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Editorial

Predictive Biomarkers for Alzheimer's Disease Using State-of-the-Art Brain Imaging Techniques

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Human life expectancy is increasing steadily as a result of the significant advances made in scientific and medical research, as well as technological and economic development. With the resulting substantial increase in the aging population, there has been a concurrent increase in age-related brain disorders. Of these, Alzheimer's disease (AD) is one of the most common brain disorders, with an estimated thirty-five million people affected worldwide. AD has become a silent tsunami in the aging population and the resulting economic burden on the healthcare system runs into billions of dollars. The last decade has seen milestone developments in AD research that have been pivotal in furthering our understanding of the disease's pathobiological-mechanism. However, AD diagnosis continues to primarily rely on various neuropsychological tests, which can detect the disease only after the manifestation of clinical symptoms [1].

There is an urgent need for the development of reliable diagnostic biomarkers that can detect AD pathology at an incipient stage. Such biomarkers will not only aid in the early detection of AD, but will also pave the way to effective clinical trials. The biomarkers presently used for AD are either genetic, such as apolipoprotein E4; cerebrospinal fluid-derived, such as amyloid-β and tau; or brain pathology-linked biomarkers that are detected with brain imaging techniques, such as magnetic resonance imaging (MRI) [2], diffusion tension imaging (DTI) [3], magnetic resonance spectroscopy (MRS) [4–7], functional MRI (fMRI) [8], positron emission tomography (PET) [9], arterial spin labeling (ASL) [10], etc. Multicentric approaches, such as the Alzheimer's Disease Neuroimaging Initiative, are excellent initiatives and are playing an instrumental role in the development of novel AD biomarkers [11]. This special issue focuses on the latest strides made in identification of diagnostic biomarkers using state-of-the-art brain-imaging modalities.

Fayed et al. have provided an excellent introductory review on the application of various MRI technologies for diagnosis as well as progression monitoring of AD during clinical trials. Gold et al. have investigated the white matter microstructure integrity changes with DTI in patients with amnestic mild cognitive impairment (aMCI). They have shown that the white matter microstructural changes in aMCI patients that could not be attributed to atrophy, but are best characterized by reduced fractional anisotropy (FA), and assessment of this FA decline, thus improved the classificatory accuracy of aMCI. Teipel et al. present a large scale multicenter study that compared multicenter reliability and diagnostic accuracy of both volumetric MRI and DTI. They found superior accuracy of grey matter volume changes detected with volumetric MRI, as compared to FA changes detected with DTI, for the discrimination between AD patients and healthy controls.

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MRI-based detection of structural alterations in cognitively normal subjects can aid in the early identification of AD. Smith et al. show that volume of the anteromedial temporal brain region is reduced in normal individuals who are destined to develop MCI and propose that its volume might serve as a predictor of memory impairment. Another potential early indicator of functional cognitive dysfunction might be the compensatory changes in activity of brain networks. Using ASL, Bangen et al. show that individuals at genetic risk for AD by virtue of the APOE $\varepsilon 4$ allele, exhibit increased resting cerebral blood flow (CBF), as well as an increased CBF and blood oxygenation level dependent (BOLD) response to memory encoding in the medial temporal lobes, as compared to $\varepsilon 4$ non-carriers. Such compensatory changes in activation can provide early indication of AD pathology-induced brain dysfunction, and thus serve to identify those at risk for AD.

MRS is a powerful non-invasive imaging technique that can provide crucial information about AD pathology-induced alteration in various neurochemical levels. Using phosphorous (^{31}P) MRS, we have identified key neurochemical changes in the left and right hippocampi of MCI and AD patients as compared to cognitively normal subjects. We observed a significant increase in phosphodiester, a membrane breakdown product, and a corresponding decrease in phosphomonoester, the building block of neuronal membrane, in both hippocampi. These changes are a characteristic signature of membrane degradation and can serve to indicate onset of neurodegenerative pathology associated with AD. Furthermore, we observed that pH levels show an interesting trend of inversal, from acidic in MCI patients to alkaline in AD patients in the left hippocampus, suggesting that monitoring of pH level in the left hippocampus might provide an excellent indicator of the converting MCI-to-AD population.

