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Does the arousal system contribute to near death experience?

Kevin R. Nelson, MD; Michelle Mattingly, PhD; Sherman A. Lee, PhD; and Frederick A. Schmitt, PhD

Abstract— The neurophysiologic basis of near death experience (NDE) is unknown. Clinical observations suggest that REM state intrusion contributes to NDE. Support for the hypothesis follows five lines of evidence: REM intrusion during wakefulness is a frequent normal occurrence, REM intrusion underlies other clinical conditions, NDE elements can be explained by REM intrusion, cardiorespiratory afferents evoke REM intrusion, and persons with an NDE may have an arousal system predisposing to REM intrusion. To investigate a predisposition to REM intrusion, the life-time prevalence of REM intrusion was studied in 55 NDE subjects and compared with that in age/gender-matched control subjects. Sleep paralysis as well as sleep-related visual and auditory hallucinations were substantially more common in subjects with an NDE. These findings anticipate that under circumstances of peril, an NDE is more likely in those with previous REM intrusion. REM intrusion could promote subjective aspects of NDE and often associated syncope. Suppression of an activated locus ceruleus could be central to an arousal system predisposed to REM intrusion and NDE.

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In life-threatening crisis, some who are near death experience dissociation from their physical body, euphoria, and transcendental or mystical elements. Such accounts led Raymond Moody to introduce the term "near death experience" (NDE) in his 1975 book *Life After Life*.[1] Although the experience of being near death is as primordial as death itself, this was the first work to compile survivor anecdotes and bring the concept of NDE into the medical and popular literature. A consistent aspect of NDE accounts is the powerful transformation of personal beliefs and values.[2] Assuming even the most complex psychological process is dependent on brain function,[3] the compelling intensity of NDE and lack of neurologic understanding argue forcefully for investigating the neurophysiologic basis of NDE.

What is NDE? NDE is a response to danger and composed of several elements that are summarized in table 1. Each NDE is thought unique and contains features in various combinations with no universal element. Individual as well as age[4] and cultural[5] heterogeneity suggests the content of NDE is modified by experience and indicates that NDE is not a simple automatism.

NDE can occur with or without neurologic impairment during the time of danger. The insult is most often ischemia, hypoxia, or both. It may not be possible to distinguish NDE with and without brain impairment by the nature of the experience alone.[6] There are no reported neurologic examinations of patients during or immediately after NDE.

The incidence of NDE in the dying will surely remain unknown. Investigations necessarily contain survivors without substantial injury to the substrates of language and memory. Some studies have intentionally selected subjects with complete neurologic recovery. Although there are many causes of NDE, prospective studies have focused on survivors of cardiac arrest, with incidences of 6.3% (4/63),[7] 10% (12/116),[8] and 12% (41/344).[2]

What causes NDE? No prospective series has found an underlying condition corresponding to NDE. Cardiac arrest survivors with NDE are not distinguished by administered medications, metabolic states, psychology,[2,4,7] sociodemographic factors,[8] resuscitative interventions, or the duration of cardiac arrest or unconsciousness.[2] There is a tendency for NDE to occur in those younger than 60 years[2,8] or with higher PO_2.[7]

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Table 1 *Features of NDE in 55 subjects*

Greyson NDE scale element	n (%), n = 55
Cognitive	
Altered sense of time	34 (62)
Accelerated thought processes	24 (44)
Life review	20 (36)
Sense of sudden understanding	33 (60)
Affective	
Feeling of peace	48 (87)
Feeling of joy	35 (64)
Feeling of cosmic unity	37 (67)
Seeing/feeling surrounded by light	43 (78)
Purportedly paranormal	
Vivid senses	42 (76)
Purported extrasensory perception	17 (31)
Purported precognitive vision	16 (29)
Sense of being out of physical body	44 (80)
Apparent transcendental	
Sense of an "otherworldly" environment	41 (75)
Sense of a mystical entity	30 (55)
Sense of deceased/religious spirits	26 (47)
Sense of a border/"point of no return"	37 (67)

