]. The study has also revealed strong positive correlations between the richness of the phenomenology and theta and delta cortical activity in specific regions of interest for self-awareness and body perception, such as the TPJ. More generally, electrical brain activity of participants who reported NDEs-like showed higher complexity and overall connectivity, paralleled by greater segregation and integration, than the non-NDEs-like group. This study, which was the first to investigate electrical brain activity related to experiences resembling NDEs in a laboratory setting using a proximate cause of NDEs, in which the syncope arose from harmless vasovagal or cardiac arrhythmia, suggests that this particular brain condition occurs within a time frame that favours the emergence of a conscious experience. The findings may be consistent with the entropic brain hypothesis, which links brain activity complexity to enhanced consciousness[151].

Psychological processes

Psychological theories might contribute to our understanding of both the emergence and the experiencer's interpretation of an NDE. In terms of predisposition, studies have shown that most people who recall NDEs

Box 3 | Distressing NDEs

Phenomenological classification

According to the existing empirical literature (although sparse), distressing near-death experiences (NDEs) can be categorized into three types on the basis of their phenomenology (listed here in descending order of frequency):

- 'Inverse' experiences involving perceptions similar to those in pleasant NDEs (for example, seeing a bright light and/or a tunnel or encountering entities) but perceived as extremely frightening
- 'Hellish' experiences in which individuals encounter hell and threatening entities, and perceptions of impending torment or judgment
- 'Void' experiences involving perceptions of nonexistence, aloneness and eternal void[193–196]

Neurochemical hypotheses

We hypothesize that inverse and hellish NDEs could result from the differential influences of the two main serotonin receptors, 5-HT_{1A} and 5-HT_{2A}. Specifically, 5-HT_{1A} receptors, which are abundant in the limbic system, might account for the emotional valence of the NDE (positive versus inverse). Conversely, 5-HT_{2A} receptors, which are widely distributed in cortical areas including perception-related and associative areas, might account for the phenomenological content of the NDE (classic versus hellish). Besides specific physiological mechanisms, the possibility of experiencing a negative NDE (hellish or inverse) tends to be influenced by both aetiology and contextual factors, which could explain observations such as the over-representation of distressing NDEs in depressive suicidal attempts[194].

The identification of neurochemical explanations for void NDEs remains challenging. One can hypothesize that a particularly intense experience of ego dissolution, typically reported by NDE experiencers[197], might generate the experience of endless nothingness or void. Of note, this subtype of distressing NDEs seems to exhibit fewer prototypical features of NDEs compared with the other two subtypes of distressing NDE. Refinement of the characterization of this subtype though empirical studies should facilitate the formulation of neurophysiological hypotheses.

Although we recognize that the above-described mechanisms are probably not the sole cause of distressing NDEs (for example, an overwhelmed endorphinergic system could also have a role), we hypothesize that for each subtype of distressing NDE, the associated top–down-to-bottom–up regulation ratio could be different, leading to specific phenomenological features.

have no global cognitive functioning deficits or specific pathological disorders[5,13,152], although they might exhibit particular cognitive and personality traits. The trait that has been highlighted the most and was identified as a risk factor by retrospective[19] and prospective[4] studies is the propensity to easily and/or frequently experience non-pathological dissociation states, such as daydreaming. These observations are consistent with an early theory that conceptualized NDEs as a type of depersonalization — a sense of the self as unreal or lacking agency — that could be interpreted as a defence mechanism in response to extreme danger[153,154]. Some related traits, such as fantasy proneness[20], have also been found in the NDE population. Overall, NDE experiencers could be particularly sensitive to their internal states and have higher tendency to pick up on perceptual elements that others might miss. Importantly, however, these findings are mostly from retrospective studies, and in the few cases that were observed prospectively, the evaluation was still conducted retrospectively, albeit immediately following the experience. Acknowledging the speculative nature of these hypotheses, our aim is to provide a conceptual framework that integrates existing evidence and highlights testable hypotheses, paving the way for future empirical research to address individual variability in NDEs.

