International Psychogeriatrics (2011), Vol. 23, Supplement 2, S58–S64 © International Psychogeriatric Association 2011
doi:10.1017/S1041610211000901

An international perspective on advanced neuroimaging: cometh the hour or ivory tower?

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ABSTRACT

Over the past five to ten years, neuroimaging capability for neurodegenerative diseases has made remarkable progress. However, debate remains as to the true clinical utility of these advanced and costly investigations. Not only is the place of these tests in diagnostic algorithms unclear, but the access to them varies both within and between countries. We sought to gather informed opinion from recognized leaders in the field who can combine both an academic and a clinical perspective on the use of neuroimaging in their own countries. Opinion is presented from Scotland, Argentina, the Czech Republic, France, the USA and Australia. The emerging consensus was one of ongoing caution. While in most countries there was a sense that the use of more advanced imaging techniques was growing, their hour has not yet cometh. However, these techniques, rather than falling from the Ivory Tower, should descend slowly step by step onto fertile and receptive clinics from where better clinical guidelines will emerge.

Key words: dementia, neuroimaging, diagnosis, magnetic resonance imaging, PET scan, amyloid, Alzheimer's disease

Introduction

There is only one reason to undertake any test in medicine and that is so that, upon its completion, the practitioner will know more about the condition that they suspect is causing the ailment. Tests are therefore used either to rule a diagnosis into or to rule a differential diagnosis out of consideration. A positive result in a test known to have high specificity will help rule in a diagnosis, whilst a negative result in a test with high sensitivity will help rule out the proposed condition. Putting this into a current Alzheimer's disease (AD) scenario, the absence of ^{11}C Pittsburgh compound B (PiB) uptake on positron emission tomography (PET) scanning, which suggests that little if any cerebral amyloid is present, may help to rule out AD as the cause of cognitive symptoms. However, it remains uncertain what a positive test may mean in people with cognitive symptoms who have not yet developed dementia because the longitudinal studies reported to date in these important populations are small and of short duration (Jack *et al.*, 2009).

The other factor to consider is how much incremental benefit the test will have on the practitioner's thinking. Approximately two thirds of all dementias are subtyped as AD (Ott *et al.*, 1995). This means that, even before conducting any tests or asking any questions, the clinician will be correct about two thirds of the time in diagnosing any presenting patient with dementia as having AD. If the patient and carer then give a classical history of insidious onset of episodic memory impairment with subsequent gradual decline, preceded by apathy, disengagement and perhaps low mood, then perhaps 80% of these patients will be later shown to have AD by standard clinical criteria. To raise this to 95–100% certainty, you would need to have a very specific and very sensitive test, which probably has to exceed 95% for both measures. No such tests are currently available.

However, it is clear that patients are presenting earlier and earlier with less clear-cut histories than the symptoms described above. There is therefore much more clinical uncertainty, and in the void left by this doubt, biomarkers are being used to

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https://doi.org/10.1017/S1041610211000901 Published online by Cambridge University Press

fill the diagnostic gap. This has led over recent years to a headlong drive to develop new criteria for "disease before dementia" – sometimes described as "insidious" or "pre-manifest" dementia. In most of these proffered criteria, biomarkers play a prominent role.

Some may argue, however, that to answer a clinical dilemma with biomarkers – which have even less evidence-based validity than the clinical criteria they seek to replace – is compounding the uncertainty rather than mitigating it. This move towards a biological diagnosis is perhaps inevitable for two reasons. First, we are witnessing repeated drug failures in populations described by predominantly clinical criteria, which are forcing study designers to seek alternative ways of defining their study samples. Secondly, there is now much clearer understanding (we think) of the basic pathology of the dementias – and if we know what the pathology in these conditions is then surely we must be able to measure markers of it *in vivo* through either sampling bodily fluids or perhaps imaging.

