ABSTRACT: There are five potential major roles for neuroimaging with respect to dementia: 1) as a cognitive neuroscience research tool, 2) for prediction of which normal or slightly impaired individuals will develop dementia and over what time frame, 3) for early diagnosis of Alzheimer’s disease (AD) in demented individuals, (sensitivity) and separation of AD from other forms of dementia (specificity), 4) for monitoring of disease progression, and 5) for monitoring response to therapies. Focusing on the last role, no single imaging approach is yet ideal, as all trade-off speed, cost, and accuracy. Functional imaging (SPECT and PET) is best suited to tracking symptomatic therapy response, and anatomic (MRI volumetric) imaging or amyloid PET are more suited to reflect dementia modulation studies. The potential for imaging with respect to pharmacological studies of dementia - to provide surrogate markers for drug studies, to improve diagnosis, to speed evaluation of outcomes, and to decrease sample sizes – is huge. At the present time, however, no single measure has sufficient proven reliability, replicability, or robustness, to replace clinical primary outcome measures.

RÉSUMÉ: Les biomarqueurs en imagerie et leur rôle dans les essais cliniques sur la démence. Il existe cinq rôles majeurs de la neuroimagerie dans l’évaluation de la démence: 1) comme outil de recherche en neuroscience cognitive; 2) pour prédire quels individus normaux ou présentant une légère atteinte cognitive développeront une démence et dans quel laps de temps; 3) pour poser un diagnostic précoce de maladie d’Alzheimer (MA) chez des individus déments (sensibilité) et pour distinguer la MA des autres démences (spécificité); 4) pour suivre la progression de la maladie et 5) pour évaluer la réponse au traitement. À ce propos, aucune approche d’imagerie ne s’est avérée idéale jusqu’à maintenant, parce que toutes font des compromis en ce qui concerne la rapidité, le coût et la précision. L’imagerie fonctionnelle (TEMP et TEP - SPECT and PET) est une meilleure approche pour suivre la réponse thérapeutique symptomatique et l’imagerie anatomicque (IRM volumétrique) ou le TEP de la substance amyloïde conviennent mieux aux études de modulation de la démence. Le potentiel de l’imagerie dans les études pharmacologiques portant sur la démence est énorme : pour fournir des marqueurs de substitution pour l’étude de médicaments, pour améliorer le diagnostic, pour accélérer l’évaluation des résultats et pour diminuer la taille d’échantillon. Actuellement, aucune mesure ne s’est avérée suffisamment fiable, reproductible ou sûre pour remplacer les principales mesures d’impact clinique.

There are five potential major roles for neuroimaging with respect to dementia; 1) as a cognitive neuroscience research tool, 2) for prediction of which normal or slightly impaired individuals will develop dementia and over what time frame, 3) for early diagnosis of Alzheimer’s disease (AD) in demented individuals, (sensitivity) and separation of AD from other forms of dementia (specificity), 4) for monitoring of disease progression, and 5) for monitoring response to therapies. While we will focus on the role of neuroimaging in drug studies (#5), the other four questions have been the major focus of research to date. Clearly, the advantages of different neuroimaging modalities depends on which question is being addressed. Furthermore, the practical utility of a neuroimaging modality (ie., the clinical roles of questions 2 to 5), are a trade-off between three factors: accuracy and reliability of the method, its ease of...
use (speed and availability), and its cost. The ideal neuroimaging modality which fulfills all three elements may be elusive! The different available modalities offer a trade-off between these three components.

Use of neuroimaging parameters as outcome measures in the development of new therapies is continually advancing and this pace will continue to accelerate in the coming decade. Different modalities can offer specific advantages for clinical trials. Imaging biomarkers with high diagnostic specificity can potentially reduce the 5 to 10% of individuals included in AD trials who in fact have other forms of dementia besides AD. While the technologies for metabolic and functional measures are available, their routine use has been restricted by technical complexity, cost and lack of sufficient replicability experience to establish correlations to clinical outcome. Recent technological advances and increasingly standardized scientific data collection and interpretation will allow for their use in the mainstream of antidementia drug development.

In practice, no one technique may offer a perfect solution. The critical question is what should be the role of neuroimaging within current drug trials? In drug studies, the endpoint of interest is clinical benefit and meaningful clinical outcome - death, stroke, progression to severe dementia, institutionalization, to name a few. There are certain neurological conditions in which surrogate endpoints have come to be accepted, inasmuch as they closely parallel and accurately predict these clinical events. For instance, hypertension and serum cholesterol levels closely predict rate of occurrence of myocardial infarction and cerebral infarction. A new medication that aims to improve blood pressure, therefore, has addressed an acceptable surrogate endpoint. The utility of biomarkers, in other words, is also judged by the degree to which they reflect clinical outcomes. Applied to imaging, the issue is which measure is most directly related to disease activity, has smaller standard deviation of measures, and require fewer patients to establish between-group differences than clinical assessment. Anatomic imaging with MRI volumetrics could potentially serve as a marker for disease severity in AD disease modification studies, thereby reducing the necessary sample sizes to demonstrate a significant effect. Should neuroimaging now be accepted as a surrogate endpoint in drug trials? We will review the different potential imaging approaches (anatomic MRI, functional MRI, PET, and SPECT) and then address this crucial question.

