

Editorial

Introduction to special edition, “State of the Field: Advances in Neuroimaging from the 2016 Alzheimer’s Imaging Consortium”

The Neuroimaging Professional Interest Area (NIPIA) of the Alzheimer’s Association is honored to partner with *Alzheimer’s and Dementia: Diagnosis, Assessment and Disease Monitoring (DADM)* on this inaugural special issue: *State of the Field: Advances in Neuroimaging from the 2016 Alzheimer’s Imaging Consortium*. This special issue comprises 12 original research and review articles from the groups that were presented at the 2016 Alzheimer’s Imaging Consortium (AIC) in Toronto, a one-day preconference dedicated to advancements in the field of neuroimaging in Alzheimer’s disease (AD) and related disorders.

The work within this special edition reflects the highly relevant and timely topics emphasized at the 2016 AIC conference—Tau Imaging, Imaging Genetics, and Brain Networks and Connectomics. The research presented at the AIC conference and within this edition encapsulates cutting-edge neuroimaging studies from research groups across the globe. Data presented in the Tau Imaging session were reflective of this rapidly evolving imaging modality and spanned a diverse range of populations in which Tau pathology may be particularly relevant—including comparisons of healthy younger and older normal control subjects to typical AD dementia patients and rare microtubule-associated protein tau (MAPT) mutation carriers. In the current issue, Vemuri et al. in their study provide a thorough analysis of regional Tau uptake measured using the AV1451 radiotracer in a large cohort of young and older participants [1]. Their analyses suggest that an age adjusted normalization procedure can address signal properties that differ across brain regions and facilitate regional comparisons. Shimada et al. present a multimodality neuroimaging study of Tau (¹¹C-pyridinyl-butadienyl-benzothiazole 3 [PBB3]-Positron emission tomography [PET]), Amyloid (¹¹C-Pittsburgh Compound B [PIB]-PET), and neuronal integrity [structural magnetic resonance imaging [MRI] and ¹⁸F-Fludeoxyglucose [FDG]-PET) in participants across the aging (young and older normal control subjects) and AD spectrum [2]. These analyses revealed associations between medial temporal lobe Tau and memory among low amyloid normals, as well as the spreading of Tau beyond the medial temporal lobe that was aligned with gray matter atrophy and hypome-

tabolism as the disease progressed. The work presented in the Tau Imaging session and published herein are emblematic of the role of this modality to glean insights into disease progression, as well as to draw attention to important methodological issues that will inform the interpretation of this signal in human participants.

The Imaging Genetics session at AIC covered an array of exciting findings and innovative analytical approaches, providing excellent representation of the complex approaches that are necessary to link genetic data to imaging phenotypes. This special edition features work by Stage et al., who investigated individual a priori risk loci previously identified in the large International Genomics of Alzheimer’s Disease Consortium Project genome-wide association study (GWAS) contrasting AD patients with control subjects [3]. Although multiple risk loci have emerged from the International Genomics of Alzheimer’s Disease Consortium Project analysis, mechanisms underlying these genetic risk factors remain unknown and can be informed using large neuroimaging studies. Stage analyses revealed differential associations among individual risk variants, brain atrophy, and glucose metabolism across the disease spectrum. Work by Gispert et al. established the impact of the *APOE* $\epsilon 4$ genotype on the association between cerebrospinal fluid (CSF) markers of neuroinflammation (YKL-40 and soluble TREM2) and brain atrophy [4]. These analyses revealed, specifically in *APOE* $\epsilon 4$ carriers, that YKL-40 is elevated early in AD development and that elevated YKL-40 was associated with worse temporal lobe atrophy. Thus, in addition to *APOE* $\epsilon 4$ being a risk factor for abnormal accumulation of β -amyloid, this genotype may also exert a detrimental impact via inflammatory pathways. Overall, the research presented at AIC and covered within this edition on the topic of Imaging Genetics provides important insight into the complexity of the heritability of sporadic AD and the value of using imaging phenotypes to elucidate underlying pathways.

The final topic featured at AIC was Brain Networks and Connectomics. This session covers a wide array of topics, demonstrating how measures of network integrity evolve throughout the AD trajectory. Using an ICA approach,

Contreras et al [5]. demonstrate that subjective cognitive complaints and objective memory performance differentially map onto connectivity changes across distinct brain networks. Nuttall et al. in their study also examined integrity across multiple brain networks, focusing on measures of within and between-network connectivity [6]. This work revealed that intranetwork connectivity was associated with disease severity and that this effect was present across multiple networks. Finally, Dickerson et al. provide an alternative perspective on network involvement in AD by implicating that multiple distinct spatial patterns of atrophy exist among AD patients [7]. Specifically, this work revealed that younger AD patients (age < 65 years) had atrophy in brain networks involving the posterior cingulate, lateral parietal, and frontal lobes, whereas older AD patients (age > 80 years) demonstrated atrophy in brain networks involving anterior medial and lateral temporal cortices. Importantly, these patterns were largely nonoverlapping, reflective of distinct networks defined by resting state functional connectivity work, and consistent with a dissociation in cognitive deficits across patient groups (the younger AD dementia group was associated with an encoding deficit, whereas the older AD dementia group demonstrated a semantic memory deficit). Overall, this work spanning multiple research groups and analytic approaches provides important insight into the involvement of multiple brain networks in the AD trajectory.

In addition to the featured research topics covered at the AIC conference, this special edition also includes work that highlights the immediate clinical relevance of AD neuroimaging technologies. Vemuri et al. review the literature surrounding imaging markers of cerebrovascular disease, a topic that is relevant for understanding the impact of cerebrovascular disease on dementia risk [9]. Work by Verfaillie et al. [8] and Rana et al. [10] shows that baseline measures of gray matter atrophy predict progression to AD dementia among clinically asymptomatic participants. Along these lines, La Joie et al. in their study examined the associations between item-specific cognitive complaints and abnormal amyloid levels among nondemented older individuals and found that a specific profile of complaints may be predictive of early amyloid accumulation [11]. The ability to predict future progression and the presence of elevated abnormal amyloid among asymptomatic older individuals is of utmost importance as the field moves toward prevention strategies and aims to identify at risk individuals before clinical symptoms are present. Finally, Apostolova et al. in their study explore the "Appropriate Use Criteria" for Amyloid Imaging in AD dementia patients scanned with Flortbetapir PET [12]. This study found that early onset patients were more likely to be amyloid positive and were more likely to undergo a change in therapy based on amyloid scan results, highlighting the utility of amyloid PET imaging in the management of patients with early onset AD. Furthermore, the higher rate of amyloid-negative scans in the late onset group,

despite this group being inconsistent with the Appropriate Use Criteria, suggests a utility of amyloid PET in this population as well.

Overall, the research comprising this special edition reveal promising insights into the AD trajectory, and highlight the ability to measure these processes in living humans using neuroimaging.

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