Quantitative 7T Relaxographic, Volumetric and DCE Assessment of Thalamic Changes in Early Alzheimer's Disease

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Introduction: Longitudinal water proton (^1H_2O) relaxation time constants (T_1) have been used extensively to probe the interactions of water and macromolecules in the human brain.[1] While an increase in gray matter ^1H_2O T_1 values with age has been observed by many groups,[2] the physiological basis of this finding remains unclear. Brain tissue ^1H_2O R_1 ($\equiv 1/T_1$) values are strongly associated with macromolecular volume fraction (f_M; an intensive property)[3] which may decrease with age and precede net tissue volume loss (atrophy; an extensive property). Volume loss in the subcortical gray is a common feature of the aging brain and has recently been identified in the thalamus of subjects with Alzheimer's disease (AD).[4] Atrophic changes are associated with expansion of CSF spaces and could, through partial volume effects, lead to increased T_1 values. Vascular ultrastructure is also known to be abnormal in early AD[5] and could, through increased blood water content, contribute to altered ^1H_2O T_1 values. The aim of this study was to examine the extent to which ^1H_2O T_1 values reflect changes in tissue and/or vascular water content in the thalamus in early AD.

Methods: 3 subjects with mild AD (71 ± 5 yrs; 3 males) and 8 cognitively normal (CN) age-matched controls (64 ± 6 yrs; 4 male/4 female) provided informed consent and were enrolled. All AD subjects had onset of symptoms after age 40, Clinical Dementia Rating[6] of 0.5, MMSE 20-27, deficit in another non-cognitive domain, and progressive worsening of memory. CN subjects had no memory complaints, MMSE 28-30, and no history of neurologic disease. MR data were acquired on a 7T whole-body instrument (Siemens MAGNETOM) with 8-channel phased array RF transmit/receive head coil (Rapid Biomedical). Full volume (96 slices) IR-MPRAGE acquisitions (TR/TE= 3500/2.3 ms; FA= 6°; 114x192 matrix; slice thickness 2 mm) centered on the lateral ventricles were sampled at different inversion times (TI= 300, 1800, 3200 ms; and no inversion pulse). FOV was adjusted to provide 1.3 mm^2 in plane resolution. IR datasets were collected prior to and 10, 24, 35, and 57 min post (CR; gadoteridol; Bracco Diagnostics) injection (0.11 mmol/kg; 2 mL/s; Spectris MR Injection System, Medrad). Parametric maps were prepared after co-registration of IR image sets and voxelwise fitting of signal intensity to a two parameter single exponential IR equation using a gradient expansion algorithm. IR-MPRAGE structural images were also acquired (TR/TE/TI 2800/2.8/1100 ms; FA 6°; 256x256 matrix and FOV; 1 mm slice). Volumes of interest (VOI) were segmented automatically by application of a sub-cortical mask prepared using FIRST, part of FMRIB's software library (FSL, Oxford), after transformation and affine registration of the parametric map and structural image to MNI 152 standard space.[7] Sub-cortical volumes were normalized to total intracranial volume (estimated with SIENAX,[8] another part of FSL). ^1H_2O T_1 values were determined after fitting VOI histograms to a Gaussian function. Intravascular water fraction (p_b) was determined from an equation for two-site (blood plasma, extravascular extracellular space) exchange that assumes equilibrium transendothelial water exchange, fixed intravascular ^1H_2O lifetime (τ_b= 280 ms)[9], and negligible CR extravasation ($K^{trans} \approx 0$).[10]

Results and Discussion: Figure 1 shows a T_1 map from a 66 year old AD male with VOIs indicated. Mean ^1H_2O T_1 values for AD and CN groups are presented in **Table 1**. The values we report are in reasonable agreement with those obtained previously at 7T.[3] Compared to CN subjects, ^1H_2O T_1 values in the thalamus are increased by about 4% (P= 0.05) in AD subjects, with smaller (non-significant) increases in other structures. No effect of gender or laterality on T_1 values was found. **Figure 2** (top) shows the mean volume of subcortical structures. Compared to CN subjects, thalamic volume is reduced by 9.6% (P= 0.04) in AD subjects. No significant differences in volume were observed between groups in other structures. The lower panel in Figure 2 shows the R_1 response of tissue in the thalamus (R_{1t}) compared to blood (R_{1b}) after CR injection and the best fit of averaged group data to the two-site transendothelial exchange model. The analysis reveals no difference in p_b between AD and CN groups. Taken together, our findings are consistent with the idea that increased ^1H_2O T_1 values in the thalamus in early AD reflect, at least in part, neurodegenerative (macro-molecular loss) processes and that changes in the vasculature which increase blood water content (e.g., vasodilation or angiogenesis) if present, are small. However, our conclusions are based on only a few subjects and a model that neglects CR extravasation. A more thorough analysis is necessary to substantiate these results.

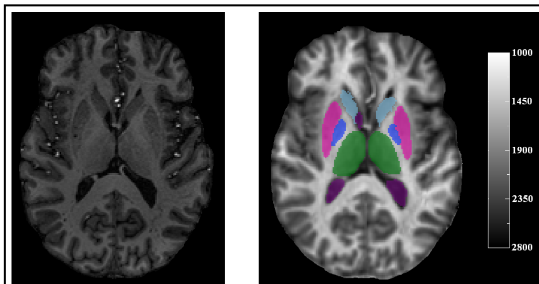

Figure 1. Application of the sub-cortical mask prepared from the structural image (left) to the pre-CR co-registered T_1 map (right) defines VOIs in thalamus (green), putamen (pink), caudate (light blue) and pallidum (dark blue).

Table 1. ^1H_2O T_1 values of subcortical VOIs

VOI	AD (N= 3)	CN (N= 8)	Difference (%)
Thalamus	1449 ± 32	1385 ± 58	4.4
Caudate	1594 ± 52	1565 ± 32	1.8
Putamen	1513 ± 26	1480 ± 30	2.2
Pallidum	1267 ± 66	1227 ± 43	3.2

[a] Mean (ms) ± sd averaged over right and left hemispheres

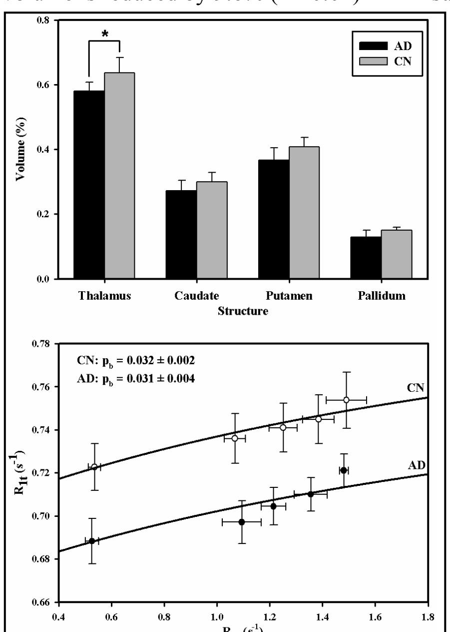

Figure 2. Volumes of subcortical structures (top) and thalamus R_{1t} vs R_{1b} fittings (lower). R_{1b} was determined from an ROI placed completely within the sagittal sinus. Estimates of thalamic fractional blood water (p_b) are shown in the lower panel corner.

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