

Chapter 2

History of the Key Disciplines

In this chapter, we will learn about the three disciplines central to population neuroscience: epidemiology, genetics and cognitive neuroscience—their beginnings and subsequent developments.

2.1 Epidemiology

In 1855, John Snow proposed that cholera is transmitted by water (Snow 1855). He reached this conclusion by getting addresses of cholera fatalities during the 1854 London epidemic and comparing them with the distribution of water sources (based on Morabia 2001). Water was provided by three different water-supply companies in the city; only one took water from a less polluted area of the Thames. The General Register Office, headed by William Farr, who created a standardized way of collecting and classifying causes of death in England, provided the addresses. Based on this database, and using “quantitative reasoning”, Snow made his inference almost 30 years before anyone discovered the disease’s causal agent, *Vibrio cholerae* (by Koch in 1884; reviewed in Howard-Jones 1984).

In mid-nineteenth-century medicine, such use of the “numerical method” was still uncommon (Lilienfeld and Lilienfeld 1982; see Text Box 2.1.). Thus, basic statistics, record keeping and careful observations and analyses of possible associations between exposures and outcomes gave rise to the science of epidemiology.

Text Box 2.1. The numerical method

The numerical method—the use of averages to characterize a phenomenon at a group, as opposed to an individual, level—was introduced by Pierre Charles Alexander Louis in 1828. William Guy, Professor of Forensic Medicine, and later of Hygiene, at the King’s College in London, and Snow’s contemporary, had this to say about the lack of numerical method in medicine: “[I]t is most worthy of remark, that the student of the exact sciences, who is familiar with the use of the most certain instruments of

calculation, has never hesitated to apply the numerical method... whilst the medical man, whose science seems most to need the application of such a method, and to offer abundant occasions for its employment, still doubts its efficacy and prefers the obscurity of general phrases to the clearness and precision of numbers.” [(Guy 1839), as quoted in (Lilienfeld and Lilienfeld 1982)].

In the ensuing 100 years, epidemiology developed into a discipline concerned with both proximal causes of diseases, such as exposures to infectious agents, and their distal causes, such as living conditions associated with the transmission of infectious agents and host susceptibility. Quickly, basic knowledge created by epidemiology developed into a “translational” discipline, namely public health or hygiene (Text Box 2.2.).

Text Box 2.2. Hygiene

To quote William Guy again: “As hygiene deals with mankind, not one by one, but in masses, its scientific method can be no other than that numerical method so often confounded with its leading application—statistics. If this word now meant what it originally did... then hygiene would take rank among its leading subdivisions as applying the great State-policy of prevention to health and disease” [Guy (1870), as quoted in (Lilienfeld and Lilienfeld 1982)].

In the process, generations of epidemiologists developed rigorous methodological foundations to address some of the issues fundamental to epidemiological studies, including study design (case-control and cohort studies) and the related possibility of a selection bias (representativeness), and confounding causal inference. Zhang et al. (2004) provide an illuminating review of these and other key concepts, which were reflected in classical textbooks of epidemiology published between 1935 and 1986.

In the second half of the twentieth century, epidemiology began to shift its focus away from infectious diseases, as these ceased to be the main source of mortality and morbidity in developed countries. To a great extent, this decreasing interest in infectious agents on the part of epidemiologists was due to the success of hygiene (and sanitation), bacteriology (and antibiotics) and virology (and vaccination). One may argue that many of these achievements were built on the knowledge generated by epidemiology, which also supported their implementation and evaluation.

What had to be tackled next? For many epidemiologists of the 1960s and 1970s, *social* determinants of health became the new domain of interest. This could be seen as reflecting both the growing health impact of chronic disorders—such as cardiovascular diseases—on morbidity and mortality in developed countries and

the conceptual return to the original goals of epidemiology, namely the search for distal causes of disorders (“living conditions” of the hygiene era). Departments of “Social Medicine”, “Community Medicine” or “Preventive Medicine” began opening their doors (Vandenbroucke 1990). Figure 2.1a illustrates this trend (between 1966 and 2005) as reflected in the total number of publications indexed in MEDLINE under various disease-related outcomes; chronic outcomes (rather than infectious diseases) appear most frequently (Cohen et al. 2007). When cross-referenced with subject headings indicating social factors (i.e. “residence characteristics”, “social environment”, “social conditions”, “social change”, “social