**Anatomic Imaging with Magnetic Resonance Imaging (MRI)**

Anatomic imaging with various forms of magnetic resonance imaging have moved from the laboratory to the clinic, although the most promising volumetric measures remain non-standardized and variable between centres. Magnetic resonance imaging hippocampal, cortical, and whole brain volumes have been successfully studied for their ability to predict which normal or slightly impaired individuals will develop dementia. There is clear and reliable medial temporal atrophy on MRI in early AD. Magnetic resonance imaging measures of atrophy increase with disease severity, and can be used to monitor disease progression.

Subcortical ischemic vascular disease in the white matter and basal ganglia have traditionally been evaluated by rating scales, which can be reliable and quick to apply by experienced raters, but provide only ordinal data and may be difficult to generalize. Tissue classification techniques are more labour intensive, but allow vascular disease burden, evident as hyperintense lesions on T2-weighted MRI, to be quantified and longitudinally mapped so that change over time and impact on neurobehavioural outcomes can be more objectively evaluated. Such volumetric methods allow subcortical vascular disease to become a legitimate target for intervention as well. Recent technical advances, such as diffusion tensor imaging, magnetization transfer imaging, voxel-based morphometry, arterial spin labeled MRI, cortical thickness measurement, and boundary shift measurements, will increase the sensitivity of MRI measurements in the future.

Structural MRI has not been used previously as an outcome measure in drug development largely due to technical limitations (ie., collecting similar data across many sites), but these are now being successfully addressed. Given the strong and coherent set of studies noted above, it should be possible to find convergence between clinical trials and MRI secondary measures. What sort of coherence is to be expected? There is little reason to think (and no evidence to date) that symptomatic treatment of AD ought to improve atrophy measures on MRI. Clearly, the potential role of MRI in drug trials is to demonstrate disease modification evident as slowing of the rate or degree of atrophy over time in a treated group. This role in monitoring response to therapies is new but potentially highly significant. The results to date, however, have raised many issues. Regarding Donepezil, a cholinesterase inhibitor, a major three year study failed to provide clear clinical evidence that this medication could slow progression from mild cognitive impairment (MCI) to AD. Nevertheless, a slower rate of hippocampal atrophy on MRI was documented in subjects taking Donepezil over 24 weeks and over a 52 week interval. How are we to interpret what appears to be a discordance between (lack of) clinical response and a biomarker expected to reflect it? Is this evidence that hippocampal volumes are superior to clinical assessment, or that they are, in contrast, unreliable?

The converse (and even more surprising) results have recently emerged from the Elan study of anti-amyloid immunotherapy. Recently, data was published from the interrupted Phase 2a A-beta immunotherapy trial of AN1792. MRI imaging was carried out prior to therapy and at 12 months, and volumes were collected. There were 45 treated subjects who were “antibody responders”, and these showed a favorable response over placebo in terms of cognition. On their matched MRI’s however, this subgroup in fact had greater brain volume decrease and ventricular enlargement than 57 placebo patients. The dissociation remains unexplained, and serves as a reminder that current biomarkers can “offer only an indirect measure of disease progression” (pg 1571).

There are other ways to use MR for functional neuroimaging. On H1 MR spectroscopy (MRS) there are reported characteristic abnormal metabolic profiles of Alzheimer’s patients which occur early on in the illness and even occur during the Mild Cognitive Impairment stage. MRS must be tested in longitudinal research for its potential utility in monitoring drug studies.

Functional MRI has been investigated extensively as a tool for cognitive neuroscience research. There is evidence that early changes in activation during memory tasks can precede and
predict occurrence of AD.\textsuperscript{42,43} FMRI also holds considerable promise as a tool in drug development, since it allows potentially for the assessment of the alteration in the regional blood flow response to cognitive activity, in a similar manner to oxygen-15 PET, without the attendant cost or radiation exposure. This technique could accordingly permit comprehensive dose response studies, the comparison of acute versus chronic drug effects over time, as well as evaluation of the effects of therapy over the natural history of an illness. Specific therapeutic intervention might then also be assessed non-invasively in terms of drug effects on activation patterns in specific regions of the brain. A combination of fMRI activation and drug treatment paradigms could potentially be used. It should be noted that the utility of fMRI relies on the validity of linking clinical response to blood flow changes – it is entirely conceivable that a significant cognitive improvement could occur without any concomitant change in the regional blood flow response to cognitive activity. The same improvement might only be demonstrable using measures of brain metabolism or neurotransmitter functioning (see PET section below). The realization of the potential of fMRI technology in the content of clinical trials will depend on its technical maturation, and continuing validation of its association to clinical symptom improvement.

