EDITORIAL

Non-invasive MRI windows to Neuroinflammation

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Abbreviations:

CNS=central nervous system

MEG=magnetoencephalography

MRI=magnetic resonance imaging

MS=multiple sclerosis

PET=positron emission tomography

fMRI= functional magnetic resonance imaging

The term “neuroinflammation” refers to a combination of responses that the central nervous system (CNS) puts into action to promote homeostasis, both in pathological and physiological conditions. The immune reaction in the CNS results from a complex integration of the responses of most CNS cell types, with a key role played by microglia, but with an also well-established participation of neurons, macroglia, and infiltrating leukocytes (Carson et al., 2006).

Inflammatory reactions can be both beneficial and detrimental to the brain, depending on the strength of their activation in various stages of neurodegeneration (Sochocka et al., 2017). A successful inflammatory response would, for instance, eliminate invading pathogens, promote lesion healing and angiogenesis; by contrast, chronic inflammation resulting from a failure to resolve the initiating insult or from an abnormal response of the recruited immune system, could evolve into dangerous pathological processes. In fact, it has been shown that a strong activation of glial cells

gives rise to cytokine overexpression/dysregulation, which accelerates neurodegeneration (Sochocka et al., 2017).

This neurotoxic mechanism has been involved in the pathogenesis of several neurodegenerative and psychiatric disorders (Dheen et al., 2007), making neuroinflammation a hot topic in brain research. For example, a sustained inflammatory response has been associated with multiple sclerosis (MS) (Lassmann et al., 2012), Alzheimer's and Parkinson's diseases (Glass et al. 2010). More recent examples demonstrate involvement of the brain immune system in social behavior (Filiano et al., 2016), and even in the regulation of infection at mucosal barriers and gut defense (Ibiza et al., 2016).

To improve diagnosis and therapy monitoring, as well as guide the development of novel treatments, it is fundamental to clarify the role of neuroinflammation in the aforementioned conditions, characterize its neuroprotective versus neurotoxic component and the causality of the link between the disease and the inflammatory response. To effectively address these questions in the basic research and clinical settings, it is necessary to develop novel, non-invasive methods to investigate neuroinflammatory processes. Magnetic resonance imaging (MRI) offers a non-invasive framework to characterize neuroinflammatory responses *in vivo*, with high translational value. In addition, MRI possesses unique flexibility, as the same basic physical principle can be employed to measure different tissue properties, from anatomy to function (Albrecht et al., 2016). This *special issue* aims at exploring the potential of MRI to uncover and investigate inflammatory processes in the CNS; the 13 reviews and empirical papers selected for this issue cover a variety of MRI approaches and different types of disease where neuroinflammation plays a major role, in animals as well as in human subjects.

Several papers focus on MS and on its neuroinflammatory aspects (Tommasin et al., 2017; Stickland et al., 2018; Fleischer et al., 2017; Toschi et al., 2019; De Santis et al., 2018). MS is a chronic neurological disease characterized by the interplay between inflammation and degeneration in both white and gray matter. In the past twenty years, MRI has played an increasing role in MS management and has become a fundamental tool for early diagnosis and for monitoring response to treatment, as

detailed in Tommasin et al. (2017). Recent evidences suggested that MS could be an immunological convolution between an underlying primary degenerative disorder and the host aberrant immune response, raising the hypothesis that the disease may originate from degeneration rather than from inflammation (Tommasin et al., 2017). In this context, advanced diffusion-based MRI discussed in this issue hold great promises to increase sensitivity and specificity to axonal pathology in MS (De Santis et al., 2018; Toschi et al., 2019), and can help characterizing axonal degeneration from the earliest stages of the disease.

Besides characterizing both focal and diffuse structural alterations, MRI can also successfully inform on the functional impairment in MS patients. MRI-based network analysis has emerged as an innovative tool to investigate network disconnection and disruption in MS, and importantly, the mechanisms of adaptation and compensation underlying the demyelinating lesions (Fleischer et al., 2017). Along the same line, another study in this issue reports a preserved neurovascular coupling in MS, despite altered neuronal and vascular responses (Stickland et al., 2018).

Beyond MS, neuroinflammation has been shown to be relevant for a number of brain pathologies which would benefit from non-invasive monitoring tools. For example, a diffusion MRI study reports an interesting correlation between white matter microstructure and blood markers of neuroinflammation, such as the neutrophil-to-lymphocyte ratio, in early Parkinson's disease patients, reopening the interesting discussion around the contribution of neuroinflammation to the pathogenesis of this disease (Haghshomar et al., 2017). Also investigating myelin integrity in Huntington's patients, using a multi-contrast MRI approach (Bourbon-Teles et al., 2017), other authors were able to unveil damaged WM pathways of the basal ganglia and motor systems in early stages of the disease, and discuss the possible role of myelin breakdown in triggering neuroinflammation.

Neuroinflammation has also been associated to the onset of a number of psychiatric disorders. One prototypical example is the major depressive disorder, and some contributors discussed exactly this topic in their review (Woelfer et al., 2017). Major depression symptoms can occur during therapies involving the use of interferon-alpha, as the latter is known to rapidly engage immune-brain communicatory pathways and,

importantly, MRI can be used to monitor the microstructural alterations induced by the interferon-alpha in the brain (Dowell et al., 2017).

Preclinical models are especially relevant in MRI research, as the imaging sequences are highly translatable from basic research to clinical settings, and provide the necessary conditions to investigate the neurobiological mechanisms underlying the MRI changes. Indeed, one of the articles included in this issue shows that MRI can be successfully used to monitor cerebral injury following maternal lipopolysaccharide-induced inflammation in rodents (Sharabi et al., 2018), opening new exciting scenarios for the development of new therapies to treat the consequences of maternal/fetal inflammation.

Combining MRI with other techniques allows to capitalize on the complementary strengths. In this issue, we present several multimodal approaches, including hybrid PET/MRI (Aiello et al., 2018), MEG/fMRI (Stickland et al., 2018) and the use of iron oxide nanoparticles in combination with MRI to visualize neuroinflammation (Millward et al., 2017). Finally, in the issue we discuss a potential “missing piece of the puzzle” when trying to understand neuroinflammation: the microbiome. The gut-brain axis has received a lot of attention recently, with several studies suggesting that the immune system plays a fundamental role in this bidirectional communication. A "Perspective" article discusses recent efforts to combine data on the gut microbiota with the features that can be obtained from the conversion of brain images into mineable data (De Santis et al., 2017).

Even if MRI has helped clarify many aspects of the inflammatory response in disease, there are still many open questions to address. We identify two main challenges: 1) the lack of specificity of current MRI measures to sub-compartments of the tissue, necessary to gather information on the neurobiological mechanisms underpinning brain inflammation; and 2) the necessity to develop a proper framework to combine large amounts of data, and extract relevant patterns that can improve diagnosis and therapy monitoring, stratify patients, as well as guide the development of novel and, maybe personalized, treatments.

We hope that this issue will stimulate further research along these lines, increase interest into this intriguing topic and foster new collaborations in this highly multidisciplinary theme.

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