

# Six Landmark Case Reports Essential for Neuropsychiatric Literacy

Sheldon Benjamin, M.D., Lindsey MacGillivray, M.D., Ph.D., Barbara Schildkrout, M.D., Alexis Cohen-Oram, M.D., Margo D. Lauterbach, M.D., Leonard L. Levin, M.S. L.I.S., M.A.

Well-described clinical case reports have been a core component of the neuropsychiatry literature and have led to: a deepened understanding of brain-behavior relationships and neuropsychiatric phenomenology, new paths for research, and compelling material for physicians who are studying neurology and psychiatry. Six landmark neuropsychiatry cases were selected for being well described, paradigmatic, and illuminating of brain-behavior correlations: Phineas Gage, Louis Victor Leborgne ("Tan"), Auguste Deter, Solomon Shereshevsky ("S"), "JP," and

Henry Gustav Molaison ("HM"). Each case and its neuropsychiatric lessons are summarized from primary sources, highlighting some less appreciated aspects. Case reports continue to be a valuable resource for neuropsychiatric education. Yet only four of the 10 highest impact factor psychiatry journals accept case reports for publication.

*J Neuropsychiatry Clin Neurosci* 2018; 30:279–290;  
doi: 10.1176/appi.neuropsych.18020027

The study of individual patients is an essential component of the neuropsychiatric literature, a springboard for paradigm shifts in research, and a cornerstone of physician training in neurology and psychiatry. This article revisits six landmark case reports that challenged the field of medicine to expand its understanding of pathophysiology and changed the trajectory of scientific conversation. We commend them as fundamental to neuropsychiatric literacy.

## METHODS

Because we found no concise, published list of historically significant neuropsychiatric cases, we contacted thought leaders in neuropsychiatry, behavioral neurology, neuropsychology, and the history of medicine for opinions as to the "most important" individual cases. Criteria were that the cases be well-described, paradigmatic, and focused on brain-behavior correlations. Six "landmark" cases were selected: Phineas Gage, Louis Victor Leborgne ("Tan"), Auguste Deter, Solomon Shereshevsky ("S"), "JP," and Henry Gustav Molaison ("HM"). Utilizing primary sources whenever possible, we summarize and discuss each case, highlighting underemphasized or underappreciated aspects of each.

## CASES

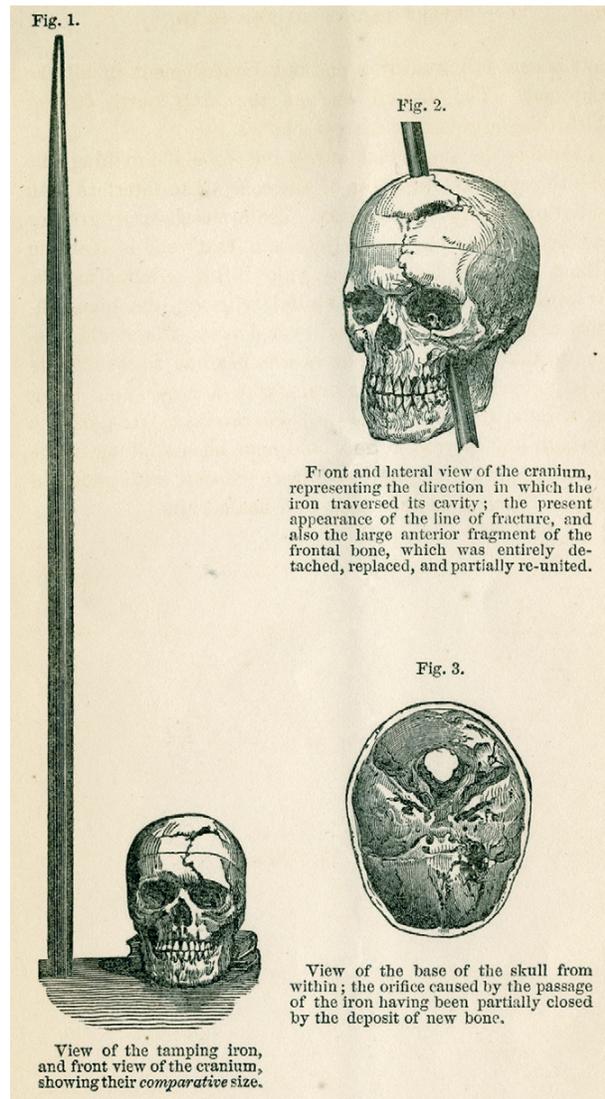
### Phineas Gage

It is due to science, that a case so grave, and succeeded by such remarkable results, should not be lost sight of; that its

subsequent history, termination, and pathological evidences, in detail, should have a permanent record. —John M. Harlow<sup>1</sup>

In 1848, Dr. John Martyn Harlow, a 29-year-old country doctor who had recently graduated from Jefferson Medical College in Philadelphia, wrote a letter to the *Boston Medical and Surgical Journal* that would influence the future of neuropsychiatry. Harlow's letter<sup>2</sup> and a brief follow-up note in January 1849<sup>3</sup> reported the case of Phineas Gage, whose survival and recovery after a severe, penetrating brain injury seemed so improbable that eminent physicians of the day dismissed it as a falsehood. The surgeon, Dr. Henry J. Bigelow, even financed Gage's travel to Boston in 1850 in order to examine the patient and ascertain whether the story was true.<sup>4</sup> Though often misrepresented, one would be hard-pressed to find an introductory psychology textbook that does not make reference to this seminal case.<sup>5</sup>

At 4:30 p.m. on September 13, 1848, a premature blast at a railroad construction site in Cavendish, Vermont propelled a 43-inch long, 13.5-pound iron rod through the skull of Phineas Gage, a 25-year-old foreman. Before this accident, Gage was described as being of "vigorous physical organization, temperate habits, and possessed of considerable energy of character."<sup>2</sup> The 1.25-inch diameter, smooth, tamping iron entered Gage's skull beneath the left zygomatic arch, passed through the left orbit and left frontal lobe, and exited the top of his skull "in the median line, at the juncture of the coronal and sagittal sutures."<sup>2</sup> (Figure 1). The rod landed yards behind Gage and was "afterwards picked up by his men, smeared with blood and brain."<sup>1</sup> Whether or not Gage

**FIGURE 1. Phineas Gage's Tamping Iron in Relation to His Skull<sup>a</sup>**

<sup>a</sup> This illustration is in the public domain.<sup>1</sup>

sustained a brief loss of consciousness is unclear; observers noted a few impact convulsive movements of his upper extremities and that he spoke within minutes. "A great favorite" to his men, they drove Gage, sitting erect in an ox cart, for three-quarters of a mile to the Adams Hotel in Cavendish, Vt.<sup>2</sup> While sitting on the hotel porch, Gage told Dr. Edward Williams who first attended him, "Doctor, here is business enough for you."<sup>4</sup> He then walked up the stairs with the doctor.

At 6:00 p.m., about 90 minutes after the accident, Dr. Harlow took over Gage's care and attended him for months, making careful notes about his physical condition and fluctuating mental state. Initially lucid, Gage became transiently delirious 2 days later. Harlow noted that at times Gage was childish, but his orientation to time was good, and his

memory for the accident was excellent.<sup>2</sup> Against all odds, Gage returned home 74 days after the accident. Harlow commented that aside from loss of vision in the left eye and partial paralysis of the left side of his face, Gage was in good physical health after recovery.

It was only in a follow-up paper 20 years later that Harlow described Gage's behavioral changes after recovery. Gage had not been rehired as foreman because he had become disinhibited, with the "animal passions of a strong man," "impatient of restraint or advice" and, "indulging at times in the grossest profanity (which was not previously his custom)."<sup>1</sup> Having formerly been regarded as smart, efficient and capable, Gage's friends famously stated that after the accident he was "no longer Gage."<sup>1</sup>

Gage traveled to Valparaiso, Chile in the late 1850s where he worked as a stagecoach driver. Dr. Henry Trevitt, who was well acquainted with Gage in Valparaiso, reported that Gage had no impairment of mental faculties.<sup>6</sup> Given the cognitive and motor skills needed to manage a six-horse stagecoach and deal with paying passengers, it can be assumed that Gage did experience additional recovery during the years after his accident. Gage later rejoined his family in California and worked as a farmhand at a succession of farms, "finding something that did not suit him in every place he tried."<sup>1</sup> He died in February 1860, 12½ years after his accident, apparently from status epilepticus.