In 2011 we are at a crossroads. Despite spending billions of dollars over the last decade on drug development and basic science research into the dementias (almost exclusively AD), we are still ordering the same tests, doing the same neuropsychometric assessments, organizing the same psychosocial interventions and prescribing the same drugs as we did ten years ago in our clinics for patients with dementia. Undoubtedly, progress has been made in raising awareness of mild cognitive impairment as a clinical concept. Despite much research and discussion, however, it remians unclear how best to define this condition and how to diagnose it (Matthews *et al.*, 2008; Stephan *et al.*, 2010). Neuroimaging may, however, be one of the strongest candidates to address some of this uncertainty.

Have things moved on then in the Neuroimaging Ivory Tower of academia to the extent that we should be embracing new technologies when we see our patients? Is it now appropriate to lobby our healthcare purchasers to direct money to our services to pay for new, more expensive but worthwhile and accurate scans?

AD is a global and major healthcare issue. Here we attempt a global perspective with international snapshots from clinical academics working in Scotland, Argentina, the USA, France, the Czech Republic and Australia.

Scotland

The Scottish National Dementia Strategy confirms the rise in the priority given to recognizing and treating people with dementia in Scotland, although the feasibility of making significant short-term gains in the current economic environment can be questioned. As is the case in many developed countries, the greatest percentage growth in the population is in the very elderly (those aged over 75 years) and in the absence of any clear preventive treatment the number of people with dementia will continue to rise inexorably over the next 25 years. The Scottish Strategy identifies improvements in the provision of post-diagnostic support and management of people with dementia in general hospitals as the main priorities rather than early diagnosis and management. However, over the past three years, a Health Efficiency and Access Target (HEAT) has driven a gradual increase in the identification of people with dementia.

The geography of Scotland is such that although 50% of the population are concentrated on 10% of the land mass, a significant number of people live in semi-rural environments and small towns. Memory clinics are not uniform and the traditional model is the source of some debate (Pelosi *et al.*, 2006). In this environment, the use of neuroimaging is far from uniform (Foy, 2008). Since publication of the paper by Foy (2008), government-led initiatives have reduced waiting times for investigations such as computed tomography (CT), magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT), and many hospitals have developed protocols to allow general practitioners (GPs) direct access to CT, particularly for the investigation of headache. Despite this, the use of imaging to help establish a diagnosis of dementia is not routine. Foy (2008) found that CT was the most common investigation and in the majority of cases was carried out for the exclusion of diagnoses of apparently atypical cases. Few centers use MRI, most commonly available as 1.5T scanners.

Centers involved in the Scottish Neuro-imaging Network (SINAPSE) have acquired 3T MRI machines, PET-CT scanners and other state-of-the-art machinery, allowing cutting edge research to be undertaken. Currently, we have no clinical Old Age Psychiatry academic departments to drive increased use of scanning for people with dementia either at research or service level. If fMRI, PET or PET-CT machines were to become more routine or hippocampal measurement to become the norm there would be a need for major educational initiatives to ensure that Old Age Psychiatrists in Scotland become aware of the value of these tools. Currently we need significant persuasion to improve the use of routinely available structural or functional scans at a clinical level. Without more ivory in Scotland, more esoteric scanners will remain out of reach.

https://doi.org/10.1017/S1041610211000901 Published online by Cambridge University Press

Argentina

Argentina has a high prevalence estimate of dementia in the population aged over 65 years. It is similar to that found in many developed countries, with a prevalence of 11.5% for all dementias (Kalaria *et al.*, 2008). The most common types are AD and vascular dementia (VaD), with prevalence rates of 5.85% and 3.86%, respectively (Pages Larraya *et al.*, 2004).

Dementia care, like health services generally in Argentina, is divided between the public and private sector (union systems, private insurance). In general, the public sector provides diagnosis and treatment to low- and middle-income populations. This is mainly hospital-based. The private system provides services to middle- and high-income populations, which often also includes home-based assessment and treatment. Standard structural CT and MRI scans are mainly available in urban areas and in the private sector. Currently, it is very difficult to access advanced neuroimaging for dementia, such as SPECT and PET scans. PiB PET scans and Isoflupane (^{123}I) SPECT are not yet available.

Cometh the hour . . . but, when and how?

