Emery N. Brown, M.D., Ph.D., Recipient of the 2015 Excellence in Research Award

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EMERY N. Brown, M.D., Ph.D., is an accomplished anesthesiology researcher, clinical anesthesiologist, computational neuroscientist, and the recipient of the American Society of Anesthesiologists 2015 Excellence in Research Award. He is the Warren M. Zapol Professor of Anaesthesia at Harvard Medical School/Massachusetts General Hospital (MGH), a practicing anesthesiologist at MGH, and the Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience at the Massachusetts Institute of Technology (MIT). Dr. Brown has made significant contributions to the neuroscience of general anesthesia and to the field of computational neuroscience.

Dr. Brown received his B.A. (magna cum laude) in applied mathematics from Harvard College, his M.A. and his Ph.D. in statistics from Harvard University, and his M.D. (magna cum laude) from Harvard Medical School. He completed his internship in internal medicine at the Brigham and Women's Hospital and his residency in anesthesiology at MGH. In 1992, Dr. Brown joined the staff in the Department of Anesthesia at MGH and the faculty at Harvard Medical School. In 2005, he joined the faculty at MIT.

In 2007, Dr. Brown became the first anesthesiologist to receive a National Institutes of Health (NIH) Director's Pioneer Award for his application entitled, "A Systems Neuroscience Approach to the Study of General Anesthesia." Awarded annually to 10 to 15 individuals, the Pioneer Award supports "individual scientists of exceptional creativity who propose pioneering approaches to major challenges in biomedical and behavioral research that have the potential for producing an unusually high impact." Dr. Brown set up an interdisciplinary team of anesthesiologists, neuroscientists, bioengineers, statisticians, imagers, and mathematicians to focus on understanding how anesthetic drugs work in the brain to produce the states of general anesthesia and sedation. The key step that Dr. Brown has taken in his research has been to combine knowledge of the molecular targets at which the anesthetics are known to act with the anatomy and neurophysiology of neural circuits in the relevant brain regions. He has used this framework to develop the first specific neural circuit hypotheses regarding anesthetic action.

This framework is detailed in analytic reviews he wrote for the *New England Journal of Medicine* in 2010 with Drs. Ralph Lydic and Nicholas Schiff[1] and for the *Annual Review of Neuroscience* in 2011 with Drs. Patrick L. Purdon and Christa Van Dort.[2] An important issue that Dr. Brown clarifies in these analyses is that general anesthesia is a drug-induced reversible coma distinct from sleep.[1] For the five major classes of anesthetics (GABAergic agonists, *N*-methyl-D-aspartate antagonists, opioids receptor agonists, α-2 adrenergic agonists, and dopaminergic antagonists), this work provides the first detailed neural circuit analyses of how each anesthetic creates altered states of arousal.[2] These analyses have provided the conceptual framework for his subsequent research.

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Working with Dr. Purdon at MGH and Nancy Kopell, a mathematician at Boston University, Dr. Brown has developed detailed neurophysiologic characterizations of how propofol induces unconsciousness. Their research uses high-density electroencephalogram (EEG) recordings,[3] multi-electrode recordings,[4] and functional imaging in humans,[5] along with mathematical modeling[6–9] and newly developed signal processing algorithms.[10–13] The fundamental insight gained from these studies has been that unconsciousness produced by propofol likely results from well-defined oscillatory changes in the brainstem, thalamus, and cortex. In the case of propofol, these prominent α oscillations (8 to 12 Hz) most likely represent a sustained coherent rhythmic activity between the thalamus and the prefrontal cortex mediated through its actions at GABAergic synapses,[3,6,10,14] whereas the slow oscillations (0.1 to 1 Hz) are markers of intracortical fragmentation.[4] These observations suggest that a key

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component of how anesthetics work is by producing highly organized oscillations that disrupt normal communications among brain regions.[15]

