Anesthetizing the Self

The Neurobiology of Humbug

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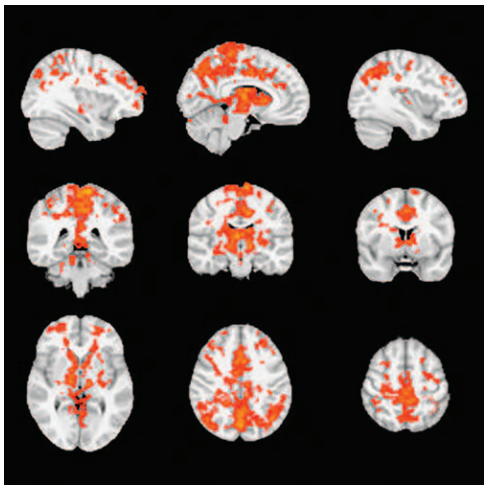
THE field of anesthesiology was born of some irony that continues to be a clinical problem and scientific challenge. On October 16, 1846, William T. G. Morton made history by anesthetizing Edward Gilbert Abbott for the surgery performed by John Collins Warren, who purportedly declared "Gentlemen, this is no humbug." Although I cannot help but agree with the imprimatur of the first public demonstration of surgical anesthesia, we must admit that the event was, in fact, beset by a bit of humbuggery. What, you might ask, is humbug, and why should we still care about it in the 21st century? The *Oxford English Dictionary* defines it as "deceptive or false talk or behaviour," and the historical context of Warren's alleged proclamation was the misinterpreted "deception" of the bungled demonstration of a tooth extraction under nitrous oxide by Horace Wells in 1845. Nitrous, unlike poor Wells, fully recovered from the embarrassment, having now survived two centuries and just as many ENIGMA trials. However, the humbug to which I refer is not the deceptive behavior of a suspected snake oil salesman, but rather the deceptive behavior of unresponsiveness. As was reported in the academic publication by Henry J. Bigelow describing the first ether anesthetics,[1] Abbott was not completely insensate but rather experienced and remembered events related to the surgery. The humbug of unresponsiveness with preserved consciousness has persisted since 1846 as the clinical problem of intraoperative awareness.



"They offer a provocative explanation [that] unresponsiveness can occur despite ongoing states of consciousness: ... anesthetics are not necessarily suppressing conscious events but rather the self that experiences them in a coherent way."

The scientific challenge of this humbug comes into play when determining the neural correlates or neural causes of anesthetic-induced unconsciousness. Even in the absence of neuromuscular blockers, the subjective state beyond unresponsiveness is unknown. If a volunteer in a study of propofol, for example, stops following a command, he or she could be (1) conscious of the command but unable or unwilling to respond, (2) unconscious of the command but conscious of something else (as in a dream state), or (3) completely unconscious (as we most often assume). As such, we have begun to question more rigorously the subjective state with which we are making correlations.[2–5] The article by Warnaby *et al.*[6] addresses the underlying neurobiology of unresponsiveness *versus* unconsciousness with a multimodal neuroimaging study.

The investigators conducted a secondary analysis of a preexisting dataset derived from healthy volunteers who underwent a slow titration of propofol-induced unresponsiveness while simultaneous functional magnetic resonance imaging (fMRI) and electroencephalography were performed.[7] Noxious laser stimuli, computer-generated tones, and auditory word tasks were presented during the administration of propofol. To avoid artifacts associated with the magnetic resonance imaging, parallel experiments with electroencephalography were performed in a different location but with otherwise similar methodology. For this study, the investigators analyzed changes in stimuli-evoked neural

Image: Oxford Centre for Functional MRI of the Brain, University of Oxford.

Corresponding article on page 766. This article has an audio podcast.

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responses, fMRI-based functional connectivity, and electroencephalographic synchrony across the lateral frontal-parietal network (using data collected independently of the fMRI).