The diagnosis of dementia has evolved in recent years like never before in the history of the disease. Neuroimaging is one of the main reasons for this development. It allows us to make better differential diagnoses, thus allowing for more accurate prognosis and tailored treatments. Undoubtedly, clinicians today prefer to have the information from a brain CT scan or MRI to give a diagnosis of dementia. Twenty years ago, an editorial in this journal might have been titled: "Brain CT scan for dementia: cometh the hour or ivory tower?" I think we all know the answer now.

Today, we have new technologies and compounds (such as Isoflupane (^{123}I) SPECT scan, PiB PET scan and florbetapir PET scan) which allow us to refine the diagnosis even more. In the near future, these new technologies will also help us monitor treatment response and identify which at-risk populations are suitable for prevention strategies. It will also raise the profile of these important illnesses and provide a new incentive for research in this area. In a developing country, there are many unmet needs and new technologies will stay in the ivory tower for a longer period. Currently, we still do not know the cut-off points for many of these tests; their validity and specificity, and – until we can count on new treatments – the costs will probably not justify the benefits from a health economic perspective. However, there will be many patients and families who will start requesting these new technologies to clarify their diagnosis and the private sector will work to meet this demand. Clinicians in the private sector will also start ordering these investigations in private institutions for complex cases carrying important emotional or economic burden. Eventually, these new technologies will become more widely available, extending into the public sector, and will slowly become part of routine practice.

Cometh indeed the time and it is very welcome . . .

USA

An estimated 2.5–5 million Americans are currently living with AD and at least as many have impaired cognition that is greater than expected for age (Cognitive Impairment Not Dementia; CIND) (Plassman *et al.*, 2008). Clinical diagnostic criteria (NINCDS-ADRDA) for AD, established in 1984, standardized the clinical diagnosis but did not specify clinical or laboratory testing for evaluation. In 2001, the American Academy of Neurology (AAN) released practice parameters for evaluation of dementia and recommended use of CT or MRI in the evaluation of patients. Today, almost all patients in the USA being evaluated for dementia receive some type of neuroimaging, with most receiving MRI. A survey by the Organization for Economic Co-operation and Development (OECD) reported that the number of MRI units per million population in the USA doubled from 12.3 in 1995 to 26.5 in 2006 (Iglehart, 2009). The median for other OECD countries, by contrast, is 7.7 MRI units per million population. This explosion in imaging technology has resulted in increased utilization so that MRI/CT or PET scans of some body part were ordered in 4.1% of all ambulatory care visits in the USA for patients over the age of 65 years (National Center for Health Statistics, 2010). Has all this imaging led to improvements in diagnosis or care? The answer to this question is unknown.

Although animal models with features of AD exist, Alzheimer's remains solely a human disease. Neuroimaging has provided a timeline of pathologic change in AD identifying decrements in cerebral glucose metabolism and amyloid accumulation that precede cognitive decline, which has led to a greater understanding of the pathogenesis of the disease. Volumetric analysis of MR images has demonstrated that subjects with MCI who have decreased hippocampal volume are at high risk for progression to dementia. Modern MRI also provides accurate detection of masses, vascular abnormalities, hydrocephalus and microvascular changes, and aids in diagnosis of VaD, normal pressure hydrocephalus, infections, inflammatory

https://doi.org/10.1017/S1041610211000901 Published online by Cambridge University Press

disorders, and Creutzfeldt-Jakob disease. In the clinical trenches, however, neuroimaging tends to be the beauty contest which is subject to the radiologist's perception of normal. The phrase "age-appropriate atrophy" and semi-quantitative descriptions of T2 and FLAIR hyperintensities related to microvascular disease are commonly found in radiology reports, but are difficult to operationalize into a clinical diagnosis. Evidence of hippocampal or focal atrophy is often noted in reports, which can aid in confirming a dementia diagnosis, but may be absent or minimal in mildly affected individuals where diagnostic accuracy is poorest. Serial imaging to detect interval volume change can be useful, but accurate quantification is difficult to achieve when performed using different scanners and imaging protocols. We await reports that quantify assessments and standardization of imaging procedures. Like Moses, we can see the "Research Promised Land", but from a clinician's viewpoint, we are not there yet.

