

DORSAL COLUMN**Grey Matter****Brenda Milner on her 100th birthday: a lifetime of 'good ideas'****Kate E. Watkins¹ and Denise Klein^{2,3}**

1 Department of Experimental Psychology, University of Oxford, Oxford, UK

2 Centre for Research on Brain, Language and Music, McGill University, Montreal, Canada

3 Cognitive Neuroscience Unit, Montreal Neurological Institute, McGill University, Montreal, Canada

Correspondence to: Kate E. Watkins

Department of Experimental Psychology, University of Oxford, Oxford, UK

E-mail: kate.watkins@psy.ox.ac.uk

Brenda Milner—the renowned neuroscientist who changed our understanding of brain and behaviour—celebrates her 100th birthday this year on St Swithun's Day: 15 July 2018. We have known Brenda for the past quarter of that century initially as postdocs at the Montreal Neurological Institute (the MNI or the 'Neuro') and latterly as colleagues and friends. In this article, we summarize the impact and legacy of Brenda's work.

Brenda's early life and career have been well documented (Milner, 1998). She grew up in Manchester, England. Her father was the music critic of the Manchester Guardian and died when Brenda was 8 years old. Brenda's mother, who died aged 95, endowed her with longevity, a love of languages, and taught her French so she could advance at school. Brenda won a scholarship to study at Newnham College, Cambridge University, initially to read Mathematics. She claims to have realized quite quickly that she would not excel in that subject and, fortuitously, took the decision to switch to Psychology. Under the influence of Frederic Bartlett, the head of department, and Oliver Zangwill her young supervisor, Brenda had her first exposure to the effects of brain lesions on human behaviour.

Brenda, together with Peter Milner, moved to Canada at the end of World War II. Peter was to work on atomic energy research and the project was due to last 1 year. Brenda initially taught psychology at the Université de Montréal in French (grateful to her mother for language lessons) and there established a rat behaviour laboratory (Fig. 1). She soon came into the sphere of Donald Hebb, recently appointed to head the psychology department at



Figure 1 Brenda Milner's rat lab at the Université de Montréal 1944–52, Faculty of Philosophy. One rat was called 'Tworil', which stands for two nips on right ear and one on left used to identify the rat. Photo from Peter Milner's files. Used with permission of Brenda Milner.

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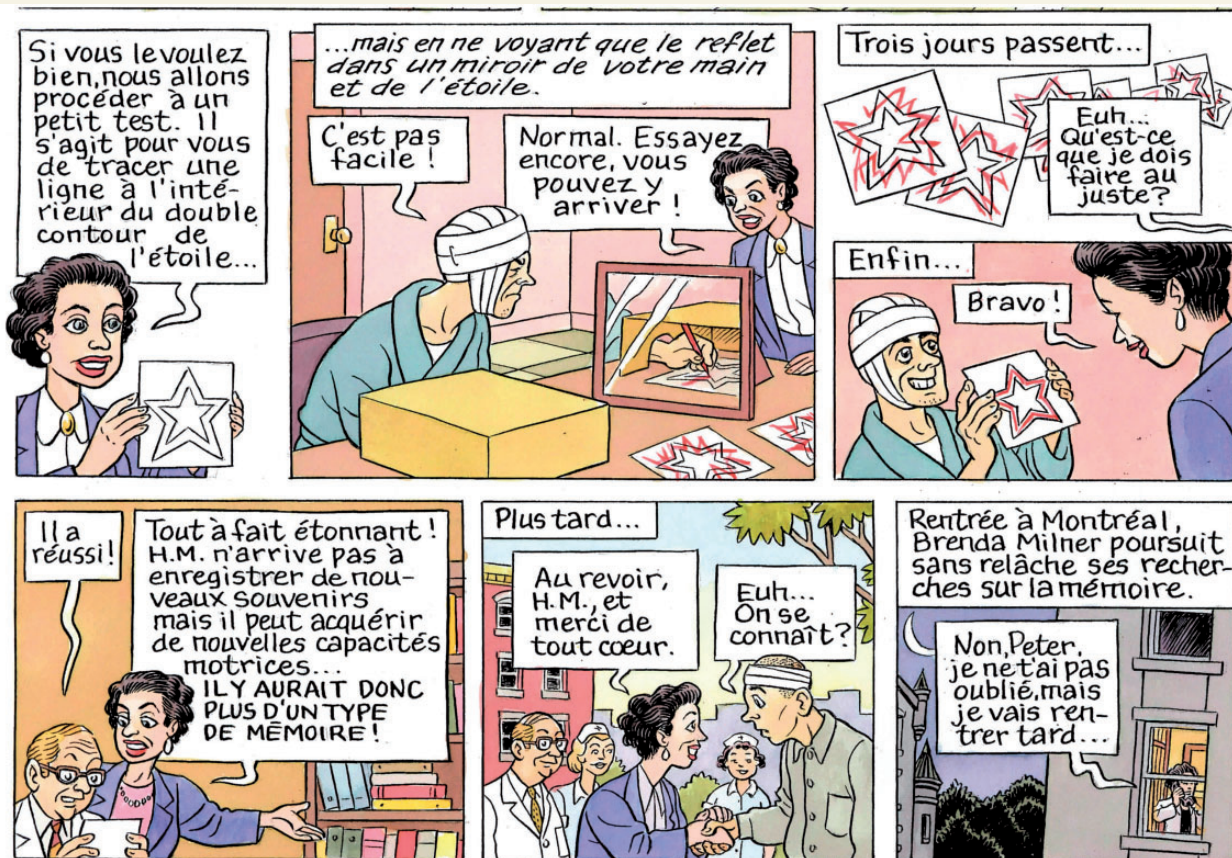