Psychological theories might also be pertinent to the potential mechanisms at play during life-threatening events. Top–down processes could be particularly active when sensory (bottom–up) information is ambiguous or lacking, as in cardiac arrest conditions or other stressful or life-threatening situations. Of note, similar activation might occur during neuraxial anaesthesia, which produces substantial sensory deafferentation. These top–down processes include pre-existing knowledge, beliefs and expectations[112], and they could permit individuals to construct meaning about their experiences. Like most of our perceptual experiences, NDEs are shaped by a dynamic interplay between top–down and bottom–up processes, with the top–down influences that may become dominant when sensory information is degraded or ambiguous, as in life-threatening situations.

The aforementioned psychological mechanisms might form part of a defence cascade that is automatically activated by phylogenetically preserved neurophysiological responses to threats when fight-or-flight behavioural responses are no longer possible[27]. People could enter a state of mental dissociation, allowing attention to be focused on internally oriented fantasies, to help them cope with and survive life-threatening situations.

NDEs and death determination

In the general population, the biological concept of death, in particular the distinction between circulatory death and brain death (also known as death by neurological criteria), is poorly understood. The traditional view that death equals the cessation of heart activity shifted to a cerebrocentric view with the advent of modern intensive care and resuscitation medicine in the 1950s. In the cerebrocentric model, the irreversible cessation of all brain functions is considered as the definitive criterion, both necessary and sufficient, to establish human death (Box 4). This condition is legally recognized as indicative of death, despite the potential for continued extracranial blood circulation and life-support systems to maintain organ functions other than those of the brain. The absence of brain activity precludes the possibility of consciousness and, hence, NDEs, which are survived events by definition. Moreover, survival alone is not enough to recall an NDE; the person must survive with a good level of cognitive function, allowing them to store the experience in their memory, retrieve it and report it in an eloquent manner.

In recent years, the study of the dying brain has begun to connect with the NDE literature. In a pioneering study published in 2009, Chawla et al.[155] observed transient electrical spikes in critically ill patients, which occurred after a continuous decline in EEG indices following loss of blood pressure and, according to the authors, "approached levels normally associated with consciousness." Despite major limitations, such as the use of indices generated by a proprietary algorithm, this finding is consistent with later research in rodents, which showed that cardiac arrest or acute asphyxia was associated with a transient global increase of functional connectivity in gamma oscillations[31,156]. Gamma synchrony across the midline of the brain seems to be important for learning, information integration and perception[157–159].

In a 2017 study, Lee and colleagues[160] found a marked decrease in power across all frequency bands but an increase in functional connectivity between the bilateral frontal and visual cortices in rats immediately preceding cardiac arrest. Subsequent studies in humans confirmed a similar pattern of activity in recordings taken immediately before the cessation of EEG activity[161,162]. These two studies have confirmed that global hypoxia increased gamma power and gamma coupling with slower oscillations. Furthermore, Xu and colleagues[162] showed that two of their four patients exhibited increased interhemispheric functional and directed connectivity in the gamma band, which seems to be important for memory recall[163]. Cholinergic brainstem nuclei are thought to modulate this gamma activity[164,165] and are fundamental to REM sleep. Importantly, gamma rhythms characterize arousal not only in the awake state but also during REM periods[166]. Interestingly, these two patients also exhibited surges of functional connectivity within the temporoparietal–occipital hot zone junction, which is considered by some[35,167] to be the minimum requirement for conscious perception. Although intriguing, these findings should

Box 4 | Redefining death: insights from animal brain resuscitation

Recent advances in animal brain resuscitation research are challenging traditional assumptions about the irreversibility of brain death. Groundbreaking studies demonstrated that perfusing a blood substitute into pigs several hours after circulatory death could restore cellular activity in several organs[198], including the brain[199]. Although this intervention restores metabolic activity, however, it does not lead to full functional recovery, emphasizing the crucial distinction between metabolic viability and recovery of higher brain functions, including consciousness. Such advances in resuscitation could redefine what constitutes irreversible brain injury. From a clinical perspective, this shift requires a careful distinction between when function will not be restored and when it cannot be restored[200], reflecting our evolving understanding of resuscitation limits and suggesting that death should be determined by the irreversibility of loss of function. The applicability of this research to the human brain remains elusive, especially given the ethical concerns that it raises. The fact that restoring cellular and metabolic activity does not guarantee that cognitive function, such as conscious awareness and the ability to experience emotions, will return is an important consideration. Nevertheless, these findings open new avenues for exploring the limits of recovery of brain function and highlight the need for further research to refine resuscitation techniques and improve our understanding of death.

be interpreted cautiously as no interview was possible owing to the imminent death of the patients.