The nature of the oscillations depends on the brain sites that the anesthetics target and the neural circuits connecting those sites.[15–18] Anesthetics that target similar receptors, and hence the same brain circuits, produce similar oscillation, whereas anesthetics that target different receptors and circuits produce different oscillations.[15] A clinically significant corollary of this observation is that each anesthetic has a different neurophysiologic signature that is readily visible in the EEG and that can be used to assess patients' level of unconsciousness in the operating room.[15,19] Moreover, these oscillations change dramatically and systemically as a function of age; the oscillations are very different in very young children, reflecting the different stages of brain development.[20,21] Similarly, the oscillations are different in the elderly.[22–24]

As a consequence, Drs. Purdon and Brown have proposed a new approach to monitoring the brain states of patients during general anesthesia that entails teaching anesthesiologists how to read the unprocessed EEG and its associated spectrogram. The spectrogram is the decomposition of the EEG signal into its power as a function of frequency over time. This new paradigm differs from the current approach that tracks the brain states of anesthetized patients using EEG-based indices and assumes that the same index value corresponds to the same anesthetic state irrespective of the anesthetic being administered. We are testing this new paradigm at MGH; thanks to the web-based program developed by Drs. Purdon and Brown, which is now available online to the anesthesiology community for free at the website www.anesthesiaeeg.com.

Over the next few years, this new paradigm could transform clinical practice by allowing anesthesiologists to administer anesthetics and infer level of unconsciousness or sedation by monitoring EEG signatures that relate to the anesthetics' mechanisms of action in the brain. This approach should make it possible to reduce significantly the amount of anesthetic administered—particularly to elderly patients—while being certain that the patient is unconscious and not at risk for awareness. Because the new paradigm could lead to more judicious and informed anesthetic administration, it could help reduce delirium and postoperative cognitive dysfunction, an issue of increasing concern for elderly patients. Finally, when full developed, the new paradigm could also help reduce anesthetic exposure in children. In the short term, this may help mitigate concerns about the neurotoxic effects of anesthetic agents in children until definitive findings are available on this controversial issue.

In collaboration with Dr. Ken Solt, Dr. Brown has also developed a new approach for inducing emergence from general anesthesia. Currently, emergence from general anesthesia is a passive process in which a patient emerges because the anesthesiologist times the dosing of the drugs and allows their effects to wear off. Drs. Solt and Brown hypothesized that instead of allowing passive emergence, it should be possible to administer agent(s) to actively induce emergence, a process they term reanimation. Through a series of highly successful rodent studies, Drs. Solt and Brown have demonstrated that the state of general anesthesia can be rapidly and reliably reversed by administering methylphenidate (Ritalin). Their work has shown that reanimation with methylphenidate is most probably achieved by increasing the brain's dopamine levels, thereby switching the largely inhibitory state of unconsciousness during general anesthesia to an excitatory state that leads to recovery of consciousness.[25–28] Drs. Solt and Brown demonstrated that reamination could be induced by direct electrical stimulation of the ventral tegemental area, the origin of the dopaminergic mesocortical pathway,[28] and optogenetic stimulation of dopaminergic neurons in the ventral tegemental area. Drs. Solt and Brown have initiated a Food and Drug Administration–approved phase I clinical trial to test the safety and efficacy of methylphenidate for inducing reanimation of humans from general anesthesia.

General anesthesia–induced burst suppression, a state of unconsciousness and profound brain inactivation in which the EEG shows bursts of electrical activity interspersed with periods of suppression, is being actively studied by Dr. Brown and coworkers[7,29,30] for basic science and clinical purposes.[31] Burst suppression is commonly maintained by continuous intravenous administration of propofol as a therapy to reduce intracranial hypertension in patients after a traumatic brain injury or to arrest seizure activity in patients with status epilepsy. This therapeutic state is termed a medically induced coma. Currently, medical coma is maintained by intensive care unit staff manually changing the anesthetic infusion rate, a task that must be often carried out for several days.

Dr. Brown and coworkers have developed in a rodent model a highly accurate closed-loop anesthetic delivery system for second-to-second burst suppression control for the purpose of maintaining a medically induced coma.[11,12,32,33] They achieved these results by combining a parsimonious pharmacokinetics model of burst suppression with the design and implementation of real-time signal processing and control algorithms. These results offer a principled, automated approach to managing medically induced coma[34,35] as well as for designing the closed-loop anesthetic delivery systems to control states of general anesthesia.