Figure 2 Discovering multiple memory systems. Brenda Milner testing HM on mirror drawing. Excerpt from *Les grands Débrouillards*, 2001, volume 4: 11 *Histoires Scientifiques En Comics*. Permission granted for use. Credits to Johanne David (research and script) and Réal Godbout (script and drawing).

McGill University. Hebb had trained under Karl Lashley and suggested to Brenda that she study the effects of neurosurgical lesions in the patients of Wilder Penfield at the MNI. Brenda and Peter Milner were to remain living in Montreal for the rest of their careers, each recognized for major contributions in separate fields in behavioural neuroscience (see Peter Milner's work on reward systems in the brain; Olds and Milner, 1954). Peter died this June, 2018, just days before his 99th birthday.

Brenda Milner's name is most famously associated with the amnesic Patient HM, who we now know since his death was called Henry Molaison. His life and contribution to science were well documented by Brenda's former doctoral student Suzanne Corkin who, from her lab at MIT, continued to work with HM throughout his lifetime (Corkin, 2013). Brenda's major contribution to our understanding of human memory was to demonstrate that HM was able to learn a new skill despite the severe amnesia resulting from his bilateral medial temporal lobe damage. Her discovery of multiple brain systems for memory was recognized by being jointly awarded the Kavli prize in 2014 with John O'Keefe and Marcus Raichle. It was also captured in a comic strip (Fig. 2). Brenda would be quick to

point out, however, that her observations of the amnesic syndrome were obtained initially from two of Penfield's patients at the Neuro, Patients PB and FC, which predated her work with HM. These two patients had unilateral temporal lobe excisions that resulted in anterograde and some retrograde amnesia. The impairment was presumed due to existing and undetected pathology in the unoperated side, which was later confirmed at post-mortem. It was the presentation of these cases at a conference that led Scoville to contact Penfield, and Brenda to visit his patients—including HM in Hartford, Connecticut—with her battery of neuropsychological tests. The rest, as they say, is history (Scoville and Milner, 1957).

Brenda's careful observations of patients like HM, PB and FC reflect characteristics of her personality in terms of a genuine interest in people and natural curiosity or 'nosiness': simply put, she notices things about people. These are hallmarks of a good psychologist, no doubt, but in her case were usefully combined with knowledge of the work of others around her, and a quick grasp of its relevance for her own studies. Brenda was quick to realize how the non-human primate work of her McGill classmate and good friend Mortimer Mishkin (among

others) might be usefully applied to her studies of patients with brain damage. In her own words 'what is good about me is I noticed quirks in behaviour and wanted to measure them, I had good ideas'. Brenda's work with HM and other patients with temporal lobe lesions was foundational for neuropsychological studies of human memory. She pioneered the use of neuropsychological tests for understanding relationships between brain and behaviour not necessarily for the sake of the patient, but as Zangwill had instilled in her, to understand the 'normal'.