France

Memory clinics in France have been established to facilitate the accuracy and timeliness of the diagnosis of dementia in primary care. Recommendations have been published by the French government concerning AD and related disorders (http://www.has-sante.fr). Dementia should ideally be diagnosed as soon as the first symptom appears, with early diagnosis involving a detailed cognitive evaluation, preferably carried out in specialized centers (memory consultations in expert centers). Practitioners (neurologists, geriatricians and psychiatrists) should use DSM-IV-TR for the diagnosis of dementia and the NINCDS-ADRDA diagnostic criteria for the diagnosis of AD or other specific criteria for related conditions. These criteria are currently being revised. Neuropsychological evaluation and paraclinical investigations (biomarkers) are also requested, including brain imaging. The brain scan is first performed to ensure that causes of dementia other than degenerative processes or potentially reversible contributors to the clinical syndrome are not overlooked (e.g. intracranial expansive process, normal pressure hydrocephalus, stroke, etc.) and to investigate atrophy and changes associated with vascular lesions.

MRI with T1-, T2- (including FLAIR), and T2*-weighted sequences is recommended. In some cases (e.g. where no MRI scans are easily accessible, old age and poly-pathology in very old) a brain CT scan without injection of contrast agent can be used. A recent brain scan should not be repeated without good reason, or when the patient is involved in a research program.

Functional imaging, including SPECT, ^{123}Isoflupane (DATscan^{R}) and PET are not recommended as routine procedures for diagnosing AD, but can be useful for differential diagnosis in patients with atypical presentations.

Finally, while this diagnostic procedure should be conducted in university and general hospital outpatient settings, the actual role of the primary care practitioner in the management of the dementia patient in relation to specialized memory clinics is not yet clear. Furthermore, the initial evaluation is limited by the availability of head-dedicated scanners, by regional localization of the scanners and by the proximity of cyclotrons (for PET ligand manufacturing) to the centers. As compared to other European countries, France has one of the lowest numbers of MRI scanners per million inhabitants (8.7). A total of 543 MRI and 800 CT scanners were available in France in 2010, and 70–80 locations have PET-scanners though these are frequently dedicated to cancer. However, it is anticipated that the number of brain procedures will increase in the next few years.

In addition to the standardized clinical guidelines, active research is conducted by a significant number of groups in France. Recent guidelines have been proposed concerning earlier stages in the disease process – i.e. mild dementia, mild cognitive impairment or pre-dementia stages. The recent advances in the use of reliable AD biomarkers that provide *in vivo* evidence of Alzheimer's pathology has stimulated the development of research criteria (Dubois *et al.*, 2010). Pre-dementia and dementia stages are defined through cross-sectional and, in particular, longitudinal clinic-based, epidemiological, and population-based research projects. It is difficult to summarize work carried out over recent years involving neuroimaging in dementia in France. Some groups have focused on morphological approaches and atrophy, showing that early hippocampal atrophy is found in AD, leading to an automated approach (Chupin *et al.*, 2007), while another, in comparing morphological and functional neuroimaging, has discussed the "hippocampal paradox" (Villain *et al.*, 2010). Here, the sequence of events (e.g. hippocampal atrophy, posterior cingulate and frontal hypometabolism, white matter tract disruption) is complex. Other studies, from population-based cohorts, have shown the impact of white matter lesions on cognition (van de Pol *et al.*, 2009; Ritchie *et al.*, 2010). Finally, a recent project will focus on how cognitive reserve can mediate the relationship between age- or AD-related pathology and the clinical impact of

https://doi.org/10.1017/S1041610211000901 Published online by Cambridge University Press

that pathology, combining functional (fMRI) and structural neuroimaging approaches.

Finally, many European groups are linked via the European consortium on Alzheimer's disease – E-ADNI – in order to unify the sequences and to compare the different populations. European links have already led to publications in the field of dementia and biomarkers (Nobili *et al.*, 2008; van de Pol *et al.*, 2009).

The impact of much improved access to amyloid PET imaging will certainly modify our different approaches, but the tracers used to label amyloid (florbetapir, florbetaben or flutematamol) are not yet available in France.