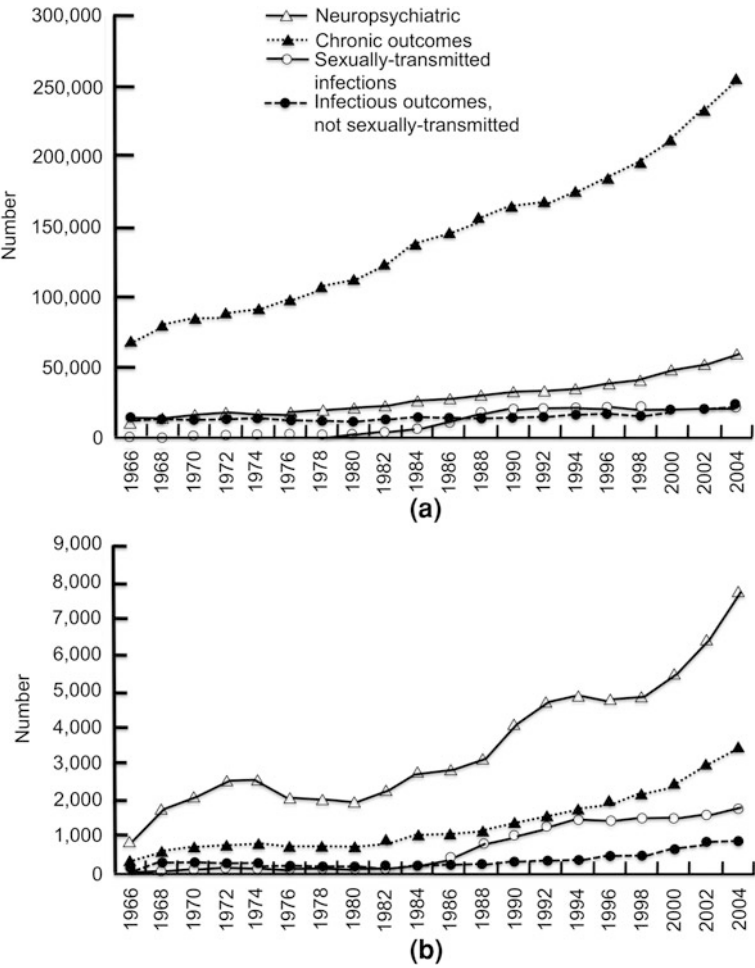


Fig. 2.1 (a) Number of citations per year indexed by Medline from 1966 to 2005 under subject headings related to important non-infectious, neuropsychiatric, infectious and sexually transmitted diseases. (b) Number of citations in the same disease categories additionally cross-referenced with subject headings related to social factors. From Cohen et al. (2007)

problems” and “social welfare”), psychiatric conditions and chronic disorders prevail (Fig. 2.1b). As we will note in (Sect. 10.1), many of these conditions are behind the growing gap between life expectancy (life span) and *healthy* life expectancy (health span). In the same analysis, Cohen et al. (2007) showed that the majority of review articles on social determinants and disease (published by November 2005) addressed cardiovascular diseases (28 %), cancer (15 %) and obesity (12 %).

The shift to social epidemiology and the work on socio-economic gradients of health, the role of social networks or the influence of built environments—to name but a few topics—represented a move away from “focusing on clinical diseases, one at a time” to the consideration of “psychosocial and cultural forces that compromise a person’s ability to withstand insult” and establishing “the link between social forces and biologic processes” (Leonard Syme in Boyce 2011). The hope for preventive medicine represented the same “translational” aspiration of social epidemiology/medicine as that of the “hygienic” movement at the turn of the previous century.

In parallel with the emergence of social epidemiology, other strong trends were taking shape: molecular epidemiology (Kilbourne 1973; Schulte and Perera 1993) and genetic epidemiology (Morton et al. 1978; Khoury et al. 2004). The former returned primarily to the problem of infectious diseases, while the latter turned its attention to the study of genetic cases of non-infectious diseases, often the same ones studied by social epidemiologists. More recently, building on the successes of the Human Genome Project (HGP) (see Sect. 2.2), epidemiology joined forces with genomics to embark on “human genome epidemiology” (Khoury et al. 2004, 2010); the work discussed in the two editions of the Khoury et al. book is directly relevant to the topic of population neuroscience.

