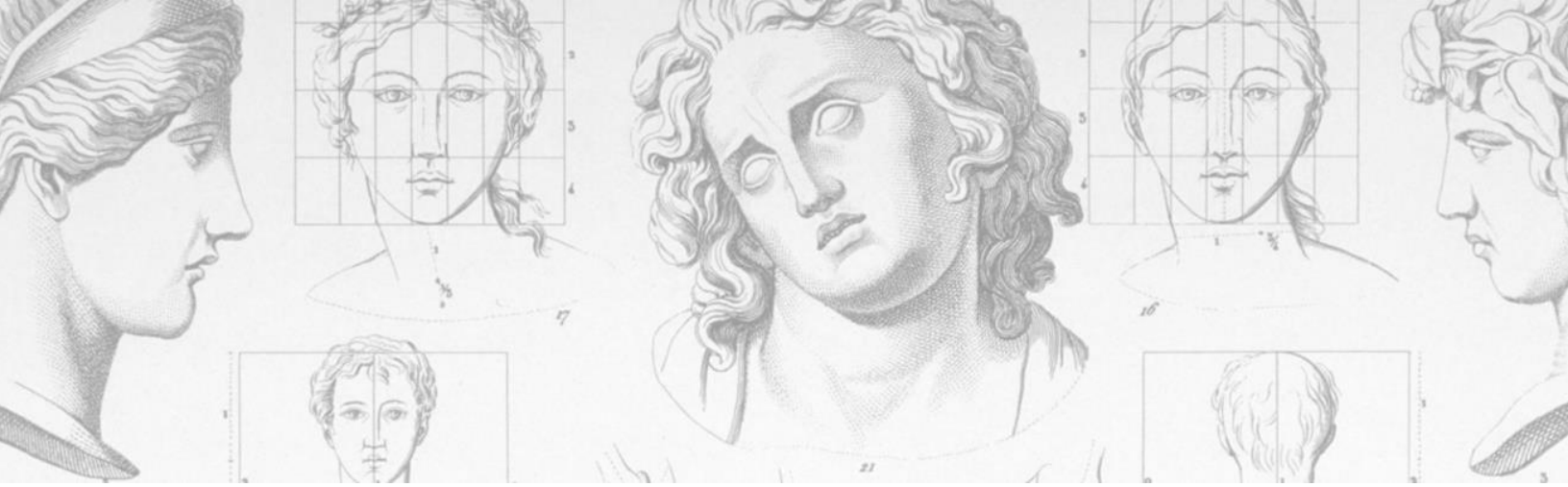

The History of Neuroscience in Autobiography
Volume 2

Edited by Larry R. Squire
Published by Society for Neuroscience
ISBN: 0-12-660302-2

Brenda Milner

pp. 276–305

https://doi.org/10.1016/S1874-6055(99)80012-7

Brenda Milner

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Brenda Milner first described patient H.M., thereby discovering the memory functions of the medial temporal lobe. She has carried out pioneering neuropsychological work on the topics of memory, hemispheric specialization, and the functions of the frontal lobes.

The History of Neuroscience in Autobiography, Volume 2

Brenda Milner

Background (1918–1939)

There was nothing in my background to predict a career in the sciences. I was born in Manchester, England in July, 1918, the only child of Samuel Langford, musical critic on the Manchester Guardian, and Leslie Doig. My father came from a family of market gardeners, but it has been said that he had a romantic rather than a business interest in gardening. I grew up in an old house surrounded by a large, overgrown garden, where my father grew delphiniums for the sake of their color rather than their market value.

As a young man, my father had played the organ in the local parish church, and it was there that his musical talent was spotted; a scholarship fund was raised to send him to study music under Carl Reinecke in Leipzig, where he stayed for 4 years, returning to England in 1900 to earn his living as a professional journalist, music teacher, and occasional concert pianist. Apart from his musical training, he was largely self-educated and expressed distrust of formal education as inhibiting the creative spirit. His wide-ranging library of prose and poetry made me a precocious reader but contained no scientific writing.

My mother, who was 23 years younger than my father, came from a broken home; as a result she had had to leave her high school in Birmingham at the age of 14 and as a young woman take a clerical job in Manchester, where she stayed with family friends. While in Manchester, she took singing lessons from my father, and subsequently married him, much to the surprise of his family who had thought of him as a confirmed bachelor.

Their life together was dominated by music, and it was a bitter disappointment to them to discover that I had absolutely no musical aptitude, and, in fact that I was practically tone deaf. Once this had been accepted, my childhood became much happier. Since my father was at home during the day, he took charge of my early education, which included arithmetic, a great deal of Shakespeare, and even a little German. At the age of seven, I began to attend a small private primary school, where we had to speak French on all social occasions (a foretaste of things to come), and where I struggled to improve my handwriting, which, like other motor skills, lagged far behind my reading ability.

When I was 8 years old, my father died of tuberculosis, after a relatively short illness, and my whole life changed. My mother secured a place for me

at Withington Girls' School, where I remained for the next 10 years, and we moved to a more modern house nearby.

One incident stands out from my early years at Withington. Thanks to my father's teaching, I found myself far in advance of my class in several core subjects, so that my mother asked if I could skip a class. The school agreed but warned her that I would be behind in French as a result. My mother took this as a challenge and taught me French grammar solidly all summer, so that when I returned to school in the fall I found that I knew enough French for the next 3 years. This excellent groundwork led me to develop a great love of French language and literature, which was to stand me in good stead when I came to live and work in Montreal, many years later.

The British school system then (and probably even now) requires specialization quite early, so that by the age of 15 I had to choose between science and the humanities. It was a difficult choice, but with my love of Latin I would have opted for classics (and a totally different life), had my school offered Greek. Since it did not, I chose to study mathematics and physics, on the science side. This was partly because I greatly enjoyed my high school mathematics, but also because I believed (and still do) that it is possible to develop one's knowledge and enjoyment of foreign languages and literature on one's own, but that once you give up science you abandon it forever. My headmistress was angered by my choice because she thought, quite rightly, that this would make it more difficult for me to get a scholarship to Oxford or Cambridge (but my mother, to her everlasting credit, supported me, although she herself would have preferred me to opt for the humanities). I had certainly gambled on my future, but thanks to an excellent physics teacher, I managed to get into Newnham College, Cambridge in 1936 and supported myself there on a Manchester City Scholarship, supplemented by a small grant from my college.

I had not been long at Cambridge before I realized that I would never distinguish myself in mathematics. Therefore, at the end of my first year, I decided to change fields. I was, however, still attracted by the elegance of mathematical reasoning and toyed with the idea of switching to logic and philosophy, in the Moral Sciences Tripos. But I was soon dissuaded from such a plan, as senior members of my college pointed out to me that nobody could earn their living in philosophy, and hence that it was a subject strictly for people of independent means. Instead, they suggested that I might consider psychology, which in those days was still classed as a moral science. F. C. Bartlett, already famous for his research in memory, was the professor, and his wife was Director of Studies in psychology at Newnham. She proved quite welcoming and gave me Murcheson's encyclopedic *Handbook of Experimental Psychology* for summer reading to prepare myself for this new field.

As I had feared, my mother was extremely disappointed by my news. Although she had originally hoped that I would have a career in the human-

ities, she had a great respect for mathematics and therefore had reconciled herself to my choice. Psychology was another matter, for outside the universities this discipline was still relatively unknown in England.