Xu and colleagues reported that global hypoxia stimulated gamma activity, especially in the right hemisphere, consistent with a role for this hemisphere in mediating sympathetic function[162,168]. This hemispheric response might involve the occipital cortex, in which hypoxia-induced excitation of visual cells could trigger perceptions such as light or tunnel vision[22,23,169,170]. However, it is important to note that the light and tunnel visions experienced in NDEs typically involve more complex imagery and intricate visual patterns, similar to the hallucinations of REM intrusions, compared with the relatively simple loss of peripheral vision observed in classical hypoxia–ischaemia-induced excitation[171,172]. Collectively, these studies suggest that the near-death state generates transient surges of functional activity in key brain regions that are relevant to consciousness[155,161,162,173].

Although NDEs and the cellular mechanisms of the dying brain are distinct phenomena, studying them in combination can enhance our understanding of both phenomena. The comprehension of the mechanisms of death and the slow recovery of brain activity following resuscitation might provide a window to gain a further understanding of the neural correlates of NDEs. However, the path forward remains complex, especially regarding the duration and biological purpose — if any — of the above-mentioned transient high-frequency surges at near death and their ability — or lack thereof — to account for the rich phenomenology of NDEs. Intracellular recordings in a rodent model by Schramm and colleagues[174] challenge the hypothesis that high-frequency oscillations occur during the resuscitation period and instead suggest that the slow recovery of brain function following resuscitation could represent a more relevant time window for generating NDEs. Therefore, extensive electrophysiological research will be needed to elucidate the precise timing of NDEs and the progression of brain deterioration.

Findings of electrical surges occurring after circulatory arrest and just before the cessation of EEG activity challenge traditional assumptions about the complete cessation of neural functioning during organ procurement. The traditional 'no-touch' period might not ensure the absence of residual neuronal activity, raising ethical concerns about donor integrity. Although normal brain function cannot be restored at this stage, safeguards might be needed to address potential residual awareness without compromising organ viability, as prolonged waiting periods can jeopardize transplant outcomes. Real-time neuromonitoring such as EEG offers a promising avenue, not necessarily to delay procurement but to assess the effects of systematic sedation, which could serve as an ethical safeguard, aligned with the precautionary principle while preserving donor dignity. Pinpointing the precise and irreversible moment of death holds importance for many, offering a sense of certainty when facing the loss of a loved one. In this context, phenomena such as NDEs, as well as other understudied phenomena such as terminal lucidity[175], could be unhelpful in the context of death determination, as seeing people in a state close to death but reporting a rich experience in situations that we otherwise would associate with an absence of awareness can seem paradoxical.

NEPTUNE: a new model for NDE

Building on this Review, we propose the Neurophysiological Evolutionary Psychological Theory Understanding Near-death Experience (NEPTUNE; Fig. 3), a comprehensive model that includes and extends previously suggested theories. For the sake of clarity, the model focuses specifically on the prototypical scenario cardiac arrest, which seems to be the most common triggering aetiology for NDEs[5,7–10] and is less prone to variability in neurophysiological patterns than other triggers.

Glossary

Agonal
A phenomenon occurring in the final stages of life, typically associated with severe physiological distress or the process of dying.

Atonia
A clinical sign characterized by a reduction in or complete loss of tone and contractility, most often referring to muscle tone.

Aura
The initial symptom of a focal epileptic seizure, reflecting localized abnormal brain activity before it potentially spreads.

Default-mode network
(DMN). A set of brain regions that show correlated functional activity and are typically active during the resting state.

Dissociation
A psychological state in which an individual experiences a disconnection between their thoughts, sensations, memories or sense of identity.

Ego dissolution
A temporary state characterized by the blurring or loss of boundaries between the self and the external world, often accompanied by disruption of self-identity.