The numbers and percentages given reflect nonweighted scores in each area. To determine if an experience meets near death experience (NDE) criteria, responses are weighted for the 16 NDE elements, yielding a maximum possible score of 32. A minimal score of 7 is necessary for an NDE.[79]

The clinical features of NDE should provide an indication of their physiologic basis. Extraordinary light is very common with NDE. Also, in some NDEs, the subject is immobilized, alert to the surroundings, and "aware of being dead."[1] Both of these observations are similar to aspects of the REM state. The REM state can intrude into wakefulness as visual hallucinations with sleep onset (hypnagogic) or upon awakening (hypnopompic). REM intrusion can also be auditory as well as atonic with sleep paralysis (SP) or cataplexy. During crisis, the atonia of REM intrusion could reinforce a person's sense of being dead and convey the impression of death to others.

The REM stage of sleep is defined by rapid saccadic eye movements and comprises cortical activation (EEG desynchronization), atonia, and pontogeniculo-occipital (PGO) waves. PGO waves are the established marker that the visual system has been activated. Originally proposed by Hobson et al.,[9] the pontine arousal system controls the transition in and out of REM sleep through a reciprocal interaction between the REM promoting cholinergic pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei, which are counterbalanced by REM-inhibiting actions of the serotonergic dorsal raphe (DR) and noradrenergic locus ceruleus (LC) nuclei. REM dissociative states arise as individual components of the REM state can be isolated by stimulation and inhibition. Lesions of the PPT impact the phasic portions of REM but not the atonia[10] as regions mediating atonia[11] and PGO waves[12] differ. Arguments favoring a contribution by REM intrusion to NDE follow five lines of evidence.

1. REM intrusion is a frequent normal occurrence. The intrusion of REM state into normal wakeful consciousness frequently occurs but is infrequently recognized. Cultures with specific linguistic references have a high prevalence of SP.[13] Other groups have lower rates. Ohayon et al. found a 6.2% lifetime SP rate in nearly 14,000 of the general European population,[14] which agrees with the 6% found by Aldrich in normal North American control subjects.[15] Takeuchi et al.[16] deliberately elicited sleep-onset REM periods (SOREMs) in normal subjects and provoked SP, sometimes with complex visual and auditory hallucinations. Commonly SP occurs with visual or auditory hallucinations.[13,16-18] SP is facilitated by stress, fatigue, and sleep deprivation.[13,17] Cataplexy has a lower estimated prevalence in general populations of 1.2%[14] to 3.2%.[19] Sleep-related hallucinations are found in 19% of a healthy population.[15] In large surveys, the prevalence of hypnagogic hallucinations is 24 to 28%.[14,18]

2. REM intrusion underlies other clinical conditions. Narcolepsy is fundamentally a disorder of state boundary control with persistent REM intrusion.[20] Upwards of 50% of narcoleptic individuals experience sleep paralysis.[15] Narcoleptic patients have frequent hypnagogic or hypnopompic hallucinations,[15,21] typically during sleep's first REM period[22] and particularly if REM is of rapid onset.[21]

Complex visual hallucinations caused by lesions near the midbrain cerebral peduncles was first recognized by Lhermitte, who later wrote that peduncular hallucinations are an "expression of a dissociated sleep associated with release of dream images."[23] The imagery can assume tunnels with a "golden gate" at one end,[24] angels,[25] and feelings of levitation.[26] Lesions causing peduncular hallucinations are concentrated in the mesopontine paramedian reticular formation,[24] suggesting injury to the raphe nuclei facilitates physiologic release of intact PPT/LDT.

In delirium tremens (DT), Tachibana and colleagues[27] first observed an EEG akin to stage I sleep, with REMs and tonic muscle activity suggesting a dissociated REM state. A pattern of EEG and eye movements similar to DT is also found during hallucinations in several neurodegenerative conditions, including Parkinson disease (PD). REM intrusion during daytime naps is documented in patients with PD,[28] and disordered sleep is known to associate with PD hallucinations.[29] Arnulf and colleagues hypothesize that visual hallucinations in PD result from a narcolepsy-like REM state disorder,[30] observing that hallucinations correspond to recorded daytime SOREM. REM states were also recorded dissociated from muscle tone, with bursts of muscle activity during REM sleep and atonia during sleep without REM. Others have found hallucinations in PD during REM without atonia.[31] In narcolepsy, DT, and

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PD,[30] it is sometimes difficult to distinguish between REM sleep and wakefulness.

