Article

Aligning the Criterion and Tests for Brain Death

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Abstract: Disturbing cases continue to be published of patients declared brain dead who later were found to have a few intact brain functions. We address the reasons for the mismatch between the whole-brain criterion and brain death tests, and suggest solutions. Many of the cases result from diagnostic errors in brain death determination. Others probably result from a tiny amount of residual blood flow to the brain despite intracranial circulatory arrest. Strategies to lessen the mismatch include improving brain death determination training for physicians, mandating a test showing complete intracranial circulatory arrest, or revising the whole-brain criterion.

Keywords: brain death; whole brain criterion; brain death tests; brain death determination

I. Statement of the Problem

Brain death is the common term for human death determined by the irreversible cessation of all brain functions. Despite persisting areas of controversy and differences in its bedside determination among countries, the worldwide acceptance of brain death continues to grow.[1] One important topic of continued controversy that has been given only sporadic attention is the discordance between the criterion and tests for brain death.[2] Here, we analyze this discordance and offer options to prevent and reduce it.

Many analyses of the conceptual foundation for brain death stratify and order three hierarchies of understanding: definition, criterion, and tests. The definition of death attempts to distill the meaning implicit in our consensual usage of the common word "death" that has been rendered ambiguous by technological developments, particularly cardiopulmonary resuscitation and tracheal positive-pressure ventilation. The criterion of death, a general standard suitable for inclusion in a death statute, is chosen to satisfy the definition by being both necessary and sufficient. The bedside tests determining death are selected and validated by physicians to show that the criterion of death has been fulfilled. These sequential steps are essential in any analysis of death, but particularly so in an analysis that justifies the validity of brain death.[3]

Consensus has been achieved in most countries that accept brain death that the whole-brain criterion best satisfies the definition of death.[4] The whole-brain criterion requires the irreversible cessation of all functions of the entire brain, namely those of the cerebral hemispheres, diencephalon (thalamus and hypothalamus), cerebellum, and brain stem. The whole-brain criterion has been incorporated into death statutes, most notably in the United States, in the Uniform Determination of Death Act.[5] The language of this model statute or a variation of it has been enacted in every state.[6] In addition to being the legal standard of brain death, the whole-brain criterion is the medical standard of brain death—the basis for physicians' bedside tests determining brain death that have been accepted as national benchmarks.[7] Therefore, any cases instantiating a mismatch between physicians' tests to determine death and the whole-brain criterion of death must be scrutinized to identify the grounds for the mismatch.

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II. Evidence of Discordance Between the Whole-Brain Criterion and its Tests

Although most patients declared brain dead satisfy the whole-brain criterion, the alignment of the criterion with bedside tests for brain death remains imperfect. For years, physicians have reported isolated cases in which patients declared brain dead have been found, on later examination, to demonstrate signs of brain functions. Insights into these cases may impact the coherence of the whole-brain criterion and its tests.

In a recent article, we collected and analyzed published cases in which patients who had been declared brain dead were found later to demonstrate signs of neurological function.[8] Some of these cases showed what we judged to be spinal cord functions which did not conflict with the prior determination of brain death. Similarly, other cases showed neurological signs of unclear origin that could have arisen from either the central or peripheral nervous system that thus also potentially remained consistent with brain death. But disturbingly, there were also cases that showed unequivocal evidence of brain functions, such as brain stem reflexes or breathing. Because these cases unmistakably demonstrated brain functions, they were incompatible with the whole-brain criterion of death and thus, with the previous determination of brain death.

Among the most unequivocal cases of mismatch were those showing evidence of persisting hypothalamic function, particularly the continued neurohormonal secretion of vasopressin preventing diabetes insipidus, that should not be expected to occur according to the whole-brain criterion.[9] Vasopressin peptide prohormone is produced by the magnocellular neurosecretory neurons of the paraventricular and supraoptic nuclei of the hypothalamus. It is converted to vasopressin and by axonal transport, transported to the posterior pituitary gland where it is secreted. The global cessation of brain functions required by the whole-brain criterion should encompass the absence of this hypothalamic control. These cases represented the most frequent instances of retained brain function despite the prior determination of brain death. Although the findings in these cases have been published for many years, some scholars have unjustifiably discarded them claiming they were irrelevant to brain death.

