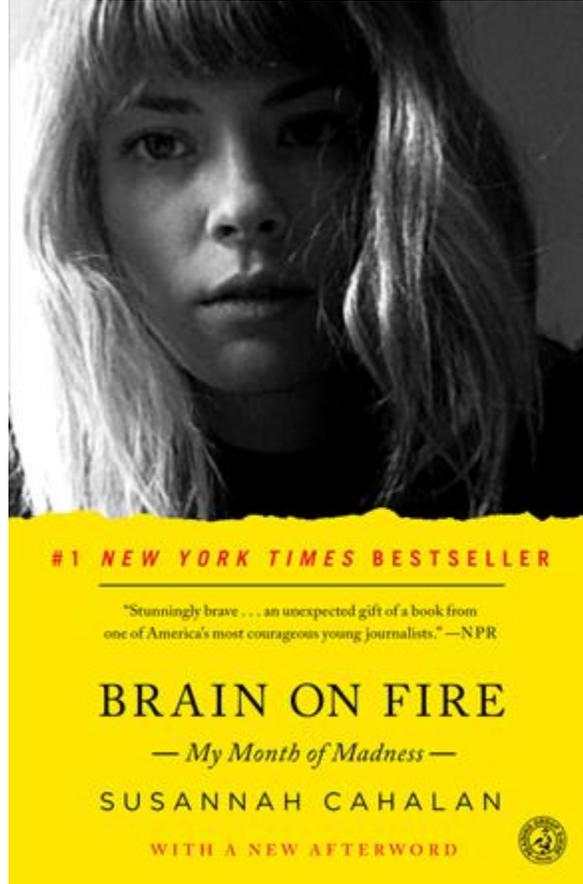


To Hell and Back
Review: Brain on Fire: My Month of Madness

Review by David Lynch, M.D., Ph.D.



Suppose you thought that you were losing your identity—changing almost overnight and doing things you could not explain? This inexplicable scenario helps launch *Brain on Fire: My Month of Madness*, in which Susannah Cahalan chronicles her experience with the rare disorder anti-NMDA-receptor encephalitis. The onset of this newly identified entity results from the production of antibodies against the N-methyl-D-aspartate (NMDA). The NMDA receptor regulates synaptic plasticity in the brain and is critical for learning and memory. The syndrome evolves over days to weeks and presents as a psychosis similar to that seen in schizophrenia. Cahalan, who suffered from seizures and other neurologic symptoms, creates a medical detective story from a patient's perspective as she captivatingly describes her descent into madness. The result is entertaining reading that gets us to think about the biological origins of our own personalities.

Cahalan presents her experience as a remembrance three years after the onset of her disorder. At the book's beginning, she is a young reporter struggling to find story ideas that will resonate with her editors at the *New York Post*. Over several weeks, she gradually finds her personality changing as she begins suffering from paranoia and hallucinations and withdraws from her friends and colleagues. She describes her thoughts (as she perceives them at the time) and confusion about the origin of her symptoms. Associated with her uncertainty is the realization that the medical community has no explanation for her rapid change.

Eventually, Cahalan develops the neurological features that lead to a correct diagnosis by a medical team at the NYU Langone Medical Center. After weeks of downward spiraling, the team puts all the facts together and arrives at the answer: anti-NMDA-receptor encephalitis, a multistage, autoimmune disease that varies wildly in its presentation. Cahalan slowly recovers after undergoing immunomodulatory therapies (steroids, IVIG treatment, and plasmapheresis) in the hospital for a month, plus six months of outpatient follow-up.

For a neuroscientific audience, Cahalan's story stimulates readers to think about the essence of the brain and the personality on several levels. First is the way that she portrays the early events of her encephalitis. She is never sure whether her bizarre behavior is being driven by a disease or is the result of reactions to stress or other events. These reactions include irrational fears of jealousy, emotional lability, and even illusions that she can sense other people's thoughts. Almost all of her friends attribute these behaviors to the demands of her job or to psychological issues, but she later

realizes that they are subtle early symptoms of anti-NMDA-receptor encephalitis. To a neuroscientist, Cahalan's attempt to decipher her symptoms represents the core of the discussion about where the neurological features of disease end and those of psychiatry begin. It also shows the overlap between these disciplines. In addition, with treatment, the changes in Cahalan's personality reverse not immediately but over long periods of time. This is consistent with the idea of a resilient, structural basis of memory and personality that is attacked by anti-NMDA-receptor encephalitis but is then slowly rebuilt. One issue, which Cahalan describes, is that anti-NMDA-receptor encephalitis is associated with a significant amnesia for the period of acute illness. Cahalan was able to trigger exquisite firsthand details about the experience by revisiting her family's notes, diaries, and recollections, and she points out that it is difficult to tell where her personal memory ends and others' memories begin. This paradox gives readers fascinating insight into the way that people constantly construct their own perceptions.

Brain on Fire is also very effective as an illustration of the diagnostic odyssey of an individual with an unknown disease. Cahalan's signs seem so clear as she presents them three years later, now that the number of individuals reported with anti-NMDA-receptor encephalitis has risen from several hundred to many thousands and the disorder is no longer a research curiosity. Cahalan was diagnosed and treated only after weeks of progression, after finally being admitted to a specialized neurology service in a tertiary care center—and even at that center, the tale is presented as if only one specialist was familiar with the condition. Viewed from that perspective, Cahalan could be considered lucky even to have received the correct diagnosis. The author does not condemn physicians unaware of the diagnosis, as she recognizes the difficulty in staying abreast of new developments in medicine. The book is dedicated to undiagnosed patients, a group that goes far beyond anti-NMDA-receptor encephalitis. Even in the age of whole-genome sequencing, the medical community lacks much information about even common diseases, much less rare ones. Good news is that the NIH Undiagnosed Diseases Program is currently undergoing revision and expansion, in recognition of the number of disorders that remain unknown and might become recognizable.

In some ways, Cahalan oversimplifies the medical and scientific communities. For example, she essentially attributes her diagnosis and the original discovery of anti-NMDA-receptor encephalitis to single individuals. This presentation fails to recognize the manner in which medical care is delivered

by interactive teams and the collaborative way that science moves forward. But the perspective presented provides insight on how people outside the medical and scientific communities view their work, and suggests that there is a need for broader education on the collaborative nature of the scientific and medical fields, particularly as the available time for such collaboration decreases.

Another misperception reflects the increasing incidence of anti-NMDA-receptor encephalitis. As Cahalan notes in her discussions with neurological experts, it is easy to speculate that this disorder might be responsible for many episodes of demonic possession or mental illness throughout history. However, this speculation does not match present medical observations, as untreated anti-NMDA-receptor encephalitis is an almost uniformly debilitating disease; scientists have identified few spontaneous survivors who did not have ICU-level care in the acute period. Thus, it seems unlikely that this specific disorder caused such reversible events throughout history, though an as-yet-unappreciated variant conceivably could have done so.

After reading Cahalan's riveting account, neuroscientists may wonder about the specific molecules that influence memory and personality, while physicians may contemplate where the next new disease will arise.