Semiology and Mechanisms of Near-Death Experiences

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Abstract

Purpose of Review Near-death experiences (NDEs) are conscious perceptual experiences, including self-related emotional, spiritual, and mystical experiences, occurring in close encounters with death or in non-life-threatening situations. The origin of NDEs remains unknown. Here, we review recent advances in the understanding of NDE semiology and pathophysiology.

Recent Findings Recent prospective studies confirm that NDEs reflect a spectrum of highly distinctive memories which are associated with negative or positive emotions and can be influenced by the nature of the causal event, but the temporal sequence with which these images unfold is variable. Some drugs, notably ketamine, may lead to experiences that are similar or even identical to NDEs. New models extend previous neural network theories and include aspects of evolutionary and quantum theories.

Summary Although the factual existence of NDEs is no longer doubted and the semiology well-described, a pathophysiological model that includes all aspects of NDEs is still lacking.

Keywords Brain death · Cardiac arrest · Coma · Consciousness · Death · Out-of-body experiences

Introduction

Near-death experiences (NDEs) are life-changing events, occurring in close encounters with death such as during cardiac arrest, traumatic brain injury or major surgery, as well as in non-life-threatening circumstances including syncope, meditation, rapid eye movement (REM) sleep, and after consumption of drugs, particularly, *N,N-Dimethyltryptamine* (DMT) and ketamine [1, 2•, 3]. NDEs are unique and rich in individual details but share the so-called "core experience", characterized by recurrent items including feelings of extreme peace (or fear), altered time perception, seeing a dark tunnel with bright light, and out-of-body experiences [1, 2•, 3]. Based on these features, Ring, 1980 [4], and Greyson, 1983 [5••], introduced numerical scales to quantify these experiences. The most widely used is the Greyson Near-Death Experience

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Scale (GNDES) which consists of 16 questions. Each answer is rated with 0, 1, or 2 points, and the (arbitrary) cut-off for NDEs is 7 points (out of a maximum of 32 points) [5••].

Since the introduction of the term "near-death experience" by Moody in his book *Life after Life* from 1975 [6], the interest in NDEs has grown, and reports on NDEs have been collected from all regions in the world and from many different cultures. However, descriptions of experiences associated with the process of dying occur in texts dating back to the Middle Ages (e.g., the *Ars Moriendi*, a Latin text from the fifteenth century; and the *Bardo Thodol*, the "Tibetan book of the dead" from the fourteenth century) or even longer (e.g., the *Bible*). These accounts have involved descriptions of seeing a bright light, perceptions of peacefulness, and love but also fear and emptiness, separation from the body, meeting spirits, and deceased relatives. Indeed, the imagery of NDEs is deeply rooted in religion, the arts, and the literature [7] (Fig. 1).

The etiology of NDEs remains unknown. Several theories and models have been proposed without satisfying scientific proof [8]. Much of the scientific and philosophic discourse centers around the archetypical mind-body problem. On one side, reports of NDEs occurring in life-threatening and non-life-threatening situations have been interpreted as evidence suggesting that the materialistic, reductive approach to consciousness must be overcome [9, 10]. On the other side, reports of NDEs during situations in which brain physiology

was objectively impaired, such as with cardiac arrest, have spurred the interest to investigate the possibility for neuronal function in circumstances in which biological dogma holds that such function is absent [11•, 12, 13••].

The aim of this review is to give a concise analysis of the recent literature on the semiology and etiology of NDEs. We will discuss new data considering established and more recent theories and models. Finally, we will briefly discuss what is needed for future research.

Methods

We performed a review of the most recent literature (2014–2019) using a predefined search strategy to identify novel aspects of the semiology and etiology of NDEs.