3. NDE elements can be explained by REM intrusion. The literature suggests that NDE requires a confluence of events. Noyes et al. described the psychological responses to danger in motor vehicle accident survivors.[32] Feeling detached from the world or body was a cardinal feature. The detachment is referred to as psychological dissociation. Survivors felt enhanced arousal and "unusual alertness," with thoughts speeded up, sharp, or lucid. A sense of greater control was common, and psychological dissociation is likely an adaptive response to danger that improves survival by diminishing panic. A group of self-reported NDE subjects, similar to those reported by this study, were found to have nonpathologic psychological dissociation consistent with a traumatic event.[33] Interestingly, feelings of detachment are also common during cerebral ischemia of syncope in the absence of danger.[34] Many NDEs are reported with little or no collaboration by medical data. Consequently, Owens et al.[6] evaluated the medical records of 58 subjects who had memories of when they believed themselves near death. On review, 28 subjects had serious illness possibly leading to death without medical intervention. The remaining 30 were in not in medical danger and therefore had psychological dissociation alone. The groups were remarkably similar in most measures. One of the few differences was the enhancement of light in the medically threatened group.

The often-cited light of NDE could be based on visual activity promoted by REM mechanisms during retinal ischemia. With hypotensive syncope, tunnel-like peripheral to central visual loss develops over 5 to 8 seconds, while other cortical functions remain.[35] Lambert and Wood confirmed retinal ischemia as the origin of syncopal blackout by preserving both vision and retinal perfusion using vacuum goggles to decrease intraocular pressure during arterial hypotension. In the absence of retinal input, pontine REM mechanisms predominantly influence lateral geniculate firing.[36] Cortical ischemia alone would not impede REM visual expression. The cortically blind are capable of visual dream imagery,[37] and during REM, the primary visual cortex is deactivated[38] while the extrastriate visual cortex is activated.[39] Moreover, simple and complex visual hallucinations are reported by a majority during ischemia from induced syncope.[34]

Autoscopy is a feature typical of NDE and has a recognized association with the REM state. Narcoleptic individuals often give account of autoscopy,[40,41] which occurs during REM and lucid dreams.[42] Sleep paralysis with autoscopy was disclosed by several normal respondents in a large survey.[18] Autoscopy is directly produced by stimulating the region of the nondominant angular gyrus[43] or amygdala[44] and is found with many clinical conditions. Surprisingly, autoscopy is a common experience. In a large European survey, 5.8% reported at least one autoscopic experience.[45] Autoscopy occurs with danger alone[46] and does not distinguish those who are or are not medically near death.[6] Syncope without danger provoked autoscopy in 4 of 42 subjects.[34] In epileptic patients, autoscopy was reported in 6% and independent of seizure type.[47] The intriguing recall of autoscopy during generalized tonic-clinic seizures[47,48] may have parallel with autoscopy during NDE from cardiac arrest. It is unknown when the memory of the autoscopic experience is established.

The reward system could influence feelings of rapture, peace, or euphoria often present with NDE. The PPT/LDT are considered instrumental in promoting reward behavior,[49] with fibers projecting to the ventral tegmental region.[50] Lesions of the PPT reduce reward-seeking behavior for many strong stimuli including food[51] and self-administered heroin.[52] The limbic and paralimbic regions active in REM sleep are also important in the reward system.[53] Pleasant or positive feelings are also common with syncope.[34]

