A survey of neuroimaging research in European neurological departments

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Introduction

Since the invention of computerized tomography (CT) of the brain, neuroimaging has become a rapidly growing field that has profoundly transformed the practice of neurology, at least in western industrial countries (Masdeu, 1997). Yet, direct involvement of neurologists is variable and often impeded by organizational structures and cost and reimbursement aspects that tend to confine the use and interpretation of neuroimaging techniques to radiology, neuroradiology, or nuclear medicine (Brillman et al., 1997). The growth of research activities is well documented in the scientific literature and by the inception of specialty journals, such as NeuroImage and Human Brain Mapping, in the past 20 years. However, integration of such research activities into clinical neurological practice poses a special challenge to financial resources and organizational structures. Thus, the goal of this survey was to assess the status of neuroimaging research in clinical neurological departments in Europe.

The primary role of neuroimaging in neurology has been to identify lesions, such as ischaemic infarcts, tumours and degenerative and inflammatory processes of the brain or the spinal cord. This has become widespread standard in clinical diagnostic work-up. In addition, recent research dealt with in vivo investigation of the pathophysiology of such lesions, and with the neural basis of higher brain functions (Iacoboni et al., 1999).

Investigation of the pathophysiology of ischaemic infarcts employs methods to determine cerebral blood flow and metabolism, such as positron emission tomography (PET), single photon emission computerized tomography (SPECT) and magnetic resonance spectroscopy (MRS) (Heiss and Herholz, 1994), complemented by non-invasive assessment of the large cerebral arteries with Doppler ultrasound or magnetic resonance angiography. Such studies have contributed to develop and improve new therapeutic measures, such as thrombolysis of acute ischaemic infarcts (Baron, 1999; Heiss et al., 1999; Tong and Albers, 2000). Functional magnetic resonance imaging (MRI) techniques, such as perfusion and diffusion weighted MRI (Baird and Warach, 1998), as well as dynamic spiral CT (Kuszyk et al., 1998) provide detailed information on the haemodynamic status. The metabolic characteristics of brain tumours can be studied with PET, SPECT and MRS, providing more detailed information on prognosis and the effects of therapy (Di Chiro et al., 1982; Fulham et al., 1992; Herholz et al., 1998). Functional imaging techniques can be used to identify eloquent brain areas prior to surgery (Thiel et al., 1998; Bittar et al., 1999). Degenerative brain diseases, such as Parkinson and Alzheimer disease, are associated with specific alterations of metabolism and neurotransmitter systems that can be imaged by PET (Rapoport, 1991; Brooks, 1997), and to some extent also with SPECT and MRS (Bartenstein et al., 1997; Ross et al., 1998).
The burden and consequences of the demyelinating inflammatory lesions of multiple sclerosis, many of which are clinically silent, can be demonstrated by MRI (European Study Group on Interferon-beta-1b in Secondary Progressive, 1998), which also demonstrated the efficacy of new drugs to reduce progression of this disease.

The investigation of the neural basis of cognitive functions is the fundamental basis in the history of neuropsychology, a special field of inquiry with a very long lasting tradition in Europe. The early period (from Broca's observation to the First World War) was, with a few exceptions, characterized by 'localizationist' doctrines. This era was followed by a period of supremacy of 'globalist' theorizing, which denied scientific status to the study of anatomoclinical correlations altogether. The renaissance of interest in the neurological side of neuropsychology is relatively recent, starting from the 1960s, and can be considered as the consequence of several factors. In the first place, the developments of neurophysiology, showing the high degree of specialization present at each level of the nervous system, have finally discredited the idea of 'equipotentiality' of nervous tissue. The influence of European researchers, such as Hecaen, Luria and many others, must not be neglected; besides their personal contributions, they prompted a rediscovery of the large body of anatomoclinical knowledge which had disappeared from the scientific arena during the 'globalist' period.