Transgenic animal model with AD pathology can be imaged at higher magnetic fields, and thus provide an excellent means of validating *in vivo* AD biomarkers involving neurochemical alterations. Mlynarik et al. have performed MRS studies at 14.1T on transgenic 5×FAD mice; they report an increase in myo-inositol, and decrease in N-acetylaspartate and γ-aminobutyrate concentrations, which is typical of human AD pathology. Utilization of MRS technique requires the effective signal processing scheme from different metabolites for accurate data analysis [12]. Cudalbu et al. have reviewed the various methodologies for macromolecules estimation in *in vivo* ^{1}H MRS and suggest that the addition of *in vivo* measured macromolecule spectrum in the quantification step significantly improves the reliability and accuracy of metabolite concentrations.

While MRI provides anatomical information about the brain, fMRI provides crucial information about the brain regions involved during the performance of a specific task. fMRI can aid in deciphering the neural basis of cognitive impairment in AD and MCI patients, and can detect the changes in functional activation and connectivity in these patients.

We review the diagnostic potential of monitoring functional network alterations related to visuospatial perception deficits in AD. We summarize the scope and key advantages of utilizing the functional brain activation correlates of visuospatial perception processing deficits in AD as an early diagnostic as well as a progression tracking biomarker for AD. In a complementary review, Yamasaki et al. describe the neuroanatomy of visual processing and discuss the proposed neural mechanisms for visual processing deficits in individuals with AD. They present a review of event-related potential and fMRI findings related to visual perception in AD and MCI and discuss these finding in context to their own work in this field. In addition to network activation associated with specific cognitive tasks, neural activity is also present in the "default network" during resting state. Dr. Sperling and colleagues provide a comparative review of monitoring task-dependent activation and default activity in revealing the functional alterations associated with healthy aging as well as MCI and AD.

The selection of brain templates has a profound effect on the result of data analysis from fMRI as well as other imaging studies. We provide a comprehensive review of the most commonly used brain templates, highlighting the methodology utilized to generate such templates. We discuss the immense applicative uses of population- and disease-specific brain templates during standardization and data analysis of various neuroimaging studies, and stress the need for generating the two major pending population-specific brain atlases from the Indian and African populations.

Moreover, it is also important to utilize the appropriate data processing and analysis methodology. Abdi et al. present a study that utilized Multiblock Barycentric Discriminant Analysis (MUBADA), which integrates multiple regions of interest (ROIs), to analyze regional CBF data obtained with PET/SPECT (single-photon emission computerised tomography) from AD, frontotemporal dementia, and elderly normal subjects. They report that MUBADA, in addition to classifying these subject groups, can also provide

additional information about the best discriminative ROIs and voxels.

Richard and colleagues' article presents a thought-provoking case for a paradigm shift in dementia research and biomarker development and argues for a rethink of the age-old hypotheses (i.e., the amyloid cascade hypothesis) and assumptions (i.e., the emphasis on the role of plaques and tangles) in dementia research, which only serve to limit the scope of biomarker development. In addition to aiding in early and accurate diagnosis of AD, imaging modalities such a MRS and fMRI can provide an invaluable tool for examining the molecular and functional therapeutic effects, respectively, of potential AD treatments. In a preliminary study using functional connectivity MRI, Zaidel et al. demonstrate that treatment of mild AD patients with donepezil, a cholinesterase inhibitor, led to a significant increase in interhemispheric functional connectivity of the left and right dorsolateral prefrontal cortices.

Further, imaging techniques, such as electroencephalography and fMRI, can also provide an interactive interphase between brain signals and environment. Liberati et al. propose a non-invasive brain-computer interface that relies on a classic conditioning paradigm to detect a patient's emotional and cognitive state—rather than the standard invasive brain computer interface that relies on voluntary modulation of brain activation—for AD patients who have lost the ability to communicate and higher cognitive function. Such technology would not only enable a means of basic communication but also be able to provide vital information about the effect of clinical drugs on brain function and cognition.

