



Review article

Histological and MRI markers of white matter damage in focal epilepsy

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ABSTRACT

Growing evidence highlights the importance of white matter in the pathogenesis of focal epilepsy. *Ex vivo* and post-mortem studies show pathological changes in epileptic patients in white matter myelination, axonal integrity, and cellular composition. Diffusion-weighted MRI and its analytical extensions, particularly diffusion tensor imaging (DTI), have been the most widely used technique to image the white matter *in vivo* for the last two decades, and have shown microstructural alterations in multiple tracts both in the vicinity and at distance from the epileptogenic focus. These techniques have also shown promising ability to predict cognitive status and response to pharmacological or surgical treatments. More recently, the hypothesis that focal epilepsy may be more adequately described as a system-level disorder has motivated a shift towards the study of macroscale brain connectivity. This review will cover emerging findings contributing to our understanding of white matter alterations in focal epilepsy, studied by means of histological and ultrastructural analyses, diffusion MRI, and large-scale network analysis. Focus is put on temporal lobe epilepsy and focal cortical dysplasia. This topic was addressed in a special interest group on neuroimaging at the 70th annual meeting of the American Epilepsy Society, held in Houston December 2–6, 2016.

1. Introduction

Epilepsy has been long considered a disorder of the grey matter. However, in recent years there has been a rapid increase of converging findings pointing out the importance of the white matter in this condition. In this review article, we aim to provide an overview of most recent findings in the study of white matter, derived from histology, *ex vivo* and *in vivo* MRI, and connectomics. We will focus on investigations in temporal lobe epilepsy (TLE) and epilepsies related to focal cortical dysplasia (FCD), the most frequent forms of pharmacoresistant epilepsy.

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2. Histopathology of the white matter

White matter (WM) pathology is a hallmark feature of well-defined focal epilepsies, such as FCD type IIB and cortical tubers (Blümcke et al., 2011). The existence of similar but more subtle or diffuse

abnormalities in “normal-appearing” WM as potential biomarkers for disease, has recently gained attention and been subjected to greater scrutiny (Liu et al., 2014a; Mühlebner et al., 2012; Reeves et al., 2016; Scholl et al., 2017; Schurr et al., 2017; Zucca et al., 2016). Pathological changes identified mainly correspond to abnormalities of myelination, axons or alteration of cellular composition.

The basic constituents of normal WM can be readily distinguished and quantified on histology sections from surgical epilepsy resections using a variety of standard techniques (Table 1, Fig. 1). It is important to consider the developmental maturation of the WM as well its capacity for regeneration and repair (Fancy et al., 2011; Semple et al., 2013). Completion of myelination in the human brain proceeds over several decades (Kinney et al., 1988) from pools of lineage-specific oligodendrocyte progenitor and precursor cells (OPC) that continue to differentiate into mature oligodendrocytes throughout adulthood, to maintain and repair myelin (Jakovcevski et al., 2009). Rates of myelination are influenced by neuronal activity (Jakovcevski et al., 2009) and axonal size (Fancy et al., 2011) among other factors and progress in a tract-dependent manner (Ullén, 2009), ultimately influencing axonal conduction velocity. The immediate subcortical region between the

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Table 1
Neuropathology studies and markers used for the investigation of white matter pathology in epilepsy.

Structure/ cell types	Components	Stains/Markers	Techniques of quantification	Examples of studies
Axons	Size Fibre density	Neurofilament (Light, medium and heavy chain) (e.g. SM31)	Quantitative Immunohistochemistry	(Shepherd et al., 2013)
Myelin and oligodendroglial lineage	Myelin sheath	Luxol fast Blue stain Myelin Basic protein CNPase	Electron microscopy Quantitative Immunohistochemistry e.g. labelling index Quantitative MRI correlation (in-vivo and ex-vivo)	(Garbelli et al., 2012) (Lockwood-Estrin et al., 2012; Mühlebner et al., 2012; Shepherd et al., 2013; Thom et al., 2012) (Lockwood-Estrin et al., 2012; Reeves et al., 2016; Thom et al., 2012)
	Oligodendrocytes (mature/ precursor cells)	Olig1, Olig2, Myelin basic protein CNPase NogoA	Quantitative/qualitative immunohistochemistry	(Lockwood-Estrin et al., 2012; Mühlebner et al., 2012; Scholl et al., 2017; Shepherd et al., 2013; Thom et al., 2012; Zucca et al., 2016)
Astroglia	Oligodendroglial progenitor cells	Tppp7/p25 NG-2, PDGFRα, PDGFRβ, Ki67	Stereology 2-d cell counting Immunohistochemistry/double labelling to quantify proliferative cell fractions 2-d cell counting Quantitative Immunohistochemistry e.g. labelling index	(Scholl et al., 2017) (Scholl et al., 2017; Shepherd et al., 2013) (Lockwood-Estrin et al., 2012; Reeves et al., 2016; Thom et al., 2012)
	Mature	GFAP	Quantitative Immunohistochemistry	(Reeves et al., 2016)
White matter neurones	Immature, reactive glia	Nestin,	Quantitative Immunohistochemistry	(Eriksson et al., 2006; Hardiman et al., 1988; Liu et al., 2014a)
	All neuronal types	Cresyl Violet (Nissl) NeuN Map2	Stereology/3d cell counting 2-d cell counting WSS image analysis	
	Inhibitory interneurons subsets	Calbindin, Parvalbumin, calretinin, NPY, Somatostatin,	2-d cell counting	(Richter et al., 2016; Suárez-Solá et al., 2009)
	Immature, subplate	Tbr1	2-d cell counting	(Richter et al., 2016)

These markers have been used in comparative investigation with normal control white matter, mainly using light microscopy on fixed tissue specimens. Cited studies exclude those on vascular structures and inflammatory microglial cells. The main methods employed include quantitative immunohistochemistry to evaluate the 'labelling index' of a structure, stereology (3D cell counting) to quantify cell density and whole slides scanning analysis (WSS) to study wide regions of brain rapidly and automatically.

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