Types of Studies

We evaluated all cross-sectional or longitudinal, retrospective or prospective, observational clinical and research studies as well as interventional trials, case reports, and reviews reporting on NDEs. We excluded interviews, editorials, opinions, and news articles. Also, studies suggesting theories underlying NDEs such as anoxia and/or hypercarbia, brain neurotransmitter actions as well as quantum mechanics and psychological hypothesis were included. We excluded studies on
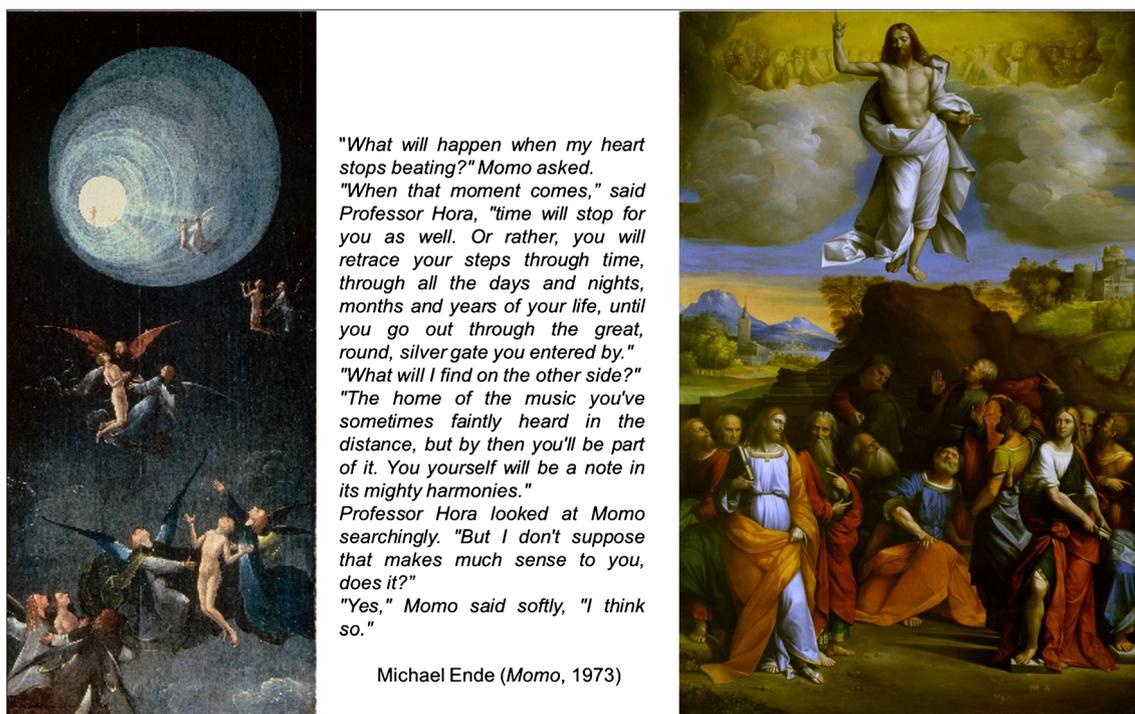

"What will happen when my heart stops beating?" Momo asked.
"When that moment comes," said Professor Hora, "time will stop for you as well. Or rather, you will retrace your steps through time, through all the days and nights, months and years of your life, until you go out through the great, round, silver gate you entered by."
"What will I find on the other side?"
"The home of the music you've sometimes faintly heard in the distance, but by then you'll be part of it. You yourself will be a note in its mighty harmonies."
Professor Hora looked at Momo searchingly. "But I don't suppose that makes much sense to you, does it?"
"Yes," Momo said softly, "I think so."

Michael Ende (*Momo*, 1973)

Fig. 1 Examples of near-death experiences from the visual arts (left; a reproduction of Hieronymus Bosch's "Ascent of the blessed", 1505–1515), prose (middle, a citation from "Momo", a 1973 children fantasy book; note the description of a life review), and religion (right; a reproduction of Benvenuto Tisi da Garofalo's "Ascension of Christ", 1510–1520). Reproduced with permission from the *Ministero dei beni e delle attività culturali, Galleria dell'Accademia*, Venice, and the *Gallerie Nazionali di arte antica*, Rome (Italy)

NDE aftereffects, studies focusing on out-of-body experiences or use of recreational drugs without reference to NDEs.

Participants

All subjects aged ≥ 18 years, at the time of the experience or of the study, reporting NDEs associated with life-threatening events (cardiac arrests, suicide attempts, traumatic brain injuries, surgeries, coma) as well as non-life-threatening situations (migraine, meditation, REM sleep, syncope, drugs) were included.

Electronic Literature Search Strategy

We searched MEDLINE (PubMed) and Scopus for relevant literature from 1st January 2014 to 5th of April 2019 (2014–2019 for Scopus), using the search terms 'near-death experience' and 'out-of-body experience'. For search examples and filters, refer to *Supplementary Files 1 (Protocol and Appendix)*. Non-English literature was included only if an English abstract and a reliable translation of the manuscript into English were available. Reference lists were manually screened for further relevant articles.

Data Collection and Analysis

After reviewing titles and abstracts, relevant studies were assessed on a full text basis. Data were extracted by the first author and cross-checked by the senior author; any uncertainties concerning data extraction and interpretation were resolved by consensus.

Results

The primary search yielded 885 titles, including four manually added. After screening and removal of 59 duplicates, 42 met the inclusion criteria for the final review. A detailed flowchart is available from Supplementary Files 1. Table 1 provides an overview on study design, recruitment methods, and demography from those studies for which demographic data were available.

Semiology

NDEs were labeled as positive, neutral, or negative [1, 2•, 20, 24•, 27, 33], according to associated emotions and features [27, 33]. Positive NDEs were recorded more often (11 out of 13 papers, 86%), including a higher frequency of positive emotions among a general cohort of people with NDEs (between 82% [1, 2•] and 88% [24•]). Frequent positive elements included out-of-body experiences or the perception of the absence of a physical body; a brilliant universal light; entering a tunnel of light; peacefulness and love; altered time perception; exceptionally vivid senses; being in an unearthly/spiritual realm; life reviews; and, less commonly, meetings with spiritual beings and deceased relatives (Table 2).

