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Review

In vivo imaging of neuroinflammation in schizophrenia

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ABSTRACT

In recent years evidence has accumulated to suggest that neuroinflammation might be an early pathology of schizophrenia that later leads to neurodegeneration, yet the exact role in the etiology, as well as the source of neuroinflammation, are still not known. The hypothesis of neuroinflammation involvement in schizophrenia is quickly gaining popularity, and thus it is imperative that we have reliable and reproducible tools and measures that are both sensitive, and, most importantly, specific to neuroinflammation. The development and use of appropriate human *in vivo* imaging methods can help in our understanding of the location and extent of neuroinflammation in different stages of the disorder, its natural time-course, and its relation to neurodegeneration. Thus far, there is little *in vivo* evidence derived from neuroimaging methods. This is likely the case because the methods that are specific and sensitive to neuroinflammation are relatively new or only just being developed. This paper provides a methodological review of both existing and emerging positron emission tomography and magnetic resonance imaging techniques that identify and characterize neuroinflammation. We describe \how these methods have been used in schizophrenia research. We also outline the shortcomings of existing methods, and we highlight promising future techniques that will likely improve state-of-the-art neuroimaging as a more refined approach for investigating neuroinflammation in schizophrenia.

1. Introduction

Schizophrenia is a severe psychiatric disease, noted for its chronic and often debilitating processes, characterized by delusions and hallucinations, cognitive impairment, and blunted affect (Bleuler, 1950; Kraepelin, 1971). Onset is during adolescence or young adulthood, and it is often lifelong and chronic. Although progress has been made in delineating brain abnormalities in schizophrenia (Fitzsimmons et al., 2013), the etiology, pathogenesis, and biological course still remain elusive, with evidence suggesting a variety of deficiencies and abnormalities, including neurodevelopmental and neurodegenerative abnormalities, as well as a number of dopaminergic, myelin, oligodendrocyte, and volumetric alterations in a number of brain regions that are not proximal but may reflect an underlying anatomical and or functional connection (*e.g.*, see reviews in Harrison, 1999; Jaaro-Peled et al., 2010; Kubicki et al., 2005; Shenton et al., 2001).

The involvement of neuroinflammation in schizophrenia has long been hypothesized (Torrey and Peterson, 1973; Vartanian et al., 1978; Pandey et al., 1981; DeLisi et al., 1984; Ganguli et al., 1987). It is only recently, however, that evidence from neuropathological and neuroimaging studies has emerged to suggest the possible role of neuroinflammation in the etiology of schizophrenia (see recent reviews: Chew et al., 2013; Kahn and Sommer, 2015; Monji et al., 2009; Monji et al., 2013; Najjar and Pearlman, 2015). Neuroinflammation is a normal, albeit, nonspecific response of the brain's immune system to harmful stimuli such as tissue damage or pathogen invasion (Streit et al., 2004). While neuroinflammation is important for a healthy functioning brain, it has been suggested that in neurodegenerative disorders, chronic neuroinflammation likely induces adverse effects, and may be responsible for some of the symptoms that persist for many years during the course of schizophrenia (Streit et al., 2004; Streit, 2006). Similarly, recent studies in schizophrenia have investigated the hypothesis that neuroinflammation is an early indicator of pathology in the etiology of schizophrenia, which may later lead to neurodegeneration (Muller et al., 2004; Feigenson et al., 2014; Najjar and Pearlman, 2015).

Neuroinflammation is observed in many brain disorders, especially in those with a neurodegenerative course such as Multiple Sclerosis, Alzheimer's disease and Parkinson's disease (Weiner and Selkoe, 2002; Schwartz, 2003). The brain parenchyma is separated from the periphery by the blood brain barrier (BBB), which, under normal conditions, prevents immune cells that are in the blood from entering brain

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tissue (Schultzberg et al., 2007; Zlokovic, 2008). Instead, the brain has its own innate immune system that operates mainly through the function of astrocytes and microglia, where neuroinflammation is defined as the activation of this system (Schwartz, 2003). Excellent reviews of the structure and function of glia cells are available and the reader is referred to these for further details (*e.g.*, Fontana et al., 1987; Streit et al., 1988; Rock et al., 2004; Schwartz et al., 2006; Tilleux and Hermans, 2007; Allaman et al., 2011). Briefly, microglia are the resident macrophages of the brain and are usually the initial responders to tissue insult or damage. Receptors on the microglia respond and activate the cells. When active, the cells change their shape and function and initiate phagocytosis. In addition, activated microglia, in concert with astrocytes, emit cytokines that lead to a cascade of events that modulate the neuroinflammatory response. As part of this process, the glia cells also emit oxidative and nitrosative products, as well as excitotoxic metabolites that can damage surrounding tissue. An acute, or short-term neuroinflammatory response is likely important for a healthy functioning brain and contributes to the repair of damaged or infected tissue. However, when the inflammatory process continues for a long period of time (weeks, months or even years), damage to the surrounding brain tissue may become substantial. For example, a prolonged neuroinflammatory response in the white matter may damage oligodendrocytes, and the myelin sheath surrounding axons, thereby affecting network connectivity in the brain (Deng, 2010; Chew et al., 2013). Exposure to oxidative, nitrosative, and excitotoxic metabolites may also result in the loss of neuronal cell bodies and reduced extracellular matrix, evident as brain atrophy (Versijpt et al., 2005; Jacobs et al., 2012; Bigler, 2013; Frodl and Amico, 2014). Tissue degeneration, in turn, reactivates neuroinflammation, forming a "vicious circle" of neuroinflammation and neurodegeneration (Jacobs et al., 2012).

