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Perspective

Perspective on Neurobiological and Clinical Early Indicators of Mild Cognitive Decline and Alzheimer's Disease

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Abstract

There is a need for early diagnosis, monitoring and treatment of Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI). Traditional assessments of cognitive decline have been found to lack sensitivity and accuracy in differentiating varying stages of Dementia and cognitive decline as well as being time consuming in their administration. Key components of cognition namely memory and executive function have been identified as most predicative of AD status. Brief cognitive screening tools such as the Montreal Cognitive Assessment have been recommended both as a primary clinical and research assessment offering more sensitivity in differentiating AD and MCI. However, overlapping clinical features and impairments in cognitive processing suggest a need for biological risk factors. Neurobiological indicators of cognitive deterioration have been identified implicating measures of cerebrospinal fluid and temporal lobe atrophy as potential biomarkers of early clinical phases of AD and predictors of cognitive decline. Evidence shows the utility of automated classification methods in processing and analysing multivariate neuroimaging data which improves our accuracy for the prediction of conversion of MCI to AD. In this review, we discuss the clinical usefulness of such approaches and the need for Big Data and multi-site studies in improving our understanding of AD neuropathology and confirming pathophysiological mechanisms that can reliably be used to differentiate MCI and AD and predict disease progression and cognitive decline.

Keywords
Alzheimer's disease; Mild cognitive impairment; Neuroimaging; Screening and Diagnosis; Mental Health assessments

Introduction

Alzheimer's disease (AD) affects nearly 47.5 million people worldwide with the world health organisation reporting there are 7.7 million new cases every year [1]. It was in 1906 that Alois Alzheimer identified amyloid plaques, neurofibrillary tangles, and arteriosclerotic changes in the brain of his patient Auguste D, a woman who died at age 51, with a five-year history of progressive cognitive impairment, hallucinations, delusions, and severe social impairments [2]. More than a century later, there is definitive recognition for this pathological entity named after Alois Alzheimer. AD is the most common dementia worldwide and the most disabling and burdensome health conditions of later life. This syndrome is further hallmarked with impairments in numerous cognitive domains including memory, executive function, attention, and language. According to recent estimates of associated disability and mortality dementia is the 9th most burdensome condition for people aged 60 years and over. The percentage disability adjusted life years estimates increase from 1990 to 2010 for dementia is 113% and is among the largest for any disease or disease group, comparing with 28% for ischaemic heart disease, 22% for stroke, 27% for all cardiovascular diseases, 79% for diabetes, 35% for cancer, 23% for digestive diseases, 46% for sensory impairment, and 55% for musculoskeletal diseases. Numbers of people with dementia is projected to increase to 74.7 million by 2030 and 131.5 million by 2050 [3]. Dementia also has enormous health care, economic as well as devastating social consequences [4]. Reports suggest AD and other dementias are projected to be among the top four causes of burden of disease by 2030 [5].

There is a diverse range of neurocognitive changes associated with normal aging and AD. These variations comprise differing neurocognitive dissociations, cognitive deficit profiles and gradients of structural decline in terms of grey and white matter atrophy [6]. Therefore, this variation cannot be merely described as accelerated aging but, on the contrary, represents a unique classification.

There is a clear need for early diagnosis, assessment, and treatment of AD which has resulted in classification of an AD prodrome in a subgroup of patients meeting criteria for "mild cognitive impairment" (MCI) [7]. MCI is associated with high risk for progression to AD [8]. MCI is characterised by multiple cognitive deficits which, although insufficient for a diagnosis of dementia [9], significantly impair activities of daily living and reduces the quality of life for patients [10]. Follow-up studies have demonstrated that 80% of persons with MCI convert to AD within six years of initial symptoms onset [11]. Commonly used diagnostic criteria including clinical and cognitive assessments for MCI lack predictive value for conversion to AD, which may be facilitated in part with the input of biological information such as structural magnetic resonance imaging (MRI) [12].

