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Editorial

Physiological MRI of the brain: Emerging techniques and clinical applications

The most widely used brain MRI techniques include anatomic MRI (e.g. T1, T2-weighted), diffusion MRI and functional MRI. Compared to these more well-established techniques, physiological MRI is an emerging field. But it is also one of the most active and vibrant areas of neuroimaging research.

Physiological MRI spans a broad range of techniques that aim to provide quantitative and biologically interpretable measures of the brain (i.e. beyond simple MR signal intensity) that have direct relevance to basic and clinical neuroscience. The quantitative nature affords these techniques many advantages. First, their outcome measures are generally related to a *single* biophysical or physiological parameter of the brain; thus these measures are independent of MRI platforms or hardware configurations. Such measures are hence ideally suited for use as biomarkers in multi-site clinical trials. Second, physiological MRI does not rely on the selection of reference tissue or region; thus they can be readily used for both focal and diffuse diseases. Even a global measure has meaningful information. Third, effect sizes of pathology on these parameters are often substantial. For example, the effects of malignant brain tumor on certain metabolites (e.g. 2-hydroxyglutarate) can be several-fold (Choi et al., 2012). Arterial stenotic disease can reduce the brain's vascular reserve by up to 90% (Kunieda et al., 2017). The permeability of the blood-brain-barrier (BBB) in hippocampal subregions of patients with mild cognitive impairment is 53% greater than that in age-matched controls (Montagne et al., 2015). The sensitivity of physiological MRI to detect brain abnormalities is expected to benefit from these relatively large effect sizes. Finally, physiological changes of the brain are thought to be more modifiable compared to structural changes. For example, it has been shown that brain perfusion in stroke patients can be restored by pharmacological or mechanical clot-removing procedures (Kidwell et al., 2013; Lansberg et al., 2012). BBB disruption in multiple sclerosis can be altered by medications (Cohen et al., 2012; O'Connor et al., 2011). Therefore, physiological MRI biomarkers have important potential roles in monitoring the effects of treating brain diseases.

In recent years, there have been major advances in physiological MRI. One reason for this success is because researchers in the field have reached consensus on several techniques, so that the MRI manufacturers can incorporate the most appropriate sequences in their product and the broader community can start using these techniques without struggling on choices of technical details. For example, the recent ASL white paper has been a major driving force in facilitating a surging interest for clinical applications of ASL perfusion MRI (Alsop et al., 2015). Similarly, the MR spectroscopy (MRS) community have also released their consensus guidelines for proton MRS in brain diseases (Oz et al., 2014). There are also parallel initiatives from the Radiological Society of North American (RSNA) to establish a series of Quantitative Imaging Biomarkers Alliance (QIBA) to harmonize imaging biomarkers for clinical trials and practice (Sullivan et al., 2015). These collective efforts are undoubtedly enhancing the impact of physiological MRI in many related fields.

Despite these successes, further technical development and clinical demonstrations are needed in order for physiological MRI to become a mainsteam MRI technique for routine clinical use (e.g. clinically billable MRI) and for their inclusion in major international imaging initiatives (e.g. the UK Biobank study (Miller et al., 2016), the US Adolescent Brain Cognitive Development (ABCD) study (Casey et al., 2018)). Toward these goals, this Special Issue consists of a combination of review articles and original research that focus on emerging techniques and promising clinical applications of physiological MRI.

The Issue begins with a series of physiological MRI techniques to measure the brain's baseline physiological parameters. Hernandez-Garcia et al. reviewed recent progress in measuring cerebral blood flow (CBF) with ASL MRI (Hernandez-Garcia et al., 2018). Hua et al. examined various MRI techniques to assess cerebral blood volume (CBV) (Hua et al., 2018). Quarles et al. provided a critical summary of hemodynamic imaging techniques using Gadolinium-based contrast agent, including dynamic susceptibility contrast (DSC) and dynamic contrast enhanced (DCE) MRI (Quarles et al., 2018). Le Bihan outlined basic concepts, biophysical models, and technical requirements of the intravoxel incoherent motion (IVIM) MRI technique (Le Bihan, 2017). Viessmann et al. demonstrated a technique to use EPI BOLD data to assess cardiac-induced vessel pulsatility in the brain and tested the technique in the context of aging (Viessmann et al., 2018). Ghassaban et al. reviewed a range of MRI methods to quantify iron content in the brain and their applications in neurodegenerative diseases (Ghassaban et al., 2018).

The next set of articles focusses on techniques probing dynamic properties of the brain. Liu et al. provided a technical review of cerebrovascular reactivity (CVR) measurement using a CO2 challenge (Liu et al., 2018). Gauthier and Fan provide a timely update of our current understanding of neurovascular coupling and BOLD fMRI signal, as well as experimental methods for quantitative evaluation of neural activation (Gauthier and Fan, 2018). Bright et al. described latest advances in multiparametric measurement of cerebral physiological parameters using calibrated fMRI techniques (Bright et al., 2017). Germuska and Wise reviewed practical issues and potential challenges in absolute quantification of cerebral metabolic rate of oxygen (CMRO2) using gas challenges (Germuska and Wise, 2018). Champagne et al. demonstrated the feasibility to use simultaneous hypercapnic and hyperoxic gas inhalation to probe multiple hemodynamic processes such as bolus arrival time and blood flow redistribution (Champagne et al., 2017). Whittaker et al. developed a technique to probe vascular autoregulation by using negative pressure as a challenge inside the MRI (Whittaker et al., 2017).

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Murphy et al. provided an intriguing review of the application of MR elastography (MRE) in the brain to probe brain stiffness in multiple sclerosis, dementia, and tumor (Murphy et al., 2017).

The final set of articles have a strong focus on clinical applications of these physiological techniques. Juttukonda and Donahue provided a thorough review of current evidence of the utility of vascular reserve in patients with cerebrovascular diseases (Juttukonda and Donahue, 2017). Chen summarized applications of physiological MRI in aging and age-related neurodegeneration (Chen, 2018). Vasung et al. provided a comprehensive review of structural and physiological neuroimaging in early human development (Vasung et al., 2018).

In summary, physiological MRI has an enormous potential in basic and clinical neuroscience. However, much work is still needed in order for these techniques to make their way to routine clinical practice. We hope this Special Issue provides an up-to-date summary of several promising techniques, introduces them to clinicians and scientists who have not considered these methods, and enhances the role of physiological MRI in understanding our brain and improving brain health.

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