A major breakthrough has been the development of structural neuroimaging methods (CT, MRI). These tools have provided a new impulse to the study of the neural basis of cognitive function. The advent of functional neuroimaging techniques (PET, SPECT and recently fMRI) have extended the field of inquiry from lesions to functional investigations of brain activity in normal subjects engaged in cognitive tasks (Frackowiak et al., 1997). Neuroimaging research programs in neuropsychology, with the aim of identifying the cerebral functional correlates of cognitive processes in normals and disease condition, now have a well-establish tradition in Europe. In parallel with methods for the in vivo study of brain function, the assessment of neurotransmission systems has become gradually possible (Sawle and Brooks, 1990). Significant progress in the field has enabled emission tomographic methods (SPECT and PET) to be unique tools in the evaluation of brain neurochemistry. Studies of neurotransmission systems open a new perspective in the research related to the studies of cognitive functions in normals (Koepp et al., 1998) and neurological diseases and the effect of therapeutic interventions (Pizzamiglio et al., 1998; Piccini and Brooks, 1999).

Methods

A task force was set up to represent neurological expertise in all relevant neuroimaging techniques, as well as to cover Europe geographically. The task force members (see Appendix) identified departments with known or suspected scientific activity in neuroimaging. All institutions listed in European Federation of Neurological Societies (EFNS) membership list were considered. In March 1999, 174 departments received a questionnaire to be completed by themselves or to be passed on to other scientifically active colleagues at the same institution, if they themselves were not able to report on the whole institution.

Within 9 months, by end of 1999, 100 completed questionnaires were returned (Table 1) and could be evaluated (57.5% of those sent out). In addition, three addressees could not be reached under the listed address and 10 questionnaires were returned claiming no neuroimaging research activities or an inability to complete the questionnaire, increasing the return rate to 64.9%.

Questionnaires were evaluated using SPSS for Windows (Release 8.0.0). With regard to disciplines, techniques, diseases, funding sources and equipment, the frequency of positive answers was assessed. Complete chapters without positive answers were regarded as missing in the evaluation. Questions with more than 10% missing answers are identified specifically in the results section. Since most quantitative data concerning resources for neuroimaging research were skewed with many low and few very high values, median values and interquartile ranges (in brackets) were reported. Most variables were compared with the budget available by

<table>
<thead>
<tr>
<th>Number sent out</th>
<th>Number completed</th>
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<tbody>
<tr>
<td>Austria</td>
<td>19</td>
</tr>
<tr>
<td>Belgium</td>
<td>5</td>
</tr>
<tr>
<td>Switzerland</td>
<td>6</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1</td>
</tr>
<tr>
<td>Germany</td>
<td>37</td>
</tr>
<tr>
<td>Denmark</td>
<td>5</td>
</tr>
<tr>
<td>France</td>
<td>20</td>
</tr>
<tr>
<td>UK</td>
<td>24</td>
</tr>
<tr>
<td>Italy</td>
<td>25</td>
</tr>
<tr>
<td>Norway</td>
<td>3</td>
</tr>
<tr>
<td>Netherlands</td>
<td>5</td>
</tr>
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<td>Poland</td>
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<td>Sweden</td>
<td>5</td>
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<td>Spain</td>
<td>10</td>
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Four questionnaires were sent to countries not listed above, without returns.
Spearman rank-order correlation or by $\chi^2$-test. Only significant ($P < 0.05$) findings are reported.