For me, however, experimental psychology proved a fortunate choice, providing a friendly laboratory environment and the tools with which to satisfy my growing curiosity about the behavior of organisms. Under Bartlett's leadership, the Cambridge department had acquired a strongly biological orientation, stemming from the tradition of Sir Henry Head. We also shared a building with Professor E. C. Adrian's Physiological Laboratory, where I had the privilege of hearing Carl Pfaffmann present his early work on taste in one of our joint seminars. For my future career, however, the most important influence was that of Oliver Zangwill, who was my supervisor from 1937 to my graduation in 1939. It was he who first taught me the value of studying the behavioral effects of brain lesions, because he believed that through an analysis of disordered function one could gain insights into the functioning of the normal brain.

The War Years (1939–1944)

On the basis of my examination results, I was awarded the Sarah Smithson studentship by Newnham College, which would enable me to pursue postgraduate research in experimental psychology at Cambridge. My project was to explore how subjects behave in situations of sensory conflict, for example, in situations in which visual information was in apparent disagreement with information derived from proprioception. With the outbreak of World War II in September 1939, this project was redirected to the war effort. I became part of a team developing and administering selection tests for air crew with a focus on the supposedly different qualities required to be a fighter or a bomber pilot. Although the whole laboratory was on a war footing, Bartlett was very skilled in keeping his scientists out of uniform, which meant that we could give our opinions to Air Marshals without running into problems of rank.

When my studentship ran out, I had to leave Cambridge and I was recruited by C. P. Snow to work as an experimental officer for the Ministry of Supply at the Radar Research and Development Establishment situated in Christchurch, near Bournemouth, on the south coast. At that time I was one of only three women officers in this large establishment, the other two being librarians. My job was to evaluate different methods of display and control for radar operators. This is where I met Peter Milner, an electrical engineer from Leeds University, who had been designing a trainer for radar operators which allowed one to compare the tracking accuracy of direct laying, aided laying, and velocity laying, as well as different forms of display. I was billeted in the home of a factory worker and had little or no social contact with the mathematicians and physicists who made up the bulk of

the scientific staff. I was, however, allowed frequent visits to Cambridge "to consult the Professor" and took full advantage of these short respites from my rather dreary existence in Christchurch.

The return train journey from London to Christchurch at night also had its own interesting possibilities, since most of the names of the stations had been removed, and in the country all the signposts were pointing the wrong way, to confuse invading Germans. At this time, in the spring of 1942, there was fear of possible parachute raids to carry off "brains" and it became evident that the establishment ought to be moved to a safer place. On one of my trips to Cambridge, I received an urgent telephone call from one of my friends, telling me to return to Christchurch immediately, with no further explanation. I did so, only to discover that within a few days the whole establishment was to be moved to Malvern, a small country town in the West Midlands, in the heart of the fruit-growing district.

The radar research establishment at Malvern soon took on the atmosphere of a college campus and the next 2 years were happy ones. Yet from a work point of view, this was for me a discouraging period of simply marking time, since the problems I was working on had no general theoretical interest. But by the late summer of 1944, it was apparent that the war in Europe would soon be over and it was time to think about one's peace-time career. I was therefore delighted to be invited to return to Cambridge to work with Kenneth Craik once the war had ended.

At this point something totally unexpected occurred that was to change the course of my life. Peter Milner was invited to join a small group of physicists, under the leadership of Sir John Cockcroft, who were due to leave for Montreal to initiate atomic energy research in Canada. The project was to last 1 year. On the spur of the moment, Peter and I decided to get married and about 2 weeks later we set sail from Glasgow on the Queen Elizabeth, which had been converted into a troopship for the duration of the war. We were accompanied by a large group of British war brides who had married American soldiers stationed in Britain and were now on their way to the United States, and on the first night out we (i.e., all the women) were addressed by the ship's captain and told not to harass the men. We had expected to land in New York, but in fact landed in Boston, to the delight of a young Bostonian anxious to rejoin her family for Thanksgiving. All the way across the Atlantic, we zig-zagged to avoid submarines, and all the time in complete black-out (as we had been in England for the previous 5 years). In Boston, the war brides received a warm welcome from the Red Cross, and we were included in that welcome and driven to the Copley-Plaza Hotel for planked steak, ice-cream, and a good night's rest. But what I remember after the darkness of wartime England, and the even deeper darkness of the North Atlantic, was the brilliantly lit streets of Boston. Peter and I found this light quite intoxicating, only to be told that this was the American black-out! Next day, after a brief tour of MIT physics labs, we

took the train to Montreal, little knowing how long we would stay in Canada.

Montreal (1944–1952)

In Montreal, the first academic opportunity that presented itself to me was in the francophone Université de Montréal, where the head of the newly formed Institut de Psychologie, Father Noël Mailloux, was a Dominican priest whose somewhat unconventional approach to psychology combined the teachings of St. Thomas Aquinas with those of Freud. He began by asking me to give 20 lectures on Bartlett's theory of memory, and he subsequently employed me to teach laboratory courses in experimental and comparative psychology. I found these assignments initially very challenging, since I had had little opportunity to speak French since my high-school days, although fortunately I had read a great deal. The challenge had to be met, however, and I found it a most stimulating experience. Moreover, I was only a few years older than my students and I formed some friendships that have lasted to this day. Nevertheless, as I became used to teaching in French, I realized that there were other difficulties in the way of communication. Most of the students had completed the classical baccalaureate degree and were interested in studying clinical psychology. They also had a Cartesian approach, expecting to know in advance what an experiment would demonstrate. My more empirical approach left them dissatisfied. I began to feel that it was time to make a change.

When we first arrived in Canada, the Psychology Department at McGill University was in a run-down state, having been reduced by the war to an absentee chairman and one half-time lecturer. In 1946, Robert MacLeod was appointed to the Chair, with a mandate to get the department back on its feet. MacLeod had carried out important research on the perceptual constancies in Germany before World War II and was strongly influenced by Gestalt psychology and phenomenology. This material was familiar to me from my undergraduate days at Cambridge, and I began to participate in his seminars, as an interesting change from my regular work at the Université de Montréal.

True to his mandate, MacLeod quickly recruited two senior faculty members, George Ferguson from Edinburgh in statistics, and Donald Hebb from Orange Park in what was then called physiological psychology. Hebb arrived with his book, *The Organization of Behavior,* still in manuscript; during his first seminar, we discussed this book chapter by chapter and did the relevant background reading, which covered Lorente de Nò, Marshall and Talbot, Hilgard, Lashley, and Sperry. The graduate students in this seminar included Mortimer Mishkin, Lila Ghent (Braine), Herb Lansdell, and Woodburn Heron, and discussion after the seminars often continued late into the night. It was an exciting time and hastened my decision to do a Ph.D. at McGill. By this time, the Atomic Energy project had moved from Montreal

to Chalk River, Ontario. I wrote to Peter enthusiastically about the Hebb seminar, with the result that he decided on a career change.

In 1948, MacLeod left McGill for Cornell University and Hebb reluctantly took over the Chairmanship, a position that I think he soon came to enjoy. In 1949, I persuaded him to accept me as a graduate student, and I set about designing experiments to explore tactual concept formation in the congenitally blind.