Entropic brain hypothesis
A theory suggesting that the subjective quality of a specific experience is reflected in the measurement of brain entropy (greater diversity of brain activity patterns), positing that increased complexity of brain activity correlates with an expansion in some key property of consciousness.

Experiencers
People who have recalled a near-death experience.

Glomus cell
Specialized cells located in the carotid and aortic bodies that act as peripheral chemoreceptors, sensing changes in blood oxygen, CO_2 and pH levels and helping to regulate breathing.

Out-of-body experiences
(OBEs). Subjective experiences in which the self is perceived as existing outside the boundaries of a body (disembodiment), sometimes accompanied by the perception of one's body from an extrapersonal space (autoscopy).

Phenomenology
The lived, first-person experience of reality as it is directly perceived, including sensory, emotional and cognitive elements, shaped by personal context and perspective.

Self-representation
The mental process or cognitive ability by which individuals represent themselves, including their characteristics, values and role within the social and physical environment.

Thanatosis
A behaviour in which an animal 'plays dead' by entering a state of immobility or paralysis, typically in an attempt to avoid predators.

Vasovagal syncope
A common type of fainting caused by a sudden drop in heart rate and blood pressure, leading to reduced blood flow to the brain.

NEPTUNE assumes a cascade of concomitant psychological and neurophysiological processes, which might start with systemic hypotension, oxygen deprivation, elevated CO_2 levels, disruption of ATP production, and a decreased pH, culminating in cerebral acidosis. Triggered by cellular energy deprivation, these intricate processes can set off a chain reaction of complex cellular responses, ultimately leading to increased neuronal excitability in cortical associative regions in the mesiotemporal lobe, occipital lobe, insular cortex and temporoparietal–occipital hot zone junction, permitting the perceptual

