Profile of Emery N. Brown

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“The frontier in anesthesiology lies in neuroscience,” (1) says Emery N. Brown, a statistician, neuroscientist, and anesthesiologist who is leading development of a new joint center between the Massachusetts Institute of Technology (MIT) and Massachusetts General Hospital (MGH). The center aims to use anesthesia research to design novel approaches for controlling brain states. Brown, a member of the National Academy of Sciences, is at the forefront of research on neurophysiological mechanisms of general anesthesia and has developed signal-processing algorithms to study how neural systems represent and transmit information. In his Inaugural Article (IA), he analyzed the brain states of COVID-19 patients who experienced prolonged recovery of consciousness (2). With coauthor Nicholas Schiff of Weill Cornell Medical College, he postulated that neuroprotective mechanisms similar to those observed in anoxia-tolerant vertebrates might exist in humans and could open the possibility for new therapeutic strategies to enhance recovery from coma.

Background in Statistics and Medicine

Brown was raised in Ocala, FL by his parents, who were high school and junior-high math teachers active in their community. Both taught African American students during the “separate but equal” legal doctrine period in Florida that upheld racial segregation. In segregated schools through the sixth grade, Brown excelled academically with the support of his family, church, and the African American community. He developed an interest in romance languages after listening to his older brother’s language instruction albums and went on a 6-week homestay program in Spain after completing ninth grade.

The following year, he attended summer school at Phillips Exeter Academy, where he continued his education through grade 12, including the academy’s year-abroad program in Spain. He says that, while language studies remained his focus at the time, “Attending medical school was always my long-term plan. I figured I would become a doctor working for Médecins Sans Frontières or the World Health Organization.” One role model was Brown’s pediatrician, Dr. Burcher. Brown says, “He was the coolest guy around. I was sick a lot as a child, and every time I saw him, I got better.”

He entered Harvard College in 1974, intending to major in romance languages. Influenced by his roommates’ interests in economics and statistics, Brown, a math aficionado, switched his major in his junior year and earned a bachelor’s degree magna cum laude in applied mathematics in 1978. At Harvard, he met statisticians and National Academy of Sciences members Kenneth Wachter and Frederick Mosteller, who recognized his potential. Mosteller, a pioneer of his field, became one of Brown’s mentors and undergraduate thesis advisor. Brown studied mathematics as a Rotary Fellow at the Institut Fourier des Mathématiques Pures in Grenoble, France before returning to Harvard to earn Master of Arts and PhD degrees in statistics and an MD magna cum laude from Harvard Medical School.

Brown’s postdoctoral training included serving from 1987 to 1988 as an intern in medicine at Brigham and Women’s Hospital and, the following year, as a research fellow in the hospital’s division of endocrinology and hypertension. MGH anesthesiologist and Harvard Medical School (HMS) professor of anesthesiology Bucknam “Jack” McPeek had introduced him to anesthesiology during his senior year in college. Brown appreciated anesthesiology’s connection to real-time physiology and pharmacology, as well as the opportunity it provided to directly help patients.

He accepted a residency in anesthesia at MGH in 1989 and in 1992 joined the HMS faculty in the department of anesthesia. Brown is now the school’s Warren M. Zapol professor of anesthesia. He is also currently the Edward Hood Taplin professor of medical engineering, professor of computational neuroscience, and professor of health sciences and technology at MIT; an investigator with the Picower Institute for Learning and Memory at MIT; and, since 1992, an anesthesiologist at MGH.

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**Circadian Rhythms, Neural Signal Processing**

While studying circadian rhythms for his doctorate, Brown first observed the juxtaposition of statistical and mathematical models representing dynamics. He says, “There was this one question that bothered me that I had worked on, and it had me appreciate that you could have a dynamical systems representation for [simulations] but when you looked at the real data, you should have a statistical representation to capture that dynamical formulation as closely as possible” (3).

Brown has since developed algorithms using multiple approaches, including likelihood methods (joint probability of the observed data as a function of the parameters of the chosen statistical model), Bayesian statistics, state-space modeling (all possible states of a system), time series (data collected sequentially, usually at fixed intervals), and point process (time series of binary observations). Statistician Peter Huber, formerly at Harvard and MIT, and former Harvard statistician Victor Solo influenced Brown’s methodological thinking. Regarding Solo, Brown says, “My engineering perspective on signal processing came from him.”

Applying these approaches to the study of circadian rhythms, Brown and colleagues determined that the human circadian pacemaker is much more sensitive to light than previously recognized (4), such that exposure to bright light and darkness can help treat physiological problems associated with working at night (5). Brown and colleagues additionally found that the intrinsic period of the human circadian pacemaker averages 24.18 hours (6). His research on circadian rhythms has enabled Brown to relate models used extensively in applied statistics, such as the harmonic regression signal plus noise model, to dynamical systems models used in circadian simulations (7, 8).

Brown has developed the state-space point process paradigm to solve longstanding neuroscience data analysis challenges. He and colleagues showed in a rodent model that hippocampal neurons maintain a dynamic representation of an animal’s spatial location in their ensemble spiking activity (9). Brown and colleagues used state space algorithms to analyze data from experiments with nonhuman primates, dynamically characterizing the link between neural activity changes and behavior during learning (10).