To assess the scientific status of neuroimaging research in the neurological literature, a MEDLINE search was performed in major neurological journals. This was done via the Internet using the PubMed facilities and MeSH keywords provided by the US National Library of Medicine (http://www.ncbi.nlm.nih.gov). Articles reporting the results of neuroimaging techniques were identified by using the following MeSH keywords: CT: ‘tomography, X-ray computed’; MRI: ‘magnetic resonance imaging’; SPECT and PET combined: ‘tomography, emission-computed’; SPECT: ‘tomography, emission-computed, single-photon’; ultrasound: ‘ultrasonography’; MRS: ‘nuclear magnetic resonance’. There is no separate MESH keyword for fMRI and thus included in MRI. The following journals of clinical neurology were identified and the frequency of articles published in 1999 was determined: *Annals of Neurology, Neurology, Archives of Neurology, Journal of Neurology, Neurosurgery and Psychiatry, Journal of Neurology, European Neurology* and *Brain*. An additional analysis was performed for the journal *Stroke*, with respect to high clinical relevance of ischemic cerebral disease. The *European Journal of Neurology* could not be evaluated because its content was not indexed by MeSH keywords. Impact factors of these journals were obtained from the Institute for Scientific Information, Philadelphia, PA, USA. The search included all publications, independent of the country of origin. Therefore, it was not limited to publications from the European Institutions that were covered by this survey, but rather provides data on the global status of neuroimaging research in the scientific neurological literature.

**Results**

**Questionnaire**

Of the 100 questionnaires returned, 77 came from university hospitals, 11 from other teaching hospitals, nine from research institutions and only two from non-teaching hospitals and one from other institutions. In 70 cases, the primary discipline was neurology, in 11 clinical neuroscience. The rest were completed by departments of nuclear medicine (five), neurosurgery (four), radiology (two), neurophysiology (two) or others (six).

The most frequent types of funding were regular institutional budgets (72%) and governmental funds (71%). Industrial funds (64%) and hospital funds (55%) were also available for research in most institutions, whereas charity funds (45%) and EC funds (28%) were less frequently available. Figures for the total annual budget available for neuroimaging research were provided by 47% of institutions. The median was €150 000 [€80 000–€800 000], 11 Institutions reported larger budgets of €1–8.8 million. Budgets were grouped as small (<€100 000), medium (<€1 million), or high (€1 million or more). There were no significant differences amongst budget groups with respect to the availability of institutional and hospital funds. The use of governmental funds and charity funds increased significantly with budget (the frequencies in the three budget groups were 41.7, 83.3 and 81.8% for governmental, and 41.7, 58.3 and 90.9% for charity funds). There was also a tendency for more frequent use of EC funds (16.7, 41.7 and 54.5%, $P = 0.063$) and industrial funds (58.3, 75.0 and 90.9%, $P = 0.076$) in higher budget groups.

Neuroimaging research is a highly interdisciplinary endeavour. Typically 8 (5–10) disciplines were involved at each institution. In addition to neurology, this was most frequently neuroradiology (84%), neuropsychology (73%) and neurosurgery (68%). Nuclear medicine (65%) and neurophysiology (64%), clinical neuroscience (54%), psychiatry (54%) and medical statistics or computing (52%), were also involved at most institutions. Less frequently, general radiology (41%), rehabilitation medicine (40%) and geriatrics (18%) were involved. Twenty-one respondents mentioned additional disciplines not listed in the questionnaire. In particular, radiochemistry (four), clinical physics (three), epidemiology (two), computer graphics (two) and audiology (two) were mentioned more than once. The number of disciplines involved was related to the budget ($r = 0.44, P = 0.002$). In particular, institutions with a high budget more frequently involved neurosurgery (41.7, 66.7 and 90.9%), nuclear medicine (33.3, 66.7 and 81.8%), psychiatry (16.7%, 45.8% and 90.9%), clinical neuroscience (25.0, 58.3 and 90.9%), and medical statistics/computing (50.0, 66.7 and 90.9%) as co-operative disciplines than groups with low budget.