After learning of Gage's death, Dr. Harlow obtained permission from Gage's family to have the body exhumed and Gage's skull sent to him along with the tamping iron that had been Gage's "constant companion" after the accident.<sup>1</sup> The skull and tamping iron were donated by Harlow to the Museum of the Medical Department of Harvard University.

### Importance

Gage is remembered as the index case of frontal lobe damage causing personality change, though the story that is told typically stops with the acute changes described by Harlow. Gage's story teaches about behaviors associated with acute prefrontal injury as well as about the possibility of recovery from serious frontal damage in adulthood. That Gage later enjoyed some degree of functional recovery is perhaps as striking as his having survived the accident itself.

The case of Phineas Gage also added evidence for localization of mental functions. Dr. Harlow's two reports bracketed in time Paul Broca's report of "Tan" and the localization of language. We can assume Harlow had become aware of Broca's work before writing his second paper about Gage. Thus, Drs. Harlow and Bigelow's interest in Gage was part of a larger medical discussion regarding localization of mental functions.

Harlow's descriptions of Gage were of great scientific value. He carefully described the circumstances of the accident, distinguishing his own observations from information that was derived from other sources. Harlow's work was also exemplary in that he documented the anatomy of the injury as well as Gage's mental status, then preserved the skull for study by future scientists.

In contrast to Harlow's careful scientific reporting, other authors have distorted and embellished Gage's story over the years. The extent of Gage's personality change has been grossly overestimated, leaving the impression that he had become a sociopath.<sup>5,7</sup> Other authors have adhered to the myth that the iron rod was still lodged in his brain when he was brought to the doctor in Cavendish.<sup>8</sup> The case of Gage reminds us of the importance of detailed, accurate reporting of clinical encounters and of consulting primary sources when looking to the past.

### Louis Victor Leborgne ("Tan")

We speak with the left hemisphere. —Pierre Paul Broca<sup>9</sup>

In 1861, French physician Pierre Paul Broca published his classic case of expressive aphasia: the patient was Louis Victor Leborgne, a 50-year-old man, now famously known as "Tan." On April 11, 1861, Leborgne was transferred to the surgical ward at the Bicêtre Hospital in Paris because he had developed gangrene of his right leg; Broca was called to see him.

Broca made note of the patient's history, including that he had been a long-term patient at Bicêtre and that he had been admitted because he had "lost the ability to speak." On admission, it had been noted that Leborgne "differed from a sane man only in the loss of articulated speech." According to Broca, Leborgne "understood almost everything that was said to him," "but regardless of the question addressed to him, he always responded: 'tan, tan.'" This verbal stereotype was "accompanied by a gesture of his left hand."<sup>10</sup> At the hospital, apparently the patient was commonly called Tan.<sup>11</sup>

Ten years after Leborgne's initial loss of expressive language and admission to Bicêtre, he gradually developed complete paralysis of his right arm followed by paralysis of his right leg. Leborgne was bedridden during the last 7 years of his life, finally succumbing to gangrenous bed sores.<sup>11</sup>

Broca reasoned from the evolution of Leborgne's symptoms that "[the] probable diagnosis was therefore: original lesion in the left anterior lobe, propagated to the striate body of the same side."<sup>11</sup> Broca deduced that Leborgne's expanding hemiparesis had been an extension of the original lesion that had produced his expressive language deficit. From what was known at the time about motor control, Broca reasoned that the seat of expressive language had to be in the left hemisphere.

Leborgne died 6 days after Broca first saw him. When Broca had the opportunity to examine Leborgne's brain at autopsy, he observed "a loss of substance of the cerebral mass" in the left anterior frontal lobe to which he attributed the loss of expressive language. A "softening extended well beyond the limits of the cavity" and these, presumably newer lesions, extended to the parietal lobe, the "temporal-sphenoidal" lobe, the insula and extraventricular nucleus of the striate body, the last of which caused paralysis of Leborgne's right limbs.<sup>10</sup> 150 years after the publication of Broca's famous paper, medical historians located Leborgne's

death certificate and medical records which allowed access to more complete information about the patient and the course of his disease.

Leborgne, born on July 21, 1809, was one of six children in a middle class family. Like his educated siblings, Leborgne was likely somewhat educated himself.<sup>12</sup> It is known that Leborgne suffered from epileptic attacks beginning about age 24, but he was able to work. He was employed as a formier, an individual who creates wooden molds for hat or shoe manufacture.<sup>11</sup> In 1833, Leborgne was admitted for 6 days to the Hôtel-Dieu with headaches, diagnosed as "inflammation of blood vessels."<sup>13</sup> In the years after this first brief hospitalization, he eventually became unable to work, and his family declined to support him. Leborgne lost his expressive language ability; it is not known precisely when this occurred nor whether the loss was sudden or gradual. It is known that Louis-Maurice de Belleyme, the Prefect of Police of Paris, arranged for Leborgne's residence at Bicêtre Hospital in Paris; Leborgne resided there from December 1834 until his death in 1861.<sup>13</sup>

There is now evidence that Leborgne "voluntarily transferred to the psychiatric ward" at Bicêtre and resided there from November 1852 to August 1853.<sup>13</sup> Broca did not discuss this transfer, and the details of any behavior that might have led to it are unknown. However, in 1861 Broca did describe Leborgne as "egoistic, vindictive and mean."<sup>13</sup> Broca did not attempt to connect these observations with the area of Leborgne's brain damage. The association of Broca aphasia with catastrophic reactions would not occur for nearly one hundred years.<sup>14</sup>

One hundred and forty-six years after Broca's report, an MRI of Leborgne's preserved brain revealed that the left hemisphere lesion extended more medially than had been appreciated by Broca.<sup>15</sup> The cause of Leborgne's malady remains uncertain, although an inflammatory vascular etiology, possibly meningovascular syphilis, could explain the late progression of deficits in the same vascular territory as the initial deficits.

### Importance

Broca's presentation of Leborgne and, later that same year, another patient named Lelong, supported the concept of cerebral lateralization of language. Although "*it is customary to speak of Broca's discovery as if it came like a clap of thunder from a clear sky,*"<sup>16</sup> Broca was not the first to suggest asymmetry in localization of cognitive functions. Marc Dax had argued 25 years earlier that certain brain functions were asymmetric, presenting cases of "aphemia" associated with left-sided brain damage, albeit without autopsy confirmation.<sup>17</sup> Broca also was not the first to associate language deficits with right hemiparesis; Hippocratic writers of 400 BC first made that observation.

In 1825 Jean Baptiste Bouillaud suggested the anterior localization of language.<sup>18</sup> On April 4, 1861, just one week before Broca first examined Leborgne, he had attended a meeting of the Anthropological Society of Paris and had

heard Bouillaud's son-in-law, Ernest Auburtin, argue for the frontal localization of language. Auburtin described his examination of a Mr. Coulerier whose failed suicide-by-gunshot had exposed the left frontal region of the patient's brain. When Auburtin compressed Mr. Coulerier's left frontal lobe with a spatula, he observed a speech arrest; release of the spatula allowed the return of language.<sup>18</sup>

When Broca presented Tan, he did not initially argue for the lateralization of language but rather for consideration of the cerebral convolutions in groups or functional regions. Broca's main achievement was that he published a total of seven additional cases of aphasia after that of Leborgne, with careful autopsy correlation that ultimately provided evidence for the left inferior frontal gyrus as the seat of language.<sup>9</sup> Broca's application of the clinico-anatomic method stands as a paradigmatic example of how to establish functional localization. In addition, the important role of history-taking in clinical reasoning is an often-overlooked feature of Broca's work. He also anticipated the concept of neuroplasticity by suggesting that other brain regions might take on language functions during recovery from aphasia.<sup>19</sup>

In Leborgne's postmortem examination, Broca took care to incise only the pia mater, noting: "as for the deep parts, I abstained from studying them so as not to destroy the specimen."<sup>10</sup> Broca had the foresight to save this historically important brain for future study; by depositing Leborgne's brain, along with fragments of dura mater and skull, in the anatomical museum in Paris,<sup>12</sup> he enabled the further elucidation of cerebral language networks that became possible when modern science developed advanced imaging probes.

