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Mathematical models for the diffusion magnetic resonance signal abnormality in patients with prion diseases

Matteo Figini[a,b], Daniel C. Alexander[c], Veronica Redaelli[d], Fabrizio Fasano[e], Marina Grisoli[a], Giuseppe Baselli[b], Pierluigi Gambetti[f], Fabrizio Tagliavini[d], Alberto Bizzi[g,*]

[a] Neuroradiology, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milano, Italy
[b] Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milano, Italy
[c] Centre for Medical Image Computing, Department of Computer Science, University College London, London, United Kingdom
[d] Neuropathology, Fondazione IRCCS Istituto Neurologico, Parma, Italy
[e] Department of Neuroscience, Università degli Studi di Parma, Parma, Italy
[f] National Prion Disease Pathology Surveillance Center, Department of Pathology, Case Western Reserve University, Cleveland, OH, USA
[g] Neuroradiology, Humanitas Research Hospital IRCCS, Rozzano, Milano, Italy

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ABSTRACT

In clinical practice signal hyperintensity in the cortex and/or in the striatum on magnetic resonance (MR) diffusion-weighted images (DWIs) is a marker of sporadic Creutzfeldt–Jakob Disease (sCJD). MR diagnostic accuracy is greater than 90%, but the biophysical mechanisms underpinning the signal abnormality are unknown. The aim of this prospective study is to combine an advanced DWI protocol with new mathematical models of the microstructural changes occurring in prion disease patients to investigate the cause of MR signal alterations. This underpins the later development of more sensitive and specific image-based biomarkers. DWI data with a wide a range of echo times and diffusion weightings were acquired in 15 patients with suspected diagnosis of prion disease and in 4 healthy age-matched subjects. Clinical diagnosis of sCJD was made in nine patients, genetic CJD in one, rapidly progressive encephalopathy in three, and Gerstmann–Sträussler–Scheinker syndrome in two. Data were analysed with two bi-compartment models that represent different hypotheses about the histopathological alterations responsible for the DWI signal hyperintensity. A ROI-based analysis was performed in 13 grey matter areas located in affected and apparently unaffected regions from patients and healthy subjects. We provide for the first time non-invasive estimate of the restricted compartment radius, designed to reflect vacuole size, which is a key discriminator of sCJD subtypes. The estimated vacuole size in DWI hyperintense cortex was in the range between 3 and 10 μm that is compatible with neuropathology measurements. In DWI hyperintense grey matter of sCJD patients the two bi-compartment models outperform the classic mono-exponential ADC model. Both new models show that T_2 relaxation times significantly increase, fast and slow diffusivities reduce, and the fraction of the compartment with slow/restricted diffusion increases compared to unaffected grey matter of patients and healthy subjects. Analysis of the raw DWI signal allows us to suggest the following acquisition parameters for optimized detection of CJD lesions: $b = 3000$ s/mm^2 and TE = 103 ms. In conclusion, these results provide the first in vivo estimate of mean vacuole size, new insight on the mechanisms of DWI signal changes in prionopathies and open the way to designing an optimized acquisition protocol to improve early clinical diagnosis and subtyping of sCJD.

1. Introduction

Prion diseases are transmissible, rapidly progressive and fatal neurological diseases. Despite their rarity and the lack of an effective treatment, prion diseases draw exceptional scientific interest, mainly because of their peculiar transmission mechanism, involving the presence of a misfolded isoform (PrP^{Sc}) of the cellular prion protein (PrP^{C}) and unique histological lesions. Sporadic Creutzfeldt–Jakob disease (sCJD), the most common human prion disease, has a wide spectrum of clinical and histopathological phenotypic heterogeneity that has

Abbreviations: ADC, apparent diffusion coefficient; BIC, Bayesian information criterion; CJD, Creutzfeldt–Jakob disease; CNR, contrast to noise ratio; DWI, diffusion weighted imaging; EEG, electroencephalogram; EPI, echo-planar imaging; FOV, field of view; GSS, Gerstmann–Sträussler–Scheinker syndrome; MPRAGE, magnetization-prepared rapid acquisition gradient-echo; PrP^{C}, prion protein cellular; PrP^{Sc}, prion protein scrapie; ROI, region of interest; RPE, rapidly progressive encephalopathy; sCJD, sporadic Creutzfeldt–Jakob disease; SS-SE, single shot spin-echo; TE, echo time; TI, inversion time; TR, repetition time

* Corresponding author at: Neuroradiology, Humanitas Research Hospital IRCCS, Via Manzoni, 56, Rozzano, Milano 20089, Italy. Tel: +39 02 82246663.
E-mail address: alberto.bizzi@humanitas.it (A. Bizzi).