One of the attractions for Hebb in returning to McGill was the interdisciplinary aspect, with colleagues such as Hank Mackintosh in physiology, and Wilder Penfield and Herbert Jasper at the Montreal Neurological Institute (MNI). Shortly after his arrival, Hebb had extracted a promise from Penfield that he could send one graduate student to the MNI to study the patients undergoing brain surgery for the relief of epilepsy. Under this arrangement, Donald Forgays had just completed a short project showing that patients were usually less impaired right after surgery than a few days later, when postoperative edema had set in, a finding that complemented his main research, which was with rats. Hebb then asked me if I would like to do my thesis research at the MNI, investigating the effects of temporal lobe lesions, since I was supposed to be inteested in the thought processes. Fascinated as I had become by my work with the blind, this could not compete with the attraction of Penfield's patients. In June, 1950, I began to carry out research at the MNI, and knew immediately that this was the kind of work I wished to pursue, whatever the practical difficulties. Meantime, the only advice Hebb gave me was to make myself as useful as I could and not to get in anyone's way. He also bequeathed me a few tests. The rest was up to me.

During those first months at the MNI, I was impressed, as no one could fail to be, by the experience of being present in the gallery of the operating room while Penfield stimulated the exposed cortex in awake patients who had reported complex hallucinatory experiences as part of their epileptic seizures. In a small number of such cases, Penfield was able to elicit reports of complex experiential phenomena that sometimes, but not invariably, resembled those occurring during their habitual seizures.

On the basis of such meticulously documented clinical observations, Penfield had become convinced that with his stimulating electrode he had managed to excite part of the neural substrate of past experience. Frequently, the experience he evoked by cortical stimulation could in fact be linked to some well-documented event, or at least to some recurrent feature of the patient's everyday life. Hence came his postulate that somewhere in the brain of each of us, there is a continuous, ongoing record of the stream of consciousness (that is, of everythig we attend to, not of things we are not attending to) extending from birth to death.

To me, as an experimental psychologist, and a student of Bartlett, this tape-recorder notion of memory seemed highly implausible since I had been trained to think of remembering as a reconstructive rather than a

reproductive process. Later I often talked to Penfield about the difficulties I had with this view. He used to say "Of course this is not memory as you psychologists understand the term, when you refer to the variability of memory, with its abstractions, generalizations, and distortions. In ordinary remembering, we do not have direct access to the record of past experience in the brain."

Despite Penfield's evident interest in memory processes, I had no intention at this stage of working on memory myself, but rather chose to focus on complex perceptual tasks. Apart from an early report by Hebb in 1939 on a single case of right temporal lobectomy, and a few auditory studies, little was known at the time about the behavioral effects of temporal lobectomy in humans. My hypotheses were therefore largely based on what was known in the monkey. In particular, the dramatic demonstration by Klüver and Bucy in 1937 of a state they termed "psychic blindness" followed bilateral temporal lobectomy in the monkey led me to expect to find visual impairments in patients with temporal-lobe lesions, although the fact that the removals in the patients were unilateral made it less likely that any striking changes would be seen. Using the small battery of tasks that Hebb had left me from his days at the MNI, I planned to test preoperatively, and again 2 weeks postoperatively, all patients undergoing unilateral cortical excisions as a treatment for focal epilepsy. With such a project, it was a particular disadvantage not to be at the MNI during the day, but I still had my full-time teaching job at the Université de Montréal, on the other side of town, and therefore had to limit myself to the weekends and evenings for testing patients. It was therefore important to know ahead of time on which patient Penfield was about to operate. For this I relied on the residents, but even they could never be sure, because Penfield would often decide only at the last minute to operate on Patient A rather than Patient B. Another obstacle was the pneumoencephalogram (PEG), which David Hubel described in his memoir, and which was mandatory for all presurgical patients. This procedure (over the timing of which I had of course no control) involved removing cerebrospinal fluid and replacing it with air. Afterwards the patients felt all right as long as they were lying down, but as soon as they sat up (as they had to do for my tests), they quickly developed headache and nausea, so that testing had to be abandoned. Despite these various frustrations, I managed to accumulate enough data for a thesis by the spring of 1952; I demonstrated mild deficits on certain pictorial tasks in my temporal-lobe groups, deficits that were detectable preoperatively and accentuated after removal of the epileptogenic area. Interestingly, these deficits were seen more reliably after right temporal-lobe lesions than after left.

I saw a parallel between the deficits I was observing in patients with right temporal-lobe lesions and the selective impairment of visual discrimination learning that was being described by Mishkin and Pribram after bilateral removal of the inferotemporal cortex in the monkey. Similarly,

some years later, I was to uncover an impairment on simple melodic discrimination tasks after right anterior temporal lobectomy (but not after left) that resembled the auditory discrimination deficits seen after bilateral lesions of the superior temporal cortex in the monkey.

As I was writing my thesis, I became aware of several further avenues I wished to pursue. First, I needed to see more patients if I was to demonstrate the special contributions of the right temporal lobe. It was still hard to convince people that the results were not due to the surgeon making larger removals from the right than the left hemisphere, or that the right-temporal deficit was not simply a consequence of an upper-quadrant visual-field defect (although this could hardly account for the preoperative findings).

Secondly, I had been listening to the patients' complaints and realizing that those with left temporal-lobe lesions complained of poor memory, but that when I questioned them further, the examples they gave were always from the domain of verbal memory. They forgot what they heard and what they read. It seemed that, whether I liked it or not, I ought to begin investigating memory. This conclusion was further reinforced by my first encounter with a case of postoperative global amnesia.

Hebb had assumed that upon completing my thesis in the summer of 1952 I would return to full-time academic work at the Université de Montréal. When I told him that I was planning to give up a tenured position there in order to pursue my research with Penfield's patients, he attempted to dissuade me, assuring me that "no psychologist could survive for long at the MNI." However, when he saw that my mind was made up, he offered to support me for a year as a postdoctoral fellow based in the McGill Psychology Department. To my astonishment, before the year was out, Penfield had told me that he needed me at the MNI and he had provided me with an office with easy access to patients and a small stipend (but no research funds). This gesture ensured the future of neuropsychology at the MNI and was, I think, brought about by the fact that in fairly rapid succession we had seen two cases of severe memory loss following unilateral anterior temporal lobectomy.

Memory Loss after Bilateral Medial Temporal-Lobe Lesions

In the early days of temporal-lobe surgery, Penfield had usually confined his removal to the anterior neocortex, but this limited resection was rarely effective in controlling the patient's seizures; by the time I arrived on the scene, most temporal-lobe removals included the anterior hippocampus and parahippocampal gyrus, together with the amygdala, with no striking behavior change resulting from what by then had become a routine procedure. During this period, several patients with unilateral neocortical removals returned with continuing seizures, requiring completion of the temporal lobectomy.

In one such case, that of a civil engineer (P.B.), this second operation, which involved only the medial structures of the left temporal lobe, was followed by a severe, persistent, and generalized impairment of recent memory unaccompanied by other cognitive deficits. The impairment was manifest clinically as a profound anterograde amnesia, such that the experiences of daily life were forgotten as soon as the patient's attention shifted to a new topic. In addition, there was a retrograde amnesia covering the salient events of the previous few months. P.B.'s unexpected memory loss was a troubling outcome of elective surgery; he remained a single puzzling case until November, 1952, when another patient (F.C.), a 28-year-old glove cutter, exhibited a similar amnesic syndrome after a one-stage left temporal lobectomy that included the amygdala, uncus, and anterior hippocampus and parahippocampal gyrus. In his case, the retrograde amnesia extended back 4 years.

