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Interactive comment on "Transferring principles of solid-state and Laplace NMR to the field of *in vivo* brain MRI" *by* João P. de Almeida Martins et al.

Anonymous Referee #1

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This manuscript describes a new approach to simultaneously measuring T2 and diffusion for characterization of microstructure in central nervous system tissue. An experimental protocol is set up to directly explore T2 relaxation and the diffusion tensor without model fitting. A unique aspect of this study is that diffusion in the voxel is interpreted as distributions of axially symmetric diffusion tensors with mean diffusivities and tensor anisotropy, Ddelta. What makes this work very different from more conventional diffusion studies is that the gradient trajectories are designed to refocus signal from voxels which have distinct diffusion tensor shapes. The measurement protocol is designed to extract 5 parameters for each voxel: T2, Dpar, Dper, theta, phi. The results are presented in 3 D plots of T2, MD, Dpar/Dper.

This manuscript is one of a series several recent publications by this group and applies

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the technology to human brain for the first time. Both the measurement and the analysis are quite sophisticated- this is an impressive accomplishment and a challenging manuscript to review due to the large number of unconventional steps in the experimental design.

All in all, this reviewer finds this work both exciting and impressive. It scores very high marks for novelty. The most exciting single result for this reviewer was the observation that grey matter generally is represented by two tensors which have similar Diso's but different tensor shapes. This work shows results from a single healthy volunteer; hence I see this as a glimpse of what might be possible with this technology. Clearly much more work is required to establish what happens in normal and, later, what happens with different brain pathologies.

I have a few comments, presented here in the order they appear in the manuscript.

1) The voxel size required for this measurement is large at 2x2x6 mmˆ3 or 2.3x2.3x5 mmˆ. This is bad enough in normal brain, but it may hamper its capability to extract microstructural information from small brain lesions. Is there potential for improved resolution?

2) I didn't see how long it took to do the analysis. Minutes, hours or days? The description of the analysis approach around line 150-155 is quite brief; is it possible to describe how weighting of points is determined?

3) The results in figure 3 are focused on the description of the 3D plots for GM, WM and CSF. Can the authors speculate more on the anatomical interpretation of these plots, especially for GM. It's one thing to say that GM has prolate and oblate components, can this be interpreted in terms of brain cell structures(s)?

4) I appreciate that log plots are a useful way to display the 3D plots; however, it would be much more intuitive for this reviewer if the data were presented in numbers that readers are familiar with. Logarithmically scaled plots are good, but the numbers on

the axes are much easier to interpret if they are numbers we are familiar with.

5) To continue, most people think of T2 as a number in seconds. Log(R2) means little to me. It's reasonable to do the analysis and plot scales logarithmically, but I prefer to see the actual numbers in plots.

6) To continue again, the definition of the three bins: Big, Thin and Thick (around line 250) would be much easier to read if they were in a table and if the various limits were provided in units most MRI readers are familiar with.

7) The discussion on how GM, WM and CSF contributions can be separated in large voxels with partial volume effects in normal CNS tissue seems longer than necessary. Is there a solid justification for the value in separating GM and WM and CSF when, as mentioned in the manuscript, T1 weighting easily enables segmentation of these components? However, discussing the similarities and differences between these three tissues in the 3D plots is very interesting. But it seems unlikely that the T2,D approach could be better than T1 for GM/WM segmentation.

8) Near line 285, there is a discussion about R2 bins. The TE times used are 60, 80, 110, 150ms. The four R2 bins correspond to 10ms to 40ms, 40ms to 63ms, 63ms to 3.16s. There are at least a couple of concerns here: i) with the first TE at 60ms, signals from most of the lower T2 range are not measurable. ii) a more serious issue is the selection of 63 ms as a boundary point. T2 times for normal GM and WM at 3T hover around 60ms. This data could probably separate T2's at 60- 100ms from T2s over 1 second, but by using 63ms as a boundary, GM and WM T2s for most structures will be equally likely to be in one or the other bins. If this is not the case, then there may be bias problems with the T2 estimations.

9) An important recent frontier in the conventional diffusion field has been the separation of isotropic and anisotropic water environments (e.g. DBSI, NODDI, CHARM, for characterisation of edema and inflammation. In their discussion near line 315, can the authors speculate on potential advantages, or disadvantages, of using the tuned

gradient trajectory approach over conventional diffusion acquisition approaches for extracting the signal from spins that undergo isotropic diffusion?

10) In Figure 6A, there seems to be a ‘pile-up’ of signal with T2 = 30ms, which especially in the ‘Thin’ box. Is this artifact or something else?

In summary, I like this work very much and look forward to seeing more work from this team.

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