### Auguste Deter

Considering everything, it seems we are dealing here with a special illness.... There are certainly more psychiatric illnesses than are listed in our textbooks. —Alois Alzheimer<sup>20</sup>

On November 3, 1906, at a meeting of Southwest German psychiatrists in Tübingen, a psychiatrist and neuropathologist named Alois Alzheimer presented the case of Auguste Deter. Alzheimer's paper, entitled "On an Unusual Malady of the Cerebral Cortex," described the clinical manifestations of this new syndrome and also "anatomical characteristics [found in the brain on autopsy] which set it apart from all recognized cases."<sup>20</sup> Eighty-eight individuals attended the talk; no questions were asked at its conclusion.<sup>21</sup> Alzheimer's 1907 publication of the Auguste Deter case also received little attention.

In 1901, Auguste Deter, a 51-year-old woman, was admitted to the Asylum for the Insane and Epileptic in Frankfurt am Main. She had been brought to the doctor by her husband for evaluation of pathological jealousy that had progressed to rapid memory loss. In addition, she had become disoriented in her home and had a fixed delusion that someone was trying to kill her. In the asylum, she was examined by Alzheimer and found to be confused and disoriented to time and place<sup>22</sup> with reduplicative paramnesia

(acting as if the hospital was her home), intermittent auditory hallucinations, and lengthy bouts of screaming that worsened when anyone approached.<sup>20</sup> She alternated between believing that her attending physician was trying to harm her and then being overly familiar with him. Her short-term memory deficits were profound, forgetting objects shown to her almost immediately. Her language functioning was characterized by fluent, paraphasic, somewhat empty speech, with poor comprehension, impaired reading, and dysgraphia containing repeated or omitted syllables. She also was agnostic and apraxic.<sup>20</sup>

Four and a half years after admission to the asylum, Auguste Deter died at age 56, following a steady, downhill course. Alzheimer received Deter's brain for analysis from the asylum's director. He found "an evenly atrophic brain without macroscopic focal degeneration."<sup>20</sup> After preparing over 250 histological slides and utilizing silver staining methods, he identified extracellular plaques and, for the first time, intracellular neurofibrillary tangles. Alzheimer prophetically noted, "A histological examination...will gradually lead to a clinical distinction of specific illnesses from the more general categories of our textbooks and it will enable us to define them clinically in greater detail."<sup>20</sup>

For decades, the histological slides of Deter's brain were lost. Then, in 1997, a year after psychiatrists at the University of Frankfurt discovered her original hospital records, a team of researchers located a trove of slides, each labeled "Deter," in the basement of the Institute of Neuropathology of the University of Munich.<sup>23</sup> Microscopic review revealed that Auguste Deter indeed had the classical plaques and tangles that we now associate with Alzheimer's disease. Even more remarkable was the genetic analysis of DNA retrieved from these slides and published in 1998.<sup>24</sup> Auguste Deter's APO-E genotype was found to be E3/E3. Advances in genetic analysis of historical specimens may yet reveal more specific information about contributions to Deter's dementia.<sup>25,26</sup>

### Importance

Franz Nissl wrote of Alzheimer that he "was first and foremost a psychiatrist who strove to advance psychiatry by using a microscope."<sup>22</sup> At the time of Alzheimer's case report, Alzheimer's disease had not been differentiated from other forms of mental illness. As recently as 1975, Medline indexed only 40 papers in which "Alzheimer's disease" was a keyword.<sup>27</sup>

Auguste Deter was the first of several cases Alzheimer would investigate using the clinico-anatomic method, establishing the core elements of the clinical description and pathology of Alzheimer's disease that remain valid today. Auguste Deter's disease was almost certainly an aggressive, familial, early-onset variety. Its importance derives not only from Alzheimer's description of the pathology but also from the fact that Auguste Deter as well as Alzheimer's second index case (Johann F. Taglohner) presented with psychiatric symptoms, an aspect of the disease that is often omitted from textbook descriptions.<sup>28</sup>

Alzheimer's case report built on the work of scientists, including those who created innovative fixation and staining techniques, advancements in microscopy, and a scientific climate that fostered curiosity. Alzheimer also asked Gaetano Perusini to examine the clinical reports and necropsy specimens of Auguste Deter and three additional patients. Perusini published detailed findings (Figure 2) that cemented Alzheimer's description of presenile dementia.<sup>29,30</sup>

In 1910, Emil Kraepelin introduced the term "Alzheimer's presenile dementia" in his 8th edition of the *Handbook of Psychiatry*. Kraepelin, who headed the Munich Royal Psychiatric Clinic in which Alzheimer was chief of neuropathology, may have named the disease for Alzheimer to differentiate it from the more common senile-onset dementias and to promulgate the idea of biological causes of mental illness. He also may have named this disease after Alois Alzheimer so as to assert his own department's accomplishments over those of competing laboratories, such as that of Arnold Pick in Prague.<sup>21</sup> It would take decades for Alzheimer's "unusual malady"<sup>20</sup> to become recognized as a common dementia.

### Solomon Shereshevsky (S)

[I]t appeared that there was no limit either to the capacity of S.'s memory or to the durability of the traces he retained.  
—Alexander Luria<sup>31</sup>

As a young scientist, Alexander Romanovitch Luria documented the exceptional memory and unusual personality of Solomon Shereshevsky in his 1968 publication, *The Mind of a Mnemonist: A Little Book about a Vast Memory*.<sup>31</sup> This book was soon translated widely from the original Russian. The story of S. (as Luria called him), prompted renewed interest in the study of memory and also inspired journalists, filmmakers, and playwrights.

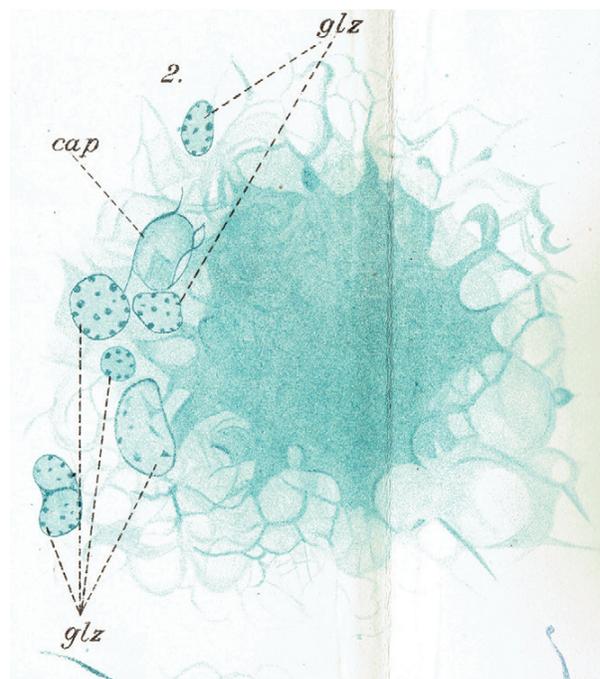
Solomon Veniaminovich Shereshevsky was born in the Russian village of Torzhok in 1896. At his father's urging, Shereshevsky briefly attended music school with the goal of becoming a violinist, but a hearing impairment impeded his musical progress. Later, he worked as a newspaper reporter in Moscow.

Each morning the editor would meet with the staff and hand out assignments for the day.... The list of addresses and instructions was usually fairly long, and the editor noted with some surprise that S. never took notes. He was about to reproach the reporter for being inattentive when, at his urging, S. repeated the entire assignment word for word.<sup>31</sup>

The editor suggested that Shereshevsky undergo psychological testing, and thus, at age 29, Shereshevsky met Luria who was 24 years old and just embarking upon his career in psychology. The two would work together for almost 30 years.