Dr. Brown has been widely recognized for his research accomplishments. He is the recipient of a National Institute of Mental Health Independent Scientist Award, an NIH Director's Pioneer Award, an NIH Director's Transformative Research Award, the 2011 Jerome Sacks Award for Outstanding Cross-Disciplinary Research from the National Institute of Statistical Science, and a 2015 Guggenheim Fellowship in Applied Mathematics. Dr. Brown is a member of the Association of University Anesthesiologists. He is a Fellow of the American Institute for Medical and Biological Engineering, the American Statistical Association, the Institute of Electrical and Electronics Engineers (IEEE), the American Association for the Advancement of Science, and the American Academy of Arts and Sciences. He is the first and only anesthesiologist to be elected to the American Academy of Arts and Sciences. Dr. Brown is 1 of only 19 people who are currently members of the National Academy of Medicine (formerly the Institute of Medicine), the National Academy of Sciences, and the National Academy of Engineering and the first and only anesthesiologist to be elected to all 3.

Dr. Brown has been a mentor to many medical students, graduate students, fellows, and junior faculty, many of whom have gone on to highly successful careers in medicine and science. Examples include Dr. Loren M. Frank, Associate Professor of Physiology, and Howard Hughes, Medical Institute Investigator at University of California in San Francisco; Dr. Riccardo Barbieri, Associate Professor of Bioengineering, University of Milan; Dr. Patrick L. Purdon, Associate Bioengineer at MGH and 2009 NIH Director's Pioneer Award recipient; Dr. Ken Solt, Associate Professor of Anaesthesia, MGH/Harvard Medical School, McDonnell Scholar; Dr. Uri T. Eden, Associate Professor of Statistics, Boston University and National Science Foundation Career Award Winner; Dr. Maryam Shanechi, Assistant Professor of Electrical Engineering, University of Southern California and MIT Technology Review 35 under 35; Dr. Srideva Sarma, Associate Professor of Bioengineering at Johns Hopkins University and National Science Foundation Career Award Winner; and Dr. Laura Lewis, Junior Fellow, Harvard University Society of Fellows.

Dr. Brown has a long history of public service. From 2013 to 2014, he served on the NIH BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative Working Group.[36] Currently, he is a member of the NIH Council of Councils, the NIH BRAIN Multi-Council Working Group, the National Science Foundation Mathematics and Physical Sciences Advisory Committee, the Board of Directors of the Burroughs-Wellcome Fund, the Board of Trustees of the International Anesthesia Research Society, International Anesthesia Research Society–Food and Drug Administration SmartTots Advisory Panel, and the Scientific Advisory Committee of CURE Epilepsy. He serves on the editorial boards of *eLife*, *IEEE Transactions in Biomedical Engineering*, the *Journal of Neurophysiology and Neural Computation*.

Dr. Brown has been actively educating the lay public about the neuroscience of anesthesia. His research has been featured on National Public Radio, in *Scientific American,* the MIT *Technology Review,* in Serious Science, the WGBH Public Broadcasting System, the *New York Times,* in TEDMED 2014, and at the recent National Academy of Sciences induction ceremony (http://www.nasonline.org/news-and-multimedia/video-gallery/152nd-annual-meeting/research-briefings.html). One delightful consequence of these publicly available presentations is a growing number of high school, college, and medical students who are interested in becoming anesthesiologists.

In addition to his several accoomplishments in the neuroscience of anesthesia, Dr. Brown has a parallel and highly successful career in computational neuroscience where his research has focused on developing signal processing algorithms to characterize how neural systems represent and transmit information. Dr. Brown recently coauthored with Dr. Robert E. Kass at Carnegie Mellon University and Dr. Uri Eden at Boston University the first textbook on statistics for neuroscience data analysis entitled, *Analysis of Neural Data* (Springer, 2014).

Dr. Brown is one of the most creative thinkers in anesthesiology today. His research is providing a fundamental neurophysiologic understanding of anesthetic mechanisms that will have significant impact on the practice of anesthesiology and that will allow anesthesiology to contribute new insights into clinical and basic neuroscience.

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Competing Interests

The author declares no competing interests.

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