The recent highly publicized case of Jahi McMath may represent a false-positive determination of brain death. Given the medical data available in the public sector, it seems clear that her brain death determination was made competently and in accordance with the accepted tests for brain death. Yet following continued mechanical ventilation and other treatment at her mother's insistence, later examiners claimed that Ms. McMath exhibited brain functions and had MRI evidence of intact brain regions.[10] The essential difficulty in analyzing and understanding her case is that relatively little medical information about her later condition has been published or is publicly available for scholarly review, and a postmortem analysis of her brain has not been performed. Thus, there remains uncertainty about the exact nature of her condition during the several-year period between the declaration of brain death and the final cessation of her systemic circulation.

III. Understanding the Causes of the Criterion-Test Mismatch

The first step in understanding the cause of any alleged brain death criterion-test mismatch is to exclude those cases resulting from an erroneous determination. If the determination of brain death was erroneous, the presence of signs of brain

functions on subsequent examination is readily explained and cannot be considered an example of criterion-test mismatch. Although the tests and optimal techniques for brain death determination have been established and accepted by the medical profession, there is reason to believe that some physicians do not follow them assiduously, a practice that produces false-positive diagnostic errors. Some diagnostic errors result from the failure to exclude conditions that mimic brain death.[11] The most important mimics are potentially reversible metabolic and toxic encephalopathies, such as those caused by drug intoxication and induced by therapeutic hypothermia.[12] Several neurologists who contacted us after our recent article was published argued that diagnostic error most likely accounted for the majority of the cases we collected.

The exact incidence of diagnostic error in brain death determination is unknown, but survey data assessing unjustified brain death determination practice variations makes us suspicious that diagnostic errors may be more common than we have previously assumed.[13] One reason the diagnostic error rate remains unknown is that once brain death is determined, all treatments, including ventilator support, are withdrawn. The absence of breathing quickly leads to the irreversible cessation of circulation. In only a tiny minority of cases is treatment continued at the insistence of family members.

Even assuming that the determination of brain death was conducted properly, it is possible that not all brain activities have ceased in every case. It is instructive to review the usual pathophysiology of brain death to understand how this can happen. Most cases of brain death result from traumatic brain injury, intracranial hemorrhage and other strokes, hypoxic-ischemic neuronal damage during cardiopulmonary arrest, or meningoencephalitis. These primary causes of brain damage produce massive brain edema which elevates intracranial pressure because the cranium has a rigid and fixed volume. When raised intracranial pressure exceeds systemic mean arterial pressure, blood flow no longer can perfuse the brain. During this interval of absent brain blood flow, the majority of neurons that had not been damaged by the primary disorder become damaged by this secondary global ischemic insult.

Yet, some brain neurons may survive despite a very low blood flow state. Coimbra coined the term "ischemic penumbra" to describe this condition.[14] This mechanism may explain the outcome of the Jahi McMath case. Many of those surviving neurons in low blood flow states are located in the brain stem and hypothalamus, which, because they are phylogenetically older, are less metabolically active than the phylogenetically newer neurons of the cerebral cortex. As a result, they require less blood flow and hence may preferentially survive low blood flow states.[15]

In most cases of brain death, the markedly elevated intracranial pressure produces lateral and downward shifts of portions of the brain, a lethal phenomenon known as transtentorial brain herniation. This pathological process usually traps and severely compresses the midbrain and brain stem, blocking circulation to it. When transtentorial brain herniation has been completed, the signs of brain stem failure are easily elicited by bedside examination. But if brain herniation remains incomplete and some brain stem or hypothalamic neurons survive the secondary process of reduced or ceased intracranial blood flow resulting from intracranial hypertension, some brain stem or hypothalamic functions could continue despite the determination of brain death. This mechanism is likely responsible for many of the cases of whole-brain criterion-test mismatch.