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made its clinical recognition difficult. Four main neuropathological features of sCJD have been described: astrocytosis, neuronal loss, intracellular spongiform degeneration and PrP^{Sc} accumulation in extracellular space (Puoti et al., 2012). A great variability on lesion distribution, spongiform degeneration and PrP^{Sc} accumulation is influenced by the genotype at codon 129 and the PrP^{Sc} type (Gambetti et al., 2003). In particular, fine spongiosis with small vacuoles is characteristic of the most common phenotypes (MM1, MV1 and VV2), whereas coarse spongiosis with large vacuoles is found in the MM2C and MV2C subtypes (Parchi et al., 2012). For example, the vacuole average diameter in sCJDMM1 is 5.8 ± 1 μm, while in sCJDMM2, an sCJD subtype which can be difficult to distinguish clinically from sCJDMM1, the average vacuole diameter is larger than 15 μm. The subtypes have quite different prognosis (Gambetti et al., 2011), so a non-invasive technique for the estimation of vacuole size would have a great importance. However, currently, definite diagnosis of sCJD and its subtypes can be made only by brain tissue examination. Clinical criteria for the diagnosis of probable sCJD require the presence of at least two clinical signs out of (i) dementia, (ii) cerebellar or visual, (iii) pyramidal or extrapyramidal, (iv) akinetic mutism, and at least one of three tests 14-3-3 protein in CSF, periodic sharp-wave complexes in the EEG, or abnormally high signal on Magnetic Resonance Imaging (MRI) must be positive (Zerr et al., 2009). In particular, asymmetric MRI hyperintensities on diffusion-weighted images (DWIs) and T_2-weighted Fluid Attenuated Inversion Recovery (FLAIR) in at least three non-contiguous gyri or in the striatum or both are highly suggestive for the diagnosis of sCJD. DWI is the best among standard MRI sequences (Young et al., 2005; Kallenberg et al., 2006; Galanaud et al., 2010; Vitali et al., 2011) with a diagnostic accuracy above 90% (Shiga et al., 2004; Young et al., 2005; Satoh et al., 2007; Bizzi et al., 2009; Galanaud et al., 2010; Vitali et al., 2011). However, even though DWI hyperintensity is currently used as a marker of prion disease (Puoti et al., 2012), the tissue alteration underlying this imaging signal remains unknown. It has been reported that DWI sensitivity may vary among prion diseases and sCJD subtypes (Krasnianski et al., 2006), which opens the possibility to use it for early diagnosis of sCJD subtypes. Therefore, the identification of the histopathologic substrate associated with the DWI signal abnormality is important, because it can guide the precise choice of MRI protocol to maximize diagnostic power.

A few authors have looked for a correlation between neuropathological changes and DWI hyperintensity or reduction in apparent diffusion coefficient (ADC). According to some groups (Geschwind et al., 2009; Manners et al., 2009) DWI hyperintensities may be correlated with spongiosis and PrP^{Sc} deposition rather than with gliosis and neuronal loss; Lodi et al. (2009) found that patients with fatal insomnia, a prionopathy associated with little or no spongiform changes (Parchi et al., 1999), did not exhibit hyperintensities on DWI thus pointing to spongiosis as the principal determinant of DWI signal hyperintensity. On the other hand, Russmann et al. (2005) found no significant correlation between ADC and the degree of spongiosis, gliosis or neuronal loss.

The sensitivity of DWI to the random displacements of water molecules in biological tissues makes it useful as a probe of tissue microstructure. Previous MRI studies of prion disease have focused (qualitatively or semi-quantitatively) on the apparent hyperintensity on T_2-weighted FLAIR and DWI, or quantitatively on the ADC (Demaerel et al., 2003; Tschampa et al., 2003; Lin et al., 2006; Galanaud et al., 2008; Hyare et al., 2010a, b). Only a recent study (Caverzasi et al., 2014) performed a slightly more sophisticated analysis, by evaluating the fractional anisotropy (which did not show significant differences between patients and controls) and characterizing the evolution of ADC with the pathology progression, which revealed a non-linear trend.