In summary, epidemiology traces its roots to the application of the “numerical method” (i.e. statistics) in the search for causes of epidemics and, in general, determinants of population health. From its initial interest in infectious diseases, it quickly expanded its scope to non-infectious diseases and, in the past 50 years, brought in tools and concepts from other disciplines, thus establishing new “hybrids”, such as social epidemiology and genetic epidemiology.

2.2 Genetics

In 1866, Gregor Mendel formulated the laws of inheritance and introduced the concept of the allele as a fundamental unit of heredity (Mendel 1886). He used the “numerical method” to derive statistical rules explaining the pattern of observations made during his experimental work on plant hybridization; this work was carried out in a garden of an Augustinian monastery (Brno, Moravia, present-day Czech Republic) between 1856 and 1865. Unfortunately, Mendel’s publication was missed by the mainstream science of the times, and his laws on inheritance

were rediscovered only in 1900 by de Vries, Correns and von Tschermak. In the subsequent 50 years, a number of discoveries were made, laying down the biological foundations of genetics. Thus, in 1902, Walter Sutton suggested that "... the association of paternal and maternal chromosomes in pairs and the subsequent separation during the reducing division ... may constitute the physical basis of the Mendelian law of heredity" (Sutton 1902, as quoted in Crow and Crow 2002).¹ The subsequent work established that "genes" do indeed reside on chromosomes (1910), that chromosomes contain DNA (1933) and that genes code for proteins (1941). Then, DNA was purified (1944), its first picture taken with X-ray diffraction (1952), and its 3D structure, a double helix, solved by Watson and Crick (1953; Fig. 2.2).

The next 20 years saw, among other discoveries, the cracking of the genetic code (1966)² and the isolation of restriction enzymes, a key discovery allowing the "cutting and pasting" of DNA. The following 20 years introduced two key methodological advancements, namely an electrophoresis-based method for DNA sequencing (1977) and polymerase chain reaction (1983) that enabled most of the work carried out in the 1990s by the HGP. The first disease-causing gene was identified (1989; cystic fibrosis trans-membrane conductance regulator), and the idea of doing genetic "fingerprinting" based on DNA polymorphisms was put forward (1989).

In 1990, the U.S. National Institutes of Health (NIH) and Department of Energy (DOE), together with their international partners, launched the HGP. Over the next 15 years, and with an annual budget of \$ 200 million provided by the NIH and DOE, the HGP's plan was to map and sequence the 3.2-billion-nucleotide-long genome: creating genetic and physical maps of the human genome, identifying all genes and sequencing the entire DNA (Watson and Jordan 1989). The initial plan for the *genetic map* envisaged one containing ~1,000 highly informative markers, so-called microsatellites, placed—on average—with an interval of ~2–5 million nucleotides. The physical location of these markers, and genes, had to be specified in real "mile stones" placed on the genome's road: The plan called for the creation of a *physical map* to be based on the sequence-tagged sites³; a total of 30,000 of such sites were planned initially. The protein-coding genes were to be identified by synthesizing DNA complementary to messenger RNA, the complementary DNA or cDNA. The plan was to create a library of cDNA clones corresponding to all protein-coding genes in the human genome. At the time, the number of genes in the human genome was unknown, the estimates varying between 35,000 and 100,000 genes (Watson and Jordan 1989; Lander 2011). Finally, the goal of mapping the full DNA sequence of the human genome—that is, the sequence of its

¹ Students reading this text may find it interesting that Sutton made his discovery during his graduate studies, which he did not finish; he became a surgeon instead (Crow and Crow 2002).

² Unique triplets of messenger RNA nucleotides [i.e. codons] specify each of the 20 amino acids from which the proteins are built.

³ Sequence-tagged sites (STSs) are short segments of DNA that occur only once in a genome.

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey¹. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

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The previously published X-ray data^{5,6} on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

Fig. 2.2 Two excerpts from the one-page report by Watson and Crick on DNA structure. From Watson and Crick (1953)

3.2 billion bases—by 2005 was clearly highly ambitious, especially given that the critical breakthroughs in parallel sequencing technology came only after the completion of the HGP (Lander 2011).

