

Understanding the impact of anti-A β immunotherapy on myeloarchitectural organization

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INTRODUCTION

Anti-amyloid immunotherapies (AAI) can trigger treatment-specific tissue alterations with poorly understood biological mechanisms. Characterizing myeloarchitectural remodeling may identify imaging biomarkers sensitive to upstream immunotherapy effects. The aim of the current study is to map myeloarchitectural alterations in Tg2576 mice following 12-week immunotherapy using ultra-high resolution multi spin echo (MSE) based quantitative transverse relaxation (qT2) and myelin water fraction (MWF) imaging.

METHODS

Eighteen-month-old Tg2576 mice (n=7/group) received weekly intraperitoneal injections of either 3D6 (anti-A β_{1-5} , IgG2a; 10 mg/kg) or isotype control IgG (IgG2a; 10 mg/kg) for 12 weeks, followed by ex-vivo qMRI on a 9.4 T preclinical scanner (Bruker BioSpin, GmbH, Germany) equipped with an ¹H cryogenic surface coil. MSE was used to obtain highly detailed, T2 and MWF maps. The MRI data was processed using custom built computational pipelines and voxel-based analysis (VBA) was performed for each qMRI parameter.

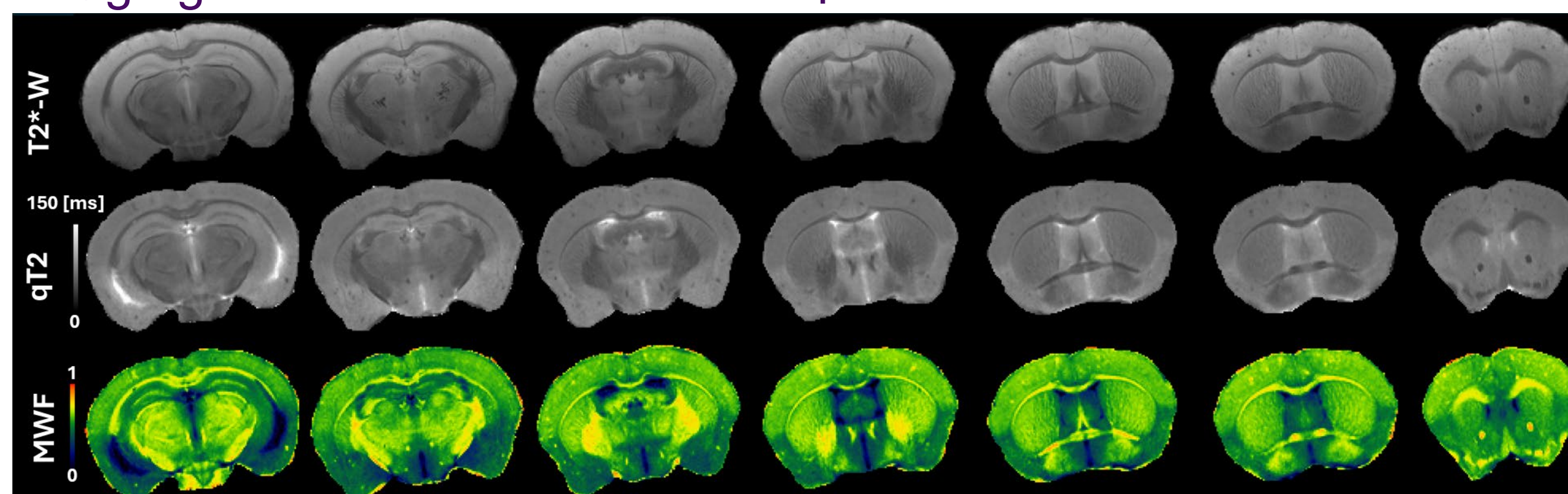


Fig 1: T2*-W, qT2 and MWF maps from a representative Tg2576 mouse treated with 3D6