To account for these two instances of memory loss after a unilateral temporal-lobe removal, we hypothesized that in each case there had been a preexistent, but preoperatively undetected, atrophic lesion in the medial temporal area of the opposite hemisphere, so that when Penfield removed a large part of the hippocampus and parahippocampal gyrus in the left hemisphere he effictively deprived the patients of hippocampal function bilaterally. The reason we emphasized the hippocampal region was that P.B. had had his temporal lobectomy in two stages, and it was only after the medial temporal-lobe removal that the memory loss was seen. In this case, our hypothesis was to be confirmed 9 years later, when P.B. died of a pulmonary embolism and the autopsy findings revealed the presence of a long-standing right hippocampal atrophy. In contrast, on the operated (left) side, the 22 mm of hippocampus that remained appeared to be normal.

We reported these two cases at the 1955 meeting of the American Neurological Association, in Chicago, and Dr. William Scoville, a neurosurgeon from Hartford, Connecticut, read our abstract. He immediately called Penfield and said that he had seen a similar memory disturbance in a patient of his (H.M.), in whom he had carried out a bilateral medial temporal-lobe resection, also in an attempt to control epileptic seizures. As a result, I was invited to go down to Hartford to study H.M. and other patients of Scoville with similar removals.

Scoville had designed the operation of bilateral medial temporal-lobe resection as an alternative to frontal lobotomy in the treatment of seriously ill schizophrenic patients. Because of the known connections between the medial temporal region and the orbital frontal cortex, he had hoped that this procedure would prove psychiatrically beneficial, while avoiding the undesirable side effects of a frontal lobotomy. As it turned out, the operation did little to alleviate the psychosis, and any memory changes went undetected until much later, when I had the opportunity to examine eight of these patients. Although some were difficult to test, I did manage to estab-

lish the presence of anterograde amnesia in all cases where the removal had encroached upon the hippocampus and parahippocampal gyrus, but not where the removal was limited to the uncus and amygdala.

Scoville had first become aware of the risk to memory in his operation in 1953, when he carried out a radical bilateral medial temporal-lobe resection in a 27-year-old epileptic patient (H.M.), whose frequent major and minor seizures had failed to respond to near toxic doses of anticonvulsant medication. This frankly experimental procedure had been proposed because H.M., an assembly-line worker by trade, had become unable to work or lead a normal life. The operation did in fact control the epilepsy, but at far too high a price. Already within the first few postoperative days, it was clear that H.M. had a serious impairment of recent memory. He could not remember what he had had for breakfast, and he could no longer find his way around the hospital or recognize members of the hospital staff (apart from Scoville, whom he had known for many years). He also showed a patchy retrograde amnesia for the events of the past 3 years, but his earlier memories appeared to be intact, his speech was normal, and his social behavior entirely appropriate.

On my first encounter with H.M. in April 1955, it was apparent that his memory disorder was of the same kind as that shown by Penfield's two patients, but even more severe. Again, there had been no intellectual loss; in fact, H.M.'s IQ had risen postoperatively, from 104 to 117, presumably because he was now having far fewer seizures and was on considerably reduced medication.

As with P.B., H.M.'s capacity for sustained attention was also remarkable. For example, I found that he could retain the number 584 for at least 15 minutes by continuous rehearsal, combining and recombining the digits according to an elaborate mnemonic scheme. Yet the moment his attention was diverted by a new topic, the whole event was forgotten. This pattern seemed to suggest that he might be able to retain a simple memorandum indefinitely, provided that no other activity claimed his attention. What I failed to realize at the time was the key role played by verbal rehearsal in this holding process. My graduate student, Lilli Prisko, was later to show, using a delayed paired-comparison task, that simple nonverbal stimuli were forgotten by H.M. in less than a minute, a finding subsequently confirmed by Murray Sidman and his colleagues in an elegant delayed-matching paradigm. These and other related studies have concurred in showing that H.M. can register perceptual information normally, but that the information ceases to be available to him within 30–40 seconds. Such results appear to support the distinction between a primary memory process with a rapid decay and an overlapping secondary process (impaired in H.M.) by which the long-term storage of information is achieved.

H.M.'s inability to retain even verbal information after a single exposure, if he was distracted in the interval, did not necessarily mean that he

would be unable to master a new task with extensive practice. Accordingly, before my next trip to Hartford, I picked up two different learning tasks from the McGill experimental psychology laboratory and then spent 3 days administering them to H.M. One of these tasks, a 28 choice-point stylus maze, proved to be impossibly difficult for him to learn, since by the time he reached the end of the maze he had completely forgotten the beginning, saying each time "I am having a little argument with myself: should it be this way or should it be that?" In contrast, and much to my surprise, H.M. had no trouble at all in learning the other task, mirror-drawing, which involved the acquisition of a new visuo-motor skill. In this case, H.M. was presented with a five-pointed star, with a double contour, and was instructed to trace a path around it, keeping within the narrow border created by the contour lines. What made the task difficult was that he only saw the star, and his own hand, as reflected in a mirror. Under these conditions, we all tend to move the hand in the wrong direction when we reach the points of the star, but we gradually improve with practice over many trials. I took H.M. through 30 trials, spread over the 3 days of my visit, and he showed a typical learning curve. Yet at the end of the last trial, he had absolutely no idea that he had ever done the task before. This was learning without any sense of familiarity. Nowadays we are well aware that such dissociations are possible following a discrete brain lesion, but for me at the time it was quite astonishing. It was also early evidence of the existence of more than one memory system in the brain.

H.M.'s success on the mirror-drawing task led me to speculate that other kinds of motor skill might also be acquired independently of the medial temporal-lobe system. By this I had in mind such activities as learning to dance or swim or to pronounce a foreign language correctly. Such skills are built up gradually without our being able to describe just what we are learning, and the attempt to introspect is likely to impair performance. It seemed reasonable to suppose that such kinds of learning (later termed "procedural" by Cohen and Squire) would not require the participation of a conscious, cognitive memory system.

This generalization has held up whenever it has been tested, although the skills sampled so far have been few and of limited complexity. But it soon became clear that motor skills were only a part of a large collection of learning and memory abilities that are spared in H.M. and other amnesic patients with similar lesions. Thus, in 1968, Warrington and Weiskrantz found that amnesic patients could learn to identify fragmented drawings of objects and animals with progressively fewer cues, even though they did not remember having seen the drawings before, a finding that I was subsequently able to replicate in H.M. This long-term effect of a prior visual experience, which I called "perceptual learning," is an instance of what is now known as priming, a kind of learning distinct from motor skill, and which, in this case, is probably mediated at the level of the visual cortex.

Interest in human memory processes and their neural substrates has grown steadily over the past 30 years, and the early pioneering work with H.M. certainly provided some of the impetus for this growth. Nevertheless, the findings had a somewhat mixed reception at the time, largely because of difficulty in establishing a suitable animal model for human amnesia. For years we were perplexed by the seeming lack of confirmation from work with monkeys, where, for example, animals with bilateral medial temporal-lobe resections similar to what had been described in H.M. showed normal performance on visual discrimination-learning tasks, even when concurrent trials on a different task were interpolated as potential distractors. This led many investigators to question the human findings, or even the validity of cross-species comparisons. What we had not considered at the time was that ostensibly similar tasks may be solved in different ways by humans and monkeys, and that a visual discrimination task learned by the monkey over many trials was an example of procedural learning and therefore not a good test for amnesia. It was not until much later that the concept of multiple memory systems became widely accepted and hence that it became clearer which memory tasks were appropriate to give to experimental animals. An important breakthrough came in 1978, when Mishkin demonstrated a severe deficit in monkeys with bilateral medial temporal-lobe lesions on a one-trial task of object recognition memory (delayed nonmatching to sample). This is of course what we should have predicted from H. M.'s failure on single-trial, nonverbal delayed matching tasks, and represents a convergence of findings from monkey to man.

