SCIENCE AND SOCIETY

Death, unconsciousness and the brain

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Abstract | The concept of death has evolved as technology has progressed. This has forced medicine and society to redefine its ancient cardiorespiratory centred diagnosis to a neurocentric diagnosis of death. The apparent consensus about the definition of death has not yet appeased all controversy. Ethical, moral and religious concerns continue to surface and include a prevailing malaise about possible expansions of the definition of death to encompass the vegetative state or about the feared bias of formulating criteria so as to facilitate organ transplantation.

> Do we have the right to stop treatment using criteria that pretend to know the boundary between life and death?
>
> *P. Mollaret and M.Goulon*[1]

> Only a very bold man, I think, would attempt to define death.
>
> *H. K. Beecher*[2]

Throughout history, society and medicine have struggled with the definition and determination of death (BOX 1). In ancient Egypt and Greece, the heart was thought to create the vital spirits and the absence of a heartbeat was regarded as the principal sign of death[3]. The first person to consider irreversible absence of brain function to be equivalent to death was Moses Maimonides (1135–1204), the foremost intellectual figure of medieval Judaism, who argued that the spasmodic jerking observed in decapitated humans did not represent evidence of life as their muscle movements were not indicative of presence of central control[4]. However, it was not until the invention of the positive pressure mechanical ventilator by Bjorn Ibsen in the 1950s, and the widespread use of high-tech intensive care in the 1960s that cardiac, respiratory and brain function could be truly dissociated. Patients with severe brain damage could now have their heartbeat and systemic circulation provisionally sustained by artificial respiratory support. Such profound unconscious states had never been encountered before, as, until that time, all such patients had died instantly from apnoea.

The earliest steps towards a neurocentric definition of death were European[5,6]. In 1959, French neurologists Mollaret and Goulon first discussed the clinical, electrophysiological and ethical issues of what is now known as brain death, using the term 'coma dépassé' (irretrievable coma)[1]. Unfortunately, their paper was written in French and remained largely unnoticed by the international community. In 1968, the *Ad Hoc* Committee of Harvard Medical School, which included ten physicians, a theologian, a lawyer and a historian of science, published a milestone paper defining death as irreversible coma[7]. The report "opened new areas of law, and posed new and different problems for theologist and ethicist ... it has made physicians into lawyers, lawyers into physicians, and both into philosophers"[8]. Some years later, neuropathological studies showed that damage to the brainstem was critical for brain death[9]. These findings initiated the concept of "brainstem death"[10] and led UK physicians to define brain death as complete, irreversible loss of brainstem function[11,12]: "if the brainstem is dead, the brain is dead, and if the brain is dead, the person is dead"[10].

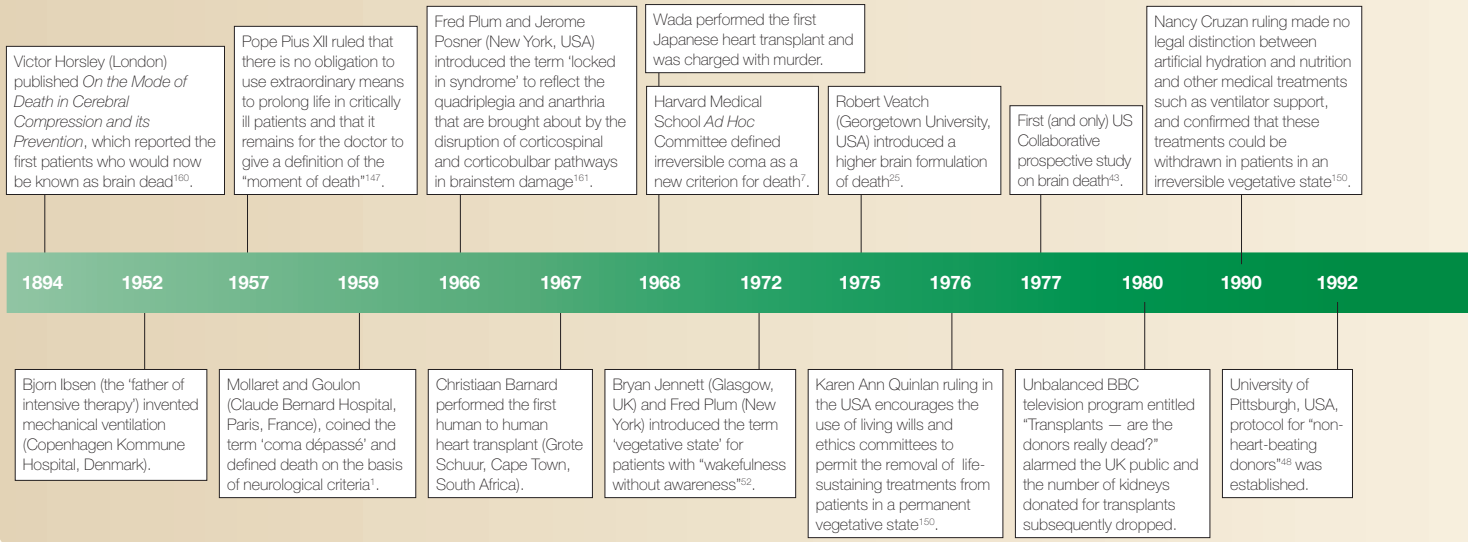
The tragic death of Terri Schiavo, misused by both 'right-to-life' and 'right-to-die' activists, recently illustrated to the world the difficulties that surround death in the vegetative state[13–15]. Many uneducated commentators have inaccurately referred to Schiavo's condition as 'brain dead' or 'neocortical dead', and her gravestone reads, "Departed This Earth February 25, 1990" — that is, the date on which her brain was damaged (although this was not total, and she was, therefore, not dead), whereas it was on March 31 2005 that her entire brain died and her heart irreversibly stopped beating.

This article has a broad ambit. It discusses the medical, philosophical, legal and ethical issues that are involved in the determination of human death. The brain-centred definition of death has a whole brain, brainstem and neocortical formulation. At present, only the two former concepts have an accepted medical basis. According to the consciousness- or personhood-centred neocortical definition of death, patients in a vegetative state are considered dead. This article emphasizes that brain death equals death; focuses on the differences between brain death and the vegetative state; argues that the neocortical definition of death cannot be implemented on the basis of reliable anatomical criteria or clinical tests; and briefly discusses the law and ethics of death and the end of life.