Luria's initial impression was that Shereshevsky was "a rather disorganized and dull-witted person."<sup>31</sup> Shereshevsky was puzzled as to why he had been sent for testing and had no awareness that his memory was different from anyone

FIGURE 2. Auguste Deter's Pathology as Drawn by Gaetano Perusini<sup>a</sup>



<sup>a</sup> A plaque: The surrounding tissue gradually is transformed into the thickened plaque. Formalin fixation: Successive treatment with Weigert's myelin mordant. Staining of axons according to Kaplan, brief differentiation. Inferior limit of the first cell poor layer of cortex. From case D. cap=capillary; glz=glial cell. The vertical line through the center of the illustration is from being folded and bound as an insert to the printed issue. This illustration is in the public domain.<sup>30</sup>

else's. In fact, Shereshevsky's memory proved exceptional. According to Luria, Shereshevsky could "easily remember any number of words and digits" and "equally easily he memorizes whole pages from books on any subject and in any language."<sup>32</sup> He could accurately quote information from a decade earlier, including tables of numbers and strings of nonsense words. Luria turned from measuring S.'s memory capacity to studying how the presence of such a remarkably developed memory affected S.'s personality, behavior, and inner world. He devoted himself to "the study of one man," to learn all that he could from this "experiment of nature."<sup>31</sup>

What Luria learned was that Shereshevsky's memory differed from that of the vast majority of individuals; time did not erode his memories. Neither did a new stimulus affect his memory of an earlier one. In addition, his recall for the first item or the last item in a series was no better than his memory for other items on the list.

For memory tasks, Shereshevsky relied primarily on visual imagery, augmented by synesthetic experiences. Anything Shereshevsky saw or heard reacted simultaneously with all of his senses... "to him any sound or thing has its own color, temperature, weight, shape and so on."<sup>32</sup> For Shereshevsky, "there was no distinct line, as there is for others of us,

separating vision from hearing, or hearing from a sense of touch or taste.”<sup>31</sup> Luria surmised that synesthetic perceptions were “a background for each recollection, furnishing him with additional, ‘extra’ information that would guarantee accurate recall.”<sup>31</sup>

If Shereshevsky were given a few moments between items he was to remember, each item would summon a vivid image. He could then mentally distribute these images along a street conjured in his mind. Later, even years later, he need only return to the route, beginning at either end, to find the images where he had left them. Shereshevsky’s performance at recall was not perfect, but his errors were, invariably because he had initially placed the image “in an area that was poorly lit or in a spot where he would have trouble distinguishing the object from the background against which it had been set...”<sup>31</sup> Thus, Luria noted that any omissions were errors of perception rather than of memory.

Shereshevsky’s visualizations allowed him to readily solve certain kinds of problems that others found difficult. However, his mode of experiencing the world also had its drawbacks. For example, Luria noted that “none of us have to deal with the problem of how to forget. In S.’s case, however, precisely the reverse was true.”<sup>31</sup> Also, if given a table of numbers that was generated by a simple rule, Shereshevsky would not notice the underlying principle, although, for others, this was what made memory of the numbers possible. Because each word conjured a unique and vivid set of sensations, Shereshevsky was especially troubled by synonyms, double-entendres, or metaphors. Abstract ideas such as “infinity” or “nothing” perplexed him. “In order for me to grasp the meaning of a thing,” Shereshevsky said, “I have to see it.”<sup>31</sup>

Shereshevsky also became confused reading or listening to a story if he did not have sufficient time to register each word; the flood of synesthetic associations would obscure the storyline. He had to work at avoiding verbosity and sticking to the point in communicating the complexity of his experiences. He also had a poor memory for faces, as each expression would give rise to a multitude of sensory experiences.

Luria also noted that Shereshevsky’s experiences were so vivid that the line between imagination and reality was blurred. He could speed his pulse by picturing himself running to catch a train; he could raise the temperature in one hand while imagining touching a hot stove and simultaneously lower the temperature in the other hand by imagining holding an ice cube. Shereshevsky would feel confused when something did not turn out the way he had expected, so real had been his envisioning. Luria noted that Shereshevsky “gave himself up to dreaming... far more than to functioning in life.”<sup>31</sup>

Shereshevsky married, had one son, and worked in a variety of jobs, including: reporter, broker, vaudeville actor, efficiency expert, taxi driver, herbal therapist. He is best known for delighting public audiences with demonstrations of his remarkable memory and for being the subject

of Luria’s important book. Solomon Shereshevsky died in Moscow in 1958 at the age of 62.

### Importance

Shereshevsky’s exceptional mental capabilities stimulated interest in the neurobiology of memory and also in synesthesia. Luria’s description of S. is a reminder that superb cognitive abilities in one domain may come at the expense of another.

Luria applied the scientific method over an extended period of time. He asked colleagues to examine Shereshevsky independently; he preserved voluminous notes for examination by future scientists. Luria’s work was facilitated by his relationship to the Vygotsky school, an environment that supported careful inquiry.

Luria’s approach to the case method was itself a paradigm shift by virtue of the depth and length of his scientific study of Shereshevsky, the collaborative nature of their relationship, and the fact that Luria wrote his book for an audience that included nonprofessionals. In addition to cataloguing S.’s cognitive abilities, Luria looked at the human dimensions of his patient’s life and how S.’s exceptional visual memory and synesthesia affected his whole personality.

### JP

[M]an cannot elaborate his social sense so that it can become part of his total self without “the great nerve net” of his frontal lobes. —Spafford Ackerly and Arthur Benton<sup>33</sup>

In 1933, Spafford Ackerly, M.D., a psychiatrist at the University of Louisville, evaluated a 19-year-old boy (JP) who had been arrested for car theft. JP’s parents and lawyer were hoping that Dr. Ackerly could find mitigating circumstances that might keep the patient out of prison. JP had had a long history of stealing cars, but in a most peculiar fashion. Seeing keys in the ignition, he would take a car and drive in whichever direction it happened to be facing until it ran out of gasoline. Then he would abandon the car, find a telephone, and call his parents to pick him up.

JP was born in December of 1912, the 11.5-pound product of a normal pregnancy and gestation, followed by a 22-hour labor and a difficult delivery requiring instrumentation.<sup>33</sup> He developed normally through age 2. At 2 1/2, JP developed a tendency to wander blocks from home, entirely without fear. Often, he was returned to his parents by police. This behavior was undeterred by his father’s scolding or corporal punishment. JP’s wandering continued. During young adulthood he would travel thousands of miles, ascribing his meanderings to impulse.<sup>34</sup>

At age 4, JP fell off a bed and struck his head on the floor. About an hour later, he began to “say queer things,” and talk “like a smart alec.”<sup>33</sup> He then lost consciousness and, simultaneously, developed left-sided convulsive movements that abated spontaneously several hours later at the hospital just before he was to have had an exploratory craniotomy. By the next morning, reportedly, he was fully recovered.<sup>33</sup>

JP's intelligence appeared normal. When he applied himself, JP apparently learned his school-work rapidly, though his reading skills far exceeded his arithmetic skills. However, his behavior in school was incorrigible. In second grade "he took a classmate's glove and rubber, defecated in them, and replaced the glove in the child's coat pocket."<sup>33</sup> That same year, upon being caught after exposing himself to two little girls in the class, JP "denied it vigorously, saying haughtily, 'I beg your pardon, Sir!'" JP's manners were described as "Chesterfieldian," "distinguished by an over-politeness and a smooth ingratiating manner toward adults." Even as a preschooler he appeared shallow and superficial.<sup>33</sup> JP was boastful, bossy, and unphased by the disdain in which he was held by his classmates.<sup>33</sup>