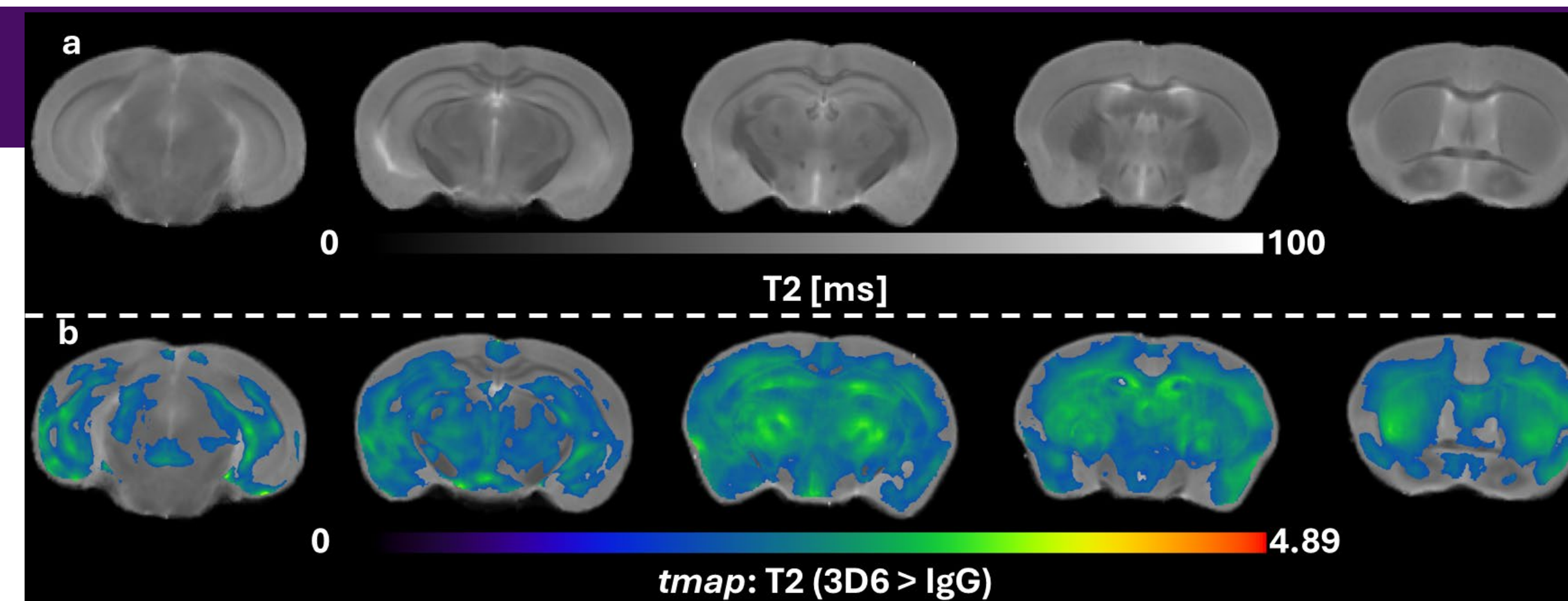


Fig 2: VBA of T2 detected increased T2 in 3D6 treated mice relative to IgG administered mice. (a) T2 based study specific template (SST). Image resolution: 76x76x200 μm^3 (b) Representative depiction of T2 differences across the brain between 3D6 treated and IgG administered mice. Group comparisons were conducted using VBA, permutation-based statistics were performed using 5000 permutations. The p -values were corrected using Threshold-Free Cluster Enhancement option in randomise (FSL) and a corrected p -value of 0.05 was considered significant. T-tests were performed for group comparisons. Results are presented as t maps. The color scale indicates the t -score ($p < 0.05$, family-wise error corrected: FWE), for which significant regions were superimposed on the SST.