The cause of neuroinflammation and its association with neurodegenerative disorders is not yet known. Moreover, in most neurodegenerative disorders (*e.g.*, Multiple Sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease), the reason for the initial inflammatory response is also not well known. This is also the case in schizophrenia, where maternal and prenatal infections (Anderson and Maes, 2013), brain injury (Chew et al., 2013), autoimmune disorder (Fineberg and Ellman, 2013), and stress response (Vogel et al., 2011), have all been hypothesized, among other possible causes (Kirkpatrick and Miller, 2013; Meyer, 2013), as the source of neuroinflammation. The duration of neuroinflammation, whether it is chronic or acute, its location and extent, as well as its relation to symptoms, are also not known in schizophrenia. Nevertheless, if neuroinflammation is indeed an earlier pathology that may lead to neurodegeneration, and if it can be reliably detected, then it can potentially be treated, making the study of neuroinflammation in schizophrenia an important and active field of research.

A key to understanding the involvement of neuroinflammation in schizophrenia, as well as in other brain disorders, is our ability to monitor neuroinflammation with respect to when it begins and as it progresses. However, monitoring neuroinflammation *in vivo* in the brain is challenging. Currently inflammatory signs in schizophrenia are mainly identified in blood and cerebrospinal fluid (CSF) markers. Yet these markers may be limited in their sensitivity and specificity (Feigenson et al., 2014), with CSF markers requiring highly invasive lumbar punctures. Additionally, these markers cannot identify the location and extent of neuroinflammation in the brain. It is therefore important to develop *in vivo* imaging methods that are sensitive and specific to neuroinflammation.

This paper is focused on existing and emerging neuroimaging methods that can identify and characterize neuroinflammation *in vivo*, by targeting different chemical, physical, and geometrical changes that occur in the neuroinflammatory cascade. Methods reviewed include positron emission tomography (PET), magnetic resonance spectroscopy (MRS), anatomical and quantitative magnetic resonance imaging (MRI), and diffusion MRI. These methods are depicted in Fig. 1. To date, most of the evidence for neuroinflammation in schizophrenia comes from *ex vivo* neuropathological studies, with only a small number of studies that have tried to utilize neuroimaging for the identification of neuroinflammation in schizophrenia (Feigenson et al., 2014; Najjar and Pearlman, 2015). The advancement of such neuroimaging methods is critical for our ability to identify and to monitor neuroinflammation *in vivo* in schizophrenia, as well as in other brain disorders.

2. Identifying neuroinflammation with PET

PET is currently the main neuroimaging modality used for the identification of neuroinflammation *in vivo* (Jacobs et al., 2012). The PET scanner produces 3D images representing levels of detected gamma rays emitted by tracers, which are radionuclides chemically incorporated into a biologically active molecule and introduced to the body (Muehllehner and Karp, 2006)

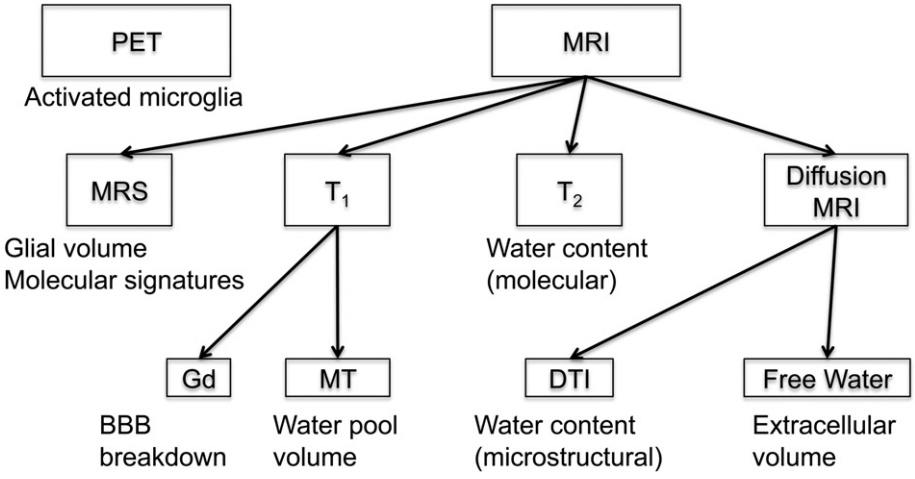

Fig. 1. Overview of imaging methods useful for neuroinflammation identification. Positron emission tomography (PET) uses ligands that bind to activated microglia, which initiate the inflammatory cascade. Magnetic resonance imaging (MRI) provides several methods: MR spectroscopy (MRS) can identify metabolites that are sensitive to glial volume, and to other molecular signatures of neuroinflammation; and Gadolinium (Gd) enhanced T_1 can identify blood–brain-barrier (BBB) breakdown, which occurs in severe cases of neuroinflammation. Other MRI based methods can identify changes in water content, which is expected to increase due to neuroinflammation, these include: Magnetization transfer (MT) that can identify changes in the volume of the water pool *versus* the macromolecular pool; T_2 weighted imaging that can identify water content changes through molecular interactions; and diffusion tensor imaging (DTI) that can identify the water content changes through microstructural changes that affect the diffusivity of water molecules. More advanced diffusion MRI based methods, such as free-water imaging, can identify the extracellular volume, which is likely more specific to neuroinflammation than water content changes.