Innovations in neuroimaging lead to important medical applications to aid clinicians

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The current special issue of *Technology and Innovation, Journal of the National Academy of Inventors*, Volume 18, Number 1 (all open access), is devoted to the evolution of neuroimaging technology, with seven articles chronicling the latest advances in this critical area. In addition, the journal's regular features include the article by the U.S. Patent and Trademark Office (USPTO), which discusses the key pillars of patent quality, and the NAI Fellow Profile, which focuses on biochemical engineer Dr. Frances Arnold (California Institute of Technology) and her important work in innovation, invention, and teaching.

In the issue's editorial, guest editor Robert H. Paul (Missouri Institute of Mental Health at the University of Missouri-St. Louis) leads off the discussion on the evolution of neuroimaging. Paul notes that, heretofore, "clinical applications in brain science have progressed at a glacial pace when compared to other medical disciplines." The recognition by the medical community of this lag in clinical applications, a problem that has only been exacerbated by an aging population at risk for degenerative brain diseases, has created a push for improved technologies. "Fortunately, technical advances in the field of neuroimaging offer new promise," he says.

Paul discusses the evolution and the future of neuroimaging investigation, particularly in clinical populations such as those with Alzheimer's disease, and reviews articles in the special issue.

"[The] articles highlighted in this issue describe cutting-edge applications...using diffusion tensor imaging, diffusion-based tractography, and positron emission tomography," says Paul. "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."

The effort to find ways to detect and diagnose preclinical Alzheimer's disease (AD) has taken a big step forward with the use of positron emission tomography (PET) for imaging processes in the body when PET is coupled with a special 'tracer' that can detect clinically relevant aspects of AD when the tracer binds to amyloid plaques in the brain, an abnormality characteristic of AD. According to author Ann D. Cohen, the use of biomarkers such as Pittsburgh Compound B (PiB) can reveal cognitive deficits seen in normal aging as opposed to those seen in AD. This distinction has become critical, she says, since the advent of AD prevention trials. Her review focuses on the use of PiB-PET across the spectrum of AD, from the earliest PiB studies where PiB retention in the brain was shown to be higher in patients when amyloid plaques were present than when they were not present. Prior to these findings, only post-mortem studies could confirm amyloid plaques.

"Neuromodulation is a growing industry that promises to treat many disabling psychiatric and other neurologic disorders," writes David F. Tate et al. The review article focuses on current findings concerning three commonly used neuromodulation methods: cranial electrotherapy stimulation (CES), transcranial direct current stimulation (tDCS), and transcranial magnetic stimulation (TMS). "The effort to validate these methods using state-of-the-art MRI is in its infancy," say the authors. However, "there are a growing number of studies that demonstrate objective MRI findings that illustrate therapeutic effects." The authors review the potential benefits of using MRI in the study of the biological underpinnings of neuromodulation effects and make suggestions for

future research.

Lauren E. Salminen et al. discuss the in vivo observation of human brain tissue using neuroimaging, specifically turning their focus on diffusion tensor imaging (DTI), which can be used to reveal subtle micro-anatomical abnormalities associated with a variety of diseases and also employed to delineate normal age-related changes in brain tissue across the lifespan.

The technique faces challenges, as "imaging artifact in DTI remains a significant limitation for identifying true neural signatures of disease and brain-behavior relationships," observe the authors. Cerebrospinal fluid (CSF) contamination is a main source of error on DTI scans, they explain, so several methods that have been proposed to correct for the CSF contamination error are discussed. The paper also reviews what the authors call no-b-zero, or NBZ, approaches, which have been shown to be effective in suppressing the CSF signal in DTI data and subsequently reducing errors and improving measurement of the brain tissue. "This approach and related techniques have the potential to significantly improve our understanding of "normal" brain aging and neuropsychiatric and neurodegenerative diseases," suggest the authors.