IV. Preventing or Reducing the Criterion-Test Mismatch

The obvious first and most important step is for physicians to avoid any instances of erroneous brain death determination producing false-positive errors. The medical standards for the proper determination of brain death have been clearly established.[16] Diagnostic errors result from physicians' substandard performance or interpretation of the bedside tests. Physicians must be trained to perform the standardized tests assiduously and accurately, and to rigorously exclude potentially reversible conditions.

One of us recently outlined the elements for proper brain death education and training.[17] First, video-assisted learning modules created by brain death experts that show how the tests are properly performed should be viewed and a test passed. Second, brain death simulation training should be conducted under supervision, culminating in brain death determination credentialing. Finally, all physicians conducting a brain death examination should complete a checklist that requires ticking off each step and that provides a written record of all of the tests that were performed and their results.

Yet, even when the brain death tests are performed and interpreted correctly, inevitably, cases will occur in which some brain functions persist, such as the hypothalamic control of vasopressin secretion. These cases constitute true examples of brain death criterion-test mismatch. The most probable mechanism at work in these cases is that the interval of intracranial hypertension causing brain circulatory arrest is not severe or long enough to cause complete transtentorial brain herniation and the cessation of functions of the whole brain. Given these examples of criteria-test mismatch, some scholars have attacked the validity of the whole-brain criterion of death.[18] We believe that these cases do not invalidate the whole-brain criterion of death so much as they show that the positive predictive value of accepted brain death tests may be insufficient to satisfy the criterion.

Two possible strategies for reducing the whole-brain criterion-test mismatch are to tighten the tests or to loosen the criterion.[19] Each strategy represents a change from current thinking: changing the tests disrupts the medical consensus on the optimal bedside tests while the criterion change disrupts the current legal and medical consensus on the validity of the whole-brain criterion. Because the two strategies are mutually independent, a third strategy might be to pursue them both.

The intent of tightening brain death tests is to prove the whole-brain criterion of death by requiring a neuroimaging procedure showing intracranial circulatory arrest. But physicians must first validate the required neuroimaging procedure by proving that zero forward blood flow measured by the neuroimaging procedure correlates perfectly with complete intracranial circulatory arrest. Currently, the performance of laboratory or imaging "confirmatory" or "ancillary" tests for brain death is optional in most test batteries around the world.[20]

The benefit of such an added requirement would be to restrict the determination of brain death to only those cases with demonstrable intracranial circulatory arrest thus fulfilling the whole-brain criterion. This requirement would likely reduce the number of patients declared brain dead because not all patients declared brain dead have intracranial circulatory arrest. One risk of this requirement is that by reducing the number of brain death determinations, it would thereby reduce the overall number of organ donations. Organ donation is a valuable outcome of brain death determination but as an instrumental goal, it should neither drive death

determination nor define its medical tests. This option would also convert determining brain death from being a purely clinical determination to one that also requires a neuroimaging procedure, although certain confirmatory tests already are required in some countries.

The second strategy is to revise the whole-brain criterion by no longer requiring all brain functions to cease in brain death but only a set of critical functions. For example, in this strategy, the continuation of hypothalamic control of vasopressin secretion may be justifiable in a brain death determination if this function were classified as non-critical. This change reconceptualizes the whole-brain criterion as the brain-as-a-whole criterion. In other words, instead of requiring all functions of the brain to cease, as implied by the term "whole-brain," it would require the cessation of only certain critical brain functions that serve the brain-as-a-whole. This relaxation of the whole-brain criterion is not as radical as it first seems because it already prevails in practice in cases in which brain death is determined despite the absence of diabetes insipidus.

