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REPLY TO LETTER

Reply to: Early white matter changes on diffusion tensor imaging in amyotrophic lateral sclerosis

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We thank Dr Finsterer and colleagues for their comments[1] on our paper.[2] They raise a number of interesting points.

Firstly, they suggest that we should differentiate between patients with bulbar and limb onset. In our sample, 15% had bulbar onset and 85% limb onset (of the 143 subjects where this information was available), indicating that the samples overall were reasonably representative of amyotrophic lateral sclerosis (ALS) clinic cohorts.

However, our data-driven approach requires large sample sizes to disentangle the temporal heterogeneity of ALS. We would be underpowered in this study to analyze small subgroups, including bulbar onset versus limb onset, especially as we do not know of any specific imaging biomarker that reliably discriminates between these categories.

Secondly, Dr Finsterer and colleagues suggest that people with familial ALS might have a differing disease course from those with sporadic ALS. Unfortunately, detailed and consistent data on the family history were not available for all cohorts at time of analysis, and ethics approval to carry out comprehensive genetic testing was not sought for cohorts E, F, K, and N. However, the same concerns about small group analyses apply: we conclude that, lacking definitive genetic data on all subjects, subgroup analysis (whether by history or genetic testing) would not enhance the results of our study.

Thirdly, they suggest that we should have included disease duration as a predictor. We do not consider that ALS disease duration per se as measured in absolute terms (e.g. years and months) is particularly informative for this study, as the progression rate of ALS is extremely variable. We

consider that disease 'intensity' (i.e. severity in relation to duration) is the most pertinent measure in this context. As stated in the text, disease severity at the time of scanning was assessed by ALSFRS-R. We also emphasize that the modeling process requires that we include subjects at as many different stages of the disease as possible.

Finally, Finsterer and colleagues question our inclusion of the inferior longitudinal fasciculus (ILF) as a white matter tract of interest in ALS. However, as cited in our study, recent tractography techniques have clearly demonstrated correlations between performance in cognitive tasks and diffusion tensor imaging changes in the ILF in ALS.[3] The ILF has also been shown to be involved in emotional dysfunctions[4] and verbal fluency impairments[5] in ALS, and reduced white matter integrity of the ILF has been found in ALS patients with the C9orf72 repeat expansion.[6]

Conflict of Interest

Gabel and Broad report grants from Motor Neurone Disease Association, outside the submitted work.

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