Negative experiences, including fear and distress, were noted in five studies [1, 2•, 20, 24•, 33], with a prevalence ranging from 1 to 9% [1, 2•, 24•]. Authors of one study attempted to categorize negative features by grouping them into three classes: inverse, void, and hellish [33]. The first class involved typical features (e.g., bright light, out-of-body experiences, life review) that were perceived as frightening or distressing; the second one was characterized by sensations of emptiness and darkness; and the third and least common class included perceptions of demons, infernal creatures, and agonizing sounds [33]. Negative experiences were more common with childbirth complications, surgery, trauma, suicide attempts, and infratentorial (as opposed to supratentorial) lesions [1, 27, 33]. Neutral experiences were recorded in four studies and occurred in 2–7% of NDEs [1, 2•, 24•, 27].

Depending on etiologies, some authors refer to NDEs as "classic" or "NDE-like" [1, 27, 28]. Classic experiences are related to real or perceived life-threatening events such as coma from cardiac arrest, brain injuries (e.g., cerebrovascular or traumatic), complications during major surgery, or worsening of ongoing systemic illnesses; NDE-like experiences occur during non-life-threatening situations such as sleep, meditation, syncope, and consumption of recreational drugs [1, 20, 29, 31, 32•]. The semiology of NDEs is identical in the two types [1], but NDE-like experiencers appear more prone to fantasy compared to those with classic NDEs [28]. However, although the features of NDEs are associated with a highly variable temporal order [25], more intense experiences as reflected by higher GNDES scores are associated with more detailed and rich memories [22].

Two controlled trials demonstrated how the injection of ketamine [31] and DMT [32•] led to NDEs, akin to those occurring in life-threatening circumstances, with similar GNDES mean scores: 10.7 for ketamine, 13.3 for DMT, and 13.3 for cardiac arrest patients [21•, 31, 32•]. When systematically compared, NDE narratives were found to have much in common with reports of experiences following drug consumption [2•]. Notably, experiences made during exposure to ketamine, *Salvia divinorum* and, to a lesser extent, serotoninergic psychedelics (e.g., ibogaine, ayahuasca, lysergic acid diethylamide (LSD), and N,N-Dipropyltryptamine (DPT)) were highly similar to NDEs, suggesting release of endogenous N-methyl-D-aspartate (NMDA) antagonists during NDEs [2•].

Pathophysiology

While some have doubted that NDEs are real experiences and consider illusory memory recollection to be a more likely

Table 1   List of main studies with demographic data

Article	Site	Study design	Recruitment; setting	Population/gender; age[a]
Hausheer 2014 [14]	USA, Missouri	Descriptive	N/A	Female, 20[a]
Cicoria Toni and Cicoria Jordan 2014 [15]	USA, New York	Descriptive	N/A	Male
Eben Alexander III 2015[c] [16]	USA, Massachusetts	Descriptive	N/A	Male; 54[a]
Khanna et al. *2018*[c] [17]	USA, Massachusetts	Descriptive	N/A	Male; 54[a]
Lawrence 2017 [18]	USA, North Carolina	Descriptive	Literature Search	Veteran, Male
Danon 2015 [19]	Israel	Descriptive	Retrospective; community	2F, 1M; 22–70
Bianco et al. *2017* [20]	Italy	Descriptive	Retrospective; community	4F, 2M; 46
Cassol et al. *2018* [21]	Belgium	Descriptive	Retrospective; community	11F, 23M; 49 ± 13[a]
Martial et al. *2019* [2•]	Belgium, USA	Descriptive Qualitative study	Retrospective; community	425F, 200M; 31 ± 15[a]
Martial et al.*2017* [22]	Belgium France	Observational Analytic Cross sectional	Retrospective; community	82F, 70M; 33 ± 14[a]
Royse and Badger 2017 [23]	USA, California, Indiana	Observational Analytic Cross sectional	Prospective; community	18F, 28M, 1 transgender; 47.1
Moore and Greyson 2017 [24•]	USA, Virginia	Observational Analytic Cross sectional	Retrospective; community	88F, 34M; 27.9 ± 10.9[a]
Martial et al. *2017* [25]	BelgiumFrance	Observational Analytic Cross sectional	Retrospective; community	82F, 72M; 34 ± 17[a]
Chandradasa et al. *2017* [26•]	Sri Lanka	Observational Analytic Cross sectional	Randomized; hospital	9F, 16M; 50 ± 15.42[a]
Charland-Verville et al. *2014* [1]	Belgium	Observational Analytic Cohort	Retrospective; community	50 NDE-like: 25F, 25M; 31 ± 11[a] 140 real NDE: 79F, 61M; 32 ± 15[a]
Charland-Verville et al. *2015* [27]	Belgium France	Observational Analytic Cohort	Retrospective; community	8 locked-in: 5F, 3M; 31 ± 6[a] 23 classic NDE: 12F, 13M; 31 ± 14[a]
Parnia et al. *2014* [13••]	USA, UK, Austria	Observational Analytic Cohort	Prospective; hospitals	45F, 95M; 64 ± 13[a, b]
Martial et al. *2018* [28]	BelgiumFrance	Observational Analytic Cohort	Retrospective; community	51 classic NDE: 27F, 24M; 35 ± 17[a] 57 NDE-like: 36F, 21M; 28 ± 16[a]
Martial et al. *2017* [22]	Belgium France	Observational Analytic Case-control	Retrospective; community	9F, 11M; 60 ± 6
Palmieri et al. *2014* [29]	Italy	Observational Analytic Case-control	Retrospective; community	7F, 3M; 49 ± 6.8
Goza et al. *2014* [30]	USA, Texas	Observational Analytic Case-control	Retrospective	Veterans: 3F, 17M; 36
Dakwar et al. *2018* [31]	USA, New York	Experimental Randomized controlled trial Ketamine vs Midazolam	Prospective; community	8F, 10M; 49.8 ± 5.7[a]
Timmerman et al. *2018* [32•]	UK	Experimental Non-randomized placebo-controlled trial	Prospective; community	6F, 7M; 34.4 ± 9.1[a]