At propofol concentrations associated with loss of *behavioral* responsiveness, there was still considerable *brain* responsiveness. Laser and auditory stimuli continued to evoke activity in areas such as the thalamus and primary sensory cortices. One area that was consistently suppressed after propofol-induced unresponsiveness was the right dorsal anterior insular cortex (dAIC), which became the focus of the study. At loss of behavioral responsiveness, functional connectivity—that is, the statistical correlation of activity—between the dAIC and the rest of the brain was analyzed. Reductions of connectivity were found between the dAIC and the right dorsolateral prefrontal cortex, right inferior parietal lobule, and right cerebellum. In parallel to the fMRI data, synchrony in slow activity was significantly reduced between the electroencephalographic electrodes most closely associated with the right dorsolateral prefrontal cortex (Fp2) and right inferior parietal lobule (P8; but, importantly, not a neighboring midline parietal electrode, Pz). The authors' interpretation of these data was that, at some critical threshold, propofol suppresses the activity of the dAIC, which disrupts a connectivity pattern in lateral frontal-parietal networks.

What does this tell us about the neurobiology of humbug? We cannot know for sure, but there are some interesting considerations based on past research of the dAIC and the lateral frontal-parietal system. First, the anterior insula has been suggested to be a site at which bodily (*i.e.*, interoceptive) sensations are integrated to form a "sentient self."[8,9] In the context of the study by Warnaby *et al.*, one interpretation is that the anesthetic suppression of the anterior insula blocks a point of convergence for sensory processing. This impaired integration would occur despite the fact that such processing continues beyond the initial loss of behavioral responsiveness, as evidenced by persistent stimulus-evoked activity and connectivity patterns associated with the primary sensory cortex. The result would be a brain state consistent with ongoing conscious experience, but either disconnected from the world or disconnected from the self. Furthermore, the lateral frontal-parietal networks are thought to be important for executive function and consciousness of environmental stimuli.[10] The authors hypothesize that the anterior insula is a "cortical gate" that, when closed, functionally fragments the frontal-parietal system. They offer a provocative explanation of how the humbug of unresponsiveness can occur despite ongoing states of consciousness: just over the border of responsiveness, anesthetics are not necessarily suppressing conscious events but rather the self that experiences them in a coherent way.

This is a fascinating possibility, but—like the interpretation of any study—must be regarded in light of the methodologic limitations. It is possible that there are other key areas suppressed just over the border of unresponsiveness that were not identified in this study, and we must also be circumspect in assigning a singular and exclusive function (*e.g.*, "self") to a particular neural area. Furthermore, it is not clear how, precisely, the suppression of the anterior insula would lead to the breakdown of functional connectivity between prefrontal cortex and inferior parietal lobule, especially because these areas are posited to have a direct cortical connection. It must be kept in mind that the fMRI and electroencephalographic data were not recorded simultaneously, so the precise relationship between dAIC suppression and frontal-parietal network fragmentation is unclear. This study also does not speak to possible influences from the brainstem or diencephalon—we have been appropriately reminded in the literature of anesthetic-induced unconsciousness that our nightly sojourn into sleep is mediated by changes in such subcortical activity.[11] Finally, only propofol was tested—it will be of interest to assess whether suppression of the anterior insula is related to the functional breakdown of frontal-parietal connectivity that has been observed with other anesthetics such as sevoflurane and ketamine.[12,13]

