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EVOLUTION OF NEUROIMAGING TECHNOLOGY IN THE MODERN ERA

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Clinical applications in brain science have progressed at a glacial pace when compared to other medical disciplines. Treatments for most neurodegenerative brain diseases are limited, and cure strategies remain underdeveloped. Pressure to improve clinical outcomes in the neurological sciences is exacerbated by an aging population at risk for degenerative brain diseases. Fortunately, technical advances in the field of neuroimaging offer new promise, with enhanced characterization of microstructural anatomy, network connectivity, and functional biomarkers of health and disease. Articles highlighted in this issue describe cutting-edge applications targeting these outcomes using diffusion tensor imaging, diffusion-based tractography, and positron emission tomography. Finally, the glymphatic system is reviewed as a target for future neuroimaging investigation in clinical populations such as those with Alzheimer's disease. Integration of these methods with new advances in computational science will inform mechanisms of healthy and dysfunctional brain mechanisms and ideally lead to new targeted therapeutic interventions.

Key words: Neuroimaging; Alzheimer's disease; Aging

The human brain remains one of the most puzzling mysteries in the known universe. Encased in bone and vulnerable to slight homeostatic disruption, the brain is not easily examined by observational methods or invasive experimental procedures. Early perspectives of basic structure-function relationships were informed by clinical evaluation of individuals who had survived traumatic brain injury, such as Mr. Phineas Gage (3). However, the resulting models of brain organization and physiology were incomplete due to heterogeneity in lesion location and severity across individuals and limited capacity to measure the impact of focal lesions on larger networks described in histopathological studies. New technical insights were needed to bridge the science from histopathological bench work to in vivo examinations of complex human behavior. The requisite technology in brain science would not be available for nearly a century after the clinical description of Mr. Gage.

By contrast, progress in the prevention, diagnosis, and treatment of diseases peripheral to the central nervous system (CNS) progressed steadily over this time period, with more rapid advances after the mid-1900s. Cardiovascular and cerebrovascular diseases previously known as fatal became manageable for many individuals with medications, surgery, and/or changes in lifestyle factors related to disease onset and progression (e.g., smoking, obesity). Similar breakthroughs in the prevention and treatment of other disease areas (e.g., diabetes) eclipsed the pace

of discovery in brain science. The discrepancy in treatment options for conditions above vs. below the neck contributed to a growing population of adults living longer lifespans, including a growing number of individuals with age-associated neurodegenerative diseases (8). The limited treatment options for the projected expansion of adults with neurodegenerative diseases of the brain such as Alzheimer's disease, growing healthcare costs, and increasing numbers of uninsured individuals all pointed towards an emerging health crisis.

Political pressure culminated in a Presidential proclamation signed in 1989 declaring the period from 1990-1999 as the "Decade of the Brain" (5). The initiative targeted 14 areas in the neurological sciences primed for breakthroughs in prevention, treatment, and cures for the most vexing and common neurological conditions. The Decade ended with few treatments and no interventions capable of reversing or halting common forms of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, or vascular dementia. However, innovative work in the field of neural bioinformatics and neuroimaging flourished during this period, and enthusiasm was high that neuroimaging technology seeded during the 1990s would significantly alter the cadence of brain science outcomes in the near future (10). This prediction proved accurate as borne out through subsequent research that leveraged a historical foundation in magnetic resonance imaging (MRI).

Early MRI systems introduced in the 1970s provided researchers and clinicians with vastly improved spatial resolution of brain anatomy compared to radiographic methods of the past. High field MRI using 1.5 Tesla (15,000 Gauss) became common in both research and clinical settings, followed by the introduction of 3 Tesla systems. The image resolution of 3 Tesla MRI is approximately 16 times that of 1.5 Tesla systems, allowing for significantly improved signal-to-noise ratio and improved anatomical detail. Eventually, 4 Tesla and even 7 Tesla systems were introduced at select research centers, the latter providing a magnetic field 140,000 times that of earth's gravitational force. The improvements in image acquisition at higher field strengths combined with robust post-processing algorithms improved visualization of both healthy and pathological brain tissue (11).

Anatomical detail provided by high field MRI opened a new world of brain structure-function relationships supported by the demarcation of tissue classification into cortical gray matter, subcortical white matter, and subcortical gray matter. Volumes of brain regions (e.g., frontal lobe) and specific nuclei (e.g., caudate nucleus) could be readily quantified and contrasted between patient groups and healthy controls or analyzed within groups to determine the degree of shared variance between brain volumes and measures of cognition, personality, or emotion. Landmark studies revealed reduced hippocampal volume in the earliest stages of Alzheimer's disease (6), microvascular infarcts in subcortical white matter (2), as well as numerous other clinically relevant findings. However, the focus on specific nuclei and regional lobes belied the anatomical complexity of the brain previously characterized in histological studies. Work dating back to Golgi and Cajal (1) brilliantly revealed the multiplex architecture of neural networks using relatively crude methods in the 1800s, yet modern neuroimaging studies restricted analyses to focal brain regions. In effect, the field defaulted to a digitized version of phrenology, ascribing complex and diverse human behaviors to isolated brain volumes. New technology was needed to measure brain network integrity on a larger scale.