[a] Age at NDE

[b] Only nine patients had NDEs, their demographic data were not specified

[c] These two studies are about the same patient

mechanism [42], most researches argue that NDEs are real, stored in episodic memory, and occur in altered states of consciousness [24•, 29, 43]. Table 2 provides a summary of contemporary theories on the origins of NDEs.

Assuming a certain degree of brain integrity, Lake [10] suggested a multifactorial NDE model in which precipitating physiological or psychological factors such as traumatic experiences, fear, or drugs activate dynamic networks that are highly integrated (connectomes). Further, in a case-control study, Nelson [37, 44] suggested that NDEs result from intrusion of REM sleep into waking consciousness, arising from a disruption of the physiological balance between sleep and awake states, with the involvement of the brainstem. The association of NDEs with REM sleep intrusion was supported by another study using a crowd-sourcing approach [3]. In stark contrast, several quantum theories have been advanced that included possible mechanisms for disembodied consciousness, i.e., consciousness not produced by the brain [15, 16, 38, 45], introducing terms such as "entangled states", "subliminal and supraliminal realities", and "informational field matter" [35, 39, 40].

NDE theories were also framed in an evolutionary context, including hypotheses about genetic and epigenetic components and a "survival original scope" [36•, 41]. Accordingly, a predisposition to NDEs allowed early hominids to develop complex mental imagery and adaptive responses to unpredictable and life-threatening situations, thereby increasing survival rates [36•, 41]. The predisposition to NDEs might result from direct or indirect selection, involving genetic drift as well as epigenetic factors like stress-induced brain changes [36•].

Finally, neurochemical models were suggested in three studies showing multiple similarities between drug consumption and real near-death situations [2•, 31, 32•]. Although endogenous production of DMT is considered unlikely to generate NDEs, other molecules such as dynorphin, glutamate, and serotonin might have a role [34].

Discussion

Semiology

With the introduction of the Greyson Near Death Experience scale in 1983, research on the semiology of NDEs became more objective and standardized. The most recurrent elements of NDEs were identified [22, 23, 24•, 28, 29, 32•], permitting a shift from descriptive [15, 16, 19] to more quantitative studies [13••, 32•]. However, most patients with awareness during or memories from the period of cardiac arrest do not meet the cut-off of 7 points on the GNDES, although they may report detailed memories [13••]. This suggests that the cut-off of 7 points is arbitrary and that NDEs likely reflect a continuum of experiences [13••].

Further, negative and distressing emotions, which are also part of the NDE semiology, are poorly investigated. This again may reflect a limitation of the GNDES, as this scale specifically addresses positive but not negative emotions. Three types of negative NDEs have been described: inverse, i.e., distressing perception of otherwise positive elements; void, i.e., feelings of cosmic emptiness and complete isolation; and hellish experiences, i.e., journeys through an infernal world [33, 46]. The factual features are comparable to those of positive experiences—in the inverse type they are identical—but perceptions, feelings, and surroundings are opposed: spirits are wandering, restless, and desperate; the bright light is perceived as a collision; the realm is void and empty instead of peaceful and harmonious [33].

Personal beliefs, self-perception, and cultural backgrounds may contribute to why some people have negative rather than positive NDEs, but also the locations of a possible brain injury might be involved [27, 47]. In one study, NDEs of patients with infratentorial lesions, resulting in a locked-in syndrome, were compared to NDEs of patients with supratentorial lesions, revealing that the first group had less positive experiences, possibly resulting from damage to limbic/paralimbic systems and the psychological distress of being paralyzed and anarthric [27]. Given that NDES with negative experiences appear to be underreported, more studies are necessary to examine the similarities and dissimilarities with positive NDEs [47].

Based on 154 narratives, Martial et al. [25] examined the temporality of NDE features but, despite common and recurrent characteristics, did not find a specific temporal order, suggesting that NDEs are deeply personal and unique experiences. However, although authors commonly distinguish between "real" (or "classic") NDEs, arising in life-threatening situations, from "NDE-like" experiences in non-life-threatening circumstances [1, 27, 28, 48], NDEs and NDE-like events are identical in terms of content and intensity [1, 48], suggesting that they share the same biological mechanisms [1].

