Neuroimaging Advances in Neurologic and Neurodegenerative Diseases

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Neuroimaging tools, including magnetic resonance imaging (MRI), positron emission tomography (PET), and others (computerized tomography (CT), single-photon emission computerized tomography (SPECT), etc.) can be important biomarkers for identification, tracking, diagnosis, and treatment monitoring of neurologic diseases. Widely used in neurodegenerative disorders like Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), and Parkinson's disease (PD) and associated disorders, neuroimaging methods are also applied to many other neurologic diseases to uncover important information about underlying biology, diagnostic classification, and treatment response. The most commonly used neuroimaging techniques for neurodegenerative disorders are MRI and PET, which are further described in this issue of *Neurotherapeutics* by C. Schwarz (2020) [1]. Although Dr. Schwarz's review is largely focused on neurodegenerative diseases, the methodologies described are generally applicable to all types of neurologic disease.

In neurodegenerative diseases, we observe significant patterns of atrophy on MRI that are generally disease-type specific. In addition, the advent of PET tracers that target two of the major proteinopathies in AD and other diseases, amyloid and tau, has allowed for early detection, monitoring of disease progression, and disease-specific target outcomes in clinical trials. Findings and future directions of studies of neuroimaging biomarkers in AD are explored in the review by Buckley (2020) [2]. Unfortunately, many other proteinopathies, such as TDP-43, a major cause of FTLT, and alpha-synuclein, a major cause of PD, PD dementia, and Lewy body dementia (LBD), are not yet able to be visualized using PET. In these cases, MRI is the primary tool used to assess changes in TDP-43-related dementia and alpha-synuclein-associated dementias. Findings from MRI and other imaging

tools from the different FTLT forms and the link of these differences to the underlying pathology (i.e., tau, TDP-43, etc.) are explored by Peet et al. (2021) [3]. This review captures the variability and heterogeneity in FTLT and their links to imaging patterns. Finally, Brooks (2020) provides a comprehensive review of neuroimaging in PD and related disorders (such as LBD), focusing on MRI, SPECT (i.e., DATScan), and PET findings (primarily dopamine-focused and other neurotransmitter-focused tracers) [4].

A major goal of neuroimaging tools in studies of neurodegenerative disorders is to define the best markers for therapeutic trials. For example, neuroimaging can be used to screen individuals for those at highest risk to have the pathological target of a therapeutic agent. In addition, neuroimaging tools may be used as secondary, and perhaps one day, primary endpoints of therapeutic trials. A. Schwarz (2020) reviews the use of neuroimaging in therapeutic trials, exploring these issues in depth [5]. Although the focus is on therapeutic trials of neurodegenerative conditions, neuroimaging can be used in this fashion in therapeutic trials for many types of neurologic diseases.

Given the recent approval of aducanumab (Aduhelm), a drug which directly targets and clears amyloid from the brain, as a disease-modifying treatment for AD, neuroimaging of amyloid now has clinical relevance to treatment course. Although these are early days, amyloid imaging techniques are at the forefront of the personalized care of AD and important for determining those eligible for this new drug. However, the prospect of providing amyloid status to individuals with symptoms and even perhaps without symptoms on a large scale brings up many potential ethical questions about returning these results to patients. Wilkenfeld et al. (2020) cover the findings to date on return of results, primarily of amyloid PET results, in both symptomatic and asymptomatic individuals [6]. They suggest that it is the clinician's duty to inform or at least try to provide information to hesitant symptomatic individuals and their loved ones using a transactional model of communication.

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In addition to the sporadic and familial neurodegenerative conditions primarily associated with aging, chronic traumatic encephalopathy (CTE) is a neurodegenerative condition thought to be caused by repetitive head trauma. Studies in individuals with CTE have suggested neurodegenerative changes visible on MRI, with little evidence of binding of tau tracers developed for AD. Neuroimaging and other biomarker studies of CTE are explored by Alosco et al. (2020) [7]. Unfortunately, specific biomarkers for CTE, such as CTE-tau focused PET tracers, are not yet available. Future neuroimaging research in this area will allow for a better understanding of the specific patterns and pathologies associated with repetitive head trauma and hopefully novel treatments to combat CTE.

Other neurologic disorders have been investigated with neuroimaging and other biomarker tools. In particular, neuroimaging studies are commonly used in pre-surgical planning and other studies related to temporal lobe epilepsy, as reviewed by Goodman and Szaflarski (2021) [8]. In addition, research studies investigating changes in brain functional and structural connectivity in patients with epilepsy have allowed for a better understanding of the underlying biological changes associated with disease. Other neuroimaging studies have focused on psychiatric disorders, including anxiety, depression, addiction, and psychosis. Recently, transcranial magnetic stimulation has been proposed as a treatment for and biological probe of underlying pathology in schizophrenia. Findings from neuroimaging studies related to these novel methods of treatment are explored by Brandt and colleagues (2020) [9]. Finally, non-central nervous system (CNS) diseases and associated treatments can show effects in the brain and on cognition. For example, non-CNS cancers and their chemotherapeutic and/or hormonal treatments have been associated with cognitive effects, known as cancer- and treatment-related cognitive dysfunction (CRCDD). CRCDD has been shown to relate to structural findings on MRI, which are summarized by McDonald (2021) [10]. As development of novel cancer treatments continues, the impact of therapies for cancer and CRCDD on neuroimaging-assessed brain structure and function, as well as cognition, is important to consider.

In this issue of *Neurotherapeutics*, we invited experts in neuroimaging across neurologic diseases to summarize the state of the field and propose steps needed to move the field forward. As medical science has begun to move towards the idea of personalized medicine, where assessments, diagnostics, and therapeutics are tailored to an individual's genetic background, amount and type of pathologic presentation, lifestyle, and other factors, the integration of neuroimaging into decisions about the development and

use of targeted therapeutics will continue to advance medical treatment and provide increased efficacy of life-saving treatments.

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