The introduction of diffusion tensor imaging (DTI) opened a new technical portal away from the hyper-focused regionalization of volumetric studies. DTI measures the *rate* and *direction* of water flow (i.e., hydrogen) in the brain, both of which are altered by neuronal damage (9). Common DTI outputs include scalar metrics of water diffusion, such as fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity (see Baker et al. in this issue for review). Refinement of DTI pulse sequences during the Decade of the Brain allowed researchers to visualize network connections by measuring the curvature of the diffusion metrics along known anatomical fasciculi. For the first time, the structural integrity of the brain (later referred to as the connectome) (12) could be defined. Subsequent studies developed methods to quantify the integrity of brain white matter tracts

identified using specialized processing methods for DTI outcomes. One such method, quantified fiber bundle length, is described in the current issue by Zhang. Compelling evidence demonstrates the sensitivity of quantified fiber bundle length to perturbations in cognition and to genetic risk alleles associated with reduced brain integrity (see Baker et al. in this issue). Technical improvements to DTI applications continue to develop, including advances in pulse sequences and post-processing data computations. In the current issue of this journal, Salminen et al. describe a method to improve the DTI signal by suppressing artifact generated by cerebrospinal fluid (CSF). Application of this CSF-suppression method offers improved anatomical precision of DTI-informed network models and more robust characterization of the scalar indices.

A notable limitation of both structural MRI and DTI is the absence of direct functional information about the brain. Functional information is most commonly derived from functional MRI (fMRI) or positron emission tomography (PET). fMRI was introduced in the early part of the Decade of the Brain at the Society for Magnetic Resonance in Medicine annual meeting in 1991. The fMRI signal is generated by changes in the blood deoxyhemoglobin concentration associated with cognitive activity completed by the individual while inside the MR unit. The spatial resolution of fMRI for cortical functions is quite good, but poor temporal resolution and high data processing demands have restricted widespread adoption in clinical settings.

By contrast, PET has long been the workhorse of clinical functional brain imaging. PET is capable of detecting functional properties of the brain at the level of proteins or brain regions depending on the selection of isotopes or ligands. The degree of anatomical specificity provided by PET represents an advantage over fMRI. Ligands are available for specific neurotransmitters (e.g., dopamine) and specific proteins, such as amyloid. In this issue, Cohen reviews the research and clinical relevance of Pittsburgh Compound-B (PiB), a PET ligand that selectively binds to the amyloid plaques characteristic of neuropathology related to Alzheimer's disease (13). PiB imaging is at the forefront of modern neuroimaging innovation, supported by evidence of abnormal PiB amyloid binding among older individuals at risk for future diagnosis of Alzheimer's disease (reviewed by Cohen).

In addition to serving as markers of disease mechanisms, neuroimaging tools are sensitive to changes in brain integrity following treatment. Tate et al. review evidence of changes in PET, fMRI, and DTI indices following neuromodulation methods. PET imaging targeting the dopamine system reveals a potential mechanism of action of repetitive transcranial magnetic stimulation, and DTI studies reveal improvement in fractional anisotropy in the brain ipsilateral to the treated hemisphere (as reviewed by Tate et al.). Additional randomized clinical trials are required to define the efficacy of neuromodulation and the impact of treatment on brain network function, yet the innovative methods represent an intriguing non-pharmacological approach or adjuvant treatment to maximize current pharmacological interventions.

This special issue of *Technology and Innovation* concludes with a contribution from Huffman et al. introducing a new frontier in imaging with high research and clinical relevance. The glymphatic and perivascular waste clearance systems identified recently in the brain have sparked both controversy and innovation (7). Once considered anatomically distinct from the periphery, the CNS is linked to the periphery through pathways that facilitate clearance of waste products across the blood-brain-barrier (BBB) (7). As reviewed by Huffman et al., identification of these pathways has opened a new world of discovery regarding communication between the CSF and plasma. Neuroimaging methods applied to animal models reveal waste products from metabolic functions and break-down of amyloid clear the CNS through these pathways, and, therefore, damage to this system may play a pivotal role in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease. Unfortunately, neuroimaging methods to examine this system are currently limited to animal studies. New innovation is required to translate these methods to human application and successfully define the relevance of disturbed glymphatic flow dynamics to human brain models.