Demographics

The field of NDE research is dominated by Western investigators [48, 49] (Table 1). We found only two recent studies from non-Western cultures: one from Israel and one from Sri Lanka [19, 26•]. Although the authors from Sri Lanka recorded frequencies in men and in monotheistic religions as opposed to Buddhism, the results are difficult to interpret because the authors investigated NDEs in unselected patients from a general hospital population and used a different cut-off on the GNDES (4/32). Still, there is no evidence to suggest that cultural backgrounds, geography, or religiosity substantially alter NDE characteristics [11•, 26•, 48–52].

Table 2 List of main studies with information on features and hypotheses

Article	Life-threatening event	Non-life-threatening event	Scale evaluation; score	Positive-negative	Common semiology characteristics	Hypothesis
Hausheer 2014 [14]	Iatrogenic acute respiratory failure in variant of Guillain Barre syndrome	–	–	–	Out-of-body experience; tunnel of light; peacefulness and love	–
Cicoria Toni and Cicoria Jordan 2014 [15]	Cardiac arrest after lightning strike	–	–	Positive	Out-of-body experience; brilliant light; peacefulness and love; altered time perception	Disembodied consciousness
Eben Alexander III 2015[a] [16]	Coma in E. coli meningo-encephalitis	–	–	Positive	Altered time perception; spiritual realm; melodies; bright light; no physical body; meeting with a deceased relative	Disembodied consciousness
Khanna et al. 2018[a] [17]	Coma in E. coli meningo-encephalitis	–	GNDES ≥ 7/32; 29/32	Positive	Bright light; no physical body; unfamiliar place; meeting with a deceased relative	–
Lawrence 2017 [18]	Bomb explosion	–	–	Positive	Peacefulness; tunnel of light; absence of physical body; meeting with deceased relatives	–
Danon 2015 [19]	Coma after severe asthma attack; after a close shooting; after a car accident	–	–	–	Bright light; meeting deceased relatives; altered time perception; no physical body	–
Bianco et al. 2017 [20]	2 comas after accident; 1 coma after cardiac arrest; 1 kidney infection	1 sleep; 1 meditation	GNDES ≥ 7/32	3 Positive; 3 Negative	–	–
Cassol et al. 2018 [21]	34 cardiac arrests	–	GNDES ≥ 7/32; 13 ± 5	–	–	–
Martial et al. 2019 [2]	Head injuries; anesthesia/drug use; cardiac arrest	–	–	512 Positive (82%) 50 Neutral (2%) 56 Negative (9%)	–	Endogenous NMDA antagonist's ketamine-like
Martial et al. 2017 [22]	Severe brain insults, cardiac arrests, traumatisms	–	GNDES ≥ 7/32	–	More intense NDE = more detailed the memory of it	–
Royse and Badger 2017 [23]	Burns	–	GNDES ≥ 7/32	–	Altered time perception; out of physical body; feeling of peace; more vivid senses	–
Moore and Greyson 2017 [24]	47 loss of vital signs (9 cardiac arrests);30 serious illness or injury	25 non-serious	GNDES ≥ 7/32; 16.95 ± 6.27	107 Positive (88%) 5 Neutral (4%) 6 Negative (5%)	–	Not false memory
Martial et al. 2017 [25]	–	–	GNDES ≥ 7/32; 16 ± 6	–	Peacefulness; bright light; encountering with spirits/people; out-of-body	–
Chandradasa et al. 2017 [26•]	–	–	GNDES ≥ 4/32	–	–	–
Charland-Verville et al. 2014 [1]	45 anoxic comas (cardiac arrest, near drowning); 30 traumatic comas (vehicle accidents; falls); 65 other comas (surgery; ongoing illnesses)	13 sleep; 11 syncope; 5 meditation; 3 drugs and alcohol; 18 other	GNDES ≥ 7/32	172 Positive; 16 Neutral; 2 Negative	Peacefulness; out-of-body experience; tunnel of light; altered time perception	–
Charland-Verville et al. 2015 [27]	27 comas after cerebrovascular accident; 4 comas after trauma	–	GNDES ≥ 7/32	8 Neutral; 23 Positive	LIS group: altered time perception; life review; out-of-body Classic NDE: peacefulness and joy; tunnel of light; unearthly realm	Less positive experience related to impaired pontine/ paralimbic system or emotional distress
Parnia et al. 2014 [13••]	Cardiac Arrest	–	GNDES ≥ 7/32	–	Altered time perception; feeling of peace; altered senses; separation from the body	Presence of awareness during cardiac arrest
Martial et al. 2018 [28]	51 Life Threatening	57 Non-Life Threatening	GNDES ≥ 7/32; Classical 16 ± 5 NDE-like 15 ± 6	–	NDE-like more fantasy proneness	–
Martial et al. 2017 [22]	9 anoxic comas; 3 traumatic brain injury; 8 other comas (surgery; ongoing illnesses)	–	GNDES ≥ 7/32	–	–	Specific cognitive processing leading to illusory recollection
Palmieri et al. 2014 [29]	4 traumatic injuries; 3 comas after severe medical conditions	2 isolation or existential crisis	GNDES ≥ 7/32; 16.5 ± 5.7	–	–	Not imagined or false memory; stored in the episodic memory