Amongst imaging techniques (Table 2), MRI was used most frequently, MRS least frequently. Interestingly, there were no major differences with respect to availability amongst the other techniques. Even the most expensive technique, PET, was used by 49% of all institutions. However, for this technique, the largest proportion of machines was dedicated to research only, and its actual use in terms of subjects studied per year correlated significantly with the budget ($r = 0.67$, $P < 0.001$). Complementary to this, the highest number of subjects studied was reported for ultrasound as the least expensive technique, and this number had a significant inverse relationship with the budget ($r = -0.63$, $P = 0.004$). More unexpectedly, a similar inverse relationship between budget and number of
studies was also seen for SPECT ($p = -0.50, P = 0.024$). Imaging techniques were combined with electrophysiologic techniques for fusion display by 40% of institutions, with increasing frequency related to budget (25.0, 45.8 and 72.7%). A broad range of diseases was studied at most institutions, most frequently cerebrovascular disease (82%), followed by dementia and cognitive disorders (68%), epilepsy (61%), movement disorders (61%), brain tumours (57%) and multiple sclerosis (48%). Meningitis and other inflammatory disorders (19%) and spinal diseases (22%) were studied only rarely. A significant correlation with the budget was seen for dementia (50.0, 75.0 and 100.0%) and movement disorders (50.0, 54.2 and 90.9%). Additional diseases not listed in the questionnaire were reported by 18 institutions, with psychiatric and developmental disorders (four), metabolic disorders such as diabetes and hepatic failure (three), specific cognitive deficits (three), coma (three), brain trauma (two) and pain or migraine (two) mentioned more than once.

Image data analysis relied heavily on digital image processing techniques, including the displaying of digital image data (90%), image processing computers (87%), quantitative image analysis (79%) and computer networks (70%). Image copies on X-ray film were used by 69% of institutions. A significant correlation with budget was seen for the use of image processing computers (75.0, 95.8 and 100.0%) and computer networks (50.0, 91.7 and 100.0%).

With regard to educational resources, a scientific library was available at 92% of institutions. 10 (4–25) local seminars were held per year, and five (3–10) national and five (3–10) international conferences were attended. Typically 10 (5–20) scientists had access to the Internet. These educational resources correlated significantly with the budget ($p$ ranging from 0.31–0.65).

Data on subject numbers were provided by 87 respondents. The total subject numbers studied per year varied widely amongst institutions; typically 600 (102.5–3225) patients were studied for clinical diagnostic purposes, 150 (50–400) for research purposes and 30 (0–100) normal volunteers were studied. Only 64 institutions reported studies of normal volunteers, and their number was closely related to the budget ($p = 0.66, P < 0.001$), whereas the patient numbers were not related to the budget.

Data on research staff figures were supplied by 89 respondents. Research full-time staff comprised typically two (0–5.5) scientists and one (0–5) technician. Most institutions did not employ administrative staff for neuroimaging research (median 0 [0–2]). Part time staff was slightly more numerous: two (1–4.5) senior scientists and one (0–2.5) post-doctorate student(s). Three (2–5) medical doctors and one (1–4) PhD student were typically involved in research. Few laboratories had visiting scientists from their own (0, [0–1]) or, slightly more frequently, from foreign countries (one, [0–2]). Few laboratories reported to have sent some of their scientists to other labs in the own (0, [0–0]) or foreign countries (0, [0–1.25]). With the exception of visitors from and to the own country, all personnel figures were significantly related to the budget ($q$ from 0.30 to 0.66), with the strongest correlations for senior scientists and PhD students.

Data on publication language were provided by 88 and on publication numbers by 72 respondents. Only five laboratories published most of their research in a non-English national language. Typical numbers of publications (without abstracts) in 1998 were 10 (4–21.5), with seven (4–12.5) citation-indexed papers with first authors from the imaging group. Typically two (0–3) MD and one (0–3) PhD dissertations were completed in the laboratories. With the exception of medical dissertations, all publication figures were related to the budget ($p$ from 0.52 to 0.59, $P = 0.001$). On average, budgeted costs of €22 000 (€5000–40 000) were spent per published research paper.