Brenda herself would consider her memory work to be only one of the strings to her bow. Another would be her frontal-lobe work and a third, her work on hemispheric specialization and interaction. At the Neuro, she established a small group initially with Laughlin Taylor and Doreen Kimura. She was supported as a Career Investigator by the Canadian Medical Research Council, a source of funding she enviably maintained until the programme was retired in the 1990s. Mr Taylor, 'Locky', remained Brenda's colleague for the duration of his career and into retirement, providing patient testing and a clinical service to the neurosurgeons. Up until his death in 2008, the two of them looked forward to and carefully planned for the annual international film festival in Montreal, and were avid cinema goers. Doreen was Brenda's first doctoral student and also first to apply the Broadbent technique of dichotic listening in her studies of hemispheric lateralization. Both the research group and the clinical service thrived and attracted young students and postdocs from all over, including many who stayed in Montreal, such as Michael Petrides, Robert Zatorre, Gabriel Leonard, and Marilyn Jones-Gotman, and many others who remain firm friends. Her extended scientific family frequently make special efforts to visit Montreal and attend events in Brenda's honour.

To return to the frontal lobes and the 1960s, Brenda had been testing patients with frontal lobe lesions as brain-damaged controls for her studies of patients with temporal lobe lesions. Being well trained by Zangwill, Bartlett and others, she knew it was necessary to control for brain damage or the surgery itself if she wanted to claim a specific function in relation to a temporal lobe lesion. Brenda was keen to understand the frontal lobes too. After all, this was a large portion of cortex but the widespread use of lobotomies had not contributed much to our understanding of structure-function relationships. The information provided by surgeons at the Neuro was superior in terms of details of the excision and these allowed Brenda and her team to make more precise mappings between structure and function. However, her mentor Hebb had shown a surprising lack of effect of surgical excisions on intelligence in some of Penfield's earlier patients. Brenda knew that lesion studies in monkeys were revealing frontal lobe deficits on tasks involving reversal learning and that the problem for the animal was in switching from a previously rewarded stimulus-response behaviour to a new one. She came across a study in normal controls using a card sorting

task that she thought would be ideal to use with the frontal patients (the Wisconsin Card Sorting Task) and one that would more precisely quantify the behavioural deficits she was able to observe. With no funding, Brenda wrote to the authors who sent a copy of the test, which she cut up into the cards and used to test her patients. The task requires participants to sort cards containing different numbers of different coloured shapes according to a rule (e.g. sort by colour) that changes once the rule is acquired. Brenda found large impairments on the card sorting task in patients with dorsolateral frontal lobe lesions, even in those with small lesions matched in size to those of the temporal lobe patients, who were unimpaired. Brenda's 'frontal' patients were typically unable to disengage from a previously adopted rule, making perseverative errors despite feedback. The use of the Wisconsin Card Sorting Task since Brenda's original observations has been prolific (Milner, 1963).

Brenda also noticed a quirk in the behaviour of some of the frontal lobe patients: they were friendly and cooperative but not very talkative. Again, her ability to notice these unusual behaviours and then work out how to measure them led her to test the verbal and written fluency of these patients. As she suspected, the patients showed limited fluency, i.e. they were unable to generate many different words starting with the same letter under timed conditions. Importantly, these deficits were observed when testing the patients with lesions to the language dominant, typically left, hemisphere. The roles of the left and right hemispheres were another strong feature of the body of work from Brenda's team at the Neuro. Doreen Kimura showed that patients with left hemisphere specialization for language reported more digits from those presented to the right ear than the left on the dichotic listening task. She also showed the opposite asymmetry for melodic stimuli consistent with right hemisphere dominance for non-speech auditory processing. Brenda had previously shown deficits in patients with right hemisphere lesions on tests of musical timbre and memory for tone sequences.

There was a need at the Neuro for a technique to establish presurgically whether a patient was left or right dominant for speech. This was particularly true of patients who were left-handed or ambidextrous as these were the most likely candidates for having reorganization of function to the right hemisphere. By Brenda's account, a young Japanese neurologist, Juhn Wada, suggested to Penfield that there was a way to determine before surgery whether the lesion was in the language dominant hemisphere. The 'Wada' test, which involved injecting sodium amobarbital ('amytal') into one of the internal carotid arteries to anaesthetize one hemisphere of the brain, was first introduced at the Neuro to establish language dominance in all left-handed or ambidextrous patients or right-handed ones in whom right-hemisphere speech was suspected. Summarizing the hundreds of patients tested over many years, Brenda, along with neurosurgeon Theodore Rasmussen, was able to estimate that the rate of bilateral

or right hemisphere speech was very low even in those who were not right handers but was considerably higher in those with early brain damage (Rasmussen and Milner, 1977).