Table 2 (continued)

Article	Life-threatening event	Non-life-threatening event	Scale evaluation; score	Positive-negative	Common semiology characteristics	Hypothesis
Goza et al. 2014 [30]	Active combat or surgery sequelae	–	GNDES ≥ 7/32; 10.7	–	–	–
Dakwar et al. 2018 [31]	–	Ketamine injection	GNDES ≥ 7/32; 10.7	–	–	–
Timmerman et al. 2018 [32•]	–	Injection of *N,N*-Dimethyltryptamine (DMT)	GNDES ≥ 7/32; 13.3 ± 4.55	–	Unearthly world;peacefulness; more vivid senses; harmony and unity	Implication of medial temporal lobe for content and emotions
Bush and Greyson 2014 [33]	3 childbirth; 2 attempted suicide; 2 traumata; 1 massive hemorrhage; 1 intestinal rupture; 1 heart failure; 1 hyperthermia	–	–	Negative	Inverse; void; hellish	–
Nichols 2017 [34]	–	–	–	–	–	Not endogenous DMT; but dynorphine, glutamate, serotonin
Gaiseanu 2017 [35]	–	–	–	–	–	Quantum processes
Lake 2019 [36•]	–	–	–	–	–	Evolutionary value
Nelson 2014 [37]	–	–	–	–	–	Blending of REM and waking consciousness
Radin et al. 2014 [38]	–	–	–	–	–	Disembodied consciousness, psychic perception
Lake 2016 [10]	–	–	–	–	–	Dynamically interconnected neural networks
Shan 2018 [39]	–	–	–	–	–	Consciousness as an entity with entangled states; quantum theory
Braban 2016 [40]	–	–	–	–	–	Presence of subliminal/ quantum level of reality; quantum theory
Evrard et al. 2018 [41]	–	–	–	–	–	Psychodynamic model in an evolutionary context

[a] These two studies are about the same patient

"–"Not applicable or no data available

Gender differences do not seem to influence NDEs either [11•], with the possible exception that women appear to report more vivid experiences, but this might represent an artifact due to women being more open to share experiences [6, 48]. Neither do other sociodemographic variables such as education [11•, 51, 52], marital status [51], and employment status [49] appear to change the incidence or semiology of NDEs. Also, duration and etiology of a possible brain dysfunction, i.e., traumatic or nontraumatic brain injury and systemic illnesses, do not appear to influence NDE semiology [1, 17, 19]. In contrast, personality traits may play a role, i.e., people with NDEs in non-life-threatening situations were found to be more prone to fantasy and people experiencing NDEs after receiving DMT had a greater tendency towards delusional thinking [28, 32•]. Age also appears to be important; hence, although NDEs may occur during the whole life, including childhood [53], they become less frequent after the age of 60 years [50, 52], with mean ages typically around 30–35 years (Table 1).

Pathophysiology

Whether NDEs are real or false/imagined events generated by the dying brain is still a matter of debate. Greyson and Moore [24•] compared memories of NDEs to memories of real events and of imagined events, concluding that NDE memories are perceived as "more real than real" [24•]. Further, Palmieri et al. [29] found that NDE memories are similar to those of real events in terms of richness of details, associated emotions and self-referential information, and that EEG activity obtained during recollection of either memories was similar. Conversely, Braithwaite [9] and French [54] hypothesized that NDE may be false memories generated by a disinhibited dying brain, and Martial et al. found that NDE experiencers are more prone to illusory recollection (i.e., remembering items not present), deducing that at least the richness of details of these memories might result from specific psychological mechanisms [42]. It can be concluded that the details of NDEs might be influenced by subjective psychological features, but that the core experience and its main features are perceived and stored as real events.

Different neurobiological theories of NDEs have been discussed, but authors tend to agree that the lack of empirical data and scientific evidence precludes full support for any of these [12, 45, 48, 55, 56]. We will briefly overview the most important theories.

Activity within temporal lobes of the brain, notably the temporoparietal junctions, can evoke out-of-body experiences [57–59]. A higher frequency of temporal lobe dysfunction was found in patients with NDEs from life-threatening events [60], although this dysfunction might simply have been due to the severity of the brain injury which was not adjusted for in

that study [8, 56]. Also, it should be noted that out-of-body experiences are part of only a minority of all NDEs, that they can occur outside the context of NDEs, and that they also exist on a spectrum ranging from looking at one's own body from an entirely detached perspective to more subtle perceptions of a bodily dissociation [6, 16, 56, 58, 61].

REM intrusion and the arousal system might have a role in NDE's in non-critical situations [44, 56, 62•]. Yet, REM intrusion might perhaps be less likely involved in NDEs occurring in cardiac arrest patients, where EEG activity is silent, in subjects under anesthesia, where REM is inhibited and in subjects with brain injuries, especially infratentorial ones, where the brainstem and its connections, responsible for the sleep-arousal cycle, are damaged [27, 55, 61].