A quick look at Table 2.1 shows the impressive achievements of the HGP over its first eight years and its goals for the final five years (Collins et al. 1998). The

Table 2.1 Goals and the early achievements of the human genome project (1998)

Area	Goal 1993–1998	Status as of October 1998	Goals 1998–2003
Genetic map	Average 2–5 cm resolution	1 cm map published September 1994	Completed
Physical map	Map 30,000 STSs	52,000 STSs mapped	Completed
DNA sequence	Complete 80 Mb for all organisms by 1998	180 Mb human plus 111 Mb non-human	<ul style="list-style-type: none"> • Finish 1/3 of human sequence by end of 2001 • Working draft of remainder by end of 2001 • Complete human sequence by end of 2003
Sequencing technology	Evolutionary improvements and innovative technologies	90 Mb/year capacity at ~\$0.50 per base Capillary array electrophoresis validated microfabrication feasible	Integrate and automate to achieve 500 Mb/year at ~\$0.25 per base support innovation
Human sequence variation	Not a goal	–	100,000 mapped SNPs Develop technology
Gene identification	Develop technology	30,000 ESTs mapped	Full-length cDNAs
Functional analysis	Not a goal	–	Develop genomic-scale technologies
	<i>E. coli</i> complete sequence	Published September 1997	–
	<i>Yeast</i> complete sequence	Released April 1996	–
	<i>C. elegans</i> most of sequence	80 % complete	Complete December 1998
	<i>Drosophila</i> begin sequencing	9 % done	Sequence by 2002
Model organisms	Mouse: map 10,000 STSs	12,000 STSs mapped	<ul style="list-style-type: none"> • Develop extensive genomic resources • Lay basis for finishing sequence by 2005 • Produce working draft before 2005

From Collins et al. (1998)

HGP finished in 2003, two years ahead of schedule. Through the HGP, we learned that the total number of protein-coding genes is much lower than expected ($\sim 21,000$). The genetic map contained $\sim 3,000$ markers in 1994 but, in their 1998 report, Collins and colleagues planned to cover the genome with 100,000 single nucleotide polymorphisms (SNPs) over the next five years.⁴ In the same report, Collins et al. (1998) predicted that “SNPs will be a boon for mapping complex traits such as cancer, diabetes, and mental illness”, “... make possible genome-wide association studies...” and “... permit prediction of individual differences in drug response”.

Since the completion of the HGP, a number of other genome-mapping efforts continue. For example, the International HapMap Project builds maps based on the combination of adjacent SNPs inherited together (haplotypes) and identifies SNPs that “tag” unique haplotypes; it is estimated that the human genome contains about 300,000–600,000 such haplotype-tagging SNPs, when compared with a total of 10 million common SNPs (hapmap.ncbi.nlm.nih.gov/thehapmap.html.en). Other efforts, enabled by the shift of parallel sequencing from the electrophoresis based to optical imaging based, focus on genome-wide epigenomic mapping of variations in chromatic modifications and methylation (Lander 2011).

In summary, genetics started in Mendel’s garden with the application of statistics, continued through the basic discoveries explaining the molecular and cellular mechanisms of the genetic machinery, and culminated in the mapping of human genome sequences and the cataloguing of inter-individual variations in its various features. The impressive achievements of the HGP, vis-à-vis basic knowledge about the human genome, advancements of genotyping technology and the creation of genetic databases: all set the stage for mapping the sources of inter-individual variability of complex traits, including the structural and functional properties of the human brain.

2.3 Cognitive Neuroscience

In 1861, Broca suggested in his report to the (French) Anatomical Society that the third frontal convolution of the left frontal lobe is the “seat” of “articulated” (spoken) language (Broca 1861). He reached this conclusion by evaluating the symptoms, and dissecting the brain, of a patient called *Tan*, a 50-year-old man who died in his (surgical) care, due to gangrene of a leg. The patient had been admitted to the Bicêtre Hospital 21 years previously, a few months after losing the ability to speak—since then, the only words he could utter were “tan, tan” (Text Box 2.3.). Broca performed an autopsy within 24 h of *Tan*’s death; he concluded that the

⁴ Today, over 10 million SNPs have been mapped.

centre of the pathology was in the posterior part of the third convolution of the left frontal lobe and suggested that this was the site of the original lesion that led *Tan* to lose his ability to speak, 21 years earlier (Broca 1861).

Text Box 2.3. The Patient Tan

Tan—a patient of Broca—was admitted to the Bicêtre Hospital a few months after losing the ability to speak. Reviewing medical records 21 years later (when he was treating Tan for gangrene), Broca put together a picture of a man who had been healthy and intelligent when originally admitted to the hospital, “who differed from a sane man only in the loss of articulated speech”, and whose brain pathology developed over the ensuing 21 years, affecting next the movement of his right arm then the right leg, eventually leaving him bedridden. But even on his death bed, “*Tan* understood almost everything that was said to him... Numerical responses were those that he could make the best, by opening or closing his fingers. I asked him many time how many days he had been sick? He [sic] responded sometimes five days, sometimes six days. For how many years had he been at Bicêtre? He [sic] opened his hand four times in sequence, and then pointed with a single finger; this would make 21 years, and one saw above that this information was perfectly exact” (Broca 1861).