Clinical Indicators

Currently, most scales used to assess cognition such as the Mini-Mental State Examination (MMSE) and the Addenbrooke's Cognitive Examination Revised (ACE-R) concentrate on general cognitive domains such as memory, attention and concentration, executive functioning, language and orientation. These scales, including a recent software-based screening tool (Cambridge neuropsychological test automated battery, Cantab) designed for use under clinical supervision, need to be administered/rated by trained observers, take time to complete, and may not capture clinically important effects. Individual tests of episodic memory have been suggested to be the most predictive of AD status implying assessment of a specific aspect of cognition enhances clinical utility [13]. However, these measures may not explore other important issues for people with dementia, such as measures of pragmatic day-to-day functioning. Current cognitive tests do not assess key cognitive functions associated with activities of daily living or everyday functioning relevant for dementia. The only measure to account for global functioning and behaviour linked with key cognitive domains is the everyday cognition (ECOG) test. Measures on the ECOG relevant to everyday functioning include remembering items on a shopping list (memory) or remembering things that happened recently (life events/current affairs). However, this assessment has many drawbacks, it is for sole use by carers, excluding the person with dementia from self-rating, and is also paper-based and time-consuming in administration.

Therefore, standard cognitive screening instruments used by health professionals to screen and monitor AD and MCI, including the MMSE may lack sensitivity in clinical settings in identifying cognitive impairments [14]. In comparison, recent studies have reported sensitivity levels as high as 90% and 100% for MCI and AD using the Montreal Cognitive Assessment (MoCA) [15, 16, 17]. The MoCA covers several cognitive domains: attention, executive function, memory, language, visuo-constructional skills, conceptual thinking, calculation, and orientation. The MoCA (http://mocatest.org) was introduced in 2005 as a short (10 minute) screening instrument for cognitive impairment [17], and has been shown to have excellent psychometric properties [18]. The MMSE and MoCA offer adequate diagnostic and classification accuracy as compared to the more detailed neuropsychological test battery developed by the Consortium to Establish a Registry of Alzheimer's Disease (CERAD-NB); however, as a brief cognitive screening measure, the MoCA was more sensitive and had higher classification accuracy for differentiating MCI from healthy individuals [19]. Accordingly, the MoCA has been recommended both as a primary clinical screen and a primary cognitive screen for research [20]. Furthermore, complementing the MMSE or the MoCA with the Dementia Severity Rating Scale (DSRS) an informant-based measure of functional impairment significantly improves diagnostic accuracy [19].

However, it still remains the case that the aforementioned assessments are predominately for dementia. There is paucity of MCI-specific measures for clinical use which would further increase the diagnostic specificity between AD and MCI.

Neurobiological Indicators of MCI and AD

Biological information from structural MRI has shown consistent grey matter abnormalities in AD and MCI by comparing patients to cognitively normal older adults [21, 22]. A meta-analysis of voxel-based morphometry studies of white matter volume alterations in AD by Li *et al*. clearly

identified white matter atrophy in AD, mainly in bilateral structures implicated in memory encompassing the amygdala, hippocampus complex and entorhinal cortex [23]. Grey matter alterations in AD and MCI have been revealed by a meta-analysis noting extensive grey matter deficits present in the medial temporal lobe (including entorhinal cortex, hippocampus, parahippocampus, amygdala and uncus), thalamus, temporal, parietal, frontal, cingulate and insular cortices in AD [22]. In MCI, grey matter reductions were identified in the medial temporal lobe (including entorhinal cortex, hippocampus, parahippocampus, amygdala and uncus), temporal, thalamus, and cingulate cortex. Subtraction meta-analyses show severe grey matter deficits predominantly in the left medial lobe (including parahippocampus, amygdala and hippocampus) [22]. This subtraction analysis provided evidence that the left medial temporal lobe may be a neuroanatomical marker to evaluate disease progression from MCI to AD. Sexton and colleagues conducted a meta-analysis of diffusion tensor imaging in MCI and AD and found that fractional anisotropy was decreased in AD in all regions except parietal white matter and internal capsule, while patients with MCI had lower values in all white matter regions except parietally and occipitally [24]. They also noted that mean diffusivity was increased in AD in all regions, and in MCI in all but occipital and frontal regions.

Unfortunately, while research based on MRI data has consistently found grey matter abnormalities associated with AD [21, 22], studies attempting to predict conversion from MCI to AD have reported mixed findings [12, 25, 26, 27, 28]. Ferreira *et al*. [29] in their meta-analysis of voxel-based morphometry (VBM) studies found atrophy in the left hippocampus and parahippocampal gyri across MCI groups who converted to AD, suggesting that medial temporal lobe atrophy may have significant value in evaluating risk of conversion from MCI to AD. Recent data has identified measurements of synaptic proteins in cerebrospinal fluid (CSF) as useful biomarkers to monitor synaptic degeneration. CSF neurogranin is increased during the early clinical phase of AD and predicts cognitive decline and disease-associated changes in metabolic and structural biomarkers over time [30]. Potential biomarkers for the progression to AD include low CSF concentrations of the amyloid-β 1-42 peptide, high CSF concentrations in total tau and phospho-tau, mesial temporal lobe atrophy on MRI, and temporoparietal/precuneus hypometabolism or hypoperfusion on 18F-fluorodeoxyglucose positron emission tomography [31]. This body of work highlights development in biological fluid and imaging biomarkers that will help progress the field towards preclinical detection of AD.

