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# MRI biomarkers — a precision medicine tool in neurology?

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## Abstract

Two new studies highlight the potential of neuroimaging to aid the differential diagnosis of neurodegenerative disease, for both clinical practice and emerging trials. Although this approach holds great promise, meaningful implementation of neuroimaging as part of a tailored precision medicine strategy may require additional imaging and non-imaging biomarkers.

We are entering an era of clinical trials of disease-modifying agents that target misfolded proteins that are involved in neurodegenerative disease. Strategies currently under investigation include the anti-amyloid-β (Aβ) immunotherapies aducanumab and solanezumab, along with tau-targeted agents such as C2N 8E12. Aβ and tau aggregates constitute the principal histopathological hallmarks of Alzheimer disease (AD), but can also be present in related neurodegenerative diseases such as frontotemporal lobar degeneration (FTLD), and a spectrum of parkinsonian disorders that includes dementia with Lewy bodies (DLB). To enable suitable participants to be identified for clinical trials, clinicians must be able to screen patients for the underlying pathogenesis of their disease in a feasible and cost-effective manner.

Two recent studies highlight the potential utility of MRI-based neuroimaging for the differential diagnosis of neurodegenerative diseases characterized by dementia[1,2]. Harper *et al.* applied six MRI visual rating scales, as well as a machine-learning approach based on multiple rating scales, to brain scans from 184 individuals with post-mortem-confirmed dementia (101 with AD, 28 with DLB and 55 with FTLD) and 73 healthy controls[1]. Koikkalainen *et al.* tested the capacity of a visual algorithm and automated image quantification tools to discriminate between MRI scans from healthy controls ($n$ = 118) and patients with AD ($n$ = 223), frontotemporal dementia (FTD; $n$ = 92), DLB ($n$ = 47) or vascular dementia (VaD; $n$ = 24). In the latter study, the diagnoses were assigned on the basis of clinical rather than histopathological criteria. Both reports showed that MRI data could be used to achieve accurate differential diagnoses between AD, FTLD/FTD and DLB (plus VaD in the case of the Koikkalainen *et al.* study[2]).

Unlike many previous case–control diagnostic biomarker approaches that focused on diagnostic sensitivity, these new multiclass studies simultaneously evaluated several conditions and, therefore, provided a specificity that is representative of the diagnostic decisions that must be considered in a clinical evaluation. Both studies incorporated a multicentre design and used MRI data of variable quality (1–3 T field strength), which suggests that these diagnostic approaches are robust to logistical limitations that could potentially limit alternative, more computationally complex imaging biomarker approaches.

An additional desirable attribute of these studies is the use of cross-validation procedures, which should help facilitate generalization of the proposed diagnostic approaches to patients in prospective study designs and clinical examinations.

Both studies used large cohorts (257 individuals in the Harper *et al.* study[1] and 504 individuals in the Koikkalainen *et al.* study[2]), thereby providing decent statistical power to assess a multiclass diagnostic procedure. In the Harper *et al.* study,[1] the disadvantages of a smaller sample size were offset by the benefits of histopathological confirmation, which reduces the potential 'noise' that can hamper diagnostic accuracy. For example, an estimated 20–30% of individuals with a clinical diagnosis of AD have primary histopathological evidence of non-AD pathology on neuropathological examination[3]. Indeed, the visual algorithm achieved higher accuracy in the histopathologically confirmed individuals[1] than in the clinically defined cohort[2] for discriminating between patient groups (~70% and ~50%, respectively, relative to a 20% chance rate). From this perspective, diagnostic 'error' in the clinically defined cohort might reflect a neuroanatomical distribution of brain atrophy consistent with the clinical syndrome rather than the pathological source of disease. Thus, it is difficult to determine whether the higher accuracy in the Harper *et al.* study was attributable to differences in visual assessment procedures or differences in using histopathological versus clinical criteria for 'gold-standard' diagnosis. Although neither study empirically assessed comorbid pathologies, which are estimated to be present in about 25% of neurodegenerative diseases[4], an advantage of multiclass diagnostic procedures is the ability to evaluate the probabilistic likelihood of co-occurring sources of disease, such as amyloidosis in DLB, or AD neuropathology co-existing with vascular disease.

Visual MRI ratings require little computational intervention and provide a quick clinically desirable approach, but both studies found a nearly 20% boost in accuracy when machine-learning procedures were used. This added benefit suggests that a single visual assessment approach is not quite ready for translation into the clinic. In an age of big data and cheap computation, it should be feasible to implement a machine-learning approach, or some combination of visual and computationally guided diagnosis, in clinicial practice. Indeed, Koikkalainen *et al.*[2] emphasize that a Disease State Index classifier, which is essentially a probabilistic weight of each candidate diagnosis, has the potential to be easily interpreted in a clinical context, in contrast to 'black box' support vector classifiers such as the one implemented by Harper and colleagues[1].

As the imaging approaches used in both studies are prone to error, we must consider how additional sources of imaging and non-imaging biomarkers can contribute to the accuracy of differential diagnosis. As precision medicine approaches emerge in neurological practice to tailor personalized treatments at the individual patient level, it will be critical for clinicians not only to incorporate structural MRI features into the differential diagnosis, but also to consider a multimodal combination of imaging, genetic, biofluid and clinical features[5]. For example, multimodal neuroimaging combinations of MRI and diffusion tensor imaging have been shown to improve differential diagnosis and statistical power in the context of screening of individuals for clinical trials[6]. PET imaging biomarkers, including amyloid and tau radioligands, are increasingly available, and can contribute to pathological diagnosis[7].

Cerebrospinal fluid markers also reliably distinguish AD from other neurodegenerative diseases[8].

The growing field of imaging genetics highlights how single nucleotide polymorphisms are associated with distinct sources of molecular pathology, and might influence the selective vulnerability of neuroanatomical networks[9]. Likewise, autosomal dominant genetic mutations may influence the distribution of disease within a single proteinopathy, such as FTLD[10]. Finally, the clinical features of neurodegenerative disease ultimately drive a patient to seek clinical attention, and fine-grained sources of data, such as a specific pattern of language difficulty with relatively preserved memory, provide a cost-effective and reasonably accurate screen that can complement more-expensive biomarker-based diagnostic approaches.

The new studies by Harper[1], Koikkalainen[2] and colleagues contribute to the mounting evidence that neuroimaging biomarkers have an important role in the differential diagnosis of neurodegenerative diseases. Although visual ratings may require some additional machine-learning practices beyond the bedside, the integration of imaging with additional multimodal features of neurodegenerative disease is poised to translate to the execution of precision medicine practices in the neurology clinic. In turn, this personalized approach based on the source of disease should increase the likelihood of success of future clinical trials.

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## Biography

Corey McMillan is an Assistant Professor of Neurology at the University of Pennsylvania where he also is affiliated with the Penn Frontotemporal Degeneration Center and Neuroscience Graduate Group. Dr. McMillan's research focuses on using neuroimaging, genetics, and biofluids in an effort to improve early diagnosis and prognosis of neurodegenerative diseases. His research leverages sophisticated bioinformatic and statistical approaches to integrate multiple data sources in effort to identify precision medicine approaches for treating individual patients.