Most respondents gave high ratings (on a scale from 1 to 5) for the opinion that neuroimaging research is important for patient care and that funding needs to

<table>
<thead>
<tr>
<th>Technique</th>
<th>Use in research (% of all answers)</th>
<th>Exclusive use in research (not shared with clinical duties, % of all answers)</th>
<th>Total number of research subjects studied per year (median, interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>53</td>
<td>2</td>
<td>150 (40, 400)</td>
</tr>
<tr>
<td>MRI</td>
<td>88</td>
<td>12</td>
<td>135 (50, 300)</td>
</tr>
<tr>
<td>FMRI</td>
<td>64</td>
<td>15</td>
<td>60 (20, 162.5)</td>
</tr>
<tr>
<td>MRS</td>
<td>35</td>
<td>10</td>
<td>45 (22.5, 95)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>48</td>
<td>7</td>
<td>300 (80, 550)</td>
</tr>
<tr>
<td>SPECT</td>
<td>56</td>
<td>4</td>
<td>70 (20, 100)</td>
</tr>
<tr>
<td>PET</td>
<td>49</td>
<td>16</td>
<td>50 (20, 153)</td>
</tr>
<tr>
<td>Others</td>
<td>11</td>
<td>7</td>
<td>150 (50, 300)</td>
</tr>
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</table>

Table 2 Imaging techniques
be improved (five, [4–5]). Slightly lower ratings (four, [4–5]) were given for the opinions that improvement of interdisciplinary co-operation, access to data and equipment, educational resources and availability of up-to-date neuroimaging for patient care is necessary. It was also felt that the EFNS should increase activities related to neuroimaging research (four, [4–5]). There was not a strong feeling that access of researchers to patients would need improvement (three, [3–4]). These opinions did not correlate with the budget available.

**MEDLINE search**

As illustrated in Fig. 1, MRI was the most frequently used technique. On average across all journals, it was indexed in 20.1% of all papers. MRI was followed by PET (3.8%), CT (2.9%), SPECT (1.5%), MRS (1.3%) and ultrasound (1.0%). Emission computed tomography (PET + SPECT) was used significantly more frequently in papers that appeared in journals with a high citation index ($q^* = 0.786$, $P = 0.036$), whereas the opposite was found for ultrasound and CT ($q^* = -1.0$, $P < 0.001$ and $q^* = -0.857$, $P = 0.14$).

**Discussion**

As intended, most responses were collected from departments of neurology or clinical neuroscience at university hospitals, teaching hospitals or research institutes. This spectrum appears to be representative of imaging research in clinical neurology. However, coverage of neuroimaging research activities across Europe by this survey may vary. For example, in the UK, research activities are usually performed by several relatively independent research groups, whereas most other European countries organize research mainly in hierarchically structured departments, with a chairperson who supervises all activities. The chairpersons of neurological departments were primarily addressed by our questionnaire, and they were asked to pass copies to independent researchers at their institution. However, the latter option was used in only a few instances, and thus research activities in the UK may not have been covered to the same extent as in the other countries. The members of the task force had been selected because of their familiarity with neuroimaging research activities across European countries. The high return rate of completed questionnaires probably indicates that the design of the questionnaire and selection of addressees was adequate. We were not able to locate major neuroimaging research activities in the eastern European countries, which may reflect their still limited access to the necessary financial and organizational resources. Within the limits of such surveys with voluntary reply, we assume that the present results give a fair account of neuroimaging research activities in European neurological departments.

Our data indicate reasonable access to modern neuroimaging techniques by the institutions which returned the questionnaires. MRI, including fMRI, had the highest frequency of use in research, which is in line with its representation in the scientific literature. In terms of the number of publications, PET followed at some distance. Fewer patients had been studied with this expensive technique, and, quite understandably, their number was correlated with the available budget. Investment in PET seems appropriate, because publications were preferentially found in journals with high impact factors. CT, which obviously offers less innovative aspects, appeared next in terms of publication presence, but preferentially in journals with low impact factors. SPECT and ultrasound, which are used with similar frequency, have even less impact in terms of the frequency of publications in journals of general neurology. They were preferentially used by groups with a low budget. For SPECT and MRS, the number of subjects studied and the number of publications in the literature was relatively low, suggesting a more marginal role in neuroimaging research.

