Anomalous Diffusion and Non-Monoexponential b-decay

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Introduction Significant departures from the standard monoexponential diffusion model have been reported in experimental data acquired in rats [2] and in humans [e.g. 3-4]. One suggestion for this deviation is the biexponential model in which two populations of spins with different diffusion constants are present in imaged brain tissue. However, this model involves a complex fitting problem in several parameters [4]. Here we present an alternative interpretation of non-monoexponential signal decay for diffusion in terms of the theory of *Anomalous Diffusion* [1] and show that simple scaling arguments lead to an experimentally-testable hypothesis. We reproduce the non-monoexponential decay observed previously [2-4] and obtain results that provide support for the anomalous diffusion hypothesis. Furthermore, we conclude that non-mono-exponential decay may occur due to non-locally homogeneous disorder in the diffusion environment.

Theory The standard model of diffusion in MRI is similar to mathematical models of free (or regular) diffusion such that the mean-squared displacement of a diffusing particle increases linearly with diffusion time, *t*. This model assumes local spatial homogeneity and leads to the Einstein equation from which the diffusion constant, *D* is defined. The model of anomalous diffusion differs from the standard model by allowing random walkers to explore a diffusion environment that is not locally homogeneous, but instead contains an irreducible disorder. This disorder leads to the mean-squared displacement of diffusing particles being proportional to t^{γ}, where $\gamma \neq 1$ [1], rather than *t*. In the present study we refer to γ as the anomalous exponent and are specifically interested in the case $\gamma < 1$. This case, commonly observed in porous media is known as subdiffusion. In particular, subdiffusion occurs when the mean-squared displacement increases slower than linearly with time.

In the present study we hypothesise that complex tissue microstructure will cause locally non-homogeneous random walker paths, leading to a subdiffusion where mean-squared displacement varies slower than linearly with time. Theoretically, anomalous diffusion may be defined as a time-dependent 'constant',

$$D := \frac{\langle r^2(t) \rangle}{t}.$$

Since the b-factor of a diffusion MRI acquisition is linear in time and in spatial field gradient, we propose the following scaling for *D*,

$$D := \frac{\langle r^2(b) \rangle}{b},$$

which by substitution in the Stejkskal-Tanner equation leads to,

$$\ln \frac{S}{S_0} = -bD = -b\frac{\langle r^2(b) \rangle}{b} = -b^{\gamma}.$$ The exponent, γ, may be extracted experimentally by calculating the gradient of a straight line on the log-log plot of $\ln|\ln(S/S_0)|$ against ln(b). On this plot, the power-law form we propose will be a straight line with gradient, γ. For a monoexponential dependence gradient of this line will be 1, and for a biexponential curve the gradient will be 1 in the limit of low ($b \to 0$) and high b ($b \to \infty$) with a non-linear intermediate region that is fitted to the data.

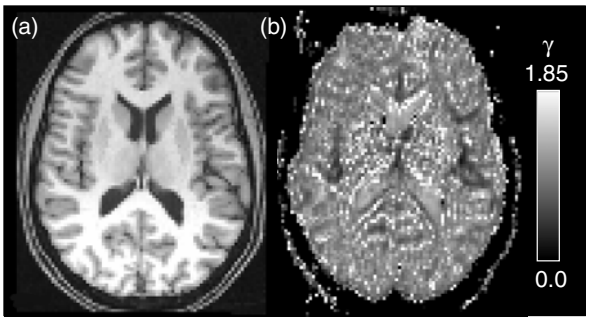

Figure 1

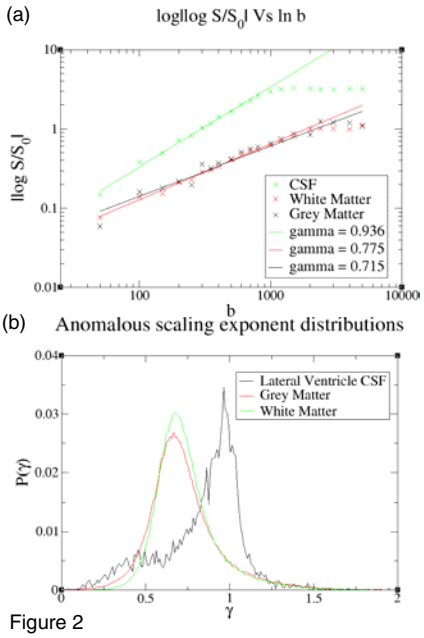

Figure 2

Experimental method *Image acquisition and preprocessing:* Data were acquired on a healthy adult male subject whose written consent was obtained prior to scanning. Diffusion weighted EPI (DWI) data were acquired on a 3T Siemens Trio MR system across 2 axial acquisitions of 32 coronal slices in 12 directions for 20 *b* values ranging between 50 and 5000 (voxel resolution $2mm^3$). The b values were chosen to be approximately evenly spaced on a log-axis. The DWIs were corrected for eddy-current distortion using FSL [5] and a T1-weighted was coregistered to the DWI data using SPM2 [6]. The coregistered T1-weighted image (Fig-1a) was segmented into grey matter, white matter and CSF [6] to allow investigation of anomalous exponents across the 3 tissue types.

Computation of the anomalous exponent: In each voxel, and for each direction, $\ln|\ln(S/S_0)|$ versus ln(b) was fitted to a straight line using a least-squares procedure to obtain the anomalous exponent γ. Only signals above the noise-floor (defined as two standard deviations above the mean background signal and measured in an empty sagittal slice of the image) were included in the fitting procedure, and only the anomalous exponents computed from 5 or more data points were further analysed. The exponents were averaged over all directions and across both acquisitions to obtain the anomalous exponent image (Fig-1b). Distributions of the anomalous exponent in grey matter, white matter and CSF were generated from the tissue segmentations computed for the coregistered T1-weighted image and are shown in Fig-2b.

Results Fig-1b illustrates the anomalous diffusion scaling exponent image and shows the dependence of $\ln|\ln(S/S_0)|$ on ln(b) When compared to the same slice through the T1-weighted image (Fig-1) the lateral ventricle CSF voxels are seen to have higher intensities (~1) than grey and white matter voxels, and the CSF spaces have more homogeneous exponents. Fig-2a shows that grey and white matter voxels contain straight lines with gradient less than 1, and that monoexponential decay observed in CSF voxels have the expected gradient of 1 (although CSF signal falls off more rapidly and exhibits a cut-off due to noise at high *b* values). The distributions of scaling exponents in different tissue types are illustrated in Fig-2b. Here the CSF distribution is strongly peaked at 0.96 (close to that expected in free diffusion), whereas the grey and white matter distributions peak at exponents of 0.73 and 0.75 respectively, indicating subdiffusion in brain tissue. There is no observed contrast between grey and white matter exponent distributions.

Conclusion The theory of anomalous diffusion and its definition for MRI data leads to a theoretical prediction of non-linear dependence of diffusion signal on time, and our initial findings indicate that this dependence appears to be present in diffusion weighted images of the brain. The power-law form leads to a more straightforward fitting problem than the biexpoential form and is able to distinguish between free diffusion (CSF) and diffusion in complex media (grey and white matter). This sub-linear *b* dependence is consistent with the theory of diffusion in porous or disordered media and provides a new insight into sub-voxel cerebral microstructure experienced by diffusing particles that are detectable by MR imaging.

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