A common lexicon as a point of reference for the clinical and research communities has to be proposed and has to be adapted, regarding, for example, the limitation of each country in terms of the number of scans dedicated to the brain and regarding the cost and the economic interest in making an early diagnosis.

Czech Republic

It is estimated that 130,000 people in the Czech Republic suffer from dementia with an incidence rate of 25,000 new patients every year, which is more than the incidence of stroke, diabetes or breast cancer (Holmerová, 2007). Alzheimer's disease (AD) accounts for approximately 60–70% of dementia cases.

The Czech Health Care System is based on obligatory public health insurance which covers most of the medical care including imaging methods. CT and/or MRI machines are widely available in most of the city hospitals and are used mainly to exclude the other causes of dementia (hematoma, hydrocephalus, tumor, etc.) and to confirm general brain atrophy. Several years ago specialized centers were founded. These memory clinics started to use structural MRI methods to detect specific volume reductions of critical brain regions with most emphasis placed on the medial temporal lobe structures and especially on the hippocampus. Among the other biomarkers of AD, cerebrospinal fluid biomarkers are frequently used. In contrast to structural CT and MRI, more advanced neuroimaging modalities are currently only available in some teaching hospitals and clinical centers. The wider use of these modalities is still limited by their higher price and lack of experience including qualified medical and radiography staff.

In the Czech Republic, MRI is a widely available and relatively inexpensive technique and new MRI-based technologies have the potential for wider use in order to contribute significantly to early diagnosis of dementia. Manual MRI volumetric analyses, mainly of medial temporal lobe structures, are used in some clinical centers in the Czech Republic, but they are time consuming and therefore not well suited to clinical practice. Automated volumetric imaging techniques (i.e. VBM), which have been recently introduced into some research protocols, seem to be more promising. Despite its potential, experience with new functional MRI based technologies (e.g. fMRI, DTI, PWI and MRS) is very limited and is used solely for research purposes.

At present, SPECT is a second-line investigation employed when MRI is inconclusive (e.g. it is used to differentiate early AD from frontotemporal dementias), but it is only available in some clinical centers (Bartoš *et al.*, 2008). Hypoperfusion may precede volume loss and thus SPECT can be useful in early cases of dementia. Dopaminergic SPECT imaging (FP-CIT or DaTSCAN; GE Healthcare, Amersham, UK) is used to differentiate AD from dementia with Lewy bodies in two centers in the Czech Republic. Currently, FDG PET is available in five hospitals in the Czech Republic with very limited use in the diagnosis of dementia because of its high price. In the future, PET imaging may become more important, especially because of the development of radioligands for *in vivo* detection of AD pathology (B-amyloid) with PiB or FDDNP, which are currently not available in the Czech Republic.

The implementation of novel neuroimaging techniques in AD research should be prompted by way of a new EU-funded International Clinical Research Center which represents a joint project between the Czech Republic and the Mayo Clinic, Rochester, USA.

Australia

Australia is geographically large but demographically small with a current population of 22 million. It is estimated that by mid-century the percentage of Australians aged over 65 years will be 25% and the number with dementia in the second most populous state (Victoria) will exceed the total number of people in Australia today. Most patients being assessed for dementia have structural imaging as part of their standard diagnostic work-up. The use of SPECT and FDG-PET scans in the initial assessment of suspected dementia patients is rare outside of a few academic centers.

Cholinesterase inhibitors have been subsidized on the nationally funded prescriber benefit scheme for some people with AD since 2001 and the availability of memory clinic services varies between

https://doi.org/10.1017/S1041610211000901 Published online by Cambridge University Press

states, with a full publicly funded assessment service available in Victoria, though waiting lists for assessment bookings are very long.

Amyloid brain imaging is available at one center in Melbourne and another in Perth and is used as a research tool. In 2006 the Commonwealth Scientific and Industrial Research Organization (CSIRO) initiated a collaboration which led to the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Ageing (Ellis *et al.*, 2009) which has assessed 1112 research subjects at baseline and at 18 months and is now more than half way through its three-year review program. One quarter of the cohort has undergone PiB PET imaging and funding arrangements now in place will ensure that the majority of the cohort gets scanned with one of the currently available amyloid imaging agents over the next 18 months.