Cerebral anoxia/hypoxia and hypercapnia may generate experiences resembling NDEs, e.g., tunnel vision, bright lights, out-of-body experiences [63–65], albeit possibly less intense [8]. Hence, blood gas measurements in cardiac arrest patients with and without NDEs have yielded somewhat discordant results. Parnia et al. [50] found higher paO2 levels in NDE experiencers but no difference in $paCO_2$, speculating that cerebral anoxia might be a protective (rather than a causal) factor [63, 65]. Klemenc-Ketis et al. [52] found a correlation between hypercapnia and NDEs but not between hypoxia and NDEs, concluding that higher levels of CO_2 might induce NDEs by altering the acid base equilibrium and that hypoxia might activate NMDA receptors as further discussed below. These findings should be cautiously interpreted due to the small sample sizes (4 and 10 subjects, respectively) and the contrasting results. However, it cannot be excluded that these factors play a role in triggering or enhancing the capability to recall NDEs [66]. Several neurochemical models have been proposed from serotonin to endogenous opioids [67, 68], but in light of new findings, we will focus on ketamine and DMT [69, 70].

As mentioned previously, the injection of ketamine and DMT in controlled trials [31, 32•] generated experiences very similar to the "real" NDEs in terms of content (GNDES scores ≥ 7/32) and semantic narratives [2•]. DMT is produced by the pineal gland, apparently during stress with neuroprotective functions [71]. However, the DMT model seems implausible as a sole cause for NDEs because the pineal gland is unlikely to excrete the high quantities required for a psychoactive effect and, even if it did, DMT would be quickly degraded by the monoamine-oxidases MAO found in cerebrospinal fluid [34]. In contrast, the ketamine model is based on the fact that stressful brain conditions such as hypoxia or hypovolemia increase glutamate release, which, via excessive activation of NMDA receptors, may damage neurons. Ketamine, by binding to NMDA receptors, is brain-protective and thus, a ketamine-like endogenous substance has been hypothesized to contribute to NDEs [2•, 72–74]. In line with this, NDEs were observed with the intake of ibogaine, a naturally occurring psychoactive substance with dissociative features [75].

Models combining several of these neurochemical theories have been proposed [76] but remain speculative [8].

Some of these hypotheses may account for NDE-like situations, where the brain is functioning and intact, but what happens in life-threatening circumstances when the brain activity apparently is absent [50, 77, 78]? Prospective studies on cardiac arrest patients have highlighted isolated cases of patients that suggest the possibility of preserved awareness during cardiac standstill, when all electrophysiological brain activity should be lost according to biological doctrine [11•, 13••, 50]. For instance, in the AWARE study, Parnia et al. reported that a 57-year old man, who survived cardiac arrest, described in detail colors, sounds, people, and the automated external defibrillator (AED) used during his resuscitation. His memories were in line with the medical records and, according to the AED algorithms, the authors concluded that the patient appeared to have been aware and conscious for at least 3 minutes during his resuscitation despite apparent absence of physiological brain activity [12, 13••]. This observation corroborates previous anecdotal reports of accurate external-world descriptions during clinical death with a flatline EEG [6, 79]. Hence, some authors have questioned the causative relationship between cortical activity and consciousness, speculating whether consciousness might be a disembodied entity rather than a physical product of the brain [11•, 13••, 50]. Alternatively (and perhaps more likely in the present authors' opinion), NDEs may arise either before or after the cardiac arrest, when brain function is still present or restored [3].

Additionally, it is disputed whether a flatline EEG is an accurate and precise index of complete neuronal inactivity. Some authors observed that scalp EEG might miss deep-seated EEG activity [80, 81] and noted that there is no definitive evidence that NDEs occur exactly at the time of EEG inactivity [9]. Further, studies in rats showed the presence of neural correlates within 30 s after the cardiac arrest, resembling states of heightened conscious processing [82] and the presence of distinctive neuronal activity, i.e., a burst in frontal coherence and a posterior shift of power as assessed by electrocorticography (ECoG). The authors suggested that this may represent a neural correlate of consciousness [83•]. Chawla et al. [84] found similar results in humans, recording surges of electrical activity in EEG of dying patients, and hypothesizing that near-death memories may be generated during these spikes of brain activity. Given that the loss of brain function around death appears to be gradual rather than binary and that a flatline EEG might not be a reliable sign of complete inactivity, for how long would the dying brain be capable of generating lucid, detailed, accurate, and long-lasting memories that can be reported as NDEs upon resuscitation [9, 12, 16, 17, 48]? More studies, including EEG/ECoG at around the time of death (animal models) or in non-life-threatening situations associated with NDEs (humans), are certainly needed.

Methodological Considerations

Most studies on NDEs are observational, typically case reports or cross-sectional studies (Table 1). In case-control studies, it is important to isolate the independent variable: cases should be exactly the same as controls, except for the presence of NDEs, i.e., patients with NDEs after life-threatening events should be compared to patients without NDEs who faced similar events [42, 56]. Further, since the recruitment is usually retrospective, authors should preferentially adjust for time passed by since the accident, although this is rarely feasible [8, 56, 85].