The primary governor of progress in brain science is the extraordinary complexity of the brain. Comprised of a dizzying number of interconnections, the brain is estimated to include as many as 10^{11} x 10^{14} synapses. Until recently, the computational methods required to capture the structural and functional complexity of the human brain in vivo were non-existent. Neuroimaging technology now permits microscopic analyses and visualization of complete tracts and systems. Functional neuroimaging methods using biologically-specific ligands such as PiB reliably identify individuals at risk for developing dementia, with new advances coming from ligands for tau and other neuropathological markers of disease. Finally, it is likely that future models of brain structure-function will incorporate waste clearance dynamics occurring through central-peripheral exchange. Once established, treatment (e.g., neuromodulation) and cure strategies can be strategically targeted against specific mechanisms of brain dysfunction.

Ambitious initiatives are underway to define the human brain connectome (12). Detailed mapping of brain circuitry provided from the connectome project will set a new water mark, with an emphasis on complete and integrated brain circuits. Delineation of brain phenotypes and endophenotypes will emerge from the integration of multiple imaging modalities, such as DTI/diffusion spectrum imaging and resting state fMRI. The neuroimaging field has already shifted in this new direction (4). The rich outcomes generated from these studies are critical to develop cost-effective options for personalized medicine and optimal patient outcomes. Undoubtedly, progress will be governed by the pace of innovation in computational science and federal funding for new research. A new political stage was set in April of 2013, with President Obama announcing the launch of the BRAIN Initiative with coordinated funding from multiple federal sources to support interdisciplinary and highly integrated brain science research. Time will determine whether the new initiative is sufficiently funded to support the development of treatments that can arrest and/or reverse neurological disease. There is little doubt, however, that the neuroimaging technology described in this issue will play a role in this next wave of strategic brain science aimed at improving the lives of individuals affected by a neurological illness worldwide.

REFERENCES

1. Albright T.D.; Jessell, T.M.; Kandel, E.R.; Posner, M.I. Progress in the neural sciences in the century after Cajal (and the mysteries that remain). Ann. N. Y. Acad. Sci. 929 (1):11-40; 2001.

2. Coutts, S.B.; Hill, M.D.; Simon, J.E.; Sohn, C.H.; Scott, J.N.; Demchuk, A.M.; VISION Study Group. Silent ischemia in minor stroke and TIA patients identified on MR imaging. Neurology 65(4):513-7; 2005.

3. de Schotten, M.T.; Dell'Acqua, F.; Ratiu, P.; Leslie, A.; Howells, H.; Cabanis, E.; Iba-Zizen, M.T.; Plaisant, O; Simmons, A; Dronkers, N.F.; Corkin, S; Catani, M. From Phineas Gage and Monsieur Leborgne to H.M.: revisiting disconnection syndromes. Cereb. Cortex 25(12):4812-4827; 2015.

4. GadElkarim, J.J.; Schonfeld, D.; Ajilore, O.; Zhan, L.; Zhang, A.F.; Feusner, J.D.; Thompson, P.M.; Simon, T.J.; Kumar, A.; Leow, A.D. A framework for quantifying node-level community structure group differences in brain connectivity networks. Med. Image Comput. Comput. Assist. Interv. 15(pt 2):196-203; 2012.

5. Goldstein, M. Decade of the brain. An agenda for the nineties. West. J. Med. 161(3):239-241; 1994.

6. Jack, C.R., Jr.; Petersen, R.C.; Xu, Y.C.; O'Brien, P.C.; Smith, G.E.; Ivnik, R.J.; Boeve, B.F.; Waring, S.C.; Tangalos, E.G.; Kokmen, E. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 52(7):1397-403; 1999.

7. Iliff, J.J.; Lee, H.; Yu, M.; Feng, T.; Logan, J; Nedergaard, M.; Benveniste, H. Brain-wide path-way for waste clearance captured by contrast-en-hanced MRI. J. Clin. Invest. 123(3):1299-309; 2013.

8. National Institute on Aging; World Health Organization. Global health and aging. Bethesda, MD: National Institute on Aging; 2011.

9. Shrager, R.I.; Basser, P.J. Anisotropically weighted MRI. Magn. Reson. Med. 40(1):160-5; 1998.

10. Tandon, P.N. The decade of the brain: a brief review. Neurol. India 48(3):199-207; 2000.

11. van der Kolk, A.G.; Hendrikse, J.; Zwanenburg, J.J.; Visser, F.; Luijten, P.R. Clinical applications of 7T MRI in the brain. Eur. J. Radiol. 82(5):708-718; 2013.

12. Van Essen, D.C.; Smith, S.M.; Barch, D.M.; Behrens, T.E.; Yacoub, E.; Ugurbil, K.; WU-Minn HCP Consortium. The WU-Minn Human Connectome Project: an overview. Neuroimage 80:62-79; 2013.

13. Vinters, H.V.; Miller, B.L.; Pardridge, W.M. Brain amyloid and Alzheimer disease. Ann. Intern. Med. 109(1):41-54; 1988.