In marked contrast to epidemiology and genetics, the science of the brain began not with statistics but from mapping “symptoms” onto anatomical features of the brain, and it continued like that for the next 50 years. These maps were often created through similar studies of single patients using the so-called “anatomo-functional” correlation. The prevailing concept in Broca’s day was that of localization of function. Various permutations of this concept—shaped both by its proponents and opponents—have continued to guide the empirical work of those interested in the relationship between the human brain and behaviour. By definition, this work has two components: the brain and the behaviour. In the course of the following 150 years, new tools and concepts emerged that refined the knowledge of the structural organization of the human brain on the one hand and the understanding of cognitive processes on the other hand.

Broca was a surgeon and an anatomist. In his report, he lamented: “One is left to be dominated by the old prejudice that the cerebral convolutions have nothing fixed about them, that they are simple folds made haphazardly, comparable to the disordered bendings of the intestinal loops” (Broca 1861). He was indeed very careful in describing the location of the lesion in *Tan*’s brain relative to the frontal convolutions (gyri and sulci). Anatomists of the late 19th and early 20th centuries spent a great deal of time mapping and naming the cerebral folds, studying their emergence during foetal development, as well as asking questions about possible relationships between the morphogenesis of the folds and psychiatric disorders (Marshall and Magoun 1998). In recent history (see below), some of this early

anatomical work has been revived through in vivo imaging studies of the human brain. Thus, gross anatomy of the human brain has been used both as a road map for the functional localization and as a window into the brain development and its disorders.

The next stage of mapping brain anatomy moved from macroscopic to microscopic level. The centre of these efforts was the Kaiser Wilhelm Institute for Brain Research, founded by Oscar and Cecile Vogt in Berlin, Germany, in 1914. In the Vogt Neurobiologisches Laboratorium,⁵ Korbinian Brodmann examined under the microscope the pattern of cellular architecture (cytoarchitecture) of the human cerebral cortex, identifying 43 distinct cytoarchitectonic areas (Brodmann 1909; Zilles and Amunts 2010). His teachers, Oskar and Cecile Vogt, used a different approach and arrived at 200 cortical areas, which differed in their pattern of myelination or myeloarchitecture (Vogt and Vogt 1919; Zilles and Amunts 2010). Today, we tend to view this work mostly as “atlas building” (reviewed in Toga et al. 2006), but its initiators were looking for (cellular) clues of functional specialization in the human brain—not unlike the mappers of the human genome searching in the DNA sequence for (molecular) clues of disorders and complex traits.

How could one examine functional specialization of the human brain without waiting for brain pathology to develop and for the patient to die in order to localize it? In 1934, a neurosurgeon called Penfield founded the Montreal Neurological Institute. There, he and his colleagues treated patients suffering from intractable epilepsy (Penfield 1977). The surgical treatment for epilepsy, which Penfield pioneered, based on a similar work done by Foerster in Breslau⁶ in the 1920s, provided unique opportunities for studies of functional specialization. First, many brain surgeries required electrical stimulation of (or recordings from) the exposed cortex in order to map out the “eloquent” cortex (to be left untouched by the surgeon) and/or the epileptogenic cortex to be identified and, subsequently, removed. In this way, Penfield and his colleagues revealed, for example, the somatotopic organization of movement (motor “homunculus”) and touch (sensory “homunculus”), and the exact extent and function of the Broca’s area of the left frontal lobe (Penfield and Rasmussen 1950; Penfield and Jasper 1954). Second, the location and extent of each surgical removal were carefully documented in a drawing that, in turn, provided the necessary information for “anatomy-functional” correlations obtained in subsequent neuropsychological assessments of the (living) patient. Brenda Milner and her students reviewed such drawings and other relevant information, and classified the patients based on the site and side of the removal. Using precisely designed psychological tests, they characterized the type of (subtle) cognitive deficits associated with particular removals of brain tissue. Using this approach, Milner and her colleagues established, for example, the role

⁵ The Laboratorium served as a nucleus for the development of the Kaiser Wilhelm Institute for Brain Research.