In cohort studies, authors typically retrospectively recruit patients with NDEs of different etiologies, e.g., life-threatening vs non-life-threatening events, and compare these groups [1, 28]. Alternatively, a cohort of subjects who might have experienced NDEs in life-threatening conditions is followed over time, i.e., prospective recruitment. In this case, investigators typically enroll hospitalized survivors of cardiac arrest or traumatic brain injuries, interviewing the subjects a few days after the event, thereby collecting more reliable data [11•, 13••, 52, 85]. Further, this type of study permits to explore medical variables during the life-threatening event, such as blood gasses, time of cardiac standstill, numbers of resuscitations; albeit, so far, none of these factors seems to influence NDEs. However, a prospective design typically requires a multicentral setting to allow recruitment of a large enough sample [13••].

Experimental studies on NDE, i.e., controlled trials, are uncommon. To our knowledge, in the last 5 years, only two such studies have been conducted: in one, investigators exposed patients to intravenous ketamine versus midazolam (double blind) [31]. Patients receiving ketamine scored higher than controls (receiving midazolam) on the GNDES with a mean of 10.7 versus 4.8, respectively [31]. In the second study, DMT was tested against a placebo (single blind) [32•]. All participants received placebo and DMT in two different sessions, blinded for the sequence of administration. All 13 subjects scored above 7/32 on the GNDES when receiving DMT, with a mean score of 13.3, but only one participant scored 7 following placebo [32•]. Both studies proved that the drugs involved may lead to consciousness states akin to NDEs. Further, they showed the possibility of inducing and potentially controlling NDEs. Hence, controlled trials offer important new approaches to the study of NDEs.

Recent Consciousness Models

A neuronal model, which resembles the disinhibition theory [9], has been advanced by Lake [10]. The author suggested the existence of patterns of dynamic brain connectivity that are genetically and epigenetically determined. Thus, psychological or physiological factors might trigger different neuronal circuits, directly or indirectly interconnected,

which in turn may operate as "releasers of phenomenal content, retrospectively interpreted" as NDE [10]. The common features of NDE would result from the activation of specific networks, carrying mental imagery, genetically transmitted and conserved over time; the subjective features instead would result from encoding or decoding of personal memories or would reflect stochastic fluctuations in network dynamics. Of note, this model is applicable if we assume that NDEs occur with a functional brain, at least to a certain degree, but this remains to be proven. In the same vein, Facco et al. suggested that the mind-brain relationship might not be unidirectional, i.e., the mind being a brain epiphenomenon, but bi-directional, i.e., the mind actively shaping brain activity and modulating its plasticity. This dynamic model might help to comprehend that NDEs are unique experiences, originated by a constant and subjective mutual influence of brain and mind [55].

Also, a phylogenetic approach has been suggested, in which NDEs are considered a human predisposition, inherited from hominids, leading to altered states of consciousness in life-threatening situations as a survival strategy [36•, 41]. The evolutionary framework seems suitable for explaining the origin of NDEs, but the occurrence of NDEs in non-life-threatening situations would then be interpreted as a "spill-over" phenomenon, which remains entirely speculative.

Finally, consistent with the quantum hypothesis of a disembodied consciousness, several quantum models [35, 39, 40, 86] have been advanced in the last years, from the presence of a subliminal, latent, level of reality called "quantum reality" to the idea that consciousness involves low-quantum entanglements that can move, returning into the brain after resuscitation [35, 39, 40, 86].

Conclusions

NDEs can be positive or negative experiences, the latter being probably underreported [27]. Despite a shared common "core", NDEs are highly personal and unique without any fixed temporal order [25]. NDEs are not influenced by (most) sociodemographic variables, except perhaps for age and gender [11•, 49, 52]. They can occur in both life-threatening and non-life-threatening situations without differences in semiology. Fantasy proneness in NDE-like experiencers and certain drugs, notably ketamine, appear to predispose to NDEs [28, 32•]. Despite this, NDEs are experienced as real events and stored in episodic memory, but the exact mechanisms, importantly including the possibility for partially preserved brain activity during periods of flatline EEG, are still debated [29]. Several neurobiological, psychological, and transcendental theories have been proposed, but none is yet sufficiently proven. A multifactorial model, combining different theories and circumstances in which NDEs might occur, is required. However, for understanding such a complex phenomenon, more knowledge

about brain functioning and consciousness at around the time of death is needed. Future research will likely lead to refined concepts of brain death and brain function during resuscitation from near death. New studies need to focus on brain perfusion and neuronal changes in the dying brain, using psychedelics to model it and extending, in large numbers of subjects, previous EEG findings [32•, 84]; the use of neuroimaging techniques such as fMRI, positron emission tomography, and ECoG in real or virtual near-death situations, should be implemented [87–90], and more prospective studies on certain populations, notably cardiac arrests patients, are required for a better understanding of death and consciousness.

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Compliance with Ethical Standards

Conflict of Interest Costanza Peinkhofer, Jens P. Dreier and Daniel Kondziella each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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