Taken as a whole, the behavioral studies provide compelling evidence that the cognitive (declarative) memory system is critically dependent upon the medial temporal region. Yet we still have much to discover about the relative importance of specific structures within that region and their mode of interaction with other brain areas. Despite the use of the word "hippocampal" in the titles of my papers with Scoville and Penfield, I have never claimed that the memory loss was solely attributable to the hippocampal lesions. Recent magnetic resonance imaging (MRI) studies in H.M. by Corkin *et al.* (1997) have shown that the bilateral medial temporal-lobe resection was essentially as described by Scoville, except less extensive (thus conforming to Percival Bailey's dictum that surgeons typically overestimate the extent of tissue excised). The lesion was bilaterally symmetrical and included the bulk of the amygdala, the perirhinal and entorhinal cortices, and about 5 cm of the hippocampal formation. The parahippocampal cortex was largely intact, as was the lateral neocortex and temporal stem. It seems likely, as Corkin *et al.* suggest, that the severity of H.M.'s memory impairment compared with that of other amnesic patients with selective hippocampal lesions may be related to the inclusion of perirhinal, entorhinal, and some parahippocampal cortex in the removal. Much current research in various centers is directed to exploring this issue.

The Growth of Neuropsychology at the MNI

In the aftermath of my work on amnesia, neuropsychology flourished at the MNI. In 1957, I was joined by two young colleagues. Laughlin Taylor, a graduate student in the McGill Psychology Department, came to help with the clinical testing of neurosurgical patients and has stayed on to head our neuropsychological services. Doreen Kimura came the next year as my first Ph.D. student, supported first by Hebb and later as a postdoctoral fellow on my own N.I.H. grant. In her thesis, Doreen demonstrated a clear impairment after right temporal lobectomy, but not after left, in recognition memory for abstract visual patterns, as well as providing evidence for subtle perceptual changes associated with epileptogenic lesions of that lobe. Meantime I myself had found a robust deficit in memory for new faces after right temporal lobectomy but not after left. The argument for a greater contribution from the right temporal lobe than the left to memory for visual patterns was thus considerably strengthened.

Doreen was the first person to use the Broadbent dichotic-listening technique to demonstrate a complementary specialization of the two hemispheres in audition. In Broadbent's version, different strings of digits were presented in pairs to the two ears, and the subject merely had to report as many digits as possible, in any order. Broadbent had found that normal subjects tended first to report all the digits for one ear, and then those for the other, rather than as a sequence of pairs. What Doreen discovered was that patients tested preoperatively, as well as normal control subjects, obtained higher scores for the right ear than for the left, a finding that she attributed to left-hemisphere dominance for speech and to the predominance of the crossed auditory pathway, from right ear to left temporal lobe, over the ipsilateral one. Evidence in support of this view came from patients with proven right-hemisphere speech lateralization, the majority of whom showed a left-ear superiority on this verbal dichotic-listening task. Doreen then went on to demonstrate, in a group of normal right-handed subjects, a right-ear superiority for digits combined with a left-ear superiority for the recognition of dichotically presented melodies, thus highlighting a dual functional asymmetry of the auditory system.

After Doreen left, Donald Shankweiler carried her auditory research further before joining Al Liberman's group at the Haskins laboratories in New York. Don had been a student of Arthur Benton and one day he received a letter from Benton telling him that a new journal, *Cortex,* was about to be launched in Milan by De Renzi's group. Only a short while earlier I had learned from Henry Hécaen of the first publication of *Neuropsychologia,* and Don and I wondered how two neuropsychology journals could survive. We would never have predicted then that both would be alive and thriving in the 1990s, together with a proliferation of other journals devoted to brain and behavior.

With Don's departure, our work on audition was interrupted for several years, although ever since my own early strong findings of impairments in tonal memory and timbre-discrimination after right anterior temporal lobectomy I had been convinced of the need for further work on music. However, I was clearly not the right person to undertake it, given my musical incompetence. Fortunately, in 1981, I was able to recruit Robert Zatorre from Brown University on an N.I.H. postdoctoral fellowship. Robert held degrees in both music and experimental psychology, and thus seemed an ideal person to conduct research on music and the brain. Robert has stayed on to become a permanent member of our group and, together with his students, is making a major contribution to our understanding of how the brain processes musical input.

In 1961, the arrival of Suzanne Hammond (now Suzanne Corkin) as a graduate student from Smith College inaugurated our program of research in somesthesis, a topic in which she expressed a surprisingly passionate interest from the beginning. Initially Sue modelled her work on that of Josephine Semmes and Hans-Lukas Teuber who had carried out meticulous sensory testing on the hands of Korean war veterans with penetrating missile wounds of the brain, but at the same time she designed tactual learning tasks analogous to visual ones developed by Doreen. Since we still had virtually no money and no technical help, Sue showed considerable initiative in driving around to various local merchants and persuading them to make up material to her specifications "for the sake of McGill."

By this time Theodore Rasmussen had succeeded Penfield as Director of the MNI; he proved to be an enthusiastic collaborator in several of our research projects. Despite an early report by Penfield and Evans of contralateral sensory defects after posterior parietal cortical excisions, Rasmussen was convinced, on the basis of his own surgical experience, that there was no lasting sensory loss after removals that spared the postcentral gyrus, unless the blood supply to that gyrus had been compromised. Sue's careful quantitative testing of sensory discriminaton on the hand combined with Rasmussen's systematic sensory mapping of the postcentral gyrus by cortical stimulation in awake patients yielded a striking confirmation of this hypothesis.

When Sue completed her Ph.D. thesis, she took up a position in Hans-Lukas Teuber's newly formed department at M.I.T., and after Lukas's untimely death in 1977, she took over the direction of the M.I.T. neuropsychology lab. Prior to Lukas's death, he and I had collaborated in further follow-up studies of H.M., both in Hartford and at M.I.T.; Sue has continued to monitor H.M.'s progress to the present day, as well as carrying out new investigations of his memory disorder.

By the mid-1960s, our lab at the MNI had acquired some financial stability for the first time. In 1964, I received a Career Investigatorship award and an operating grant from the Medical Research Council of Canada; I

have had continuous salary and research support from the Council ever since, without which most of our work could not have been done. Shortly afterward, Laughlin Taylor accepted a position as a clinical neuropsychologist on the Quebec Hospital Service, and our neuropsychology unit became more firmly established in both the hospital and the institute.

In 1960, I met Roger Sperry at a memory conference in New York, and when he heard of my special interest in the right hemisphere he invited me to go out to Pasadena and study the group of patients with cerebral commissurotomy. As a result, Laughlin Taylor and I made several visits to Caltech during the next 10 years, always with some specific experimental question in mind. For me, our most important finding was not only that the patients tested after cerebral commissurotomy were better at delayed matching of tactile patterns with the left hand than with the right, but also that they could bridge longer delays than H.M., whose commissures were intact. The fact that the mute, surgically isolated, right hemisphere could match tactile patterns correctly after a 2-minute delay seemed to me to constitute an effective rebuttal of the claim, by Sidman and others, that H.M.'s failure on such tasks after 30 seconds was due to a failure to generate the appropriate verbal labels.