At age 13, after stealing money from a little girl and repeated episodes of masturbating in school, JP was transferred to the Day School for Defective Children which referred him to the Louisville Mental Hygiene Clinic for evaluation. His intake note included the following observations: "he has no friends; lies; steals; and is known in his neighborhood as having bad sex habits."<sup>33</sup> JP attributed his social isolation to the malevolence of others. His IQ was measured at 92 on the Stanford-Binet, without inter-test scatter; his mother described his excellent memory for facts in the stories he'd read and the movies he'd seen. However, "his planning ability and capacity to modify behavior by experience" were described as "not equal to that of the average 7-year-old child."<sup>33</sup>

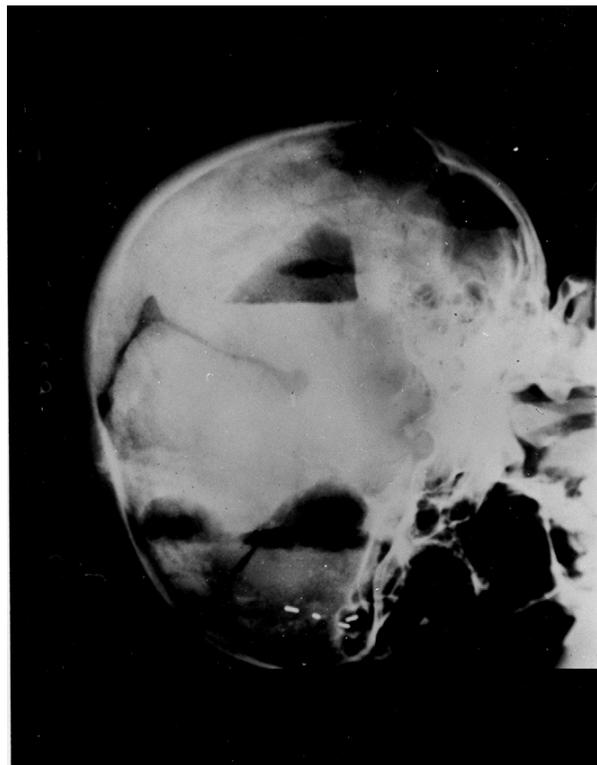
During the ensuing 6 years JP was transferred to private, public and parochial schools, and finally to an out-of-state military school. There he stole a teacher's car and served 2 years in reform school.<sup>33</sup> After his release, JP continued to wander widely and steal cars, his father making good on any damages and thereby helping him to avoid arrest. In 1933, at age 19, JP was arrested for yet another car theft.<sup>32</sup> This time he faced the possibility of prison, and the family lawyer arranged for him to see Dr. Ackerly.

The physicians who had previously evaluated JP believed that he was sociopathic. Ackerly, working with the neuropsychologist, Arthur Benton, noted that JP had a well-developed sense of right and wrong in the abstract or with regard to the actions of others, although JP's own moral judgment was impaired and his behavior antisocial. Ackerly and Benton found JP to be irresponsible, impulsive, a spend-thrift, completely free of anxiety, and unable to hold a job for more than a few months.<sup>33</sup>

He never holds a grudge nor speaks ill of anyone, never picks a fight, never tricks anyone....One is struck with the childish simplicity and superficiality of his petty lying and stealing and sex experiences which are unpremeditated. Yet these acts are never the result of pure impulse dissociated from their settings. Of all patients encountered he is by far the most stimulus bound....Everybody knows there is something radically wrong, but no one can put his finger on it.<sup>35</sup>

Ackerly's evaluation of JP included a pneumoencephalogram in October 1933 (Figure 3) that revealed severe bifrontal damage, thought to be consistent with an old brain

FIGURE 3. Pneumoencephalogram of "JP" in 1936 at Age 23<sup>a</sup>



<sup>a</sup>The scan (forehead down position) shows incompletely filled lateral ventricles and an incompletely filled left-frontal cavity consistent with massive frontal defect. Postoperative changes are present, with little change from the 1933 preoperative pneumoencephalogram description. Reprinted with permission from Kornhauser Health Sciences Library and Historical Collection, University of Louisville College of Medicine, Louisville, Ky.

abscess. Exploratory surgery confirmed that in the place of JP's atrophic right prefrontal lobe there was a large arachnoid cyst and that bands of chronic arachnoiditis were compressing his left prefrontal cortex.<sup>33</sup> Although it was impossible to tell with certainty, Ackerly believed this damage to have been present from birth.

Ackerly continued to follow JP and published a follow-up report in 1964. He describes 50-year old JP as "the same refreshingly simple, uncomplicated, straightforward, outrageously boastful or indignant little boy."<sup>34</sup> However, JP had gradually become unable to recall events as recently as five minutes in the past, the only exception being that he could retain anything having to do with automobiles, driving, and highway distances up to at least a day later. JP's father had died 5 years earlier; JP remained at home, "lording it over his mother and taking no responsibility for helping out."<sup>34</sup> He appears to have ceased his incessant wandering by that time.

#### Importance

Ackerly and Benton could not say with certainty whether JP's brain pathology was congenital or acquired in early childhood, nor could the pneumoencephalographic and

neurosurgical evidence conclusively rule out damage to other brain areas. By the time of the 1964 publication, Ackerly noted that JP's memory had progressively declined, implicating an ongoing process that may or may not have been related to JP's frontal pathology.

Despite uncertainties about the etiology of JP's pathology, through their study of JP, Ackerly and Benton were able to postulate the role of the prefrontal cortex in social learning. The case of JP demonstrated that early childhood or congenital prefrontal damage could produce lifelong behavioral changes that might not be manifest until increasing social demands bring the behavioral pathology into focus. This was in contrast to individuals with extrafrontal lesions sustained during childhood in which elemental functions tend to recover.<sup>36</sup> Ackerly and Benton's conclusion that individuals do not seem to be able to compensate for early, severe frontal damage has been borne out by subsequent authors.<sup>37–39</sup>

### Henry Gustav Molaison (HM)

Henry Gustav Molaison... left no survivors. He left a legacy in science that cannot be erased. —B.H.M. Carey<sup>40</sup>

"HM" is arguably the single most intensively studied and best-described patient in the history of neuroscience. Henry Gustav Molaison unexpectedly developed a severe impairment in his ability to form new memories following bilateral medial temporal lobe surgical resection for intractable seizures in 1953, when he was 29 years old. Postoperatively, HM's "loss was immediately apparent. ... [T]his young man could no longer recognize the hospital staff nor find his way to the bathroom, and he seemed to recall nothing of the day-to-day events of his hospital life. ... His early memories were apparently vivid and intact."<sup>41</sup>

HM, a high school graduate who worked as a motor winder, was hit by a bicycle as a child, sustaining a 5-minute loss of consciousness. There was a history of epilepsy in 3 paternal cousins.<sup>41</sup> At age 10, HM began to experience "minor" seizures; after age 16, "major" seizures developed. By 1953, despite escalating doses of anticonvulsants, HM was having up to 10 seizures daily, affecting his interictal mental functioning and his ability to work. In an effort to ameliorate HM's epilepsy, William Beecher Scoville, a Hartford Connecticut neurosurgeon with a faculty position at Yale, bilaterally resected HM's medial temporal lobes using a procedure he had developed, called "fractional undercutting." This involved suctioning the medial temporal tissue extending 8–9 cm caudally from the temporal tips through bilateral supraorbital burr holes. Scoville, who later became the founding president of the International Society for Psychiatric Surgery,<sup>42</sup> had developed this procedure as a less destructive alternative to transorbital lobotomy.<sup>43</sup> Unilateral medial temporal resection for treatment of intractable epilepsy had been pioneered by Wilder Penfield at the Montreal Neurological Institute (MNI) in 1928.<sup>44</sup> However, applying bilateral "fractional undercutting" to the treatment of HM's seizures in 1953 was, according to Scoville, "frankly experimental."<sup>41</sup>

Although HM's epilepsy did improve and his post-operative neurological examination was reportedly normal, Scoville noted "one striking and totally unexpected behavioural result"—HM's remarkable loss of ability to form new memories.<sup>41</sup> Scoville first reported this surgical result in April 1953 in a speech at the Harvey Cushing Society. His talk was published in 1954 as "The Limbic Lobe in Man" and included mention of "a very grave, recent memory loss" in two patients "undergoing bilateral resection of the entire [limbic lobe] complex including the hippocampal gyrus extending posteriorly for a length of 8–9 cm from the tips of the temporal lobes."<sup>45</sup> One of these patients was HM.