The biologic purpose of dreams remains speculative. Many ancient and modern cultures have regarded dreams an augur of the future and link to the divine and deceased. Sleep-related sensations possess characteristics easily transformed into features of NDE, such as falling into an abyss found in 16% and the sensed presence of an entity in 9% of normal people.[45] Most dreaming occurs in REM sleep,[54] and despite the possible contribution by REM intrusion to NDE, NDE and dreams fundamentally differ. NDEs are recalled with an intense sense of realness that contrasts sharply to dreams. Furthermore, NDEs lack the bizarre characteristics of dreams. Yet importantly, REM intrusion under peril does provide a mechanism for stimulating limbic and paralimbic structures believed to underlie many of the ineffable transcendental and paranormal qualities of NDE.[4] In REM sleep, amygdala and anterior cingulate gyrus activity is detected on PET scan,[38,53,55] and PGO waves propagate to the basolateral amygdala, cingulate gyrus, and hippocampus.[56] REM intrusion could form the basis of subjective phenomena[34] and "dreams"[35] frequent with syncope and strikingly similar to NDE.[57]

4. Cardiorespiratory afferents evoke REM intrusion. Successful execution of Walter B. Cannon's "fight-or-flight" responses to danger requires the arousal system to be tightly coupled with central nervous control of the cardiorespiratory systems. Undoubtedly, the autonomic responses during the NDE conditions of danger, cardiorespiratory crisis, or syncope are characterized by heightened vagal afferent activity. Afferent fibers from stretch, pressure, mechanical, and chemoreceptors transmit sensory information from the heart, vascular, and pulmonary systems to the brainstem principally by way of the vagus but also the glossopharygeal and trigeminal nerves. The cervical portion of the vagus is made up of approximately 80% visceral afferents.[58]

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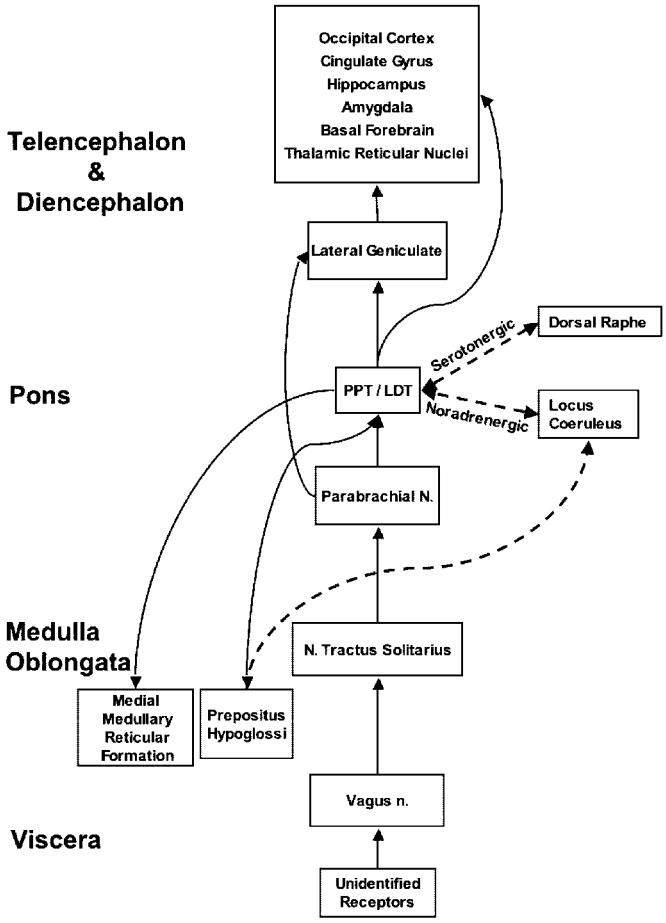

Figure. A partial summary of the relationship between vagal afferents and REM generation. Solid line = excitatory; dashed line = inhibitory; PDT = pedunculopontine; LDT = laterodorsal tegmental.

