Alzheimer’s disease affects tens of millions of people worldwide. Post-mortem analyses of the brains of Alzheimer’s patients reveal two major histopathological hallmarks, (1) the accumulation of extracellular beta amyloid plaques (Aβ) and (2) intracellular neurofibrillary tangles (NFTs). NFTs are associated with the loss of neurons, whereas Aβ is linked to dysfunction of neuronal synapses, cerebrovascular deficits, and inflammatory activity.

In addition to the above post-mortem hallmarks, in vivo imaging, magnetic resonance imaging (MRI) studies reveal structural differences between the Alzheimer’s brain and unaffected healthy subjects. This includes thinning of the cortical mantle, shrinking of the hippocampus, and enlargement of the lateral ventricles, which carry cerebrospinal fluid (CSF).

However, a link between Aβ or NFTs and these in vivo MRI hallmarks remain unclear. In this study, we applied Advanced Normalization Tools (ANTS) and Symmetrical Normalization to assess structural differences between control nontransgenic (nTg), TgCRND8, and 5xFAD mice harboring both amyloid precursor protein (APP) and presenilin mutations.

**Steps for Processing Anatomical Scans Using Non-Linear Registration to Reference Brain**

This study used scans that were collected at 11.1 Tesla MRI as part of studies to examine functional and white matter differences between Alzheimer’s disease mice and non-transgenic control mice. The data included the following:

Aged nTg CRND8 mice (n=4) and TgCRND8 mice (n=7). Also, wildtype C57BL/6J (B6) mice or B6 x DBA/2J intercrossed mice (D2), and aged match transgenic littermates with 3APP and 2 PS mutations (5xFAD)(n=4-7/group).

We used a high-resolution Turbo-RARE MRI sequence with the following dimensions: field of view 15x11x15mm, 256x192 data matrix and 25 slices. The scans covered the entire mouse brain.

**Summary**

Mice with APP mutations (TgCRND8 or 5xFAD) did not have significant anatomical differences when compared with wildtype mice.

A trend was observed in hippocampal and white matter regions of 5xFAD mice, although this varied with the background strain.

The nonlinear normalization approach was observed to work best when using a reference scan of the mouse brain.

This approach will be used to assess the role of structural differences and how this can influence results from functional MRI and diffusion MRI studies.

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