However, further VBM studies are required to confirm these findings and to explore the relationship between grey matter atrophy, CSF measures and cognitive decline in these patient groups which, despite a large body of recent research [32, 33, 34], has yet to be clarified using a large sample or been inclusive of cognitive, clinical and brain imaging measures.

Furthermore, valid methods need to be chosen to meet the objectives of early and accurate diagnoses and the predication of conversion from MCI to AD. A large part of neuroimaging research as described above so far has utilised univariate (measuring only one variable) based methods or analyses which may not be sensitive in the detection of subtle changes within the brain. A revolutionary multivariate (measuring multiple variables) pattern classification analysis is a novel and pioneering approach which goes one step further and allows the simultaneous investigation of multiple voxels.

Multivariate artificial learning algorithms capable of MR imaging based classification of patient populations is one such method which is changing the way we think about diagnosis and

classification [35, 36]. Recent studies have utilised multivariate pattern recognition techniques for the diagnostic classification of patients with Bipolar disorder based on neuroimaging data [37], and this approach has been used relatively successfully by independent groups in autism spectrum disorder [36], schizophrenia [38] and AD [39].

Multivariate analyses of MRI data in AD and controls has been shown to be somewhat efficient in the identification of MCI converters. Aguilar *et al*. used automated classification methods such as support vector machines and orthogonal projections to latent structures to examine AD patients and healthy controls and to prospectively predict the conversion of MCI to AD from baseline MRI data [40]. These classification techniques yielded 83% sensitivity and 87% specificity, whilst accuracy for the prediction of conversion of MCI to AD at one-year follow-up was 86% [40]. Nevertheless limitations in accuracy using such techniques have been identified and attributed to the data used for modelling rather than to inferior methodology. Data, which is readily available and easily interpreted such as clinical, cognitive and imaging data is optimal and can also be used and incorporated into clinical practice more efficiently [41].

In turn, these techniques may prove clinically useful in improving diagnostic accuracy of mental disorders that currently rely on clinical observation and cognitive assessment alone. Serial neuroimaging measures and novel multivariate pattern classification analyses may identify and differentiate dementia with known comorbidity. Moreover, we can build robust models with the ability to predict MCI conversion. In addition, this methodology incorporates the mechanism for generating predictions of illness at the individual level and represents a major development in bridging the gap between neuroscience and clinical practice [35]. The key objective is to generate biomarker-based support to strengthen existing clinical understanding and expertise, thus improving diagnostic accuracy.

Big Data and Multi-Site Studies

Big data refers to extensive large data sets that can be analysed computationally to reveal patterns, trends, and associations. Big data has the potential to change the process of discovery in dementia and neuroscience as it has done so for a variety of fields. Global large-scale neuroscience projects such as the European Commission Human Brain Project and the White House BRAIN Initiative mandate big data neuroinformatics approaches. These approaches include multi-scale integration of the dynamic activity and structure of the brain, brain simulation, neurotechnology and research infrastructure [42].

The Alzheimer's disease Neuroimaging Initiative (ADNI) was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a 5-year public-private partnership with a cost of $60 million. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to be valuable to researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost associated with clinical trials (http://adni.loni.usc.edu/).

The establishment of infrastructure for data collection from multiple sites and to allow sharing of all raw and processed data without restriction for scientific investigation throughout the world is one of the aims of ADNI and DOD (Department of Defense) ADNI. ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through contributions from numerous key stakeholders including Alzheimer's Association; Alzheimer's Drug Discovery Foundation; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; F.; Janssen Alzheimer Immunotherapy Research and Development, LLC.; Johnson and Johnson Pharmaceutical Research and Development LLC. The Canadian Institutes of Health Research also provides funds to support ADNI clinical sites in Canada. Moreover, the private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://adni.loni.usc.edu/).