Vagal afferents robustly promote REM intrusion. Electrical stimulation of the vagus nerve in various animal preparations enhances REM,[59-61] elicits PGO waves,[60,61] and causes atonia.[60,62,63] The transition from wakefulness to REM can be very brisk after direct vagal stimulation, which is acknowledged by the terms "reflex REM narcolepsy"[62] and "narcoleptic reflex"[60] and depicted in figure E-1 on the *Neurology* Web site (go to www.neurology.org). The abrupt shift between wakefulness and the REM state, represented in clinical circumstances by SOREM, is important in the genesis of REM intrusion.[16,21] In epileptic individuals treated with electrical vagal nerve stimulation, Malow et al.[64] have shown "ambiguous" SOREM with sleep spindles and chin electromyographic tone, indicating intrusion of REM into non-REM states. The relationship between the vagus nerve and REM state generation is partially summarized in the figure.

Vagal afferents synapse within the medullary nucleus tractus solitarius (NTS). From the NTS, fibers travel to the pontine parabrachial nuclear complex (PBN), which is the principal relay for ascending cardiorespiratory afferents to the forebrain.[65] Stimulation of the lateral PBN has profound pressor[66] and respiratory[67] effects. The lateral PBN and nearby Kolliker–Fuse nucleus have long been viewed as essential to the pontine role in respiratory system.[68]

Vagal cardiorespiratory afferents and REM state generation critically intersect in the lateral PBN region. Both the NTS and the PBN send projections to the LDT, and the NTS projects to the PPT as well.[69] The cholinoceptive dorsal portion of the subceruleus region, responsible for generating a species equivalent of the PGO wave, receives afferents from neurons scattered throughout the PBN.[70] Cholinergic stimulation of the caudal portion of the lateral PBN immediately induces state-independent PGO waves[71] and REM enhancement.[71,72] PGO-on and PGO-off cells are recorded within the lateral PBN,[73,74] and caudolateral PBN lesions impair PGO generation.[75] Both REM phase–on and REM phase–off neuronal discharges can be recorded from many neurons within the lateral PBN, including some that are tightly phase locked.[76] Although not well characterized, REM-generating regions are known to respond to hypoxia. Cholinergic neurons within the PPT increase their firing rate,[77] and c-fos activity increases in the LDT.[78]

5. Persons with an NDE may have an arousal system predisposing to REM intrusion. Under apparently similar physiologic conditions, a fraction of cardiac arrest survivors have an NDE. Are those with an NDE susceptible to REM intrusion manifested by a greater life-time prevalence?

Methods. From a registry of 446 self-reported NDEs, 64 North Americans responded to e-mail inquiry. Structured interviews were conducted in 55 consecutive volunteers who qualified with an acute episode of danger associated with an experience satisfying Greyson criteria (total score ≥ 7).[79] The proximate causes of NDE included syncope/near-syncope during peril (10), cardiac events (8), near drownings (8), motor vehicle accidents (8), head trauma (5), perioperative incidences (5), strokes (3), falls (2), hypocalcemia (2), and 1 each of carbon monoxide poisoning, drug overdose, latex allergy, and lightening strike. Nine were excluded from study because they either had an experience with Greyson score less than 7($n = 3$) or the danger was not imminent (e.g., febrile illness) ($n = 6$). REM intrusion prevalence was compared with that in similarly interviewed age- and gender-matched control subjects recruited from medical center personnel or their contacts (table 2). All gave informed consent as approved by the institutional review board. Analyses of interview responses involved χ^2 and Fisher exact tests for group differences and analysis of variance to compare REM intrusion and Greyson scores, utilizing SPSS version 7.3 (SPSS, Chicago, IL).

Results. Subjects with NDE reported significantly greater REM intrusion than matched control subjects (table 2). The difference between NDE and con-

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Table 2 *Demographic features and REM intrusion contrasted between NDE and control subjects*

