Increase of structural disorder along neurites is leading cause for diffusivity drop in acute ischemia

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Introduction: The significant decrease[1] in the water diffusion coefficient minutes after brain injury is a noninvasive diagnostic marker for acute ischemia. However, the microscopic origin of this phenomenon has long been debated[2,3,4,5]. The resolution of this problem is closely related to identifying the predominant restrictions and/or cell mechanisms responsible for the observed values of the diffusion coefficient in a healthy brain. Here we address these two related questions by focusing on the dispersive diffusivity $D(\omega)$ measured[6] in rat cortical gray matter (see Fig.1).

Methods: A striking observation from the dispersive diffusivity, as measured with the oscillating gradient spin echo technique[6], is the accuracy of the power law

$$D(\omega) = \tfrac{1}{2}\langle v(-\omega)v(\omega)\rangle \cong D_\infty + \text{const}\cdot\omega^\alpha \quad \text{with } \alpha = 1/2 \qquad (1)$$

in the velocity autocorrelation function, over the whole frequency range $\omega/2\pi \le 0.5$ kHz, both in live and ischemic (i.e., postmortem) rat (see Fig. 1). To interpret this observation, we have classified the types of structural organization ("disorder") in any medium, in terms of the long-time (low-frequency) power-law exponent α in the time-dependent diffusivity (1). At long diffusion times, the molecules travel across multiple structural features probing the statistics of spatial fluctuations of the microstructure. The DWI signal becomes sensitive to whether the microarchitecture is regular (periodic) or random, and to the degree of such randomness. For example, $\alpha = d/2$ in d dimensions[7] corresponds to the Poissonian statistics of the disorder in the positions of local restrictions (no spatial correlations). When the microarchitecture is more homogeneous (e.g. periodic or hyperuniform), the structural fluctuations average out faster with the diffusion length, so that the exponent obeys $\alpha > d/2$; for a strictly periodic system (no fluctuations), $\alpha = 2$. Conversely, structural fluctuations introduced by extended permeable membranes average out slower, leading to $\alpha < d/2$, as we showed recently[8].

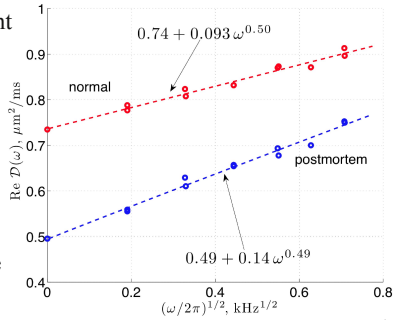

Fig.1: Measured[6] $D(\omega)$, as a function of $\omega^{1/2}$, follows Eq. (1) in live and ischemic brain.

Results: The dispersion (1) with $\alpha = 1/2$ both *before and after global ischemia* narrows down the scope of plausible changes in stroke. In particular:
(i) We exclude active water transport as a main contribution. While axonal transport, cytoplasmic streaming/microcirculation have been discussed[3] as reasons for why diffusion is enhanced in normal tissue relative to postmortem, it is unlikely that the combination of these effects could yield the dispersion (1) even in a normal brain. Indeed, the lack of a time scale in the power law means that these streaming processes must happen on multiple time scales, fine-tuned in such a way as to produce the exact power law exponent 1/2. Even if this were the case, such fine-tuning must break down after cell death with those processes switched off, causing the dispersion to change qualitatively, which contradicts the results of Fig. 1. Hence the diffusional dynamics is determined by the *passive* restrictions, and the change in their properties after injury is only quantitative, not qualitative.
(ii) As $\alpha < 2$, neither bounded motion (water confined e.g. to impermeable cells of finite volume), nor any periodic structures (e.g. periodic permeable barriers[9] or any packing with a single pronounced length scale in any dimensionality[10]) provide the dominant restrictions to diffusion. The predominant restrictions to diffusion must then be *nonconfining* (at least in one direction) and *disordered*.
(iii) The passive restrictions, while not fully ordered, are still *correlated in space* so as to yield the $\omega^{1/2}$ scaling, since in the absence of correlations, one gets the $\omega^{3/2}$ dispersion, $\alpha=d/2$ in d=3 dimensions. Moreover, the nonzero D_∞ (Fig.1) rules out the anomalous diffusion[11], e.g. in fractal geometry.