The paper by Laurie M. Baker (University of Missouri-St. Louis) and colleagues reviews methods and applications of length-based fiber bundle analysis of cerebral white matter in vivo using diffusion magnetic resonance imaging. Specifically, quantitative tractography based on diffusion tensor imaging (qtDTI) technology has been developed to help quantify aggregate structural anatomical properties of white matter fiber bundles. Current and new applications are discussed, along with insights into brain organization and function as well as opportunities for improving methodology through more complex medical models. "Advances in diffusion weighted imaging technology have allowed researchers to characterize structural integrity of white matter tissue,"

explain the researchers. Further, "highly advanced DTI methods...have significantly improved the utility of diffusion tensor measurements to detect subtle white matter changes in both healthy and diseased populations."

Song Zhang discusses diffusion imaging tractography, a type of MRI widely used to probe the three-dimensional structure of fibrous tissue—such as the brain, heart and muscles—in vivo. The shape and size of neural fiber bundles in the brain white matter can be revealed through diffusion tractography, he says, which helps researchers examine the integrity of the neural bundles. Zhang reviews the background of the methodology and the applications and discusses how water molecules in biological tissues engage in random "Brownian motion" as a result of collision with other atoms and molecules. "The motion is restricted by microstructures in the tissues," writes Zhang. "For example, in white matter, water diffuses faster along the axons...because the motion is restricted by the tightly packed multiple myelin membranes encompassing the axons; this can be captured by diffusion MRI to explore the white matter structures in vivo."

"Brain-wide pathways of perivascular flow help clear the brain of proteins and metabolic wastes linked to the onset and progression of neurodegenerative diseases," explains Jacob Huffman et al. in a paper covering the biological relevance and clinical applications of the emerging field of perivascular flow dynamics. The authors also explain how the dysfunction of delivery and clearance systems may render the brain vulnerable to the accumulation of metabolic waste and proteins, such as amyloid B, which is related to Alzheimer's disease. However, they note that current techniques are unable to fully reveal the complex functional and anatomical features of clearance pathways. Their review also discusses the biological relevance of the glymphatic and perivascular clearance systems, the innovative technology that has defined those pathways, and the potential for advancing our

understanding of degenerative brain diseases using new technology.

In a commentary titled "the Pillars of Patent Quality," United States Patent and Trademark Office writer Alex Camarota discusses the importance of patent quality in fostering innovation and the USPTO's efforts to strengthen it in recent years. Camarota notes that successful "transfer of knowledge to the public in exchange for limited monopolies" depends on the patent system's ability to "discern which inventions are legally entitled to protection in the marketplace while also protecting the ability of others to invent around and improve upon them." Camarota provides an overview of the USPTO's Enhanced Patent Quality Initiative, built around three pillars of improving patent examination policy and processes, metrics, and customer service. The article also briefly discusses the USPTO's exciting new forays into leveraging artificial intelligence and 'big data' to enhance patent quality and accelerate the examination process.

Biochemical engineer Frances Arnold, professor in the Division of Chemistry and Chemical Engineering at the California Institute of Technology, inventor on 49 U.S. patents, and author of over 200 peer-reviewed publications, has been lauded for her pioneering work in "directed evolution," which allows for the engineering of proteins through the recombination or mutation of genes followed by a careful artificial selection process to choose desired traits. The resulting proteins have the potential to revolutionize how we solve problems in health care, agriculture, and sustainable energy, among other areas.

"I am interested in the evolution of chemical novelty—specifically, how do new enzyme catalysts arise from old ones," she tells T&I. "It happened a gazillion times in nature, but it's hard to capture evolution in the act."

This profile and Q&A with Arnold touches on her training in mechanical

and space aerospace engineering, as well as on her observations regarding teaching, invention and innovation. As befits the scope of her work, her ambitions are equally expansive. "I am always looking for ways to make the products we need in a cleaner, cheaper, and more sustainable fashion, and for where that ability opens new opportunities to combat chemical waste, pollution and harm to the planet," says Arnold.

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