Despite these limitations, Warnaby *et al.* are to be commended for facing the difficult problem of how general anesthetics affect behavior, consciousness, and the self. We must also face the foundational reason *why* this is such a difficult problem: in a seemingly inescapable way, all judgments regarding states of consciousness in others are inferences based on responsiveness and behavior. Even in the normal waking state of consciousness, we can assert definitively the existence of one and only one instance of subjective experience—our own. Every other determination is an approximation based on analogy and without the possibility of direct demonstration. This is what led the deeply rigorous thinker Renee Descartes to scientifically doubt the reality of everything except the one indisputable fact that he himself was conscious. In essence, the Cartesian assertion "Cogito, ergo sum" as a firm basis for philosophy and science really meant "I think, therefore I am—*because everything else could just be humbug*." Ultimately, we must continue the efforts of Warnaby *et al.* to study the deceptive behavior of unresponsiveness, advance our clinical care and neuroscientific investigation accordingly, and hope that our best efforts fall on the right side of the shadows and the light.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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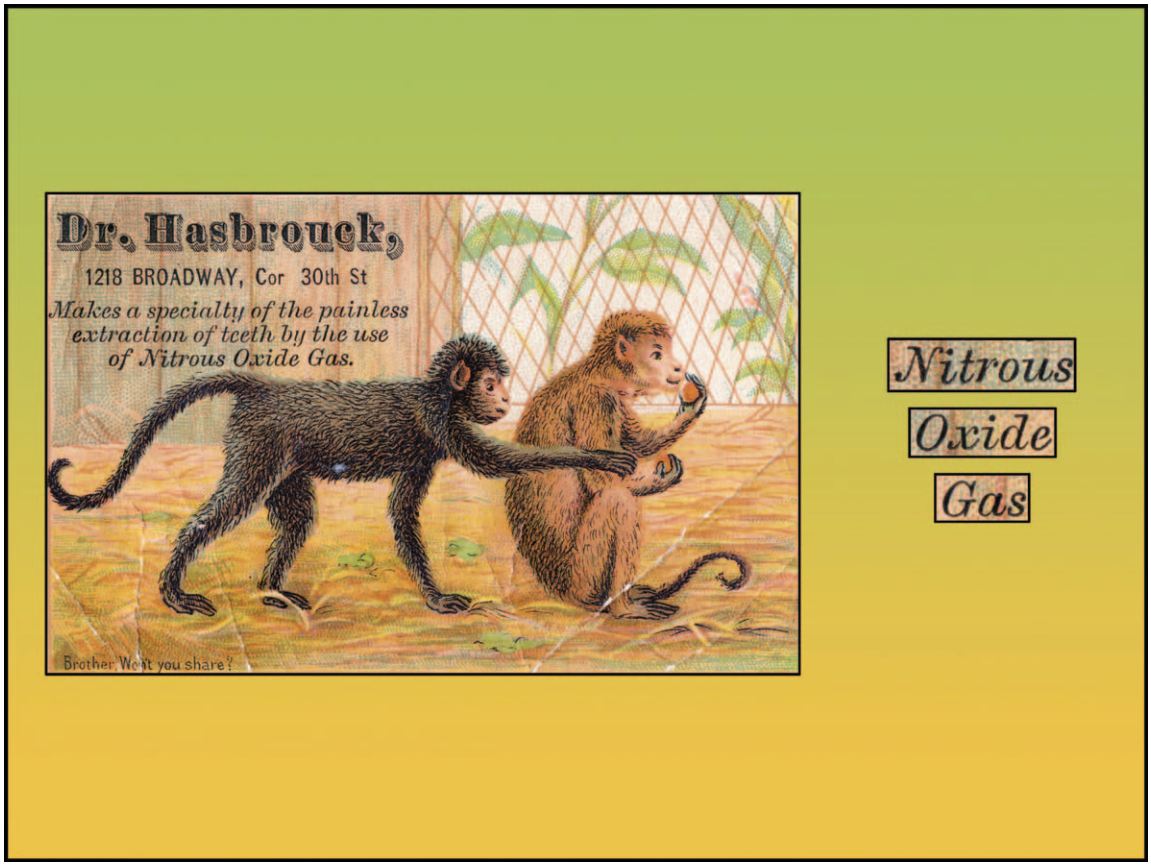
ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Ferdinand Hasbrouck's Nitrous Oxide Caper—Which One?



A Yale professor of chemistry, Dr. Benjamin Silliman, Sr., noted that nitrous oxide made "One of our gravest citizens … caper about like a monkey…." From the Manhattan corner of Broadway and 30th Street, Dr. Ferdinand Hasbrouck (1844–1904) capered off with that monkey imagery for the obverse of his dental trade card (*left*). Hasbrouck's advertising featured a squatting auburn monkey with food in each hand and with its back to a second monkey. One of Hasbrouck's most infamous capers occurred aboard the yacht *Oneida*. Onboard he administered nitrous oxide for the first stage of U.S. President Grover Cleveland's secret surgery for oral cancer. (Copyright © the American Society of Anesthesiologists, Inc.)

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