The legacy of HM's amnesia after bilateral medial temporal lobe removals meant that any patient with presumed bilateral disease was deemed ineligible for epilepsy surgery. Rasmussen saw another opportunity here for amytal and asked Brenda to develop a way to use the procedure to assess memory function in the two hemispheres, which she did. Injections of the drug that put the 'good' hemisphere to sleep resulted in patients being unable to recall or recognize material presented to them during the short-term effects of the anaesthetic. Importantly, injection into the lesioned hemisphere of a patient should demonstrate no additional impairment in memory. The materials chosen by Brenda for these tasks were 'dually encodable', i.e. they were line drawings of nameable objects. Previous work with temporal lobe patients had shown that both right and left temporal lobe patients could recall these stimuli because either the visual or the verbal mode of encoding was available to them. An amnesic patient like HM, however, would show impaired memory because of lesions affecting both hemispheres. The use of the amytal procedure became widespread and international in the 80s and 90s for presurgical workup for epileptic patients but has become less commonly used because of the opportunities offered by non-invasive imaging procedures.

The amytal procedure and Brenda's collaborative work with Roger Sperry on split-brain patients offered unprecedented means of examining the cerebral hemispheres in isolation. In some ways, these studies returned Brenda to her first love, the overlooked right hemisphere. During her PhD, Brenda had shown deficits in complex visual perception in patients with right hemisphere lesions and later impairments on tests of melody. Brenda always says we study the things that we are bad at and would not argue with the observation that she has a poor right hemisphere. Despite having strongly musical parents, Brenda by her own admission, has no musical ability and poor visuo-spatial skills. Her left hemisphere on the other hand shows superior ability; she is very verbal and talented in languages. She is fluent in English and French, knows Latin, has given scientific lectures in Italian, and has a fair acquaintance with German. Brenda is a strong advocate of multiple and early language learning.

Brenda also loves to travel and experience people from other countries and cultures. She is proud of her diverse trainees and colleagues brought to Montreal from all over the world. The 1990s were a particularly exciting time at the Neuro. Brenda and Michael Petrides received one of the prestigious awards from the McDonnell-Pew Foundation to establish a Centre for Cognitive Neuroscience at the MNI. This allowed Brenda to attract even more international post-docs to the Neuro, including one of us (Denise Klein) from South Africa, and Tomáš Paus from the Czech Republic. At this time, Brenda was already into her 70s, yet she showed

remarkable flexibility ('good frontal lobes') to deal with a changing field, the move from neuropsychology to the merging of cognition and neuroscience, moving from presentations using slide carousels to PowerPoint, and from a postal service to e-mails; it is this hallmark trait of adaptability that has allowed Brenda to stay so active as a scientist well past conventional retirement age and into her 100th year.

It is not surprising that we three bonded during the latter part of Brenda's career over the question of language organization in the brain. As brain imaging emerged as a new tool to investigate brain regions involved in language functions, we worked with Brenda using PET on the topic of bilingualism (Klein *et al.*, 1995) and to assess the role of the basal ganglia in complex control of the production of novel articulation sequences (Klein *et al.*, 2006). During the long hours of PET scanning, Brenda would spend all her time down in the unit scanning participants and engaging with the technical staff. Her willingness and interest in being part of the entire experimental process was admirable and her stamina enviable. She particularly enjoyed the early morning starts and being asked to give the bilingual participants instructions in French, which was necessary if Denise was on a school run (and Kate's French did not pass muster).

In 2018, we are still working with Brenda, well into her 100th year, on the question of interactions between the hemispheres. Her early work with Kimura and others characterized the complementary specializations of the two cerebral hemispheres. But Brenda was keen also to highlight the importance of communication between the two hemispheres for cognition. She had observed profound impairments in Roger Sperry's split-brain patients on certain kinds of memory tasks (Milner and Taylor, 1972). These findings demonstrated interhemispheric dependence, a foreshadow of current trends in the field of brain connectivity. Some 40 years later, when she won the prestigious Balzan prize, Brenda proposed to use tools in functional MRI combined with fine-grained behavioural measures to investigate hemispheric interactions non-invasively; this project is ongoing.