Brain death equals human death

Brain death means human death determined by neurological criteria. It is an unfortunate term, as it misleadingly suggests that there are two types of death: 'brain' death and 'regular' death[4]. There is, however, only one type of death, which can be measured in two ways — by cardiorespiratory or neurological criteria. This misapprehension might explain much of the public and professional confusion about brain death. Bernat and colleagues have distinguished three levels of discussion: the definition or concept of death (a philosophical matter); the anatomical criteria of

Timeline | **Medical, philosophical, ethical and legal milestones in death, dying and permanent unconsciousness**



death (a philosophical/medical matter); and the practical testing, by way of clinical or complementary examinations, that death has occurred (a medical matter)[16].

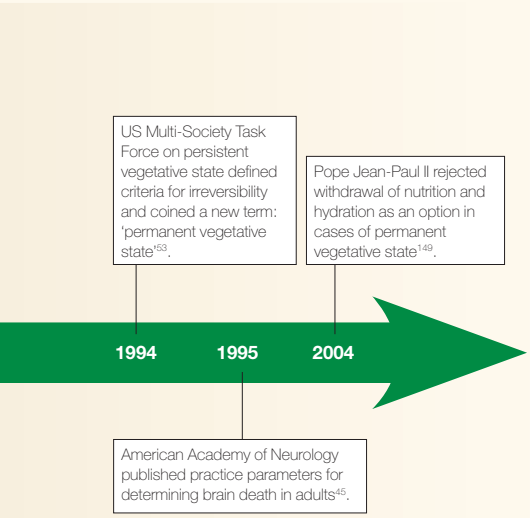
The concept of death. At present, the most accepted definition of death is the "permanent cessation of the critical functions of the organism as a whole"[17]. The organism as a whole is an old concept in theoretical biology[18] that refers to its unity and functional integrity — not to the simple sum of its parts — and encompasses the concept of an organism's critical system[19]. Critical functions are those without which the organism as a whole cannot function: control of respiration and circulation, neuroendocrine and homeostatic regulation, and consciousness. Death is defined by the irreversible loss of all these functions. The tiresome debate about whether this loss is a process[20] or an event[21] is seemingly insolvable (FIG. 1).

In this article, death is regarded as the discontinuous event (linguistically it can be understood only as an event[22]) that separates the continuous process of dying from the subsequent disintegration. The radical transition from life to death has been proposed[22] to follow a supercritical Hopf bifurcation (a bifurcation presenting a combination of continuity and discontinuity that is known from chaos and dynamical systems theory[23]) — not unlike Dehaene and Changeux's proposed discontinuities between consciousness and unconsciousness[24].

The brain-centred definition of human death has three formulations, known as whole brain, brainstem and neocortical death. Whole brain and brainstem death are both defined as the irreversible cessation of the organism as a whole, but differ in their anatomical interpretation. Because many areas of the supratentorial brain (including the neocortex, thalami and basal ganglia) cannot be accurately tested for clinical function in a comatose patient, most bedside tests for brain death (such as cranial nerve reflexes and apnoea testing) directly measure function of the brainstem alone[4]. The neocortical formulation of death, which was proposed in the early days of the brain death debate[25], advocates a fundamentally different concept of death: the irreversible loss of the capacity for consciousness and social interaction. By application of this consciousness- or personhood-centred definition of death, its proponents classify patients in a permanent vegetative state and anencephalic infants as dead. This most progressive and controversial concept of death is dealt with separately.

Some physicians[26], philosophers[27] and ultraconservative Catholic theologicians[28] have criticized the brain-centred definition and advocate a circulatory formulation of death defined by the irreversible cessation of circulation. Alan Shewmon, its most persuasive proponent, cites two lines of data to support this contention. First, he argues that the brain is merely one organ among many equally important ones and deserves no special status in death determination, as it performs no qualitatively different forms of bodily integration or homeostasis from the spinal cord[29]. In his view, a living body possesses not an integrator but integration, a holistic property that derives from the mutual interaction among all parts[26]. Second, he has presented at least 50 thought-provoking cases of children and adults with brain death who were treated aggressively and had their circulation maintained for many months or longer[30]. There have also been pregnant patients with brain death for whom continued intensive care treatment was requested until the foetus was mature enough to be born[31–34]. The most exceptional of such cases was the successful maintenance of a pregnant woman with brain death from 17 to 32 weeks of gestation[32]. These cases have been used by Shewmon to show that the neurocentric concept of death is inherently counterintuitive, because how could a dead body continue visceral organ functioning for extended periods, grow or gestate infants[30]?

In response to the integration–regulation criticism, Bernat[4] has counter-argued that the circulatory formulation has the inverse problem of the higher brain formulation. Whereas the higher brain formulation generates a criterion that is necessary but insufficient for death, the circulatory formulation generates a criterion that is sufficient but not necessary for death[35]. The homeostatic capacities of the brain are not the sole evidence of function of the organism as a whole — as previously stated, the functions of circulation, respiration and consciousness are also regarded as critical functions. With regard to the exceptional 'chronic' cases, their chronicity merely "indicates that their bodily decomposition has been delayed until their circulation has ceased"[36] and reveals heroic technological support in the modern intensive care unit — "an example of what science and technology

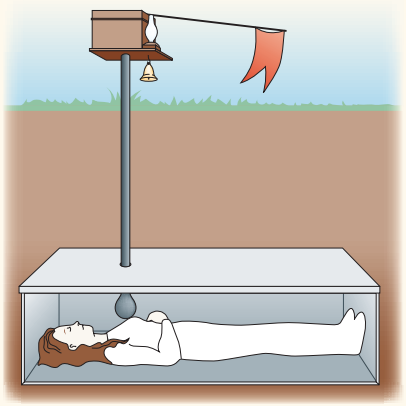


could do, but should not do"[37]. Brain death signifies death not because it is invariably imminently followed by asystole, but because it is accompanied by irreversible loss of critical cerebral functions. The concept of brain death as irreversible loss of the capacity of the organism to function as a whole that results from the permanent loss of its critical system is not invalidated by the time lag between the diagnosis of brain death and cardiac arrest[38]. From a pragmatic point of view, the advocates of the circulatory formulation have not swayed the majority, who are intuitively attracted to the brain death formulation and find it sufficiently coherent and useful to wish to preserve it as public policy[35].

Criteria of death. The whole brain formulation requires the bedside demonstration of irreversible cessation of all clinical functions of the brain, and is the most widely accepted. The brainstem formulation regards irreversible cessation of clinical functions of the brainstem as not only necessary but also sufficient for the determination of death. Pallis, one of the most eloquent advocates of brainstem death, argues that the brainstem is the through-station for almost all hemispheric input and output, the centre that generates arousal (which is essential for consciousness), and the centre of respiration[39].