He helped formulate a computationally tractable method for state-space and parameter estimation from point process observations (11) that has since been used to analyze neurophysiologic experiments involving implicit stimuli. He also developed a point process framework to determine the effects and relative importance of factors simultaneously affecting the spiking activity of individual neurons (12). With colleagues, he also developed a method for determining the signal-to-noise ratio of single neurons in stimulus-response experiments (13). The approach can be applied to nearly any generalized linear model, including those for clinical trials and evaluation of neural prostheses.

**Mechanisms of General Anesthesia**

Invited to neuroscience meetings to talk about neural signal processing and data analysis, Brown was often approached by other scientists who were curious about his work as an anesthesiologist. He says, “They would ask me, ‘How does anesthesia work?’ and I would reply, ‘We don’t know.’” Determined to find answers, he applied for and won a NIH Director’s Pioneers Award in 2007. The $2.5-million award, distributed over 5 years, supported the development of a systems neuroscience approach to study how anesthetic drugs act in the brain to create the state of general anesthesia. He subsequently led a detailed analysis of the relationships between general anesthesia, sleep, and coma (14). With colleagues, he also performed a detailed systems neuroscience analysis of altered arousal states induced by five different classes of anesthetic drugs (15).

Studying propofol, the most commonly used intravenous agent for induction and maintenance of anesthesia, Brown and his team established important components of how it induces unconsciousness. They found that the drug causes highly structured alpha (8-12 Hz) oscillations and slow-delta (0.1-4 Hz) oscillations (16, 17). They also discovered that under propofol spiking activity in cortical circuits is strongly phase limited, particularly by the slow-delta oscillations (18, 19). These oscillatory dynamics produce unconsciousness by dramatically impairing neuronal spike timing, and as a consequence, the ability of brain regions to freely communicate. Brown and his team have shown that ketamine-mediated unconsciousness is achieved with an entirely different set of oscillatory dynamics (20). He and his colleagues have also demonstrated that anesthetic management can be more precisely controlled by performing multimodal anesthesia, during which multiple analgies agents are used simultaneously to control pain and modulate the level of unconsciousness (21).

Brown’s mathematical descriptions of electroencephalogram (EEG) oscillations observed during different anesthetic states have helped uncover mechanisms of anesthesia and improve the monitoring of patients receiving anesthesia care (22). As a result, anesthesiologists can safely administer less anesthesia than would otherwise be given under standard protocols that rely more on drug-dosing conventions and indirect signs of arousal. He has worked to advance these methods throughout his field via extensive advocacy within professional societies and the sharing of free training materials (23).

Improved real-time assessment and control of anesthetics are among the longstanding objectives of Brown and his team. With colleagues, he showed that methylphenidate, whose short-acting form is the drug Ritalin, can bring about rapid emergence from general anesthesia (24). Brown and colleagues have since conducted drug trials using Ritalin, which holds promise for reducing potentially harmful side effects of anesthesia, such as cognitive dysfunction commonly observed in elderly patients following administration of general anesthesia.

In addition to their research on pharmacological agents, Brown and his team have developed electrical stimulation and optogenetic methods for controlling brain arousal states. For example, he and colleagues demonstrated that electrical stimulation of the brain’s ventral tegmental area can induce rapid emergence from general anesthesia (25). They also showed that thalamic stimulation can increase arousal (26) and reverse some neural effects of propofol-induced
unconsciousness (19). Using a stochastic control framework, Brown led development in a rodent model of a brain–machine interface that helps control medically induced coma by real-time monitoring of EEG data and adjustment of anesthetic infusion rate (27).

Frontiers for Clinical Neuroscience Research

In his IA, Brown suggests a novel approach for controlling brain arousal states, presenting a conceptual, multidisciplinary analysis to interpret the brain states of COVID-19 patients who experienced a prolonged recovery of consciousness. The authors postulate that factors contributing to such positive patient outcomes could include latent neuromodulatory mechanisms in the human brain, analogous to those documented in anoxia-tolerant vertebrates. If additional research confirms the existence of the theorized protective downregulated state in humans, new methods for enhancing coma recovery may be possible.

Brown and coauthor Schiff note that, when certain patients with COVID-19 or following cardiac arrest were in a state of unconsciousness prior to their recovery, they exhibited an EEG signature very similar to that of painted turtles experiencing a prolonged reversible coma, meaning that it was similar to that seen in hibernation. Brown says, “If we could induce states comparable to hibernation in certain very sick patients, enabling total control of their physiology, we would likely enhance their recovery.”

Brown is one of only 25 scientists—and the first African American, statistician, and anesthesiologist—to be elected to all three US National Academies. He is grateful for the work and dedication of more than 40 postdocs, graduate students, and undergraduates whom he has trained and mentored over the years.

He is also grateful for the support of his wife, a public-health nurse, and their children. Brown hopes to continue nurturing their talents and interests, as well as those of his team. “My parents would be very upset if I weren’t doing my part to help the next generation,” he says. “It is what you are supposed to do.”