To better understand this idea, an instructive analogy is that between the brain-as-a-whole and the more familiar concept of the organism-as-a-whole. Many definitions of death feature the cessation of functions of the organism as a whole. The organism-as-a-whole concept refers to those capacities ("emergent functions") of an organism that are greater than those of the sum of its parts, that cannot be reduced to any of its parts, and that contribute to the unity of the organism.[21] Thus, functions of the brain-as-a-whole may include consciousness, and respiratory and circulatory control, but could conceivably exclude arguably less critical brain functions such as vasopressin neurosecretion. Admittedly, the neurophysiological correlation of the brain-as-a-whole criterion remains vague and a list of its critical functions remains to be established.

The benefit of revising the whole-brain criterion would be to correlate it more closely to that set of brain functions whose cessation is necessary and sufficient for death. If, given prevailing practices, the implicit intent of the whole-brain criterion was the brain-as-a-whole, reconceptualizing it this way would simply make that intent explicit.[22] The risk is to disrupt the conceptual integrity of the whole-brain criterion by creating an ad hoc list of critical brain functions that excludes non-critical brain functions without first providing a biologically coherent and justified distinction between the two groups of functions.

The medical and organ transplantation communities endorse adding rigor and standardization to physicians' brain death training to assure the tests are followed carefully and to prevent any false-positive brain death determinations. But it seems likely that both communities would oppose tightening the tests for brain death to require evidence of intracranial circulatory arrest because of the negative impacts we noted. Both groups would likely be more amenable to the idea of revising the whole-brain criterion in the direction of the brain-as-a-whole because this change accommodates prevailing medical practices. But how this change would impact the legal status of brain death in those jurisdictions in which the whole-brain criterion is enshrined in the death statute remains unclear. It would demand an analysis that clarifies what the brain-as-a-whole criterion of death means, how it is measured, and how and why it is an improvement over the whole-brain criterion.

Thus, both essential questions about whole-brain death raised by the criterion-test mismatch cases remain inadequately answered: (1) The irreversible cessation

of which brain functions constitutes a necessary and sufficient criterion of death? and (2) What brain death tests are required to satisfy that criterion? What is clear is that the valid cases of criterion-test mismatch raise a nagging problem with the coherence of the current formulation of whole-brain death that requires further analysis and refinement.