In the context of the Australian healthcare system, which is a blend of both public and private sector provision, it is unlikely that investigations beyond structural MRI/CT will be routinely available in the near future. Also, definitive conclusions emerging from research such as the AIBL study are still many years away. An assessment of the accuracy of these scans, their incremental benefit over cheaper and currently more accessible tests, and a clear definition of the target population where they would be most useful is needed before any discussions can take place with healthcare funders about the possibility of purchasing such scans for some patients.

In this regard, the scans are peeking out the window of the ivory tower, but the hour when they will be used in routine clinical practice is at least a few years away.

Summary and conclusions

The transition from clinical research findings to clinical practice is always influenced by numerous factors. Early clinical research can seldom consider the eventual clinical context where the research is hoping to change or modify practice. The embedding of robust research findings in dementia into clinical practice are further hampered by the multiplicity of care pathways which exist both within and between countries. This is reflected in the views from the seven countries listed here. Each of these countries is relatively affluent and it is likely that access to expensive investigations will be even more difficult and there will be greater internal disparity in poorer and emerging economies.

All of the authors from the seven countries were invigorated and optimistic about the prospects for more advanced imaging techniques playing a role in better diagnosis of neurodegenerative disease. However, each expressed this enthusiasm with quite significant caveats: cost, accessibility and accuracy were the three main themes to emerge.

The accuracy of these tests is probably the biggest hurdle but also (perhaps) the most surmountable. How often do we read at the end of a paper: "our findings need to be replicated in a larger sample"? This remains true of advanced neuroimaging. There was, however, a general consensus that if asking a particular and specific question of the test then there was utility. Examples are using DAT scanning to identify dementia with Lewy bodies (McKeith *et al.*, 2007) and FDG SPECT/PET to distinguish between frontotemporal dementias and AD. Structural imaging will still be used predominantly to rule out other pathologies, and although volumetric, sequential MRI is of great utility in identifying AD as it affects medial temporal lobe structures, the technique is not sufficiently accessible yet for routine clinical use.

What will help move the research from the Ivory Tower?

There is a risk that we invest (with new clinical criteria; see, for example, Dubois *et al.*, 2010)) too much emphasis on biomarkers to supplant clinical criteria for neurodegenerative disease. The risk is that we imbibe the tests with a greater degree of validity and accuracy than they are currently known to have. The consequence of this may be that we then have great difficulty in divesting ourselves of them as criteria. An example of this shooting oneself in the foot was the early adoption of the ADAS-Cog as the principle outcome in AD trials. Subsequently it has been hard to wrestle this test out of the Phase 2 or 3 AD trial despite significant evidence that its psychometric properties are suboptimal (Cano *et al.*, 2010).

Rushing headlong into using tests with uncertain diagnostic accuracy because we are desperate to do something to define more accurately a homogenous clinical population may come back and bite us. It is true that clinical trials of new agents are all failing at a disappointing rate, but there may be other reasons for these, including heterogeneous sample populations in terms of language, poor trial conduct and poor choice of outcome measures.

A test that is thrown out of one of the higher windows of the ivory tower will crash and break on the ground. To be adopted by the clinical community and health care purchasers, the test must descend the tower gradually, step by step. These (research) steps are large scale, high quality primary diagnostic research, followed by systematic review and meta-analysis, health-economic studies and testing in multiple health settings and defined clinical populations.

https://doi.org/10.1017/S1041610211000901 Published online by Cambridge University Press

This hour has not yet cometh but it will – though it seems likely that it may be some years before advanced imaging techniques are being used routinely in clinical practice.

Conflict of interest

FP has sat on an advisory board for GE Healthcare, and CWR has received honoraria for chairing a neuroimaging meeting sponsored by GE Healthcare.

Description of authors' roles

Each author contributed their own section as per their country of origin. Every author reviewed the entire paper prior to submission.

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