Around this time, Penfield noted two of his patients had become severely amnesic following *unilateral*, left medial partial temporal lobectomy for refractory epilepsy.<sup>46</sup> These two patients were presented at the 1955 meeting of the American Neurological Association. Their surgical outcome had been entirely unexpected as it was in contradistinction to at least eighty other similar procedures that did not result in memory loss. After the meeting, Scoville called Penfield to tell him about HM. Penfield consulted with MNI neuropsychologist Brenda Milner, who began a career-long study of HM beginning 2 years after HM's surgery.<sup>47</sup>

In April 1955, when Milner first examined HM, he still believed the year to be 1953 (the year of his operation), and he had no recollection of the conversation he had had with Milner immediately prior to entering the interview room. Milner found that HM's IQ had actually increased by eight points to 112 on the Wechsler-Bellevue scale in comparison to postoperative testing; this improvement was thought to have been a consequence of HM being "less drowsy" because he was having fewer seizures. HM displayed a complete loss of memory for events since his surgery, partial retrograde amnesia for the 3 years before the procedure, and remarkably intact early memories.<sup>41</sup>

In their seminal paper, Scoville and Milner reported 10 temporal lobectomy patients one year after surgery, one of whom was HM. Two of their patients had no demonstrable memory impairment, five had moderate memory loss, and three, including HM, exhibited severe anterograde amnesia.<sup>41</sup> All but one of the patients had undergone bilateral surgery, eight for treatment of psychotic conditions. The other two patients in the severe category had the surgery performed for treatment of paranoid schizophrenia and manic depressive disorder. What made HM unique was that his mental status findings were "restricted to his inability to remember new episodic, autobiographical events and not confounded by other neurological or psychological disorders."<sup>48</sup>

In light of earlier reports that unilateral lesions had no impact on memory, Scoville and Milner concluded that bilateral lesions produce "persistent impairment of recent memory whenever the removal is carried far enough posteriorly to damage portions of the anterior hippocampus and hippocampal gyrus." "The degree of memory loss appears to depend on the extent of hippocampal removal." The authors

added the caveat that, since the uncus and the amygdala were always removed along with the hippocampal complex, they could not rule out the contributions of these areas to “retention of current experience.”<sup>41</sup>

In 1958, a little more than a year after the Scoville and Milner paper, Penfield and Milner published the two cases of unilateral left partial temporal lobectomy they had presented in 1955. Both patients had developed severe anterograde amnesia similar to that of HM. Penfield and Milner postulated that these two patients were unique in having had unrecognized, pre-existing, right-sided hippocampal lesions, causing the severe anterograde amnesia produced by bilateral hippocampectomy.<sup>46</sup> Postmortem examination of one of their patients in 1964 confirmed the presence of right hippocampal sclerosis that had been unrecognized prior to the left-sided surgery.<sup>49</sup>

### Importance

Prior to studies of HM, memory was believed to be a widely distributed function, associated with, rather than separate from, other cognitive and perceptual abilities. The function of the hippocampal formation was unclear, having been suspected of having roles in motor, olfactory or emotional function.<sup>50</sup> HM's case illustrated the importance of the medial temporal lobes for memory. Contrary to popular interpretation, HM's case alone did not prove that bilateral hippocampectomy resulted in complete anterograde amnesia, since the amygdalae were also removed. However, when HM was considered with their two aforementioned unilateral hippocampectomy cases, Penfield and Milner were able to conclude that removal of the hippocampi bilaterally does, in fact, result in anterograde amnesia.<sup>46</sup>

HM was the most important patient in modern memory research. As many as 100 investigators examined and tested him, first at the MNI, and later at the Massachusetts Institute of Technology laboratory of Suzanne Corkin. Corkin, a student of Milner, had met HM in Milner's laboratory in 1962. HM's willingness to participate in innumerable studies during the 55 years between his surgery and his death in 2008, confirmed the role of the hippocampus in memory formation and revealed that memory is not a unitary function.

Despite having no recall of having learned a motor task, nevertheless his performance of complex motor skills improved with repetition, establishing that procedural memory relied on different brain networks than did declarative memory. In addition, HM could retain information as long as his attention to a task was sustained by continual mental rehearsal, establishing that working memory involved extrahippocampal areas.

HM also agreed to have his brain preserved for further study after his death. An extremely detailed postmortem examination of HM's brain showed that he had approximately 2 cm<sup>3</sup> of retained hippocampal tissue bilaterally, so the surgical resections were not complete.<sup>51</sup> At the time of this writing, research projects using tissue from HM's brain

are being coordinated by David Amaral at the UC Davis MIND Institute.<sup>52</sup>

### DISCUSSION

Although there are many other seminal case reports of interest to neuropsychiatrists (Table 1), the six cases in this paper provide an introduction to the historical canon of neuropsychiatry. Each opened a new avenue of inquiry by utilizing the scientific method to illuminate important brain-behavior relationships. Ackerly, Harlow, Luria, and Milner studied their subjects over many years and published follow-up papers or monographs. Alzheimer, Broca, Harlow, and Milner preserved biological material from their patients to allow future investigators to review their cases in the light of new technological advances and advancing theoretical ideas; others documented their patient's cognitive or personality features in sufficient detail to allow later researchers to interpret the data for themselves.

Each of the six cases also is remarkable for what was neither included in the original reports nor emphasized in subsequent commentaries. Broca's work opened the door to exploration of the complex neurological basis of language. However, while Broca's aphasia is named for the expressive aphasia and associated left hemisphere lesion that Broca identified in Leborgne's brain at autopsy, modern imaging has demonstrated that Leborgne's left hemisphere had more extensive damage than is now known to be sufficient to produce “Broca's” aphasia. The case of Leborgne also may represent a missed opportunity. Leborgne's behavior as described by Broca, and the patient's transfer to a psychiatry unit, a fact omitted from Broca's report, may have been consistent with catastrophic outbursts that would later be described in Broca aphasia.

Phineas Gage, touted as the archetypal case of prefrontal behavioral syndrome, may actually be as important for demonstrating the possibility of functional recovery after severe traumatic brain damage during adulthood. It is also interesting to note that, in contrast with Harlow's original 1848 report that emphasized Gage's physical recovery, Harlow's 1868 report, published 6 years after Broca's presentation of Leborgne, drew attention to Gage's personality change.

While Deter's brain exhibited the widespread plaques and tangles now known to be characteristic of Alzheimer disease, Deter's clinical presentation was atypical for Alzheimer disease; agitation and psychotic symptomatology overshadowed her memory loss. Alzheimer's work demonstrated the value of investigating microscopic cellular pathology in association with behavioral alterations, and this has led to the elucidation of large classes of neurodegenerative diseases.