Brain death is classically caused by a brain lesion (for example, massive traumatic injury, intracranial haemorrhage or anoxia) that results in an intracranial pressure higher than the mean arterial blood pressure. This causes intracranial circulation to cease and brainstem damage due to herniation. However, using the brainstem formulation of death, unusual but existing cases of catastrophic brainstem lesion (often of haemorrhagic origin) that spared the thalami and cerebral cortex can be declared brain dead in the absence of clinical brainstem function, despite intact intracranial circulation. Therefore, a patient with a primary brainstem lesion (who did not develop raised intracranial pressure) might be declared dead by the UK doctrine but not the US doctrine[40]. Theoretical cases in which a multifocal brainstem lesion could selectively impair all brainstem function that can be clinically assessed while preserving some residual (but clinically undetectable) function of the ascending reticular activating system sufficient to warrant some residual, fluctuating form of awareness could lead to diagnostic error. In practice, no such case has ever been reported. By definition, confirmatory examinations,

Box 1 | **Public fear of misdiagnosis of death and organ donation**



People have feared being diagnosed dead while still alive for hundreds of years. The anatomist Andreas Vesalius (1514–1564) was charged with murder after he conducted an autopsy and exposed a still-beating heart[130]. Edgar Allan Poe's eloquent writings on anecdotes of being buried alive provoked fears in the nineteenth century general public[131]. Count Karnice-Karnicki, chamberlain to the Tsar of Russia, patented and marketed a device to prevent premature burial in 1896 (see panel). The apparatus allowed the buried to signal that he or she was still alive by activating a flag and ringing a bell. It could be rented for a small amount of money and, after a length of time, when there was no chance of revival, the tube could be pulled up and used in another coffin. There is no record of what the success rate of these devices might have been.

At present, defining death and organ harvesting are inextricably linked because of the 'dead donor rule'. This rule requires that patients be declared dead before the removal of life-sustaining organs for transplantation. It is consequently considered unethical to kill patients for their organs, no matter how ill they are or how much good can be accomplished for others by doing so. To avoid conflicts of interest, transplant surgeons are excluded from performing brain death examinations. In 1980, a BBC television program "Transplants — are the donors really dead?" (13 October), which alleged that patients certified as brain dead were sometimes not, was followed by a fall in the number of kidney donations[10]. Although the neurocentric definition of death originated before the advent of multiorgan transplantation (TIMELINE), the demand for donors has been a major driving factor in the popularization and legalization of brain death. Despite the current shortage of donors, our definition of death should not serve to facilitate transplantation. In the public eye, the acceptance of multiorgan donation depends on the certainty of the diagnosis of death and the confidence in the dead donor rule[129].

Some authors have recently advocated to abandon this rule[132–134]. Truog, for example, proposes that organs be taken from patients with brain damage and no hope of recovery or imminently dying patients who are 'beyond harm' with their informed consent (or that of their family) without first being declared brain dead[135].

In 1995, anencephalic infants were proposed as organ donors by the Amercican Medical Association[136]. The potential to save dying infants and to give meaning to the anencephalic infant's family were presented as providing justification for this idea[137]. As a result of the ensuing public outcry and the unresolved scientific question of consciousness in anencephaly (see REF. 138 for an example in congenitally decorticate infants) the previous recommendation banning the policy was reasserted[139].

Similarly, patients in a vegetative state have been proposed as organ donors[140–142]. The International Forum for Transplant Ethics has suggested the administration of a lethal injection before organ harvesting in patients for whom the decision had been taken to withdraw life-sustaining treatment[140]. Justifying arguments were again humanitarian, obviating the futile use of resources required to keep alive an individual with no hope of recovery, and to make available organs suitable for transplantation. The idea has not been accepted because it violates the dead donor rule[143] or requires the definition of death to be amended[144], and opposition among the general public is thought to obstruct organ donation programmes[145].

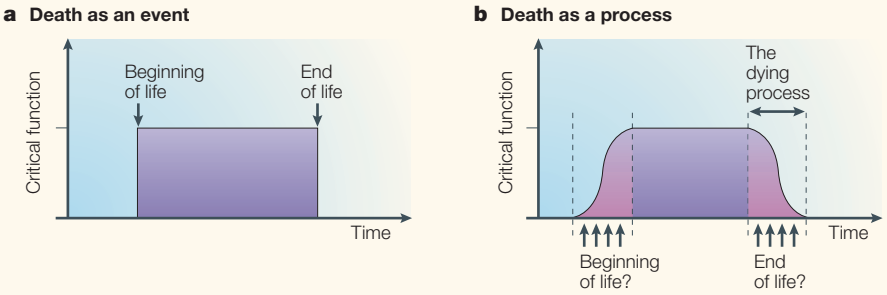


Figure 1 | **Death: event or process?** Death, which is defined as the loss of the capacity of an organism to function as a whole as a result of the irretrievable cessation of its critical functions (circulation, respiration and consciousness), has been considered to be a radical, clear-cut event (**a**) or a progressive, continuous process (**b**). The exact moments of the beginning and ending of life remain a challenge that science has not yet resolved.

such as functional imaging[41] or electrophysiology, would be needed to identify these cases, to which some authors have applied the term "super locked-in syndrome"[35,42].

Testing of death. The first (and only) prospective study validating the neurocentric criteria of death was the National Institutes of Health (NIH)-sponsored multicentre US Collaborative study of Cerebral Death[43]. Its aim was to identify tests that could be used to predict cardiorespiratory death within 3 months despite continued ventilatory and cardiac support. Of the 503 enrolled patients, 189 showed cerebral unresponsiveness, apnoea and one isoelectric electroencephalogram (EEG); 187 of these patients died based on cardiorespiratory criteria within 3 months, the 2 who survived had experienced drug intoxication. The authors recommended one re-examination at least 6 h after onset of coma and apnoea (unlike the initial 24 h re-examination required by the Harvard criteria). In 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research of the US published "Defining Death" as their first project, and recommended the use of ancillary diagnostic studies (see below) to reduce the duration of the requisite period of observation[44]. The American Academy of Neurology (AAN) published its guidelines for determining brain death in adults (BOX 2) in 1995 — including the important practical description of apnoea testing[45] — which have been used to model many institutional policies. Clinical and paraclinical diagnostic assessments have been didactically summarized elsewhere[46].