Signal in DWI depends on several parameters (Mori and Barker, 1999), including T_2 relaxation (between 80 and 120 ms in healthy brain tissue, but tends to increase with structural damage), the proton density M_0, and the water mobility within the tissue. The ADC factors out T_2 and M_0 providing a purer index of water mobility, but is still influenced by a wide range of factors. Recent trends in DWI, so-called microstructure imaging, use mathematical models to relate DWI signals to histological features; see for example Assaf et al. (2004), Barazany et al. (2009), Panagiotaki et al. (2012), and Zhang et al. (2012). However, current techniques largely consider healthy white matter tissue, so are not directly applicable to explain the grey-matter DWI hyperintensity in prion disease.

In this prospective study we examine, for the first time in consecutive patients with suspected prion disease, the potential of more sophisticated mathematical models than the simple mono-exponential model used for ADC estimation. We develop a modelling approach based on two main hypotheses on the microstructural tissue alterations that may cause DWI hyperintensity. Each hypothesis leads to a different family of mathematical models for how the DWI signal varies with echo time TE, b-value and diffusion time. Our two hypotheses are: a) reduction of hindered diffusivity caused by prion PrP^{Sc} deposition in the extracellular space; and b) restriction of water diffusing within intracellular vacuoles. The key difference between the two hypotheses is that (b) implies restricted diffusion, whereas (a) does not. In normal grey matter, a single or bi-exponential model explains the DWI signal well (Clark and Le Bihan, 2000; Kiselev and Il'yasov, 2007). For hypothesis (a), we suppose that PrP^{Sc} deposition hinders diffusion (i.e. slows down but does not trap water molecules) in the extra-cellular space: the diffusivity is reduced in the lesions but the displacement distribution is still Gaussian with a variance linearly increasing with time. Thus we use a biexponential model (Niendorf et al., 1996; Clark and Le Bihan, 2000; Mulkern et al., 2001) to represent hypothesis (a). Under hypothesis (b), the confinement of water molecules inside the vacuoles leads to restricted diffusion that has a non-Gaussian displacement distribution that depends on the average size of the vacuoles. This condition is modelled with a two-compartment model, with restricted diffusion in a spherical compartment (the vacuoles) and hindered diffusion in the other compartment, corresponding to the extracellular space in the voxel. Each more provides estimates of various parameters that contain more specific information than the ADC. Both estimate compartmental diffusivities, as well as volume fractions for each compartment. Moreover, model (b) provides estimates of the average vacuole size, which offers potential as a non-invasive biomarker that discriminates prion disease subtypes. We also tested the standard mono-exponential model (the ADC) for comparison with both of the newly proposed models.

To test and compare the different mathematical models, we designed an advanced acquisition scheme that explores the possible range of different diffusion-weightings (b-values), diffusion times and T_2-weightings as widely as possible on a clinical 1.5 Tesla MR scanner. The scheme provides a uniquely broad sampling of the possible space of measurements with which to evaluate the candidate models. The acquisition is not intended as practical to run routinely for clinical assessment, but rather to provide the best information with which to identify an appropriate model. Once we have such a model, we can use it to find an economical imaging scheme that is practical for clinical assessment, for example using the experiment design optimization algorithm described by Alexander (2008).

Overall, the study has two main aims: i) to evaluate the MR parameters of each model in healthy subjects and patients in order to see which are informative about the presence of prion pathology and to understand if the proposed models can provide more information than the ADC; and ii) to compare the models themselves in terms of fitting performance in order to see which hypothesis is more likely to explain the signal changes. Thus, (i) leads to new clinical indices of prion pathology and for a better characterization of specific features of the affected tissue, while (ii) aims for a general understanding of the pathological mechanism responsible for the signal hyperintensity.

2. Material and methods

2.1. Subjects

We recruited 15 consecutive patients with suspected diagnosis of prion disease and four healthy age-matched elderly subjects. The