One aspect of Brenda's legacy that has been somewhat overlooked is her contribution to helping trainees, or as she calls them 'the troops'. She stresses the importance of clinical training for all trainees doing research. Students who worked with patients for research were also required to participate in the clinic, with the suggestion by Brenda that they learn how to administer a neuropsychological battery and contribute by testing one patient a month (Fig. 3). The second contribution was her strong role in facilitating good writing style. Brenda was less excited about filling a blank page, but she enjoyed reading and correcting manuscripts. She offered strong advice on writing style and grammar, and came to be known as the 'Manchester filter', an aspect of her role as a supervisor that gave Brenda great pride. It is evident from reading Brenda's personal recollections of her supervision under Hebb that she 'suffered' similarly when writing her own thesis. Her legacy is that, despite the sometimes painful



Figure 3 Brenda Milner with former PhD student and trainee Ingrid Johnsrude. The image shows one of the arrays used to examine object-location memory, a test she developed with another PhD student Joelle Crane (Crane and Milner, 2005). Photo from the Montreal Neurological Institute Neuro archives; used with permission.

criticism, the importance of good writing is something all her trainees will have passed on to subsequent generations of researchers. In fact, we write this piece with some trepidation, for fear that Brenda will catch a misplaced apostrophe, unnecessary hyphen or exclamation mark (sorry Brenda!).

Brenda did not set out to be a role model for women but it is difficult to ignore the magnitude of her achievements set against the backdrop of the dominance of men in the field during the early years of her career. One has only to look at the faces in the black and white photos of the Neuro to witness this gender imbalance and in some of them the only female face, usually off to the side, is Brenda's (Fig. 4). Brenda herself feels she did not experience sexism in the workplace, only in the early years of her education when options for women to study at university were limited. She enjoys working with men and women, has trained them equally, and has certainly earned the respect of both. Nevertheless, even if it were unintended, at least a part of Brenda's legacy is to have been a pioneer



Figure 4 Neurosurgical meeting at the Montreal Neurological Institute and Hospital. Wilder Penfield in the middle, Brenda Milner at the back right. From the Montreal Neurological Institute Neuro Archives; used with permission.

and role model for women and girls; this was recently captured by her featuring (probably unknowingly) as one of many heroic women in the children's book *Good Night Stories for Rebel Girls*.

Anyone who knows Brenda well will know that with strong ideas and a strong character come strong opinions. But they will also know that she is capable of revising her ideas swiftly and embraces the similarities and differences among people. In surveying restaurant menus, Brenda is usually quick to point out when the chef introduces the same ingredient twice, she takes good note of the ambiance and decor of an auditorium in order to choose the appropriate outfit prior to giving a talk, and usually notices when someone has changed a hairstyle or purchased a new outfit. In 2008, she was asked by the Society for Neuroscience to deliver a history of neuroscience lecture. She was nervous and questioned whether people would want to hear about the old stuff. But she was cheerful when reassured that they would indeed love to hear it from 'the horse's mouth'. To understand the efforts and contributions that Brenda Milner made in forging our science, there really is nothing better than hearing it first-hand. We know we can always rely on Brenda for lively conversations about science, people, restaurants, food, clothing, with astute observations and the wisdom of many years. For these reasons and many more, we are grateful that she continues in good health and spirits as she enters her second century and look forward to many more productive years of fruitful exchange and discovery.

References

- Corkin S. Permanent present tense: the man with no memory and what he taught the world. London: Penguin; 2013.
- Crane J, Milner B. What went where? Impaired object-location learning in patients with right hippocampal lesions. *Hippocampus* 2005; 15: 216–31.

- Kimura D. Left-right differences in the perception of melodies. *Q J Exp Psychol* 1964; 16: 355–8.
- Klein D, Milner B, Zatorre RJ, Meyer E, Evans AC. The neural substrates underlying word generation: a bilingual functional-imaging study. *Proc Natl Acad Sci USA* 1995; 92: 2899–903.
- Klein D, Watkins KE, Zatorre RJ, Milner B. Word and nonword repetition in bilingual subjects: a PET study. *Hum Brain Mapp* 2006; 27: 153–61.
- Milner B. Effects of different brain lesions on card sorting. *Archives of Neurology* 1963; 9: 90–100.
- Milner B, Taylor L. Right-hemisphere superiority in tactile pattern-recognition after cerebral commissurotomy: evidence for nonverbal memory. *Neuropsychologia* 1972; 10: 1–15.
- Milner B. The history of neuroscience in autobiography: volume 2. In: Squire LR, editor. San Diego: Academic Press; 1998. pp. 276–305.
- Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J Comp Physiol Psychol* 1954; 47: 419–27.
- Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. *Ann NY Acad Sci* 1977; 299: 355–69.
- Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 1957; 20: 11–21.