The clinical set of tests for whole brain and brainstem death are identical. There are two sets of tests that can be used to ascertain death — neurological and cardiopulmonary — which test is used depends on whether or not the patient is on mechanical ventilation. In patients who are mechanically ventilated, validated neurological tests are used to assure irretrievable absence of brain (in practice merely brainstem) function. In non-ventilated patients, physicians evaluate the irretrievable absence of heart beat and breathing. Irrespective of the fact that neurological or cardiopulmonary criteria are used, there are four possible times at which death can occur. First, when circulatory or cerebral critical function stops; second, when this critical function is first examined and known to have stopped; third, when the loss actually becomes irreversible; and, fourth, when this irreversibility is known by the physician[47]. The exact duration required for the absence of circulation and respiration before death occurs has evoked controversy in relation to to the Pittsburgh protocol[48] for non-heart-beating donors. It is now debated that after 5 min of asystole the heart will not auto-resuscitate and the patient can be declared dead according to cardiopulmonary criteria, given that artificial resuscitation would not be attempted[49]. In this specific context death according to neurological criteria will occur many minutes later, when the brain has become totally infracted as a result of anoxic damage[50,51].

Box 2 | **Criteria for brain death**

The criteria detailed below are from the guidelines set out by the American Academy of Neurology[45].

- **Demonstration of coma**
- **Evidence for the cause of coma**
- **Absence of confounding factors, including hypothermia, drugs, and electrolyte and endocrine disturbances**
- **Absence of brainstem reflexes**
- **Absence of motor responses**
- **Apnoea**
- **A repeat evaluation after a further 6 h is advised, but the time period is considered arbitrary**
- **Confirmatory laboratory tests are only required when specific components of the clinical tests cannot be reliably evaluated**

Vegetative state is not brain death

Like brain death, the vegetative state is a clinical diagnosis that, when it becomes permanent, can be regarded as a tragic artefact of modern technology. When Jennet and Plum coined the term "wakefulness without awareness" in 1972 (REF. 52), they cited the Oxford English Dictionary to clarify their choice of the term 'vegetative' as: "to vegetate is to live a merely physical life devoid of intellectual activity or social intercourse" and "vegetative describes an organic body capable of growth and development but devoid of sensation and thought"[52]. BOX 3 summarizes the criteria that must be met for the diagnosis of vegetative state[53].

Unlike brain death (excluding confounding factors, such as intoxication and hypothermia, as required by its definition) the vegetative state can be partially or totally reversible. 'Persistent' vegetative state was arbitrarily coined as a vegetative state present 1 month after the occurrence of brain damage, but does not mean that it is irreversible[53]. 'Permanent' vegetative state does imply that the patient will not recover. This term was introduced by the Multi-Society Task Force on Persistent Vegetative State to denote irreversibility 3 months after a nontraumatic brain injury and 12 months after traumatic injury[53]. It is very important to stress the difference between persistent vegetative state and permanent vegetative state, which are, unfortunately, too often identically abbreviated to PVS, causing unnecessary confusion[54]. When the term persistent vegetative state was first described[52], it was emphasized that persistent did not mean

Box 3 | **Criteria for the vegetative state**

The criteria listed here comprise the guidelines of the US Multi-Society Task Force on Persistent Vegetative State[53].

- **No evidence of awareness of self or environment and an inability to interact with others**
- **No evidence of sustained, reproducible, purposeful or voluntary behavioural responses to visual, auditory, tactile or noxious stimuli**
- **No evidence of language comprehension or expression**
- **Intermittent wakefulness manifested by the presence of the sleep–wake cycle**
- **Sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care**
- **Bowel and bladder incontinence**
- **Variably preserved cranial nerve and spinal reflexes**

permanent; it is now recommended that 'persistent' be omitted and patients be described as having been vegetative for a certain time. When there is no recovery after a specified period (3–12 months, depending on aetiology) the state can be declared permanent, and only then do the ethical and legal issues that surround withdrawal of treatment arise[55,56]. The vegetative state can also be observed in the end-stages of chronic neurodegenerative diseases, such as Alzheimer's disease, and in anencephalic infants.

It might seem that the difference between brain death and the vegetative state is so fundamental that it need not be reviewed. However, in reality, both terms are all too often mixed up in the lay — and even medical — press. Part of this misunderstanding might have its origin in the interchangeable lay use of the terms brain dead and vegetable[57]. This had already started when the New York Times (August 5, 1968) announced the Harvard criteria for brain death. In the accompanying editorial it read: "As old as medicine is the question of what to do about the human vegetable … Sometimes these living corpses have survived for years … It is such cases, as well as the need for organs to be transplanted that the Harvard faculty committee had in mind in urging that death be redefined as irreversible coma"[57]. More recently, one study reported that slightly less than half of surveyed US neurologists and nursing home directors believed that patients in a vegetative state could be declared dead[58]. Below, I briefly review the clinical, diagnostic and neuropathological differences between brain death and the vegetative state.

Clinical signs. Both patients with brain death and those in a vegetative state are unconscious following severe brain injury. The first difference between the two is the time of diagnosis. Brain death can be diagnosed with an extremely high rate of probability within hours to days of the original insult[46], whereas diagnosing irreversible vegetative state takes many months at best (3 months following a nontraumatic brain injury and 12 months after traumatic injury, as stated above[53]). Unlike patients with brain death who are, by definition, comatose (that is, never show eye opening, even on noxious stimulation), patients in a vegetative state (who, it should be stressed, are not in a coma), classically have their eyes spontaneously open, which can be very disturbing to families and caregivers. Patients with brain death are apnoeic and necessarily require controlled artificial ventilation, whereas patients in a vegetative state can breath spontaneously without assistance (even if during the acute stage ventilation must sometimes be artificially assisted). Unlike patients with brain death, those in a vegetative state have preserved brainstem reflexes and hypothalamic functioning (for example, regulation of body temperature and vascular tone). At best, patients with brain death only show slow body movements generated by residual spinal activity: finger jerks, undulating toe flexion sign, triple flexion response, Lazarus sign, pronation-extension reflex and facial myokymia may be present in up to a third of patients[59,60]. Patients in a vegetative state show a much richer array of motor activity, albeit always nonpurposeful, inconsistent and coordinated only when expressed as part of subcortical, instinctively patterned, reflexive response to external stimulation: moving trunk, limbs, head or eyes in meaningless ways and showing startle myoclonus to loud noises[53]. Finally, patients with brain death never show any facial expression and remain mute, whereas patients in a vegetative state may occasionally smile or cry, utter grunts and sometimes moan or scream[53,106].