Notes

1. Wahlster S, Wijdicks EF, Patel PV, Greer DM, Hemphill JC 3rd, Carone M, et al. Brain death declaration: Practices and perceptions worldwide. *Neurology* 2015;84:1870–9.
2. Notably, several authors have discussed the issue of criterion-test mismatch. See Youngner SJ, Bartlett ET. Human death and high technology: The failure of the whole-brain formulations. *Annals of Internal Medicine* 1983;99:252–8; Halevy A, Brody B. Brain death: Reconciling definitions, criteria, and tests. *Annals of Internal Medicine* 1993;119:519–25; Veatch RM. The impending collapse of the whole-brain definition of death. *Hastings Center Report* 1993;23(4):18–24; Truog RD, Miller FG. Changing the conversation about brain death. *American Journal of Bioethics* 2014;14(8):9–14; and Nair-Collins M. Taking science seriously in the debate on death and organ transplantation. *Hastings Center Report* 2015;45(6):38–48.
3. This analysis is summarized in Bernat JL. Whither brain death? *American Journal of Bioethics* 2014; 14(8):3–8.
4. The principal exception to using the whole-brain criterion is the United Kingdom, which uses the brain stem criterion of death. In practice, the overwhelming majority of cases fulfilling the brain stem criterion also fulfill the whole-brain criterion, but there are rare cases of primary brain stem damage that fulfill the brain stem criterion but not the whole-brain criterion. See Bernat JL. How much of the brain must die in brain death? *Journal of Clinical Ethics* 1991;3:21–6.
5. The Unified Determination of Death Act provides: "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards." See President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Defining Death. Medical, Ethical, and Legal Issues in the Determination of Death*. Washington, DC: US Government Printing Office; 1981, at 55–84.
6. Pope TM. Legal briefing: Brain death and total brain failure. *Journal of Clinical Ethics* 2014; 25(3):245–57.
7. Appendix F of President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Defining Death. Medical, Ethical, and Legal Issues in the Determination of Death*. Washington, DC: US Government Printing Office; 1981, at 159–66; Wijdicks EF, Varelas PN, Gronseth GS, Greer DM. American Academy of Neurology. Evidence-based guideline update: Determining brain death in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2010;74:1911–8; and Nakagawa TA, Ashwal S, Mathur M, Mysore M, and the Committee for Determination of Brain Death in Infants and Children. Guidelines for the determination of brain death in infants and children: An update of the 1987 Task Force recommendations. *Critical Care Medicine* 2011;39:2139–55.
8. Dalle Ave AL, Bernat JL. Inconsistencies between the criterion and tests for brain death. *Journal of Intensive Care Medicine* 2018:1–9 (epub before print.) PMID 29929410. The authors grouped the cases into several categories: (1) obvious clinical brain functions that were disregarded in the test batteries; (2) cases in which brain functions may have been present, but were not detectable at the bedside; and (3) cases in which brain functions may have been absent transitorily because of confounding factors.
9. Arita K, Uozumi T, Oki S, Kurisu K, Ohtani M, Mikami T. The function of the hypothalamo-pituitary axis in brain dead patients. *Acta Neurochirurgica (Wien)* 1993;123(1-2):64–75.
10. For a recent debate on the correct understanding of the McMath case, see: Lewis A. Reconciling the case of Jahi McMath. *Neurocritical Care* 2018;29(1):20–2; and Shewmon DA. Truly reconciling the case of Jahi McMath. *Neurocritical Care* 2018;29(2):165–70.
11. For mimics of brain death, see Busl KM, Greer DM. Pitfalls in the diagnosis of brain death. *Neurocritical Care* 2009;11:276–87.

12. Webb AC, Samuels OB. Reversible brain death after cardiopulmonary arrest and induced hypothermia. *Critical Care Medicine* 2011;39:1538–42.
13. Bernat JL, Brust JCM. Strategies to produce uniformity in brain death determination. *Neurology* 2019;92:401-2.
14. Coimbra CG. Implications of ischemic penumbra for the diagnosis of brain death. *Brazilian Journal of Medical and Biological Research* 1999;32:1479–87.
15. The preferential survival of brain stem neurons during diffuse hypoxic-ischemic injury is also the mechanism by which the vegetative state is produced during prolonged cardiopulmonary arrest in cases not severe enough to produce brain death. See Bernat JL. Chronic disorders of consciousness. *Lancet* 2006;367:1181–92.
16. See texts referenced in note 7.
17. See note 13, Bernat, Brust 2019.
18. See texts referenced in note 2.
19. We discussed these ideas briefly in the article cited in note 8.
20. The relevant confirmatory tests are neuroimaging studies measuring intracranial blood flow, such as contrast angiography, intravenous radionuclide angiography, CT angiography SPECT, and transcranial Doppler ultrasound. See Robbins NM, Bernat JL. Practice current: When do you order ancillary tests to determine brain death? *Neurology Clinical Practice* 2018;8:266–74.
21. Huang AP, Bernat JL. The organism as a whole in an analysis of death. *Journal of Medicine and Philosophy* 2019 (in press).
22. From nearly the beginning of the brain death era, investigators have noted the presence of isolated EEG findings and certain movements in brain dead patients. See Grigg MM, Kelly MA, Celesia GG, Ghobrial MW, Ross ER. Electroencephalographic activity after brain death. *Archives of Neurology* 1987;44:948–54; and Saposnik G, Basile VS, Young GB. Movements in brain death: A systematic review. *Canadian Journal of Neurological Sciences* 2009;36(2):154–60.