My visits to Pasadena were enriching in other ways and led to lasting friendships with Roger and Norma Sperry, and with Joe and Glenda Bogen, as well as with many of the students in Sperry's lab. I was therefore delighted when, in 1972, during a sabbatical year in Cambridge, I was able to welcome Roger and Norma there, on the occasion of Roger's honorary degree from that university.

It was on a visit to Caltech that I first met Giovanni Berlucchi and Giacomo Rizzolatti, at a party held in their honor at the end of a year they had spent in Sperry's lab; I was later to visit them both in Italy, first in Moruzzi's lab in Pisa, and later in Parma and Verona on many occasions. During this same period, I also established strong links with Ennio De Renzi's group in Milan; it was there that he and Luigi Vignolo persuaded me to give my lectures in my somewhat halting Italian, which henceforth added another dimension to my visits to colleagues in Italy. These Italian connections have also been strengthened by visits to Dario Grossi's group in Naples, and by Valeria Cavazzuti's prolonged stay in Montreal as a visiting scientist from Bologna, as well as by Antonio Incisa della Rocchetta from Rome, who did his Ph.D. with me and who has become a firm friend of all members of our group.

The Introduction of Intracarotid Sodium Amobarbital Speech Tests

It is impressive how often the introduction of a new technique can give us new insights into brain function. We owe the introduction of intracarotid amobarbital testing to Juhn Wada, a postdoctoral fellow in neurology from

Japan. I remember the occasion when he first told us of the possibility of determining the side of speech representation by injecting a barbiturate, sodium amobarbital, into the common carotid artery of one side. It was during a preoperative EEG conference on a left-handed patient whose seizures arose from the left posterior temporal region, but who showed no postictal speech difficulty. Penfield had just remarked how wonderful it would be if only we had a means of determining ahead of time if the lesion was in the dominant hemisphere for speech, in which case he would not operate. Wada, sitting at the back of the room, suddenly spoke up, asserting that there was indeed such a way. Penfield removed his glasses (a sure sign of annoyance) and said that this was ridiculous. But Wada was quietly persistent, and soon he and Rasmussen embarked on rigorous testing of monkeys to establish the safety of the procedure. Then, from 1959 onward, all left-handed or ambidextrous patients who were candidates for a brain operation underwent preoperative intracarotid amobarbital tests to determine the lateralization of speech, as did any right-handers for whom there was reason to suspect atypical speech representation.

What these tests brought that was new was the possibility of comparing the functions of the two hemispheres of the same individual, although testing had to be simple and the time available was short. The language tests were similar to those used in conjunction with cortical stimulation in the operating room; they included both the naming of common objects and the recitation of well-known sequences, such as the days of the week forward and backward and counting forward and backward.

In a long series of amobarbital tests carried out in collaboration with Rasmussen and Charles Branch in neurosurgery, Laughlin Taylor and I confirmed the existence of bilateral speech representation in about 15 to 20% of non-right-handed patients, as well as demonstrating interesting qualitative differences between the pattern of speech disturbance from left- and right-sided injections in about 40% of such cases.

The results of amobarbital speech tests also alerted us to the importance of locus of lesion in determining whether or not an early injury to the left cerebral hemisphere resulted in the right hemisphere becoming dominant for speech. Rasmussen and I were initially surprised to find that severe early trauma to the left frontal polar region or to the left occipital lobe was compatible with left-hemisphere dominance for speech. We later realized, from a scrutiny of the distribution of lesions in the group of patients with early damage to the left hemisphere, that damage to Broca's area or to the posterior parieto-temporal speech zone in infancy was likely to bring about a functional reorganization of the brain in which the right hemisphere became dominant for language or in which there was bilateral representation, but that, in contrast, left-hemisphere lesions that spared these critical regions rarely affected the lateralization of speech.

The Initiation of Amobarbital Memory Tests

Once it had become apparent that the operation of anterior temporal lobectomy carried some risk to memory in patients with preexisting damage to the hippocampal region of the opposite hemisphere, for the next few years all seizure patients with bilateral independent electrographic abnormality, or with radiological or clinical evidence of such bilateral damage, were refused operation. Yet we realized that this policy would exclude many people whose seizures might have been controlled, or substantially reduced, by removal of the more epileptogenic area. For this reason, in the late 1960s, Rasmussen suggested that we try to adapt the intracarotid amobarbital procedure to the study of memory, thereby enabling us to screen out those patients for whom the proposed temporal lobectomy was likely to provoke an amnesic syndrome. The underlying hypothesis was that no memory deficit (as defined by our tests) should be seen after unilateral amobarbital injection, unless there was already extensive damage in the hippocampal zone of the opposite hemisphere. If there were such contralateral damage, then the temporary inactivation of the ipsilateral hemisphere by the action of the drug should produce transiently the amnesic state seen in patients, such as H.M., with known bilateral medial temporal-lobe lesions.

Attractive as this suggestion sounded, it was not at all clear to me at the time that such an extension of the amobarbital procedure from speech to memory would prove either feasible or valid. Whereas we could be confident that the carotid injection would affect the cortical speech areas, provided we obtained the expected contralateral hemiparesis, it was far less certain that the hippocampal region would be inactivated in those cases (and they would be the majority) in which the posterior cerebral artery was not filled. This question was particularly troubling because we were then still making our injections into the common carotid artery, and without angiographic control. We were thus unaware of the precise distribution of the drug in any given case. A second cause for concern was the fact that the effects of the amobarbital injection wear off in a matter of minutes, yet a short time lapse between stimulus presentation and stimulus retrieval was essential if we were to have a meaningful memory test.

In designing our original memory protocol in 1959, I was looking for a task that H.M. would fail but that an aphasic patient would be able to pass. The essential features were, first, the use of dually encodable material (line drawings of common objects) and, second, the interpolation of an effective distractor task (mental arithmetic) before memory was tested. An interesting early finding was that most patients showed very poor free recall of material presented when one hemisphere had been inactivated by the drug, even if the injection was ipsilateral to the patient's brain lesion. For this reason, and because amnesic patients fail recognition as well as recall tests, we decided to take recognition of the test items from a multiple-choice se-

ries as our criterion of successful retention. The results for our first 123 patients were encouraging for several reasons. First, we obtained a clear dissociation between aphasia and amnesia, in that patients frequently recognized later objects that they had been unable to name when presented shortly after the injection, and, conversely, patients might fail to recognize later objects that they had named correctly. Second, our main goal was achieved in that we did see a transient anterograde amnesia after 22% of the injections contralateral to a temporal-lobe epileptogenic lesion, and never (in the first series) after ipsilateral injections. This anterograde amnesia was usually accompanied by retrograde amnesia for material presented before the injection. However, once the drug had worn off, patients were again able to identify the items from the preinjection period, whereas they could still neither recall nor recognize the new material that had been presented while the drug was active. Thus the retrograde amnesia could be attributed to a retrieval block but the anterograde amnesia appeared to represent a true failure to consolidate the new experience into an enduring memory trace. I later used this as an argument against Larry Weiskrantz's interpretation of amnesia as primarily a retrieval deficit.