In conclusion, utilization of combined imaging modalities can provide a much-needed platform for identification of novel molecular, structural, and functional biomarkers for AD. In order to identify the earliest biomarkers of AD, further research is needed to understand which of the above mentioned changes (neurochemical alterations, structural changes and atrophy, or functional alterations in brain networks) is causally related to the onset of AD. It is our hope that this issue will enrich the quest for a predictive diagnostic biomarker for AD using multi-model imaging approach.

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REFERENCES

[1] Lopez OL, Becker JT, Klunk W, Saxton J, Hamilton RL, Kaufer DI, Sweet RA, Cidis Meltzer C, Wisniewski S, Kamboh MI, DeKosky ST (2000) Research evaluation and diagnosis of probable Alzheimer's disease over the last two decades: I. *Neurology* **55**, 1854-1862.

[2] Fox NC, Freeborough PA (1997) Brain atrophy progression measured from registered serial MRI: Validation and application to Alzheimer's disease. *J Magn Reson Imaging* **7**, 1069-1075.

[3] Ringman JM, O'Neill J, Geschwind D, Medina L, Apostolova LG, Rodriguez Y, Schaffer B, Varpetian A, Tseng B, Ortiz F, Fitten J, Cummings JL, Bartzokis G (2007) Diffusion tensor imaging in preclinical and presymptomatic carriers of familial Alzheimer's disease mutations. *Brain* **130**, 1767-1776.

[4] Mandal PK, Tripathi M, Sugunan S (2012) Brain oxidative stress: Detection and mapping of anti-oxidant marker 'Glutathione' in different brain regions of healthy male/female, MCI and Alzheimer patients using non-invasive magnetic resonance spectroscopy. *Biochem Biophys Res Commun* **417**, 43-48.

[5] Mandal PK (2007) Magnetic resonance spectroscopy (MRS) and its application in Alzheimer's disease. *Concepts Magn Reson Part A Bridg Educ Res* **30**, 40-64.

[6] Shonk TK, Moats RA, Gifford P, Michaelis T, Mandigo JC, Izumi J, Ross BD (1995) Probable Alzheimer disease: Diagnosis with proton MR spectroscopy. *Radiology* **195**, 65-72.

[7] Kantarci K, Petersen RC, Przybelski SA, Weigand SD, Shiung MM, Whitwell JL, Negash S, Ivnik RJ, Boeve BF, Knopman DS, Smith GE, Jack CR Jr (2008) Hippocampal volumes, proton magnetic resonance spectroscopy metabolites, and cerebrovascular disease in mild cognitive impairment subtypes. *Arch Neurol* **65**, 1621-1628.

[8] Sperling RA, Bates JF, Chua EF, Cocchiarella AJ, Rentz DM, Rosen BR, Schacter DL, Albert MS (2003) fMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **74**, 44-50.

[9] Butters MA, Klunk WE, Mathis CA, Price JC, Ziolko SK, Hoge JA, Tsopelas ND, Lopresti BJ, Reynolds CF 3rd, DeKosky ST, Meltzer CC (2008) Imaging Alzheimer pathology in late-life depression with PET and Pittsburgh Compound-B. *Alzheimer Dis Assoc Disord* **22**, 261-268.

[10] Alsop DC, Detre JA, Grossman M (2000) Assessment of cerebral blood flow in Alzheimer's disease by spin-labeled magnetic resonance imaging. *Ann Neurol* **47**, 93-100.

[11] Trojanowski JQ, Vandeerstichele H, Korecka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter WZ, Weiner MW, Jack CR Jr, Jaust W, Toga AW, Lee VM, Shaw LM (2010) Update on the biomarker core of the Alzheimer's Disease Neuroimaging Initiative subjects. *Alzheimers Dement* **6**, 230-238.

[12] Mandal PK (2012) *In vivo* proton magnetic resonance spectroscopic signal processing for the absolute quantitation of brain metabolites. *Eur J Radiol* **81**, e653-e664.