Ancillary diagnostic studies. Cerebral angiography and transcranial Doppler sonography[61] can be used with high sensitivity and 100% specificity to document the absence of cerebral blood flow in brain death[62]. Similarly, radionuclide cerebral imaging, such as single photon emission computed tomography and positron emission tomography (PET), classically show the so-called hollow-skull sign, confirming the absence of neuronal function in the whole brain[41,63] (FIG. 2). Such 'functional decapitation' is never observed in patients in a vegetative state, in whom overall cortical metabolism and blood flow are known to be substantially reduced (40–50% of normal values)[41] but never absent. Some PET studies have even reported normal cerebral metabolism[64] or blood flow[65] in individuals in a vegetative state. Furthermore, PET studies measuring cerebral metabolism at rest cannot be reliably used to differentiate between patients in a vegetative state and those who are minimally conscious[66,67].

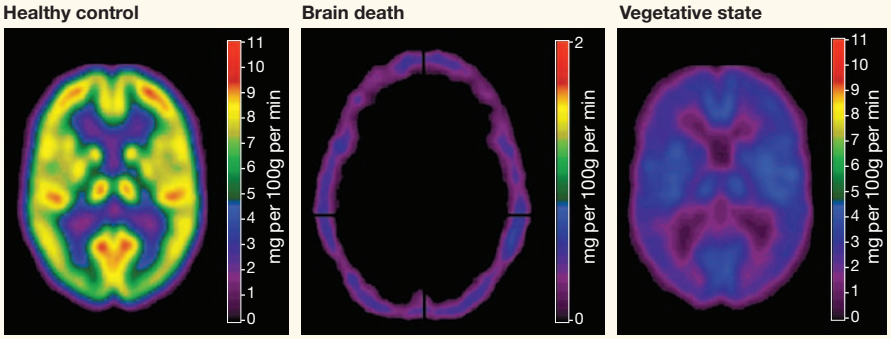


Figure 2 | **Illustration of the differences in resting brain metabolism measured in brain death and in the vegetative state, compared with controls.** The image in patients with brain death shows a clear-cut 'hollow-skull sign', which is tantamount to a 'functional decapitation'. This is markedly different from the situation seen in patients in a vegetative state, in whom cerebral metabolism is massively and globally decreased (to 50% of normal value) but not absent. The colour scale shows the amount of glucose metabolized per 100 g of brain tissue per minute.

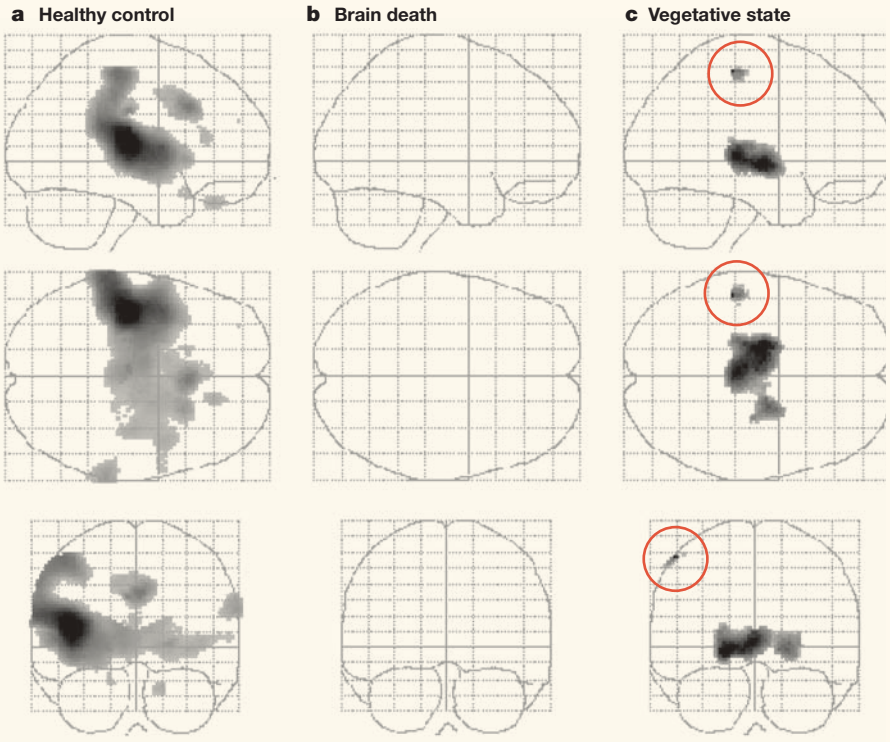


Figure 3 | **Cortical activity in response to painful stimuli in heathly controls and in patients with brain death or in a vegetative state.** Painful stimuli activate a wide neural network (known as the pain matrix) in healthy controls (**a**); in brain death absolutely no cerebral activation can be detected (**b**); in a vegetative state some subcortical (upper brainstem and thalamic) and cortical (primary somatosensory cortex; red circle) activation can be observed (**c**). The robust cortical activation observed in each and every one of the 15 patients in a vegetative state studied is not compatible with the concept of neocortical death in the vegetative state. Nevertheless, this cortical activation is limited to the primary somatosensory cortex and does not reach the higher-order associative cortices from which it was functionally disconnected. In the absence of a true understanding of the 'neural correlate of consciousness', the cortical activation seen in the vegetative state should be interpreted with caution even if the vast majority of neuroscientists would consider isolated neural activity in the primary cortex to be insufficient for conscious perception. Data adapted from REF. 71 and shown on glass brains.

The EEG in patients with brain death shows an absence of electrocortical activity (that is, isoelectric recording) with a sensitivity and specificity of 90%[68]. It is the most validated and, because of its wide availability, preferred confirmatory test for brain death implemented in many countries' guidelines. The EEG of patients in a vegetative state is only sporadically isoelectric or of very low voltage[53], most frequently it shows a diffuse slowing (that is, generalized polymorphic delta or theta rhythm)[69].

Somatosensory evoked potentials typically indicate arrest of conduction at the cervicomedullary level in brain death[70], whereas they frequently show preserved cortical potentials (N20) in a vegetative state[71]. Brainstem auditory evoked potentials usually only show a delayed wave I (originating in the cochlear nerve) in brain death[70] and preserved brainstem potentials in a vegetative state. However, there are too few evoked potential studies with detailed clinical correlations for this to be considered of validated diagnostic value.