The Challenge of the Frontal Lobes

Although by the time I went to work at the MNI, by far the most frequent brain operations were for the treatment of temporal-lobe epilepsy, this had not always been the case. Before embarking on temporal-lobe surgery, Penfield had carried out a number of operations on the frontal lobes in cases of posttraumatic epilepsy or indolent brain tumor. It was during this period, in the late 1930s, that Hebb spent 2 years as a research fellow at the MNI, where he studied Penfield's patients before and after surgery. At the time, Hebb's main interest lay in exploring the effects of these removals on intelligence, as measured by the standard tests of the day. To his great surprise, the patients he saw showed little or no intellectual change following the frontal-lobe operation, and tended to have average or above-average intelligence before the operation.

The fact that in some cases an extensive removal of epileptogenic brain tissue actually resulted in improved intellectual status (provided that the patient's seizures had been controlled) led Hebb and Penfield to formulate the notion of "nociferous cortex." This is the idea that an area of damaged and malfunctioning brain can interfere with the activity of neighboring healthy tissue, so that when the damaged area is excised, the overall level of intellectual efficiency may rise. A particularly striking example of this was provided by their famous patient K.M. who in 1928, at the age of 16, had sustained a severe, penetrating injury to both frontal lobes. He subsequently developed recurrent major epileptic seizures and exhibited a marked deterioration in behavior. On April 14, 1938, in an attempt to

alleviate the seizures, Penfield carried out a bilateral brain operation, removing an extensive area of scar tissue involving approximately the anterior one-third of both frontal lobes. This operation not only controlled K. M.'s epilepsy, but also led to a remarkable improvement in his day-to-day behavior and to a reliable increase in his IQ, which was in the average range. Such results led Hebb to argue that in the adult brain the frontal lobes contribute less to intellectual function than had hitherto been supposed.

At first my own experience with frontal-lobe patients at the MNI seemed to add further support for Hebb's view. Patients undergoing left or right frontal cortical excisions for epilepsy constituted well-matched brain-operated control groups in my temporal-lobe studies. Not only were these patients unimpaired postoperatively on the Wechsler Bellevue Intelligence Scale, they also achieved normal scores on most of the perceptual and mnemonic tasks that proved difficult for patients with temporal-lobe lesions. Nor had they any difficulty performing the Weigl color-form sorting task, or other simple pass–fail tasks on which performance had been claimed to be selectively sensitive to frontal-lobe injury.

It seemed clear that I was missing something; once again I took my cue from studies in the monkey, where Harlow and Dagnon had demonstrated an impairment in discrimination reversal learning after large bilateral frontal cortical excisions. Their animals showed normal learning of the initial discrimination problem but had great difficulty in overcoming their established response pattern, once the reward values of the discriminanda were reversed so that the previously correct choice became incorrect. With this result in mind, I decided to administer the Wisconsin Card Sorting Test to all my patients before and after operation. In this task, which was modelled by Grant and Berg on work with monkeys, the subject is required to sort a stack of response cards with reference to four key cards and to verbal feedback provided by the examiner as to the correctness of each response. After a particular mode of sorting has been established (say, to color), a new sorting principle (form or number) is imposed without warning. Whereas normal control subjects and patients with temporal-lobe lesions usually adapt quickly to the new principle, I found that patients with dorsolateral frontal lobe-lesions did not, the deficit being more consistently seen and more long-lasting after left frontal lesions than after right. These results on a quantitatively scored test provided strong support for the view that the ability to shift from one mode of solution to another is more impaired by frontal than by posterior cerebral injury and constituted my first evidence of cognitive impairment in our frontal-lobe groups.

It so happened that in 1962 I had the opportunity to carry out a follow-up study on Hebb and Penfield's patient K.M., who had sustained damage to both frontal lobes; I was able to replicate Hebb's findings for the intelligence tests that had been given 23 years earlier. K.M. had remained seizure-free, his behavior had been socially appropriate, and his Wechsler IQ was

within the average range. Yet on the Wisconsin Card Sorting Test he exhibited to an unusual degree the perseverative behavior that I had come to expect from patients with lesions to the dorsolateral frontal cortex. This case study emphasized for me that fact that the failure to find deficits after a brain lesion may merely mean that the range of tasks sampled has been too narrow, rather than that the damaged area was serving no important cognitive function.

Divergent Thinking and the Frontal Cortex

Many of my ideas for studying patients have come from having my curiosity piqued by peculiarities of behavior that I then set out to measure with carefully chosen tasks. In this sense my research has been data-driven rather than theory-driven. A salient example of this is my discovery of a word fluency deficit in patients with excisions from the left frontal lobe. These removals all spared Broca's area; the patients showed no loss on verbal intelligence tests, but I was impressed by the remarkable paucity of their spontaneous speech, even though they were typically cooperative and good-humored throughout the lengthy testing sessions, had a normal vocabulary, and were certainly not aphasic. There was thus a striking contrast between their word knowledge and their word use. I set out to test this further using the Thurstone Word Fluency Test, which requires subjects to write down as many words as possible beginning with a particular letter within a prescribed time limit. Patients with left frontal-lobe excisions were in fact impaired on this task, having a lower output than my other groups, including the patients with left temporal-lobe lesions and deficient verbal memory. My student, Marilyn Jones-Gotman, then went on to demonstrate a corresponding deficit in patients with right frontal-lobe lesions on a nonverbal fluency task, in which subjects were instructed to draw as many different unnameable designs as they could invent in a given time.

Fluency tasks are considered to be tests of divergent thinking, in that they emphasize the number and variety of responses that can be generated to a single question, unlike traditional intelligence tests, where there is usually just one answer to the question or problem set. Such tasks are held to be better predictors of creative achievement than are standard intelligence tests, and it is therefore interesting that performance on them should be impaired by frontal-lobe lesions.

Frontal Lobes and the Temporal Organization of Memory

In 1964, I was invited by Larry Weiskrantz to take part in a summer workshop at Churchill College, Cambridge to examine the various experimental methods used to measure behavioral change consequent to surgical, pharmaceutical, and other treatments. My assigned topic was that of memory disorder. As a result, I found myself trying to understand better why patients

with frontal cortical excisions failed certain memory tasks, while performing normally on others that involved the same kind of memoranda. It seemed as though the way that memory was tested was critical in determining whether or not a deficit would be found after frontal lobectomy, whereas in the case of left or right temporal-lobe removals, the nature of the stimulus material was the predominant factor.

The natural starting-point for thinking about frontal lobes and memory is the classical experiment of Jacobsen in 1935, followed by that of Jacobsen and Nissen in 1937, showing impairment of delayed response and delayed alternation in monkeys with bilateral frontal-lobe removals, the critical zone being subsequently narrowed down by Nelson Butters to the middle third of sulcus principalis. This did not, however, seem to me to be the best way to test memory in patients, because even quite long time intervals can be bridged by verbal mediation. Instead, my student, Lilli Prisko, had in 1963 adapted the Konorski delayed paired-comparison technique to bring out deficits after frontal lobectomy; the task embodied an intratrial delay as an essential feature. In her procedure, two easily discriminable stimuli in the same sense modality are presented in succession and the subject has to say whether the second stimulus was the same as, or different from, the first one, presented 60 seconds earlier. Patients with frontal-lobe lesions were impaired on those tasks on which a few stimuli recurred in different pairings throughout the test, but not on the one task in which new stimuli were used on each trial. This contrast indicated that patients with frontal-lobe lesions had a heightened susceptibility to interference from the effects of preceding trials, rather than an inability to retain new information over a short time interval.