⁶ Wrocław, in the present-day Poland.

of the medial temporal lobes in the different types of (declarative) memory, and of the frontal lobes in “executive” functions and language (Milner 1998). It is important to note that, being an experimental psychologist by training, Milner brought her knowledge of (cognitive) psychology and the rigour of experimental design to these studies, which she and her group carried out for over 50 years, thus complementing the opportunities afforded by the neurosurgeons and their patients (Text Box 2.4.).

Text Box 2.4. An interview with Brenda Milner

Brenda is a well-known scientist who lives and works in Montreal. She does psychology. Brenda was born in 15 July 1918, in Manchester, England. Her favourite subjects in school were algebra and Latin. When she was a little girl, she also learned German. Brenda’s father was 58 when she was born. Brenda did not go to school for she was taught by her father until she was 8 years old, that is when her father died. Brenda went to Cambridge University when she was 18. She was then very interested in maths but also in science. In those days, you had to decide what you want to do very early. So, she had to make an early choice whether to do maths or psychology. She picked psychology because she thought she would never be as good at maths as she was in science. Then, she got a scholarship to do psychology in England. But just then the war broke out. So, she then had to work at a radar station to find out what is the best way to design the radars. She then met her future husband Peter Milner. Peter was an engineer making the radars. Brenda was then sent with Peter to Montreal to work on an atomic energy project. Peter and Brenda quickly got married, packed, went by train to Scotland where they boarded a ferry called Queen Elizabeth and sailed to Boston. From Boston they went to Montreal. That was in October 1944. Brenda got a full time job as a professor at University of Montreal, teaching psychology. Peter went to Chaulk River to go on with his research on the atomic energy project.

Few years later, Brenda started going to interesting classes on psychology by Hebb at McGill. Brenda became very interested in what Hebb talked about. In the meanwhile, a brain surgeon Dr. Penfield was thinking about taking in one student of Hebb to test his patients. Hebb asked Brenda and she was very honoured and decided to go to the MNI.

Dr. Penfield was treating patients who had epilepsy by removing a piece of brain called hippocampus. But in one case, the patient lost his memory after the surgery. This surprised Dr. Penfield greatly because he had done this surgery so many times and yet it had never damaged the memory. Dr. Penfield then had another patient and it happened again. That frightened him! Brenda had to find out what caused it. She figured out that hippocampus is important for creating memories like what you ate today, what game you played and what you learned in class. This memory is called declarative.

Dr. Penfield and Brenda wrote a paper about what had been happening with his patients. In Hartford, Dr. Scoville read this paper and became soon interested because something similar happened to one of his patients, H.M. When he was 23, Scoville treated his epilepsy by taking out the hippocampus on both sides of the brain. After surgery, H.M lost declarative memory. He could still remember things from before the surgery because it was saved on the surface of the brain. If you would tell H.M your name and who you are and then go away for 5 min, H.M would not remember you. Brenda went to study H.M to learn more about the hippocampus and declarative memory. She tried out different memory tests with him.

Unfortunately, H.M could not go to her to Montreal all the way from Hartford so instead Brenda made the trip. Brenda had done a lot of tests with him but realized she wanted something new. So, she thought she would try the mirror drawing with him. In this test, you ask the patient to trace the outline of a star while looking at what you are doing only in a mirror. At first, you would do terribly but with practice it gets better. She tried the mirror drawing because it was something that was not used a lot and because it was easy to carry all the way to Hartford. When she first tried it with him he started out the same way as any of us would. But then later on she discovered something very amazing. Even though he did not remember he had been doing the mirror drawing yesterday she saw that he was getting better and better. Brenda Milner had proved that hippocampus is not important for all kinds of memory. What H.M could still do was to learn new skills. Like riding a bike, playing basketball, skating, skiing, tennis and mirror drawing! But he could never remember learning those skills. For that, he needed his hippocampus.

You see that I have not been using H.M's full name. That is because scientists do not want to harm the patients' feelings by being known as the patient who lost his memory, etc.

For Brenda Milner, her most interesting time at the MNI so far was in the 1950s. That was when most of scientific discoveries in psychology were made. At the end of my interview with Brenda, I asked her what the best thing about being a scientist is. She said that if you look at poetry, music or story writing, you will notice that it can be all as good a hundred years ago as it is now. But in science, the discoveries made now are always more advanced and better than the ones a hundred years ago. Science is always new and is meant to make our lives more interesting and understandable.

