MRI observation of hippocampal degeneration in Alzheimer's disease: a forgotten case

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Summary

At the beginning of the 1990s, as part of work being done for a master's degree thesis in physics, an important observation of hippocampal degeneration in Alzheimer's disease was made in Pavia. However this result was never published in a full scientific paper. This case gives an idea of how an isolated observation can, in the right setting, develop into a real scientific achievement.

KEY WORDS: Alzheimer's disease, hippocampal degeneration, MRI, neuroscience in Italy.

At the beginning of the 1990s, magnetic resonance imaging (MRI) emerged as one of the most significant advances in biomedical technology. After a history dating back some decades, the nuclear magnetic resonance technique began to have strong applications in clinical diagnostic procedures and in neuroscience research. The application of MRI appeared to offer many advantages: it was non-invasive, it used non-ionizing radiation and, by modifying the physical parameters of the machine, it could be used to obtain high-resolution, high-contrast discriminative images of soft tissues. At that time, MRI research was an extremely fertile field, seeing investigators from different specializations (clinicians, psychologists, physicists, radiologists, technicians) drawn into efforts to create a multidisciplinary approach to the brain, initially based on morphology but rapidly extended to functional analyses.

At the beginning of the 1990s, Italy, in line with other advanced European countries, had around 180 MRI whole-body apparatuses distributed in its healthcare centers. By contrast, applications of MRI in scientific research were struggling to flourish. In fact, in those years, the Italian contribution to the annual meeting of the Society of Magnetic Resonance in Medicine was in the order of 0.1% of the works presented. This contradictory situation reflected the fact that, at that time, there was yet to evolve a true Italian community of MRI neuroscientists and, as a result, each center was working independently of the others.

One of the MRI research centers in Italy was based at the University of Pavia where the phenomenon of nuclear magnetic resonance (NMR) had been a key interest at the "Alessandro Volta" Institute of Experimental Physics. In 1947 a paper by Luigi Giulotto (Giulotto, 1947) provided the first clear evidence of the phenomenon that was later correctly interpreted by Willis Lamb and came to be known as the Lamb shift; in that same year, the first NMR apparatus was already in operation in Pavia (Amaldi, 1998). However, despite these pioneering efforts, the subsequent development of NMR techniques applied to medicine occurred outside Italy. Several decades later, at the start of the 1990s, MRI technology, by this time mature, returned to Pavia with major installations at three leading scientific institutes for research, hospitalization and healthcare: the C. Mondino Foundation, the S. Maugeri Foundation and the Policlinico San Matteo.

During the academic year 1993-94, an MSc thesis in physics was discussed in Pavia. The thesis was entitled "*Applicazioni della risonanza magnetica nucleare in medicina: problemi tecnici del miglioramento del rapporto benefici/costi*" (Applications of nuclear magnetic resonance in medicine: technical problems of improving the cost/benefit ratio) and the candidate was Claudia Gandini (now Claudia Wheeler-Kingshott). Her mentor was Prof. Marco Villa, a physicist who pioneered the application of MRI physics to medicine. The thesis (Gandini, 1994), dealt with a number of applications of MRI to medicine, in particular to brain and cardiac pathology. The most important novelty of the thesis was a series of investigations on neurodegenerative disease, in particular Alzheimer's disease (AD). The MRI scans were performed with a Toshiba 0.35 T MRI scanner (ten times less powerful than current research scanners, which typically use a 3T magnetic field strength). The aim of the study was to establish a method for performing volumetric measurements of different parts of the brain, and it included the development of different sequences and imaging analysis techniques. These included two-dimen-

sional T_1-weighted scans with whole brain coverage, acquired sagittally and coronally, as well as a "high-resolution" (0.8x0.8x3mm^3) three-dimensional (3D) coronal scan, covering a volume localized specifically on the hippocampus. The total acquisition time for the whole protocol was kept below 10 minutes, in order to take into account a key factor in volumetric measurements, namely motion, which depends very much on the patient's level of comfort. The experiments were first optimized in normal subjects and then applied to patients. The results obtained in 12 AD subjects demonstrated significant hippocampal atrophy related to the clinical severity of the disease. Although the sample was small, these results provided a basis for suggesting that absolute volumes, rather than volume ratios, were correlated with the clinical state.

It is remarkable how this pioneering research, given the limited analytical power available at the beginning of the '90s (magnetic fields ten times less powerful than current ones), anticipated a cardinal element for AD neuroimaging and, more in general, for the applicability of MRI to the investigation and diagnosis of neurodegenerative diseases. However, these results never appeared as a full paper, probably because the local scientific context did not allow their exploitation. The candidate left the University of Pavia and developed her career in the UK.

This case, which seems to reflect the general situation of neuroscience in Italy at that time, also has a more general meaning. Neuroscience is an interdisciplinary field requiring the integration of expertise from different disciplines, like physics, medicine and biology. When a complex target has to be reached, it is not enough that these are individually excellent. What is needed, instead, is the development of new structures, unrestricted by academic boundaries, and the dynamic adaption of these to the specific needs of the research to be carried out. The first organized centers for neuroscience research in Pavia appeared only recently, namely the Brain Connectivity Center (activated in 2010) and the Department of Brain and Behavioral Sciences (activated in 2013).

Science demands adequate centers, contexts and targets: individual efforts are arduous unless they are effectively supported by research centers, scientific networks composed of scientists coming from different fields, and, possibly, also by clear developmental lines in terms of science policy. This is an old problem that, in the Italian research system, still seems to be awaiting a solution. In fact, Claudia Gandini continued her research career in the UK, where, in 1994, she did her PhD in fast sequence development at the University of Surrey. She has since concentrated on the development of quantitative MR methods for assessing the brain and spinal cord at University College London. She is currently the University Reader in MR Physics, and continues develop MRI methods to investigate structural, functional and metabolic substrates of neurological diseases (e.g. Wheeler-Kingshott et al., 2012, 2013; Solanky et al., 2013a,b).

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