Reflecting on these findings during the Cambridge workshop, I suggested that frontal lobectomy might interfere with the ability to structure and segregate events in memory, and hence that in a situation lacking strong contextual cues, patients with such lesions would be less able than control subjects to distinguish a stimulus presented 60 seconds ago from one appearing earlier in the same series of trials. It seemed to me that if items in memory normally carry time tags that permit the discrimination of the more from the less recent (as Yntema and Trask had proposed), then this time-marking process might be disturbed by frontal-lobe injury, so that serial-order judgements were impaired.

Some years later, in the early 1970s, another student of mine, Philip Corsi, provided a direct test of the hypothesis by constructing three formally similar recency-discrimination tasks, embodying different kinds of stimulus material (concrete words, representational drawings, and abstract paintings) and administering these tasks to patients with unilateral removals from the frontal or the temporal lobe and to normal control subjects. The results obtained confirmed the notion that frontal-lobe lesions impair the temporal ordering of recent events, as well as indicating some specialization of function related to the side of the lesion and the stimulus material.

Unlike the temporal-lobe groups, neither frontal-lobe group was impaired in simple item recognition, as measured by the ability to distinguish a stimulus that had appeared before from one that was new. These findings pointed to some separability of the processes mediating item memory and those mediating memory for temporal order.

It was not possible, on the basis of Corsi's original data, to identify a specific area within the frontal cortex that is implicated in recency discrimination, but when later, in collaboration with my former graduate student, Gabriel Leonard, I tested more patients, we found some limited support (in the case of the left frontal lobe and verbal tasks) for a critical area in the mid-dorsolateral frontal cortex, as I had hypothesized on the basis of animal studies.

By this time there was ample evidence of cognitive deficits associated with lesions of the frontal cortex, and also of a reawakened and growing interest in this part of the brain. Whereas, for me, the 1950s had been the decade of the temporal lobes, in the early 1960s the major emphasis in our work shifted to studies of frontal-lobe function, despite the relatively small number of these cases coming our way. This trend was evident also in the interests of new recruits to our unit. In 1973, Morris Moscovitch spent a year with me as an MRC postdoctoral fellow on leave from the University of Toronto; during this period he looked for proactive-interference effects on verbal memory tasks in patients with frontal-lobe lesions. He was followed by Bryan Kolb, also an MRC postdoctoral fellow, with a strong interest in the role of the frontal lobes in social communication.

In 1977, Michael Petrides came as a postdoctoral fellow from Sue Iversen's laboratory in Cambridge. Michael had a strong background in neuroanatomy but had carried out behavioral work on the frontal and parietal cortex of the monkey for his Ph.D. thesis. Michael had chosen to do his postdoctoral research with me in Montreal, because he wished to adapt some of the tasks that he had used with monkeys to the study of patients with frontal- or temporal-lobe lesions. But on arrival in Montreal, Michael also established an animal laboratory and devised simplified versions of some of the tasks that I had used with patients (including those requiring temporal-order judgments) in order to look for more precise localization of function than was possible in our work with patients. Subsequently, Michael embarked on systematic neuroanatomical studies of the primate frontal cortex with Deepak Pandya in Boston, and this work has now provided us with a valuable, detailed picture of the anatomical homologies between monkey and human frontal cortex.

New Developments and the Advent of Neuroimaging

The last few years have brought many changes. In 1990, Michael Petrides succeeded me as Director of Neuropsychology/Cognitive Neuroscience Unit at the MNI, while I continue to carry out research as the Dorothy J. Killam

Professor of Psychology, funded by the Medical Research Council of Canada. Michael's appointment means that the Institute has now committed itself to a full-time salaried professorial position in neuropsychology, and hence that the research unit that I built up will continue to flourish.

I have had many new graduate students since the early 1980s, including Dennis Rains, Donald Read, Mary Lou Smith, Laurie Miller, Julien Doyon, Virginia Frisk, Susan Pigott, Ingrid Johnsrude, and Joelle Crane. This period has seen a consolidation of my earlier work with patients, with further evidence of the complementary specializations of the two temporal lobes in memory processes, and of the important role played by the hippocampal region. In addition, with the introduction by Dr. André Olivier of the procedure of selective unilateral amygdalo-hippocampectomy as an alternative to anterior temporal lobectomy in cases of medial temporal-lobe epilepsy, it has become possible to delineate better the specific role of the medial temporal region in the performance of our memory tasks.

At this point, a whole new research prospect opened up with the establishment of the McConnell Brain Imaging Centre at the MNI, first under the directorship of Albert Gjedde, and more recently of Alan Evans. This meant that we were now able to use neuroimaging techniques of positron emission tomography (PET), combined with MRI, to measure regional cerebral blood-flow changes in normal volunteer subjects, and in individual patients during the performance of our various cognitive tasks.

The opportunity came at the right time for us, because in 1989 Michael and I were jointly awarded a McDonnell-Pew grant to establish a center for cognitive neuroscience at the MNI. This substantial financial support has facilitated a close interaction between the neuropsychology unit and that of brain imaging. It has also enabled us to attract some gifted young scientists to join our group, including Tomáš Paus, a neurophysiologist from Prague, and Denise Klein, a psycholinguist and cognitive psychologist from South Africa.

Neuroimaging work with normal subjects complements rather than replaces the analysis of the behavioral effects of brain lesions, and the underlying logic is different in the two cases. In the typical lesion study, if a lasting impairment in the performance of a given task follows damage to a particular brain region, it is assumed that the damaged area plays a critical role in normal performance of that task. In contrast, in the typical PET experiment, the regions showing significantly increased blood-flow compared with a baseline condition are assumed to have been jointly activated by the cognitive demands of the task, without performance necessarily being dependent upon the integrity of all the activated regions. The great attraction of imaging studies is that they show us the normal brain in action, and that they allow us to break our complex behavioral measures down into their component processes (as, for example, in comparing the encoding and retrieving phases of a memory task).

During the past few years, Denise Klein and I have been using PET and MRI to investigate whether performance in a second language (L2) involves the same neural substrates as that of a first language (L1) in normal bilingual subjects, who acquired L2 after the age of 5 years. To do this, we first capitalized on the bilingual (French–English) situation in Quebec, but later extended our study to two languages (Mandarin and English) that were linguistically more distinct. Still more recently, in collaboration with André Olivier, we have embarked on a series of individual studies of presurgical patients whose brain lesions bordered on critical speech cortex. Our goal has been to map not only primary speech areas, but also areas involved in higher order linguistic processing, such as synonym generation. By using tasks in the operating room similar to those used with PET, we have attempted to correlate regions of cerebral activation identified via PET with those identified by electrical stimulation of the exposed cerebral cortex in patients under local anesthesia. Our clinical aim is to reduce the risk to language in such operations.

Postscript

As I look back over the past 50 years, it seems to me that I have had a lot of luck in being in the right place at the right time, but also enough tenacity of purpose not to be discouraged when the going got rough, as it frequently did in the early days at the MNI. I am also grateful for my sense of curiosity, which led me to wish to delve deeper into phenomena that caught my eye, and which keeps me going to this day. Of course none of this work would have been possible without the active collaboration of my colleagues in neurosurgery, in particular Theodore Rasmussen and André Olivier, or without the enthusiastic support of generations of graduate students and postdoctoral fellows who contributed so much. At this stage, my own greatest satisfaction comes from seeing behavioral neuroscience so firmly established in what Hebb, some 40 years ago, considered to be unpromising soil.

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