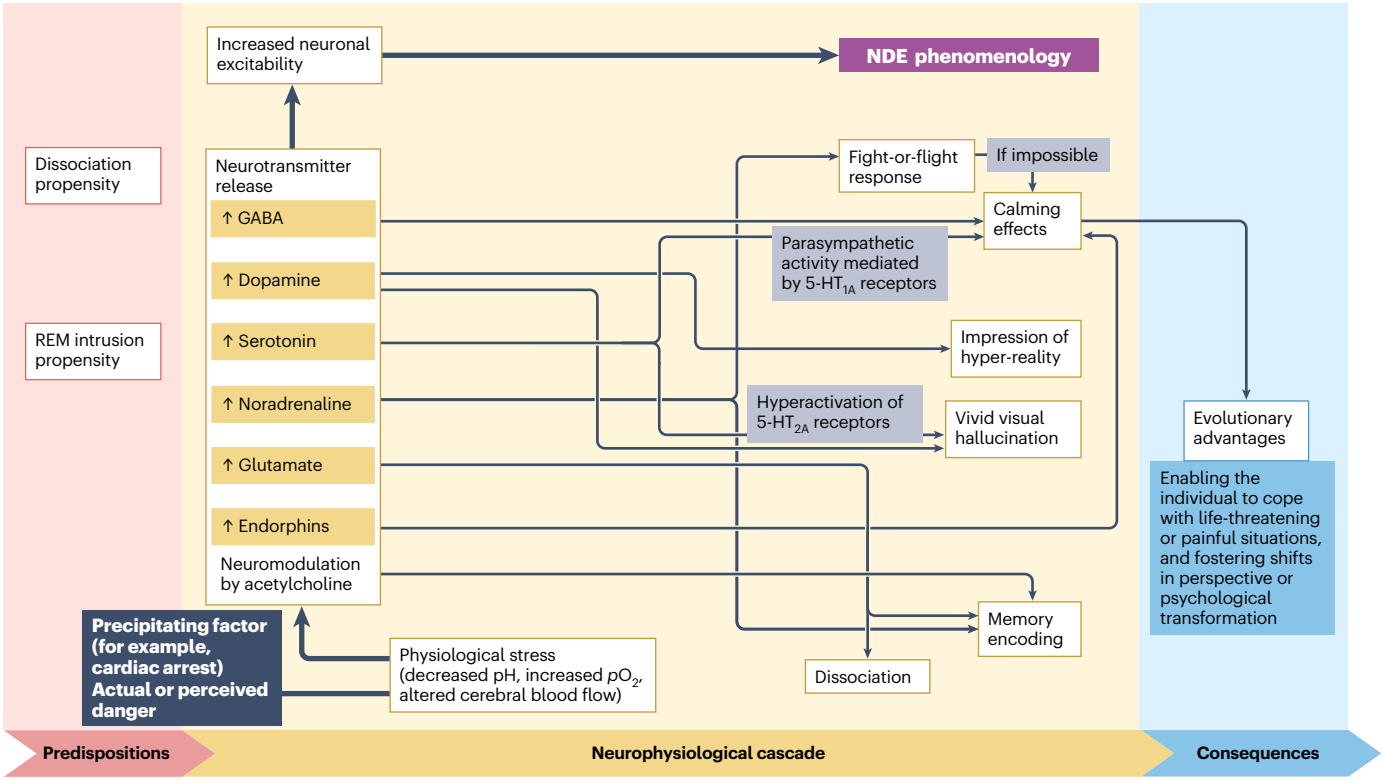


Fig. 3 | The Neurophysiological Evolutionary Psychological Theory Understanding Near-death Experience (NEPTUNE) model. This model, which is based on empirical research (including animal research), proposes a cascade of concomitant psychological and neurophysiological processes that could trigger near-death experience (NDE) phenomenology, within an evolutionary context. Oxygen deprivation and elevated CO_2 levels culminate in cerebral acidosis, and this cellular energy deprivation sets off a chain reaction that leads to increased neuronal excitability in key brain regions, including the temporoparietal junction and the occipital lobe, accompanied by massive release of endogenous neurotransmitters. Each neurotransmitter system might contribute to specific NDE features, including a sense of calm, an impression of hyper-reality, vivid visual hallucinations, memory encoding and dissociation. Individual predispositions, such as a tendency towards dissociation and REM states, might facilitate this neurophysiological cascade. Experiencing an NDE could offer an evolutionary advantage by enhancing adaptation to the environment through a dissociation process that helps individuals to cope with life-threatening situations. 5-HT, 5-hydroxytryptamine (serotonin); pO_2, partial pressure of oxygen.

content of the experience to become conscious. The neural mechanisms underlying NDEs tend to be similar to those underlying REM intrusions. Enhanced neuronal responsiveness, resulting in increased firing rates, ultimately leads to the massive release of neurotransmitters.

In tandem with other neurochemical mechanisms, we hypothesize the following key neurochemical events in NDEs. We propose that calming effects are induced by increased 5-HT_{1A} receptor availability, as well as by transient increases in endorphin and GABA levels, potentially leading to a feeling of deep peace, whereas vivid visual hallucinations are triggered by hyperactivation of 5-HT_{2A} receptors and dopamine (Fig. 2). The profound feelings of hyper-reality associated with these hallucinations could be explained by increased release of dopamine specifically. Determining the precise role of glutamate in NDEs remains challenging, but we tentatively suggest that it could be involved in cognitive dissociation. Memory encoding of this phenomenology would be promoted by release of noradrenaline, acetylcholine and glutamate, triggered by the stressful or life-threatening situation, to enhance coping. Individual predisposition to dissociation might facilitate this neurophysiological cascade, and the dissociation process can be seen as a defence mechanism to cope with the stressful or life-threatening situation, consistent with an evolutionary role.

Despite our efforts to develop a comprehensive model, some questions remain: for example, what combinations of the above-mentioned processes are necessary and/or sufficient to trigger an NDE? Also, although our model might effectively explain certain key NDE features, it does not cover other features, such as precognition.

Conclusions

Investigating the neurophysiological mechanisms underlying NDEs is helping us to clarify how these rich, deeply encoded memories might represent a phylogenetic response to physiological stress. Our NEPTUNE model, although theoretical at present, provides a foundation for the next research phase, which will entail empirical testing of each mechanism. Even if we can obtain a comprehensive understanding of all aspects of NDEs, they tend to retain a unique place in the study of human consciousness, marked by their distinctiveness and profound effects on people who experience them.

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