Pathological features. Anatomopathology in patients with brain death who are receiving maximal artificial means of support will inevitably end up showing what is known as 'respirator brain': surface vasocongestion due to venous engorgement, thrombosis in cortical veins and sinuses, subarachnoid haemorrhage, and cortical congestion and haemorrhage will be observed after about 12 h of a nonperfused state[72]. After about a week an autolysed liquefied brain will pour from the opened skull[73]. Such dramatic findings are never encountered in a vegetative state. In patients with anoxic vegetative state pathological features encompass multifocal laminar cortical necrosis, diffuse leucoencephalopathy and bilateral thalamic necrosis. Patients in a vegetative state following blunt head injury classically show diffuse white matter damage with neuronal loss in thalami and hippocampi[74].

Neocortical death myth

In 1971, Scottish neurologist Brierley and his colleagues urged that death be defined by the permanent cessation of "those higher functions of the nervous system that demarcate man from the lower primates"[75]. This neocortical or higher brain death definition has been further developed by others, mainly philosophers[25,76], and its conceptual basis rests on the premise that consciousness, cognition and social interaction, not the bodily physiological integrity, are the essential characteristics of human life. The higher brain concept produces the neocortical death criterion, in which only the functions of the neocortex, not of the whole brain or of the brainstem, must be permanently lost. Clinical and confirmatory tests for neocortical death have never been validated as such.

Based on the neocortical definition of death, patients in a vegetative state following an acute injury or chronic degenerative disease and anencephalic infants are considered dead. Depending on how "irreversible loss of capacity for social interaction"[77] is interpreted, even patients in a permanent "minimally conscious state"[78], who, by definition, are unable to functionally communicate, could be regarded as dead. I argue that, despite its theoretical attractiveness to some, this concept of death cannot be reliably implemented using anatomical criteria nor in reliable clinical testing.

First, our current scientific understanding of the necessary and sufficient neural correlates of consciousness is incomplete at best[79,80]. In contrast to brain death, for which the neuroanatomy and neurophysiology are both well established, anatomopathology, neuroimaging and electrophysiology cannot, at present, determine human consciousness. Therefore, no accurate anatomical criteria can be defined for a higher brain formulation of death.

Second, clinical tests would require the provision of bedside behavioural evidence showing that consciousness has been irreversibly lost. There is an irreducible philosophical limitation in knowing for certain whether any other being possesses a conscious life[81]. Consciousness is a multifaceted subjective first-person experience and clinical evaluation is limited to evaluating patients' responsiveness to the environment[82]. As previously discussed, patients in a vegetative state, unlike patients with brain death, can move extensively, and clinical studies have shown how difficult it is to differentiate 'automatic' from 'willed' movements[83]. This results in an underestimation of behavioural signs of consciousness and, therefore, a misdiagnosis,

which is estimated to occur in about one third of patients in a chronic vegetative state[84,85]. In addition, physicians frequently erroneously diagnose the vegetative state in elderly residents with dementia in nursing homes[86]. Clinical testing for absence of consciousness is much more problematic than testing for absence of wakefulness, brainstem reflexes and apnoea in whole brain or brainstem death. The vegetative state is one end of a spectrum of awareness, and the subtle differential diagnosis between this and the minimally conscious state necessitates repeated evaluations by experienced examinors. Practically, the neocortical death concept also implies the burial of breathing 'corpses'.

Third, complimentary tests for neocortical death would require provision of confirmation that all cortical function has been irreversibly lost. Patients in a vegetative state are not apallic, as previously thought[87,88], and may show preserved islands of functional pallium or cortex. Recent functional neuroimaging studies have shown limited, but undeniable, neocortical activation in patients in a vegetative state, disproving the idea that there is complete neocortical death in the vegetative state (FIG. 3). However, as previously stated, results from these studies should be interpreted cautiously for as long as we do not fully understand the neuronal basis of consciousness. Again, complimentary tests for proving the absence of the neocortical integration that is necessary for consciousness are, at present, not feasible and unvalidated.

As discussed above, the absence of whole brain function in brain death can be confirmed by means of cerebral angiography (nonfilling of the intracranial arteries), transcranial Doppler ultrasonography (absent diastolic or reverberating flow), nuclear imaging (absence of cerebral blood flow: hollow-skull sign) or EEG (absent electrical activity). In contrast to brain death, in which prolonged absent intracranial blood flow proves irreversibility[40], the massively reduced — but not absent — cortical metabolism observed in the vegetative state[64,89–93] cannot be regarded as evidence for irreversibility. Indeed, fully reversible causes of altered consciousness, such as deep sleep[94] and general anaesthesia[95–97], have shown similar decreases in brain function, and the rare patients who have recovered from a vegetative state have been shown to resume near-normal activity in previously dysfunctional associative neocortex[98,99].

However, proponents of the neocortical death formulation might counter-argue that because all definitions of death and vegetative state are clinical, finding some metabolic activity in functional neuroimaging studies does not disprove the concept (as these studies are measuring non-clinical activities), although this does contrast with the validated non-clinical laboratory tests used to confirm whole brain death.

Finally, proving irreversibility is key to any concept of death. The clinical testing of irreversibility has stood the test of time only in the framework of whole brain or brainstem formulations of death. Indeed, since Mollaret and Goulon first defined their neurological criteria of death more than 45 years ago[1], no patient in apnoeic coma who was properly declared brain (or brainstem) dead has ever regained consciousness[10,35,100]. This cannot been said for the vegetative state, in which permanent is probabilistic — the chances of recovery depend on a patient's age, aetiology and time spent in the vegetative state[101]. Unlike brain death, for which the diagnosis can be made in the acute setting, the vegetative state can only be regarded as statistically permanent after long observation periods, and even then there is a chance that some patients might recover. However, it should be stressed that many anecdotes of late recovery are difficult to substantiate and it is often difficult to know how certain the original diagnosis was.

Ethics of death and dying

The debate on the need to withhold or withdraw 'futile' life-prolonging treatments and the idea of 'death with dignity' was started by intensive care physicians (not ethicists or lawyers) in the mid-1970s[102]. At present, almost half of all deaths in intensive care follow a decision to withhold or withdraw treatment[103]. There is no moral or legal distinction between withholding or withdrawing[104].