Solomon Shereshevsky's remarkable memory became an example of the cognitive and social costs of a single, prodigious cognitive ability. While Luria did not address anatomic correlations, his extensive case report of S. expanded

**TABLE 1. Other Seminal Neuropsychiatric Cases**

Case Name	Presentation	Case Report
"AJ"	Eidetic autobiographical memory	Parker et al. <sup>55</sup>
"EVR"	Amoralism and acquired sociopathy in ventromedial frontal dysfunction	Damasio et al., <sup>56</sup> Eslinger and Damasio <sup>57</sup>
"GK" and "MH"	Perinatal frontal damage with antisocial behavior emerging in adolescence	Price et al. <sup>58</sup>
Monsieur X	Impaired visual imagery	Young and van de Wal <sup>59</sup>
Mary Rafferty	First report of direct cortical stimulation	Bartholow <sup>60</sup>
Merk	Simultanagnosia	Humphreys et al. <sup>61</sup>
Fräulein G	Mind-blindness	Solms et al. <sup>62</sup>
Balint's Case	Balint's original case of what became known as Balint syndrome	Husain and Stein <sup>63</sup>
Astrid L	Foreign accent syndrome	Monrad-Krohn <sup>64</sup>
Clive Wearing	Complete anterograde amnesia from herpes simplex virus encephalitis	Wearing <sup>65</sup>
"GR"	Deep dyslexia	Marshall and Newcombe <sup>66</sup>
"KC"	Autobiographical amnesia with intact declarative memory following traumatic brain injury	Rosenbaum et al. <sup>67</sup>
"WLP"	Surface dyslexia	Schwartz et al. <sup>68</sup>
"JBR"	Category-specific aphasia	Warrington and Shallice <sup>69</sup>
"EC" and "NF"	Right-hemisphere language in patients with left hemispherectomy	Burklund and Smith <sup>70</sup>
"AH"	Suprachiasmatic nucleus lesion with loss of circadian rhythm	Cohen and Albers <sup>71</sup>
The Marquise de Dampierre	Itard's first observation of what would become known as Gilles de la Tourette syndrome	Kushner <sup>72</sup>
"SM"	Bilateral amygdala lesions leading to inability to decode facial emotion and absence of fear	Adolphs et al. <sup>73</sup>
King Henri II	Fatal brain damage due to jousting injury	Martin <sup>74</sup>
Kim Peek	Prodigious recall in congenital callosal agenesis	Opitz et al. <sup>75</sup>

the field of scientific inquiry to include the effects of specific neuropsychiatric features on the whole person.

JP became the index case of the behavioral sequelae of early life prefrontal dysfunction in contrast to those with more posterior brain damage. Although there is evidence that JP had extensive frontal lobe injury, the precise extent, timing and etiology are unknown. The case of JP clarified that the timing of injury to frontal brain regions influences the patient's capacity for adaptation.

Although HM was arguably the most extensively studied patient in neuropsychiatric history and his case demonstrated that remote memory and procedural learning involved brain areas other than the hippocampus, there is still debate as to whether his hippocampi were entirely ablated and whether a small iatrogenic frontal lesion may have contributed to his amnesia.<sup>51,53</sup> Nonetheless, the case of HM had a lasting influence on the field of neuropsychiatry, demonstrating that memory was neither a widely-distributed brain function nor a unitary process.

The ideas presented in these six seminal works emerged within the context of scientific thinking, available technologies, and medical practice at the time of their publication; thus, these case reports provide insights into the origins of contemporary neuropsychiatric thought and remind us to consider our own place within the unfolding history of scientific understanding. For example, while the quest to understand localization has been a central organizing principle in neuropsychiatry for decades, functional connectivity studies are expanding our perspective by demonstrating the brain's intrinsic network organization.<sup>54</sup>

Despite the inherent value of clinical case reports, only four of the 10 highest impact journals in psychiatry routinely accepted case reports for submission in 2017. While the case report is an underappreciated stepchild in modern medical literature, it remains a cornerstone of neuropsychiatric education and a driver of neuropsychiatric inquiry.

#### AUTHOR AND ARTICLE INFORMATION

From the Department of Psychiatry, University of Massachusetts Medical School, Worcester, Mass. (SB); the Department of Psychiatry, University of Toronto (LM); the Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston (BS); the Department of Psychiatry, University of South Florida, Tampa, Fla. (AC-O); the Neuropsychiatry Program Sheppard Pratt Health System, Baltimore (MDL); and the Countway Library, Harvard Medical School, Boston (LLL).

Send correspondence to Dr. Benjamin; e-mail: sheldon.benjamin@umassmed.edu

This study was a project of the Neuropsychiatry Committee of the Group for Advancement of Psychiatry.

The authors thank Michael Gregory, M.D., for his input during multiple stages in the development of this article.

The authors report no financial relationships with commercial interests.

Received February 15, 2018; revisions received April 28 and May 6, 2018; accepted May 7, 2018; published online Aug. 24, 2018.

#### REFERENCES

1. Harlow JM: Recovery from the Passage of an Iron Bar Through the Head. Waltham, Mass, Publications of the Massachusetts Medical Society 1869, pp 3–21
2. Harlow JM: Passage of an iron rod through the head. *Boston Med Surg J* 1848; XXXIX:389–393