	NDE, n = 55	Control, n = 55	*p*
Women	36 (65%)	36 (65%)	
Age, y			
Mean	54.5	54.5	
Range	32–76	31–76	
Visual REM intrusion			
"Just before falling asleep or just after awakening, have you ever seen things, objects or people that others cannot see?"	23 (42%)	4 (7%)	<0.0001
Hypnagogic	9	2	
Hypnopompic	6	2	
Both	8	0	
Auditory REM intrusion			
"Just before falling asleep or just after awakening, have you ever heard sounds, music or voices that other people cannot hear?"	20 (36%)	4 (7%)	<0.001
Hypnagogic	9	1	
Hypnopompic	7	3	
Both	4	0	
Atonic REM intrusion (sleep paralysis)			
"Have you ever awakened and found that you were unable to move or felt paralyzed?"	25 (46%)	7 (13%)	<0.001
Atonic REM intrusion (cataplexy)*			
"Have you ever had sudden muscle weakness in your legs or knee buckling?"	4 (7%)	0 (0%)	0.12
Total REM intrusion (visual, auditory, sleep paralysis, or cataplexy)			
One or more element	33 (60%)	13 (24%)	<0.001
One element	9	11	
Two elements	11	2	
Three elements	11	0	
Four elements	2	0	

* Two of three precipitants required; laugh or joke, strong emotion or excitement, surprise or startle.

NDE = near death experience.

trol groups for cataplexy approached, but did not achieve, significance. Of the four NDE subjects with cataplexy, each had at least two additional elements of REM intrusion, and three had SP. Given the hypothesized association between REM intrusion and NDE, total Greyson scores were predicted by the presence or absence of REM intrusion events. Multiple linear regression revealed a prediction of total Greyson score by auditory REM intrusion ($R = 0.38$, $p < 0.01$). Higher mean Greyson scores were found in NDE subjects reporting visual ($t = -2.41$, $p < 0.02$) and auditory ($t = -3.02$, $p < 0.01$) intrusion. Mean Greyson scores showed no differences based on cataplexy or SP.

Episodes of REM intrusion appear to be substantially more common in the lifetime of subjects with an NDE. These findings imply that persons with an NDE have an arousal system predisposing to REM intrusion.

What becomes of the activated LC? The LC could be central to an arousal system predisposed to REM intrusion. The widely projecting LC is the brain's chief adrenergic nucleus. In addition to a role in the regulation of the wake–sleep cycle, the LC during wakefulness is paramount to behavior in vigilance[80] and stress.[81] Fear,[82] hypoxia,[78] hypotension,[83] and hypercarbia,[84] all vigorously stimulate the LC and increase tonic discharge rates. Although a causal relationship is not established, a precise and rapid correlation exists between LC discharge rates and behavior. Moderate rates strongly correspond to focused behavior, which shifts to scanning and labile attentiveness at high LC discharge rates.[85] Physiologic systems do not function in isolation. Such interdependence is classically exemplified by the yoked opposition between cholinergic and adrenergic portions of the peripheral autonomic nervous system. Although factors activating the LC have been extensively investigated, less is known about how LC activity is tempered. LC discharges can inhibited by the nucleus paragigantocellularis acting on α_2-adrenoceptors[86] or γ-aminobutyric acid from the nucleus prepositus hypoglossi.[87] Systems promoting REM powerfully inhibit the LC. Only during the REM state (or related atonia) does the LC cease discharging.[88] As LC suppression anticipates the REM state,[89] it may be that events leading to REM have the greatest influence. If scanning behavior became maladaptive or focused attention became necessary in crisis, counterbalancing inhibitory mechanisms such as the cholinergic REM system could suppress adrenergic LC activity and perhaps facilitate adaptation. Conceivably, the nature of LC suppression distinguishes those with REM intrusion and NDE.

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Conclusions. REM intrusion may underlie some of the subjective experiences of NDE and syncope. A role for the arousal system explains why various dangers lead to NDE. Because of this diversity, an inclusive NDE study such as this one bears the limitations of being retrospective and of self-reported subjects. Although preliminary, these findings encourage further investigation such as a prospective study of NDE under the special conditions of cardiac arrest. NDE would be predicted in those with prior REM intrusion. Yet challenges confront the hypothesis. The low-amplitude EEG waveforms of the REM state are likely to be obscured by the high-amplitude waveforms of cerebral ischemia.[90] REM saccades during syncope may be overridden by dominance of the vestibular system.[91] Last, patients are sometimes reluctant to report an unusual experience with intense personal meaning—meaning independent of how NDE arise.

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