As discussed above, a person who is brain dead is dead — disconnecting the ventilator will not cause him or her to die. Patients in a vegetative state are not dead, but when their situation becomes hopeless it can be judged unethical to continue their life-sustaining treatment. Unlike patients with brain death, patients in a vegetative state do not usually require ventilatory or cardiac support, needing only artificial hydration and nutrition. The internationally reported case of Terri Schiavo[13–15] centred first on opposing opinions between her husband and parents about whether she would wish to continue living in such a severely disabled state, and also on the lack of family consensus regarding her diagnosis of vegetative state. This case illustrated how hard it is for lay persons (and inexperienced physicians and policy makers) to accept the medically established ethical framework that justifies letting patients in an irremediable vegetative state die. Misinformation stemming from high-profile cases such as Schiavo's may increase societal confusion and consternation about end-of-life decision-making[105–107].

Stopping artificial nutrition and hydration to patients in a vegetative state is a complex issue, and it would be beyond the scope of this paper to cover all ethical, legal and practical dilemmas involved (see Jennett's recent monograph for an in-depth account[106]). It should be stressed that "unless it is clearly established that the patient is permanently unconscious, a physician should not be deferred from appropriately aggressive treatment"[108], and physicians also "have an obligation to provide effective palliative treatment"[109]. Several US[110–112] medical societies and interdisciplinary bodies, including the American Medical Association[108]; the British Medical Association[113] and the World Medical Association[114], have asserted that surrogate decision makers and physicians with advance directives provided by patients have the right to terminate all forms of life-sustaining medical treatment, including hydration and nutrition, in patients in a permanent vegetative state.

The moral values that underlie these guidelines are the principles of autonomy, beneficence, non-maleficence and justice[115]. Informed, mentally competent patients should consent to any treatment they receive and have the right to make choices regarding their bodies and lives. The primary factor determining the level of treatment provided for an incompetent patient should reflect the patient's personally expressed wishes for treatment in this situation. It should be noted that the principle of autonomy was developed as a product of the Enlightenment in Western culture and is not yet strongly emphasized beyond the US and Western Europe (for example, in Japan[116]). In the Western world, the main challenge for autonomy in justifying a right to refuse life-prolonging treatment comes from the vitalist religious view (mainly from orthodox Jews, fundamentalist Protestants and conservative Roman Catholics) that holds that only God should determine when life ends (BOX 4).

In the past, physicians have interpreted beneficence to mean promotion of continued life, at almost any cost. With the advancement of medical technology, medicine is now ethically obliged not to promote life at all costs in a paternalistic way but rather to enable patients to choose what type of life represents a 'good' life to them and

Box 4 | **Religion and death**

Both Judaism and Islam have a tradition of defining death on the basis of absence of respiration, but brain death has now become an accepted definition of death for these religions[146]. The Catholic church has stated that the moment of death is not a matter for the church to resolve. More than 10 years before the Harvard criteria were established, anaesthesiologists who were concerned that new resuscitation and intensive care technologies designed to save lives sometimes appeared to only extend the dying process, sought advice from Pope Pius XII. The Pope, up-to-date with (even, surprisingly, in advance of) modern day medicine, ruled that there was no obligation to use extraordinary means to prolong life in critically ill patients[147]. Therefore, withholding or withdrawing life-sustaining treatment from patients with acute irreversible severe brain damage became morally accepted.

With regard to life-prolonging treatments in chronic conditions such as the vegetative state, many have found it difficult to view artificial hydration and nutrition as extraordinary means. However, recent ethical and legal discussions have abandoned the extraordinary versus ordinary dichotomy in favour of disproportionate versus proportionate treatments. Many prominent progressive Catholic theologists have accepted the idea of therapeutic futility in patients in an irreversible vegetative state, and have defended the decision to withdraw nutrition and hydration in well-documented cases[148]. Nevertheless, Pope John Paul II, addressing an international congress on the vegetative state in March 2004 (for details see Further information), considered that the cessation of artificial life-sustenance to patients in a permanent vegetative state could never be morally accepted, whatever the situation[149]. However, many of the meeting's invited neuroscientists had more nuanced viewpoints, and some Roman Catholic theologians considered it to be at variance with Christian tradition. The moral legitimacy to inquire about the duty to treat at all cost (that is, therapeutic obstinacy), which was accepted by the Catholic Church for acute cases of severe neurological damage (irreversible coma) in 1957 (REF. 147), stands in contrast to the Church's recent refusal to allow withdrawal of life-sustaining treatment in chronic cases (irreversible vegetative state)[149]. The official Catholic position de-emphasizes the reality of irreversibility in longstanding vegetative state and does not consider artificial nutrition and hydration to be treatments. So far, it has not changed practices in the US, where withdrawal of life-sustaining treatment from patients in an irreversible vegetative state remains a settled view; a view that was endorsed by the US Supreme Court in the case of Nancy Cruzan, and that is held by many other medical, ethical and legal authorities[150] (BOX 5).

what type of life does not. Medical choices should now depend on patients' individual values and can therefore be in disagreement with physicians' personal perceptions[117]. If patients can no longer speak for themselves, having someone who knew them make decisions for them seems the best reasonable compromise. However, critics have argued that surrogate decisions are flawed. Most people would not want to continue living if they were in a vegetative state[118]. However, severely disabled patients with brain damage seem to want to go on living[119–122]. Some studies have shown the limitations of spouses' predictions of patients' desires regarding resuscitation[123], and healthy people tend to underestimate impaired patients' quality of life[124].

The principle of justice, which includes equity, demands that an individual's worth not be judged solely on social status, nor on physical or intellectual attributes. Vulnerable patients, such as those who are non-communicative and have severe brain damage, those with other handicaps, and those who are very old or young, should not be treated any differently from healthy individuals. No person's life has more or less intrinsic value than the next. Concepts of justice should trump the claims of autonomy, based on a model of medical futility[125].

Medical futility is defined as the situation in which a therapy that is hoped to benefit a patient's medical condition will predictably not do so on the basis of the best available evidence (exactly what probability threshold satisfies the standard of 'ethical acceptability' is still under discussion[126]). Since the Multi-Society Task Force on PVS, we know that the chances of recovery after 3 months for non-traumatic and 12 months for traumatic cases are close to zero. Letting patients in a permanent vegetative state die, despite being ethically and legally justified (BOX 5), remains a complicated and sensitive issue for all those involved[127].

Finally, the question remains about the mode of death. Stopping hydration and nutrition leads to death in 10–14 days[128]. Recent neuroimaging studies have concluded that patients in a vegetative state lack the neural integration that is considered necessary for pain perception[71]. Some, however, are in favour of injecting a lethal drug to quicken the dying process. At present, this practice can only be envisaged in countries or states in which euthanasia has been legalized (for example, Belgium, The Netherlands and Switzerland) and only if patients have explicitly expressed this wish previously in living wills.