**Positron Emission Tomography (PET)**

Positron emission tomography has been applied to all five questions listed at the start of this section. Positron emission tomography has been used as a cognitive neuroscience research tool in dementia.\textsuperscript{44} Studies in Alzheimer's disease have demonstrated that there are characteristic regional patterns of impaired cerebral blood flow (cbf) and metabolism\textsuperscript{45-49} and a linear relationship between them has been established.\textsuperscript{50} Metabolic changes have traditionally been correlated to regional histopathologic abnormalities.\textsuperscript{51,52} Identification of disease subgroups\textsuperscript{53} may be facilitated by this technology but verification is still needed and results have been mixed.\textsuperscript{46,54,55} PET has recently been used in prediction of which normal or slightly impaired individuals will develop AD.\textsuperscript{56,57} A considerable literature now exists regarding the role of FDG PET in the early diagnosis of AD and the progressive changes in PET metabolism with disease progression.\textsuperscript{58-61} Automatic diagnostic expert systems using FDG-PET are currently being developed.\textsuperscript{62} Biparietal-temporal hypometabolism has even been documented in those with genetic susceptibility for AD.\textsuperscript{63} This last finding underlines the potential for PET imaging to supply additional information not obtainable from clinical evaluation.

Studies of cerebral pharmacodynamics have shown the effects of neuroactive drugs on regional glucose metabolism as an index of regional synaptic activity. In terms of monitoring response to therapies, there have been a number of studies correlating response to cholinergic drugs with metabolic changes on FDG PET.\textsuperscript{64-67} There are plans to incorporate FDG PET as a secondary outcome measure in a number of current clinical trials. What is currently unclear is whether these measures are more robust than clinical outcome measures.

Activation paradigms\textsuperscript{58-70} might provide a more powerful means of quantifying specific effects of drugs on cognitive function. These paradigms include utilizing PET to image brain function during the execution of memory tasks and then assessing the effects of neuroactive drug treatments on these same endpoints.\textsuperscript{71-73}

New PET methodologies also allow for specific labeling of neurotransmitters and/or their receptors with the potential that responders to specific compounds might be identified.\textsuperscript{74} This might thus also provide a promising avenue for the evaluation of novel therapies. Most recently, the publication of a number of PET studies utilizing ligands such as PIB (Pittsburgh B compound) that successfully bind to fibrillary amyloid deposits, represents a major advance.\textsuperscript{75-77} Stabilization therapies, in particularly those targeting amyloid deposition, might focus on PET with such ligands as a major outcome measure. These exciting developments are too recent to fully evaluate whether use of amyloid PET will prove to be a molecular imaging breakthrough. A recent paper, for instance, suggests that amyloid load (measured in terms of PIB PET activity) appears to plateau in moderate to severe dementia, and may therefore not be an appropriate outcome measure for studies at this stage of the disease.\textsuperscript{78}

How feasible is PET as a more generally used outcome measure in drug trials? The cost is higher than MRI, but not impossibly so. There was previously relatively limited availability of PET units, but this is rapidly changing, particularly when ligands are used that do not require an adjacent cyclotron. Both PET and SPECT technologies produce radioactive exposure, but less so than previously, and they can certainly be used on a number of occasions for repeat monitoring of drug study outcomes. As the molecular and metabolic basis of clinical response becomes clearer, following various neurochemical systems with PET may become increasingly a common secondary outcome measure in drug studies of disease modification and of symptomatic therapies.

**Single Photon Emission Tomography (SPECT)**

Single photon emission computed tomography, a nuclear imaging technique that also measures cerebral blood flow and receptor distribution, reveals the characteristic abnormalities of Alzheimer's disease established with PET.\textsuperscript{79} Traditionally, PET has been viewed as more quantitative and SPECT as more qualitative. There are increasingly, however, semiquantitative measurement of regions of interest applicable to both SPECT and PET methodologies. Single photon emission computed tomography has been used for prediction of which normal or slightly impaired individuals will develop dementia, with varying degrees of success.\textsuperscript{80-84} It has been used for early diagnosis of AD in demented individuals,\textsuperscript{85-87} and for monitoring of disease progression.\textsuperscript{88} Regarding the monitoring of response to therapies, there has been recent success with traditional SPECT ligands measuring regional cerebral blood flow (rCBF). Cholinesterase inhibitor treatment has reliably affected rCBF in group studies.\textsuperscript{89,93}