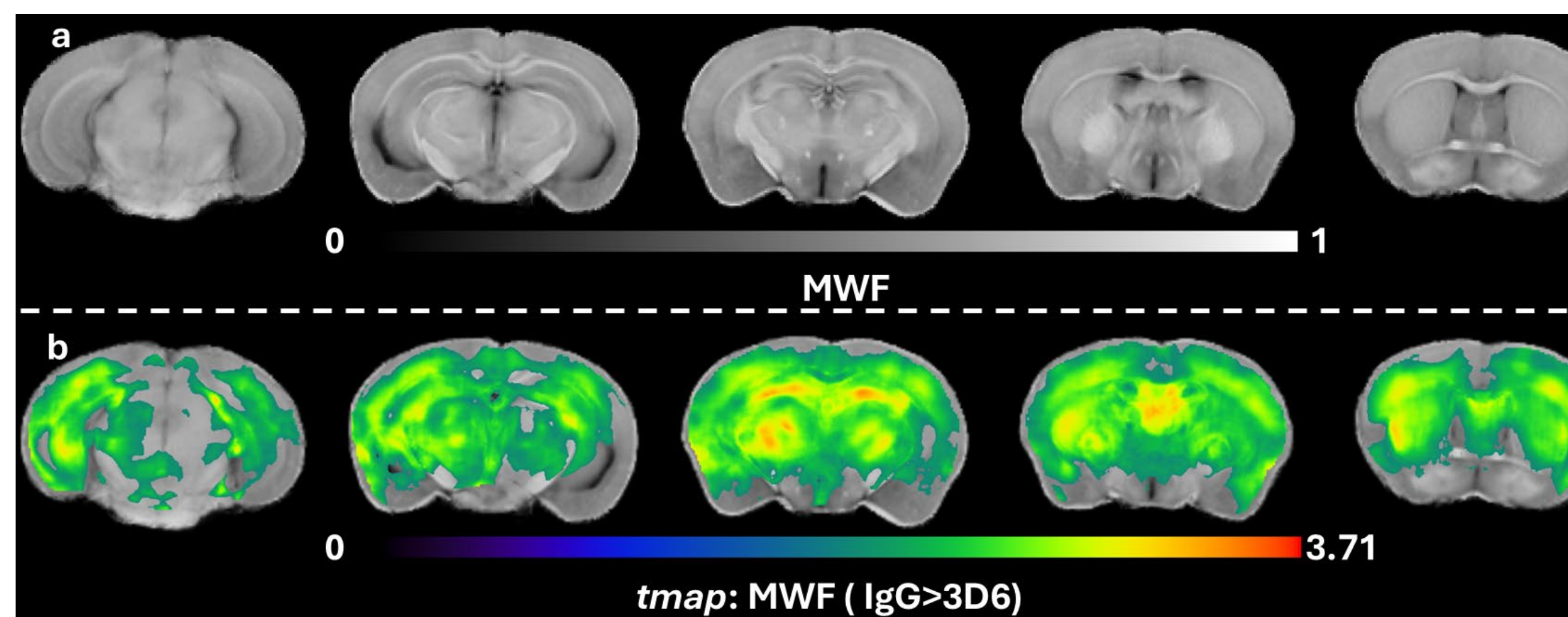


Fig 3: VBA of MWF detected reduced MWF in 3D6 treated mice relative to IgG administered mice. (a) MWF based SST. Image resolution: 76x76x200 μm^3 (b) Representative depiction of MWF differences across the brain between 3D6 treated and IgG administered mice. Results are presented as t maps. The color scale indicates the t -score ($p < 0.05$, FWE), for which significant regions were superimposed on the SST.

RESULTS

Compared to IgG control group, 3D6-treated mice exhibited significantly higher T2 across cortical and subcortical structures, corpus callosum, hippocampus, thalamic nuclei, and dorsal striatum (Fig:2). MWF was significantly lower in 3D6-treated mice, relative to IgG control in these regions (Fig:3).

CONCLUSIONS

AAI increased tissue water content and reduced MWF, suggesting 3D6-specific interstitial fluid accumulation, demyelination, or myelin remodeling. These microstructural changes may represent upstream mechanisms driving accelerated brain volume loss. Thus, qMRI may serve as a sensitive biomarker for monitoring myeloarchitectural alterations in AAI.

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