Patients in a vegetative state are not dead, even if their loss of consciousness results in our belief that they may be 'as good as dead'. However, letting patients in an irreversible vegetative state die can be the most humane option, just as abortion can be justified in, for example, cases of anencephaly, without needing the foetus to be declared dead. This is not a purely medical matter, but an ethical issue that is dependent on personal moral values, and we should accept deviating culture-and religion-dependent viewpoints.

Conclusions and future perspectives

In conclusion, brain death is death and irreversible vegetative state is not. Of the two bio-philosophical concepts of brain death (the 'whole brain' and the 'brainstem' formulation), defined as the irreversible cessation of critical functions of the organism as a whole (that is, neuroendocrine and homeostatic regulation, circulation, respiration and consciousness), the whole brain concept is most widely accepted and practised. Since their first use in 1959 (REF. 1), the neurocentric criteria of death — as compared with the old cardiocentric criteria — are considered to be "among the safest medicine can achieve"[38]. In those instances in which confirmatory tests for brain death are desirable, irreversibility can, at present, be more reliably demonstrated for the whole brain concept (for example, by measuring lack of intracranial blood flow)[40]. However, with future technological advances and a better understanding and identification of the human cerebral 'critical system', the criteria might move further in the direction of brainstem death[4].

In my view, neocortical death, as a confirmatory index for defining death, is conceptually inadequate and practically unfeasible. Clinical, electrophysiological, neuroimaging and post-mortem studies now provide clear and convincing neurophysiological and behavioural distinctions between brain death and the vegetative state. Similar lines of evidence also provide compelling data that neocortical death cannot be reliably demonstrated and is an insufficient criterion for establishing death.

Box 5 | **Death and the law**

Under the US Uniform Determination of Death Act[151], a person is dead when physicians determine, by applying prevailing clinical criteria, that cardiorespiratory or brain functions are absent and cannot be retrieved[146]. The neurocentric definition is purposefully redundant, requiring a determination that "all functions of the entire brain, including the brain stem" have irreversibly ceased[151]. The American Academy of Neurology guidelines are shown in BOX 2 **. The Canadian guidelines closely mirror these[152]. In 1971, Finland was the first European country to accept brain death criteria. Since then, all EU countries have accepted the concept of brain death. However, although the required clinical signs are uniform, less than half the European countries that have accepted brain death criteria require technical confirmatory tests, and approximately half require more than one physician to be involved[153]. Confirmatory tests are not mandatory in many third-world countries because they are simply not available. In Asia, death based on neurological criteria has not been uniformly accepted and there are major differences in regulation. India follows the UK criteria of brainstem death[154]. China has no legal criteria and there seems to be some hesitation among physicians to disconnect the ventilator in patients with irreversible coma[57]. Japan now officially recognizes brain death, although the public remains reluctant — possibly as a result of the heart surgeon Sura Wada, who was charged with murder in 1968 after removing a heart from a patient who was allegedly not brain dead[155]. Australia and New Zealand have accepted whole brain death criteria[156].**

Some legal scholars have also endorsed the neocortical definition of death[157,158] but they have never convinced legislatures or courts. A physician who believes that a patient who is permanently unconscious but breathing is dead risks criminal prosecution or a civil claim for wrongful death if he or she acted on this belief[146]. A finding that consciousness is irreversibly lost will not, by itself, under any applicable medical practice guidelines or law, justify a diagnosis of death; evidence that brainstem functions are absent is always required. However, withdrawing any treatment that is not considered to be of benefit to the patient is medically and legally accepted, and no doctor has ever been charged with murder for doing this in well-documented cases of patients in an irreversible vegetative state[106]. It should be noted, however, that N. Barber and R. Nejdl were charged with murder in California for withdrawing all treatment, including artificial hydration and nutrition, from a patient, Mr Herbert, who had been comatose for 7 days. However, their case was dismissed before trial and the patient's condition later evolved into an irretrievable vegetative state[159].

Finally, death is a biological phenomenon for which we have constructed pragmatic medical, moral and legal policies on the basis of their social acceptance[129]. The decision of whether a patient should live or die is a value judgment over which physicians can exert no specialized professional claim. The democratic traditions of our pluralistic society should permit personal freedom in patients' decisions to choose to continue or terminate life-sustaining therapy in cases of severe brain damage. Like most ethical issues, there are plausible arguments supporting both sides of the debate. However, these issues can and should be tackled without changes being made to the current neurocentric definition of death. The benefits of using living humans in a vegetative state as organ donors do not justify the harm to society that could ensue from sacrificing the dead donor principle[129].

Many of the controversial issues relating to the death and end of life in patients with brain damage who have no hope of recovery result from confusion or ignorance on the part of the public or policy makers about the medical reality of brain death and the vegetative state. Therefore, the medical community should improve educational and public awareness programmes on the neurocentric criteria and testing of death; stimulate the creation of advance directives as a form of advance medical care planning; continue to develop clinical practice guidelines; and more actively encourage research on physiological effects and therapeutic benefit of treatment options in patients with severe brain damage.

What is the future of death? Improving technologies for brain repair and prosthetic support for brain functions (for example, stem cells, neurogenesis, neural computer prostheses, cryonic suspension and nano-neurological repair) might one day change our current ideas of irreversibility and force medicine and society to once again revise its definition of death.

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doi:1038/nrn1789

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Acknowledgments

The author is Research Associate at the Belgian 'Fonds National de la Recherche Scientifique'.

Competing interests statement

The authors declare no competing financial interests.

Online links

FURTHER INFORMATION

Steven Laureys' homepage: http://www.ulg.ac.be/crc/en/slaureys.html
US National Institute of Neurological Disorders and Stroke: http://www.ninds.nih.gov/disorders/coma/coma.htm
American Academy of Neurology: http://aan.com/professionals/practice/pdfs/pdf_1995_thru_1998/1995.45.1012.pdf
American Medical Association: www.ama-assn.org/ama/pub/category/8457.html
British Medical Association: www.bma.org.uk/ap.nsf/Content/pvs?OpenDocument&Highlight=2,vegetative,state
World Medical Association: http://www.wma.net/e/policy/p11.htm
World Federation of Catholic Medical Associations and Pontifical Academy for Life: http://www.vegetativestate.org
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