Highlights of seminal research conducted using ADNI data include identification of preclinical AD based on a number of abnormal biomarkers and cognitive markers, and assessing which measures of cognitive function and brain imaging best predict change over time and conversion of MCI to AD. A set of compiled measures of executive function encompass the WAIS-R Digit Symbol Substitution, Digit Span Backwards, Trails A and B, Category Fluency, and Clock Drawing are examples of measures included in ADNI data. These composite measures in particular have shown to be very useful in understanding MCI and AD. Data from these tests show the greatest change over time, needing a 40 % smaller sample size to detect change and have been found to be the strongest predictor of AD conversion [43]. Data from AD patients pooled from two multicentre, double-blind, Phase 3 solanezumab (EXPEDITION/2) or semagacestat (IDENTITY/2) studies, and from ADNI has shown cognitive decline precedes and predicts subsequent functional decline in mild AD dementia [44]. New operational definitions of subtle cognitive decline capturing both cognitive and functional abnormalities have been produced utilizing ADNI data which is of clinical use for diagnosis and prognosis of MCI and AD. Additionally, a new approach has been identified for staging preclinical AD, based on number of abnormal biomarkers and cognitive markers [45].

The major accomplishments of ADNI also comprises the development of standardized methods for clinical tests and the assessment of alternative methods of diagnostic categorization along with MRI and CSF biomarkers in a multicentre/multi-site setting. Furthermore multimodal methods incorporating genetic information (APOE status) and longitudinal MRI has proved most highly predictive of future decline [46].

Future Directions

In order to confirm previous findings and extend our understanding of AD, further prospective and longitudinal research into conversion to AD from MCI is required. Commonly used diagnostic criteria for MCI lack predictive value for conversion to AD [47] but may be improved by the subsequent use of biological information from structural MRI [12]. The use of big data comprising multimodal methods, across sites and automated multivariate classification techniques will further help to elucidate the pathophysiological mechanisms underlying cognitive decline and the transition from MCI to AD. The potential treatment options including pharmacological interventions for AD have not shown real promise and this may be a consequence of enrolled participants in clinical trials being advanced in the illness to derive clinical benefit [31]. Essential future research directions include clinical and preclinical neuropharmacological studies at all

stages of dementia. Another key question for future research is whether the biomarkers for cognitive decline identified in previous findings are influenced by AD medications.

Conclusion

The current research expands integral areas of the AD knowledge base relating to the reliable and sensitive monitoring of cognitive decline in AD and MCI. The commonly used assessments of cognitive decline in a clinical and research setting have been found to lack sensitivity in differentiating MCI from AD and for examining activities of daily living. The current measures have also been critiqued for their time efficiency and ease of administration. Key cognitive domains such as episodic memory and executive function have been highlighted as essential for the understanding of MCI and AD. Compared to standard clinical assessments such as the MMSE, the MoCA in particular has been shown to be more sensitive and has higher classification accuracy for differentiating MCI from healthy individuals and AD. The MoCA as a brief cognitive screening tool has been recommended both as a primary clinical screen and a primary cognitive screen for research.

Potential biomarkers for the progression to AD have been suggested, these include low CSF concentrations of the amyloid-β 1-42 peptide, high CSF concentrations in total tau and phospho-tau and neurostructural biomarkers of decline, implicating the role of the temporal lobe network in predicting onset and progression of AD. However, early accurate and differential diagnosis of MCI and AD poses significant challenges to clinicians and a large body of neuroimaging literature utilises univariate analytic methods. These methods are not sensitive to subtle differences in conditions, such as overlapping clinical features and impairments in cognitive processing. At present there is a paucity of validated biological risk factors based on neuroanatomy and function. Recent advances in neuroimaging and neuroinformatics may aid the discovery of neurostructural/functional biomarkers. Automated classification methods have shown some success in accurately predicting conversion of MCI to AD. As the methodology develops, appropriate data needs to be selected and readily available for use in a clinical setting.

The use of big data and multi-site/centre studies is one solution to provide such data in advancing the Identification of biologically-valid risk and also protective factors using cutting-edge neuroimaging techniques. Programs such as ADNI have provided worldwide impact through data collection and sharing and allowed integration of ADNI biomarker and clinical data to stimulate research. This has led to numerous insights including new operational definitions of cognitive decline, identifying new approaches for staging preclinical AD, and the utility of multimodal methods incorporating imaging data which is proving to be a strong predictor of future decline. These findings will guide crucial developments towards improving clinical and functional outcomes in patients with MCI and AD. We are now faced with the challenge of integrating findings into an explanatory framework for clinically indistinguishable disorders.

Competing Interests

The author declares that no competing interests exist.

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