Magn. Reson. Discuss.,
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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 #2

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Authors present multi-dimensional (this time 5D) NMR imaging, to resolve compartments with different relaxation and diffusion properties. This is a very promising and interesting work which tackles one of the main limitations of quantitative MRI, lack of specificity.

Per-voxel diffusion MR signal is a summary statistics of multiple compartments with different biophysical properties. The conventional approaches to decompose these compartments are multi-compartment modeling or data driven signal decomposition. Propose technique is highly valuable because it adds an important degree of freedom (gained from acquisition domain) that enables tissue specific sensitization, and therefore improved specificity.

The experiment is nicely done, well evaluated and the paper is well structured and well

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written. It is in camera ready in current form.

I have below thoughts/questions:

- This work is presented as a clinically feasible acquisition, but a 45 minute acquisition is not clinical. It is described and supplemented that the work can be shorten, but all the evaluation are done and conclusion are made based on a 45 minute scan (especially given that you state that SNR boosting repletion is essential). Although 45 minute is less than a usual clinical MRI scan ($\sim$1 hour), but if one spend 45 min on DWI, there will be no room for clinically essential scans such as FLAIR, T1w, T2, T2*/SWI.

- I was wondering if you compared regions with anatomically known microstructural differences to see how your measures compare. E.g. CST vs a short U-fiber

- Any specific reason for 2x2x6 configuration? do you think isotropic acquisition affect your measurements?

- How long the parameter extraction with MC took? what was the hardware used?

- "The acquired images were not subjected to any additional corrections (e.g. denoising or motion correction) before data inversion." Do you mean you did not do motion correction at all (screaming face emoji)? This is a 45 minute scan, and regardless of how Zen your participant was, there would be motion. did you at least assess the amount of motion. In particular, I would expect that the motion correction of high b-value, spherical acquisitions would be challenging. Did you average repetitions without motion correction?

- It would be useful to know the number of unknown parameters

- The paper only mention PGSE and how old it is, it would be more fair if alternative sequences (e.g. OGSE) are compared against this approach

Few additional minor suggestions:

- "The structure of the brain is shaped by both disease and normal developments on a

wide range of length scales." This sounds a bit strange.

- "insufficient for direct observation of individual cells, chemical and cellular features", what features? Microstructural? This can be confused with functional features

- I couldn't understand why delta(D) can be negative and why the range is -0.5 to 1. Please elaborate so those new to this technique could better understand the sequence.

- it could help less familiar readers if you mention that the linear encoding (b_delta = 1) is the same as conventional PGSE

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