By Veronika Pausová (age 11), Montreal, 6 May 1998

Naturally, the work carried out in (human) patients was not occurring in a vacuum. Perhaps, the most relevant complementary knowledge was generated in non-human primates, mostly macaque monkeys, throughout the 1970s and 1980s. First of all, experiments carried out in monkeys allowed investigators to evaluate the behavioural impact of well-circumscribed *bilateral* lesions, thus “knocking

off” the entire structural unit rather than only its half (as common in human studies). These experiments also provided a way of establishing which of the structures affected in patients are critical for a particular deficit; in the monkey, small structural “units” were lesioned separately or in combination with other brain regions (e.g. amygdala and hippocampus; Mishkin 1978). Second, new techniques were introduced to study neural connectivity; tracers such as horseradish peroxidase and, later, tritiated amino acids, were injected into distinct (cortical) regions to describe the pattern of afferent and efferent connections with other parts of the brain (e.g. Pandya and Kuypers 1969). Over the years, this kind of work allowed neuroscientists to draw, for example, a “wiring” diagram of the visual cortex (Felleman and van Essen 1991) and to create databases of cortico-cortical connectivity in the macaque brain (Kötter 2004). Third, neurophysiologists developed techniques for recording the electrical activity of single neurons (“single-unit” activity) in a behaving monkey. With this tool in hand, they went on to describe various features “coded” by brain cells throughout the cerebral cortex—from the orientation of visual stimuli in the primary visual cortex (Hubel and Wiesel 1968), through rotation of the limbs at their joints in the parietal cortex (Mountcastle 1975) to size, shape and colour of visual stimuli in the temporal cortex (Gross 1969) and working memory in the prefrontal cortex (Fuster 1973). Together with the growing knowledge of brain connectivity, these studies forced neuroscientists to think about the brain as a collection of highly specialized but tightly interconnected brain regions.

In the 1980s, positron emission tomography (PET) brought an apparent revolution to the studies of brain–behaviour relationships in humans. Although PET (as we know it) was invented in the 1970s, it was not until the second half of the 1980s that neuroscientists started using PET for mapping cognitive processes in healthy human volunteers. To a large extent, this was due to a series of innovations that emerged from the group of Raichle at St. Louis Washington University (Text Box 2.5.).

Text Box 2.5. Key Innovations that Enabled the Mapping Brain Function with PET

The key innovations enabling the use of PET for studying brain–behaviour relations in healthy volunteers included: (1) the use of ^{15}O -labelled water for measuring cerebral blood flow as an index of brain activity; (2) introduction of the “subtraction” technique (Task A minus Task B) to isolate brain regions associated with a particular set of cognitive processes; and (3) statistical analysis of such differences between A and B in a group of individuals, by mapping their brains into the common 3D space, calculating a statistics for each voxel and reporting X, Y and Z coordinates of the significant voxels in a standardized stereotaxic space (Raichle 2009).

Over the next 20 years, this brain-mapping approach—and its expansion due to the development of non-invasive (radiation free) and more widely available functional magnetic resonance imaging (fMRI)—generated literally thousands of studies, reporting brain responses associated with various sensory, motor and cognitive processes. By virtue of recording task-related brain responses throughout the entire brain, functional neuroimaging both enabled and forced network-based analysis of brain function. Terms such as functional and effective connectivity were introduced to refer to different types of inter-regional relationships in the recorded signal (Friston 2002). At the same time, various forms of structural MRI opened up the opportunities for assessing structural properties of the grey and white matter, with sophisticated voxel-wise analysis of brain images carried out in an automatic “pipeline” manner. The number of participants scanned in any given study soared, from an average of seven participants per PET study (reviewed in Paus et al. 1998) to hundreds of participants enrolled in a given MRI-based population study (see Chap. 8). Perhaps not surprisingly, MRI-based imaging has become a tool of choice for high-throughput brain phenomics.

In summary, the study of brain-behaviour relationships in humans has proceeded through the mapping of clinical observations (symptoms) onto brain lesions, which were identified *post-mortem*, and cognitive test-based assessments onto the maps of surgical removals (or brain images) obtained in living patients, all the way to functional and structural neuroimaging studies of healthy individuals. The work in humans has been always informed by detailed studies of experimental animals, mostly macaque monkeys, which have provided the details of neural connectivity and revealed functional specialization of the primate brain at a single-cell level.

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