The number of subjects studied per year with ultrasound was the highest of all techniques. The obvious main application of ultrasound is in cerebrovascular disease. Correspondingly, in the speciality journal *Stroke*, which has a relatively high impact factor, the frequency of ultrasound use was 11.9%, second only to MRI (13.9%). In contrast, relatively few publications appeared in the journals of general neurology, and then mostly in those with relatively low impact factors. A similar tendency was seen with CT,
also much more frequently indexed in *Stroke* (9.1%) than in general neurology journals.

The high frequency of studying cerebrovascular disease and dementia seems appropriate with regard to the prevalence and socio-economic impact of these diseases. The contribution of neuroimaging research to the management of focal epilepsy, multiple sclerosis, movement disorders and brain tumours is also well reflected by study frequencies. The limited role of neuroimaging in meningitis is not unexpected, because investigations of CSF are much more helpful in this disorder. Yet, spinal disease appears to be somewhat neglected, given the large clinical impact of neuroimaging findings and the severity of functional impairment that may result from spinal disease.

Co-operation frequencies reflects the outstanding role of neuroradiology for neuroimaging research. Co-operation with neuropsychology and psychiatry is also frequent, and may reflect the expertise of these disciplines in clinical evaluation of higher brain functions. Nuclear medicine comes next, close to neuropsychology, which may not always have been marked as a co-operating discipline because it is integrated in clinical neurology at many institutions. The high number of disciplines involved, and their correlation with budget, suggests that structures which favour co-operation, supported by adequate funding, are important for neuroimaging research.

Monetary aspects were also evident with regard to several resources that are needed for high quality neuroimaging research. This involves many technical, statistical and computing aspects that need to be covered by co-operation or by highly qualified personnel (PhDs). Both of these resources, as well as high-tech equipment (image processing computers and computer networks) and educational resources were significantly related to the budget. The possibility of studying a sufficient number of normal subjects, in addition to clinical work, is certainly a prerequisite for innovative research, which was also related to budget.

Many groups performed their research with a small number of full-time staff: 50% had only two scientists and one technician or less. Even more critical may be that the exchange of scientists between the groups is very low or absent in most laboratories. Given the enormous role that an exchange of know-how has for the use of advanced medical technology, this may represent a major impediment to reaching or maintaining a competitive scientific standard in the field. Therefore, such exchange may be one of the most important issues for EC research politics to encourage and facilitate.

In Europe, in the last 15 years, cognitive neuroscientists, neuropsychologists and neurologists studying the neural correlates of mental operations have extensively adopted functional neuroimaging techniques to localize the components of cognitive processing in the human brain, and to image their orchestration as humans perform a variety of cognitive tasks. However, this advanced field of research was, and still is, confined to very few centres where only the efforts of individual research leaders allowed the merging in specific project plans of intellectual strengths and research facilities.

The European dimension of researchers in the field of cognitive neuroscience and neuropsychology and their relevance for the advancement of science for a European integration and scientific exchange will be only assured by establishing collaborations with several neuropsychological research groups, by running joint experiments, and by sharing facilities and experiences. A substantial contribution to this central objective is related in particular to the training of young scientists in qualified centres for neuropsychological research with the neuroimaging techniques, especially the costly PET techniques.

In summary, this survey documented neuroimaging research activities in at least 100 neurological institutions across Europe. These activities correspond with the important role of neuroimaging research in clinical neurology, which is reflected in the international scientific literature. This survey shows that European groups contribute significantly to this highly interdisciplinary research on severe and frequent diseases with enormous socio-economic impact. It also shows that many relatively small groups within major hospitals perform research activities, often with small budgets, very few senior scientists and little exchange amongst groups, which does not achieve a high degree of innovation. Thus, in addition to an improvement of funding, the improvement of collaboration amongst groups and concentration on innovative techniques and applications should be a goal for science politics in this field.

**Acknowledgements**

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Note added in proof

Since this paper was submitted, the European Journal of Neurology has been indexed by Medline. From now on, it is therefore possible to include the European Journal of Neurology among the journals to be used in the method proposed by the authors.

References