3. Harlow JM: Medical miscellany. *Boston Med Surg J* 1849; 39: 506–507
4. Bigelow HJ: Dr. Harlow's case of Recovery from the passage of an iron bar through the head. *Am J Med Sci* 1850; XXXIX:13–22
5. Macmillan M: Restoring Phineas Gage: a 150th retrospective. *J Hist Neurosci* 2000; 9:46–66
6. Macmillan M, Lena ML: Rehabilitating Phineas Gage. *Neuropsychol Rehabil* 2010; 20:641–658
7. Griggs RA: Coverage of the Phineas Gage story in introductory psychology textbooks: was Gage no longer Gage? *Teach Psychol* 2015; 42:195–202
8. Hirsch A: *Life's a Smelling Success: Using Scent to Empower Your Memory and Learning*. Mt. Shasta, Calif, Authors of Unity, 2003
9. Berker EA, Berker AH, Smith A: Translation of Broca's 1865 report: localization of speech in the third left frontal convolution. *Arch Neurol* 1986; 43:1065–1072
10. Pearce JM: Broca's aphasiacs. *Eur Neurol* 2009; 61:183–189
11. Broca P: Perte de la Parole, Ramollissement Chronique et Destruction Partielle du Lobe Antérieur Gauche du Cerveau. *Bulletin de la Societe Anthropologique*. 1861; 2:235–238
12. Domanski CW: Mysterious "Monsieur Leborgne": The mystery of the famous patient in the history of neuropsychology is explained. *J Hist Neurosci* 2013; 22:47–52
13. Domanski CW: Post scriptum to the biography of Monsieur Leborgne. *J Hist Neurosci* 2014; 23:75–77
14. Goldstein K: Language and language disturbances. *J Clin Psychol* 1948; 5:374
15. Dronkers NF, Plaisant O, Iba-Zizen MT, et al: Paul Broca's historic cases: high resolution MR imaging of the brains of Leborgne and Lelong. *Brain* 2007; 130:1432–1441
16. Head H: *Aphasia and Kindred Disorders of Speech*. New York, Hafner Publishing Company, 1926
17. Dax M: Lésions de la moitié gauche de l'encéphale coïncident avec l'oubli des signes de la pensée (lu à Montpellier en 1836). *Gazette Hebdomadaire de Médecine et de Chirurgie*. 1865; 17:259–262
18. Stookey B: Jean-Baptiste Bouillaud and Ernest Auburtin: early studies on cerebral localization and the speech center. *JAMA* 1963; 184:1024–1029
19. Lazar RM, Mohr JP: Revisiting the contributions of Paul Broca to the study of aphasia. *Neuropsychol Rev* 2011; 21:236–239
20. Alzheimer A, Stelzmann RA, Schnitzlein HN, et al: An English translation of Alzheimer's 1907 paper, "Über eine eigenartige Erkrankung der Hirnrinde". *Clin Anat* 1995; 8:429–431
21. Cipriani G, Dolciotti C, Picchi L, et al: Alzheimer and his disease: a brief history. *Neurol Sci* 2011; 32:275–279
22. Dahm R: Alzheimer's discovery. *Curr Biol* 2006; 16:R906–R910
23. Graeber MB, Kösel S, Egensperger R, et al: Rediscovery of the case described by Alois Alzheimer in 1911: historical, histological and molecular genetic analysis. *Neurogenetics* 1997; 1:73–80
24. Graeber MB, Kösel S, Grasbon-Frodl E, et al: Histopathology and APOE genotype of the first Alzheimer disease patient, Auguste D. *Neurogenetics* 1998; 1:223–228
25. Müller U, Winter P, Graeber MB: A presenilin 1 mutation in the first case of Alzheimer's disease. *Lancet Neurol* 2013; 12:129–130
26. Rupp C, Beyreuther K, Maurer K, et al: A presenilin 1 mutation in the first case of Alzheimer's disease: revisited. *Alzheimers Dement* 2014; 10:869–872
27. Boller F: History of Dementia, in *Handbook of Clinical Neurology*. Edited by Duyckaerts C, Litvan I. New York, Elsevier, 2008, pp 3–13
28. Tonkonogy J, Moak GS: Alois Alzheimer on presenile dementia. *J Geriatr Psychiatry Neurol* 1988; 1:199–206
29. Perusini G: *The Early Story of Alzheimer's Disease*. Edited by Bick K, Amaducci L, Pepeu G. Padova, Italy, Liviana Press, 1987, pp 82–128
30. Perusini G: Histology and clinical findings of some psychiatric diseases of older people. (translated) *Histologische und Histopathologische Arbeiten* 1910; III:297–351
31. Luria AR: *The Mind of a Mnemonist: A Little Book About a Vast Memory*. Cambridge, Mass, Harvard University Press, 1987, xxv, pp 160
32. Mecacci L, Solomon V: Solomon v. Shereshevsky: the great Russian mnemonist. *Cortex* 2013; 49:2260–2263
33. Ackerly SS, Benton AL: Report of case of bilateral frontal lobe defect. *Res Publ Assoc Res Nerv Ment Dis* 1948; 27:479–504
34. Ackerly SS: A case of paranasal bilateral frontal lobe defect observed for 30 years, in *The frontal granular cortex and behavior*. Edited by Akert JM, Warren K, New York, McGraw-Hill, 1964
35. Ackerly S: Prefrontal lobes and social development. *Yale J Biol Med* 1950; 22:471–482
36. Teuber H, Rudel RG: Behaviour after cerebral lesions in children and adults. *Dev Med Child Neurol* 1962; 4:3–20
37. Anderson SW, Wisniewski JL, Barrash J, et al: Consistency of neuropsychological outcome following damage to prefrontal cortex in the first years of life. *J Clin Exp Neuropsychol* 2009; 31: 170–179
38. Eslinger PJ, Robinson-Long M, Realmuto J, et al: Developmental frontal lobe imaging in moral judgment: Arthur Benton's enduring influence 60 years later. *J Clin Exp Neuropsychol* 2009; 31:158–169
39. Eslinger PJ, Flaherty-Craig CV, Benton AL: Developmental outcomes after early prefrontal cortex damage. *Brain Cogn* 2004; 55: 84–103
40. Carey BHM: Whose loss of memory made him unforgettable, dies. *The New York Times*, 2008
41. Scoville WB, Milner B: Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 1957; 20:11–21
42. Lipsman N, Meyerson BA, Lozano AM: A narrative history of the International Society for Psychiatric Surgery: 1970–1983. *Stereotact Funct Neurosurg* 2012; 90:347–355
43. Scoville WB, Wilk EK, Pepe AJ: Selective cortical undercutting: results in new method of fractional lobotomy. *Am J Psychiatry* 1951; 107:730–738
44. Feindel W: Toward a surgical cure for epilepsy: the work of Wilder Penfield and his school at the Montreal Neurological Institute, in *Surgical Treatment of the Epilepsies*, 2nd ed. Edited by Jr E. New York, Raven Press, 1991, pp 54–66
45. Scoville WB: The limbic lobe in man. *J Neurosurg* 1954; 11:64–66
46. Penfield W, Milner B: Memory deficit produced by bilateral lesions in the hippocampal zone. *AMA Arch Neurol Psychiatry* 1958; 79:475–497
47. Squire LR: The legacy of patient H M for neuroscience. *Neuron* 2009; 61:6–9
48. Dossani RH, Missios S, Nanda A: The legacy of Henry Molaison (1926–2008) and the impact of his bilateral mesial temporal lobe surgery on the study of human memory. *World Neurosurg* 2015; 84:1127–1135
49. Penfield W, Mathieson G: Memory: autopsy findings and comments on the role of hippocampus in experiential recall. *Arch Neurol* 1974; 31:145–154
50. Kaada BR: Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of rhinencephalic and other structures in primates, cat, and dog; a study of responses from the limbic, subcallosal, orbito-insular, piriform and temporal cortex, hippocampus-fornix and amygdala. *Acta Physiol Scand Suppl* 1951; 24:1–262
51. Annese J, Schenker-Ahmed NM, Bartsch H, et al: Postmortem examination of patient H M's brain based on histological sectioning and digital 3D reconstruction. *Nat Commun* 2014; 5:3122
52. Ditrich L: The brain that couldn't remember. *The New York Times Magazine*, August 3, 2016, p 34
53. Winter W: Behavioral evidence suggestive of frontal lobe pathology in the amnesic H.M. *Brain Cogn* 2018; 123:136–141
54. Opitz A, Fox MD, Craddock RC, et al: An integrated framework for targeting functional networks via transcranial magnetic stimulation. *Neuroimage* 2016; 127:86–96

55. Parker ES, Cahill L, McGaugh JL: A case of unusual autobiographical remembering. *Neurocase* 2006; 12:35–49
56. Damasio AR, Tranel D, Damasio H: Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. *Behav Brain Res* 1990; 41:81–94
57. Eslinger PJ, Damasio AR: Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. *Neurology* 1985; 35:1731–1741
58. Price BH, Daffner KR, Stowe RM, et al: The compormental learning disabilities of early frontal lobe damage. *Brain* 1990; 113:1383–1393
59. Young AW, van de Wal C: Charcot's case of impaired imagery, in *Classic Cases in Neuropsychology*, vol 1. Edited by Code C, Wallesch C, Joannette Y, et al. Hove, East Sussex, Psychology Press, 1996, pp 31–44
60. Bartholow R: Experimental investigations into the functions of the human brain. *Am J Med Sci* 1874; CXXXIV:305–313
61. Humphreys GW, Riddoch MJ, Wallesch C: Poppelreuter's case of Merk: the analysis of visual disturbances following a gunshot wound to the brain, in *Classic Cases in Neuropsychology*, vol 1. Edited by Code C, Wallesch C, Joannette Y, et al. Hove, East Sussex, Psychology Press, 1996, pp 77–88
62. Solms M, Kaplan-Solms K, Brown JW: Wilbrand's case of "mind-blindness", in *Classic Cases in Neuropsychology*, vol 1. Edited by Code C, Wallesch C, Joannette Y, et al. Hove, East Sussex, Psychology Press, 1996, pp 89–110
63. Husain M, Stein J: Rezső Bálint and his most celebrated case. *Arch Neurol* 1988; 45:89–93
64. Monrad-Krohn GH: Dysprosody or altered melody of language. *Brain* 1947; 70:405–415
65. Wearing D: *Forever Today*. New York, Doubleday Publishing, 2005
66. Marshall JC, Newcombe F: Patterns of paralexia: a psycholinguistic approach. *J Psycholinguist Res* 1973; 2:175–199
67. Rosenbaum RS, Köhler S, Schacter DL, et al: The case of K C: contributions of a memory-impaired person to memory theory. *Neuropsychologia* 2005; 43:989–1021
68. Schwartz MF, Marin OS, Saffran EM: Dissociations of language function in dementia: a case study. *Brain Lang* 1979; 7:277–306
69. Warrington EK, Shallice T: Category specific semantic impairments. *Brain* 1984; 107:829–854
70. Burklund CW, Smith A: Language and the cerebral hemispheres: observations of verbal and nonverbal responses during 18 months following left ("dominant") hemispherectomy. *Neurology* 1977; 27:627–633
71. Cohen RA, Albers HE: Disruption of human circadian and cognitive regulation following a discrete hypothalamic lesion: a case study. *Neurology* 1991; 41:726–729
72. Kushner HI: Medical fictions: the case of the cursing marquise and the (re)construction of Gilles de la Tourette's syndrome. *Bull Hist Med* 1995; 69:224–254
73. Adolphs R, Tranel D, Damasio H, et al: Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature* 1994; 372:669–672
74. Martin G: The death of Henry II of France: a sporting death and post-mortem. *ANZ J Surg* 2001; 71:318–320
75. Opitz JM, Smith JF, Santoro L: The FG syndromes (online Mendelian inheritance in man 305450): perspective in 2008. *Adv Pediatr* 2008; 55:123–170