Our analysis based on ref. 8 shows that the dispersion (1) arises due to effectively one-dimensional water motion along locally straight, narrow neurites (mostly dendrites in gray matter[6]). The structural disorder, modulating the diffusive properties along the neurites, may include spines, variations in thickness ("beads") and directionality on the ≥1μm scale in dendrites[12], as well as the synaptic boutons (varicosities), with the distances[13] between them 3−6μm, in axons. The $\omega^{1/2}$ dispersion then arises if the disorder statistics is Poissonian. This is remarkably consistent with the variance in the varicosity spacing being proportional to the mean spacing, as found in ref. 13. Ischemia causes "blebbing", i.e. more pronounced varicosities in both dendrites and axons[14], which effectively increases the disorder. The latter leads to the increase in 'const' in Eq. (1) for the $\omega^{1/2}$ contribution to $D(\omega)$, in agreement with Fig. 1. We also note that the observed 50% increase of the 'const' in front of $\omega^{1/2}$ under ischemia is inconsistent with a drop of the unrestricted water diffusivity D_0 in cytoplasm. Hence, the signature decrease in D_∞ in ischemia cannot be explained by the cell cytoplasm becoming "denser" or "more viscous" after injury. This again hints at the major changes being structural rather than molecular.

Applying our model[8] to the one-dimensional diffusion, assuming random "barriers" (narrow shafts) separating spines and beads, we obtain the reduction of the effective barrier permeability from about 0.5 μm/ms to 0.2 μm/ms after ischemia, while the distance between "barriers" increases from 2 to 3 μm, consistent with the disappearance of spines[14] and the increased role of wider-spaced and more pronounced beads.

The above analysis is also compatible with the recent observation that *in vitro* tensile stress reduces D_∞ in parallel axons.[4] As beading occurs both for tensile stress and for ischemia, ref. 4 advocated axonal beading to be the primary cause for the reduction of D_∞ in stroke and presented numerical results for a model of *periodic* beads to support this hypothesis. While D_∞ is indeed reduced in this model, it is also reduced in other proposed scenarios considered above. This type of modeling for complex media is often not definitive due to multiple adjustable parameters for which the physical values are not well known. Our approach, indeed, shows that periodic restrictions would actually lead to $\alpha = 2$, inconsistent with the measurement of Does et al.[6] We emphasize that Poissonian disorder is essential to obtain the observed dispersion along either axons or dendrites.

Discussion: The robustness of our conclusions with respect to the microscopic details highlights the value of the information contained in the dynamical exponent α, Eq. (1). Our approach underscores the value of the *functional form* of $D(\omega)$, rather than of a typically discussed single number $D_\infty \equiv D(\omega=0)$, for identifying the origin of a complex biophysical phenomenon. It augments the previously suggested picture of impermeable straight hollow cylinders[15]. The present framework may stimulate more focussed investigations of ischemic stroke, as well as of other neurological disorders.

1 Moseley *et al*, MRM 14(1990)330. **2** Benveniste *et al*, Stroke 23(1992)746. **3** Nevo *et al*, NMR Biomed 23(2010)734. **4** Budde *et al*, PNAS 107(2010)14472. **5** Ackerman *et al*, NMR Biomed 23(2010)725. **6** Does *et al*, MRM 49(2003)206. **7** Ernst *et al*, J Stat Phys 34(1984)477. **8** Novikov *et al*, Nature Physics 7(2011)508. **9** Sukstanskii *et al*, JMR 170(2004)56. **10** Novikov *et al*, NMR Biomed 23(2010)682. **11** Bouchaud *et al*, Phys Rep 195(1990)127. **12** Garcia-Lopez *et al*, J Neurosci 26(2006)11249. **13** Shepherd *et al*, PNAS 99(2002)6340. **14** Zhang et al, J Neurosci 25(2005)5333. **15** Jespersen *et al*, Neuroimage 34(2007)1473.