It is important to underline the fact that the relationship between SPECT and PET abnormalities on the one hand, and AD neuropathology on the other hand, is far from simple. Is the alteration in cbf a reflection of plaques and tangles, of neuronal loss, or of problems downstream from the microscopic pathology? In one study of MCI, for instance, it was found that
the most striking abnormality on PET was in the posterior cingulate, not previously noted as an area of intense microscopic pathology. While results on an individual level are often unpredictable, these results should encourage use of SPECT as a secondary outcome measure in future drug studies. The considerably lower cost of SPECT compared to PET, offers the possibility for a key role in the development of new treatment strategies. Realization of this potential will depend upon the development of appropriate quantification techniques. Positron emission tomography, for the moment at least, offers a wider range of ligands available to study particular neurochemical systems.

**COMBINED MULTIMODAL IMAGING**

Although major advances have been made in many neuroimaging modalities during the past 20 years, each has relative limitations in terms of spatial/temporal resolution, the specific nature of the processes measured, and cost and feasibility factors. It may be possible and even advantageous in the future to combine imaging approaches, for instance evoked responses and MRI. Combining FDG PET and volumetric MRI. With the relatively good image resolution of MRI comes the opportunity to superimpose functional images from EEG, PET and evoked potentials onto 3-dimensional anatomical maps.

**THE CURRENT AND FUTURE ROLE OF NEUROIMAGING IN DRUG STUDIES**

Should neuroimaging now be accepted as a surrogate endpoint in AD drug trials? The hope has been that these measures might prove less variable, and more sensitive to therapy, than “crude” clinical measures. Unfortunately, this point has not yet been reached. One must first consider the scientific basis for symptomatic therapies to affect brain imaging measures. There is plausible evidence cited above that functional measures – fMRI, PET, and PET activation studies – may respond to changes in cognitive networks and acetylcholine levels, and even correlate in degree of change with the improvement in cognitive symptoms. The limiting factor, however, has been a dramatic absence of replication studies and standardization, and no single functional measure is yet sufficiently validated to serve as a primary outcome measure in a symptomatic therapy trial. Nevertheless, improvement in baseline PET and SPECT measures of cfb and metabolism, and normalization of “pathologic” alterations in functional activation during memory tasks, constitute potential secondary outcome measures being considered for study in symptomatic trials.

The potential role of neuroimaging is even greater in studies of disease modification. Here it would be scientifically plausible to utilize alteration in the rate of brain atrophy, or the rate of accumulation of amyloid, as outcome measures. The limiting factor again, however, is current validation. Even MRI hippocampal volumes, the most studied imaging variable, lack the validation, standardization, sensitivity, and specificity to be used in this manner yet. Furthermore, the results of the AN19792 immunization trial have raised serious doubts about the validity of altered MRI atrophy as a measure of disease response, at least in this one form of therapy. It now appears plausible, for instance, that clinical response or stabilization might occur without a concomitant MRI or fMRI response. The variability between patients and labs may simply be too great to achieve a simple, universally accepted approach to imaging data. The establishment of the Alzheimer Disease Neuroimaging Initiative (ADNI), which seeks to build a publically available, pan North American Imaging database for structural MRI and FDG PET, will certainly help improve imaging standardization.

Nevertheless, neuroimaging measures offer considerable potential to achieve such validation in the future. Measures such as hippocampal volume, fMRI memory activation, FDG and amyloid PET (all for AD), and quantitative MRI lesion measurements (in vascular dementia), have steadily moved towards acceptable reliability. Currently a number of Phase 3 trials of stabilization therapies are using MRI atrophy measures as secondary outcome measures. Atrophy of the hippocampus and whole brain appear most reliable, with a demonstration of a significant change in the annual rate of atrophy in the treated group constituting a positive outcome of therapy. Improvement in baseline PET and SPECT measures of cfb and metabolism, and normalization of “pathologic” alterations in functional activation during memory tasks, constitute other secondary outcome measures being considered for study.

In summary, it is our opinion that while promising, these neuroimaging measures are not yet sufficiently developed to replace clinical primary outcomes. We consider these neuroimaging modalities currently to be promising biomarkers, rather than acceptable surrogate endpoints for clinical response. We would therefore suggest that such neuroimaging biomarkers be included, wherever possible, as secondary endpoints for therapeutic phase III trials of symptomatic and stabilization therapies. They should not replace clinical measures, but the presence of imaging alterations (for instance, decreased rate of hippocampal atrophy in those subjects treated with prophylactic medications) will strongly support clinical claims for altering the natural history of AD or MCI. We would strongly encourage the use of neuroimaging measures (MRI, PET) in addition to clinical evaluation and care, as secondary measures in every study, particularly those with MCI or vascular components.

**REFERENCES**


