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Reply

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The letter by Dols-Icardo et al. reports an independent analysis of [^{18}F]fluorodeoxyglucose positron emission tomography and whole-genome sequencing data from the Alzheimer's Disease Neuroimaging Initiative cohort that nicely complements our recent report[1] addressing brain structural features associated with a *REST* missense variant as well as the recent findings reported by Lu et al.[2] We found the minor allele of rs3796529 in the REST gene protective for rate of hippocampal volume loss in individuals with *APOE* ε3/ε3 genotype. Further analyses[3] in response to a letter from Dr. Yankner[4] indicated that rs3796529 was significantly associated with hippocampal CA1 subfield volume in both mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients, with minor allele carriers having larger CA1 volumes. However, rs3796529 was not associated with hippocampal CA1 volume in older adults who were in the cognitively normal control group.

By contrast, Dols-Icardo et al. found that both controls and MCI patients carrying at least one minor allele of the *REST* singlenucleotide polymorphism had increased glucose metabolism in the medial temporal region compared to noncarriers, suggesting the neuroprotective role of the *REST* missense variant extends to controls. The role of *REST* as a protective factor in controls notably supports the previous findings by Lu et al.[2] However, the influence of rs3796529 on brain glucose metabolism was found for only the left or right medial temporal region, and the statistical images were not corrected for the multiple comparisons at the voxel or cluster level. Thus, these intriguing findings warrant further investigation and ideally an independent replication.

In summary, Dols-Icardo et al.'s findings reaffirm earlier observations that the *REST* rs3796529 variant may be a protective factor for MCI. Additional longitudinal analyses would help to clarify the protective role of *REST* through the AD continuum as well as its relevance for prediction of within-subject change. Additional experimental studies are needed to determine the potential of *REST* as a target for therapeutic and preventative interventions.

References

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Potential Conflicts of Interest: Nothing to report.

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