

Impact of Smoothing Weights on Voxel-Based Quantification (VBQ) analysis

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INTRODUCTION

Voxel-based group analyses conducted in a stereotactic space enable hypothesis-free analyses over the entire brain, which is particularly beneficial for the discovery of novel insights for which there is no a priori knowledge [1]. In such analyses, data for each participant are spatially normalised to a common space, using non-linear warping algorithms, e.g. DARTEL [2]. While these algorithms can achieve a high degree of spatial correspondence across individuals, it is typical to **smooth the data to compensate for any residual mismatch between participants**. Smoothing also serves to enhance the study's sensitivity and reduce the multiple comparisons problem.

However, when dealing with quantitative data with distinct values in different tissue compartments (e.g. grey and white matter), smoothing can introduce deleterious partial volume effects at the tissue boundaries. Like the TSPoon method [3], "Voxel-Based Quantification" (VBQ) [4] has been proposed to **minimise partial volume effects by using participant-specific weights** derived from the spatially normalised tissue probability maps that additionally account for the original tissue volume.

Here we investigate whether or not these weights might introduce spurious effects due to participant-specific morphology by looking at a cohort spanning a broad age range where differential atrophy can be expected.

METHODS

A previous analysis of a cohort with a broad age range (19-75 years) identified patterns of age-related differences in quantitative MRI data using the VBQ approach [5]. The **identified effects were consistent with demyelination (via magnetization transfer, MT) and iron accumulation (via transverse relaxation, $R2^*=1/T2^*$)**.

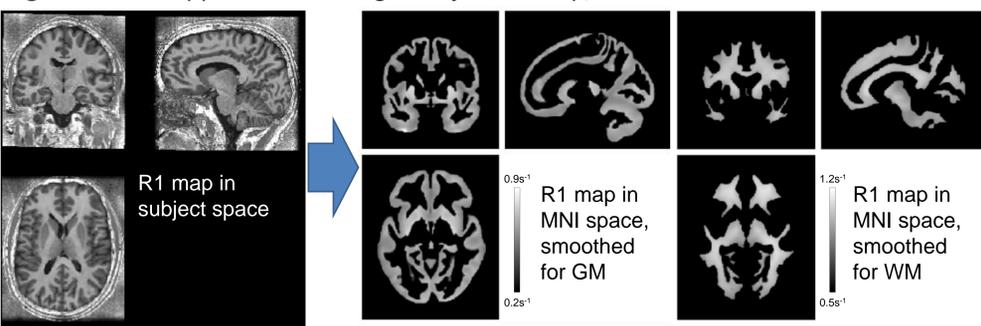
The **VBQ approach used to spatially normalize and smooth the maps, prior to statistical analysis in group space**, is given by Equation 1 and illustrated in Figure 1:

$$\text{Eq. 1: } p_j = \frac{g^*(w_j s_j) m_{\text{TPM}}}{g^* w_j} m_j$$

where

p_j	Parameter map, MT or $R2^*$, for subject indexed by j after VBQ smoothing
s_j	Subject-specific parameter map warped to group space by deformation Φ_j
w_j	Participant-specific weights given by $J_j t_j$
Φ_j	Participant-specific deformation mapping from native to group space
J_j	Jacobian determinants of deformation Φ_j
t_j	Participant-specific tissue probability map warped by deformation Φ_j
m_{TPM}	TPM-specific mask identifying voxels with probability > 5%
g^*	Convolution by Gaussian smoothing kernel (FWHM of 3mm used here)
m_j	Participant-specific mask defined as $(g^* w_j) > 5\%$

Figure 1: VBQ approach for a single subject R1 map, for GM and WM tissues.



These data were re-analysed with one change: **participant-specific VBQ smoothing weights were applied to a single parameter map, s** , according to Equation 2:

$$\text{Eq. 2: } \hat{p}_j = \frac{g^*(w_j s) m_{\text{TPM}}}{g^* w_j} m_j$$

Our hypothesis was that, since the parameter map s was identical and only the smoothing weights changed across participants, any age-related effects identified by this analysis would be spurious and driven by age-related changes in morphometry, most notably atrophy, which would be captured by the Jacobian determinants in w_j .

For the age regression analysis, explicit masks for the GM and WM were used. The GM (respectively WM) mask includes voxels having *i*) >20% chance of being GM (resp. WM) and *ii*) larger probability of being GM (resp. WM) than CSF or WM (resp. GM), on average across all subjects [5]. Voxels are deemed to be significant at $p < 0.05$, after FWER correction for each tissue class considered (GM and WM).

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CONCLUSION

The VBQ [4] or similar [3] approaches to smoothing spatially normalised data should be adopted when analysing quantitative data in a voxel-wise fashion in order to prevent partial volume effects being introduced by the smoothing process. **While this approach, available in the hMRI toolbox [9], may introduce some spurious effects, it appears to be rather robust to differential morphometry across the cohort, particularly in the cortex.**

The methodology presented here could be used to assess this effect in other cohorts.

RESULTS & DISCUSSION

Age-related effects identified in MT, Figure 2, and $R2^*$, Figure 3, using the standard VBQ approach with

- participant-specific parameter maps and smoothing weights (43,552 and 18,608 red voxels resp.), or
- a single parameter map but participant-specific weights (8,619 and 6,792 blue voxels resp.).

The magenta voxels showed significant age-related effects in both analyses. Both GM and WM results are presented and overlaid on the mean MT map in MNI space.

This successfully reproduces the previously reported pattern, in red, of age-related change consistent with demyelination across grey and white matter (MT) and iron deposit in the cortex and basal ganglia ($R2^*$). For both MT and $R2^*$, the spurious significant, in blue, age-related effects are primarily located at the boundary of the ventricles.

These spurious effects showed some overlap (magenta, Figure 2 & 3) with age-related effects identified by the standard VBQ analysis with Dice's coefficients of 0.21 and 0.03 for MT and $R2^*$ respectively. The larger Dice's coefficient in the MT case stems from the fact that age-related effects in MT were predominantly in WM, including adjacent to the ventricular walls.

Figure 2: Age regression, in GM & WM, for multiple and single subject MT map

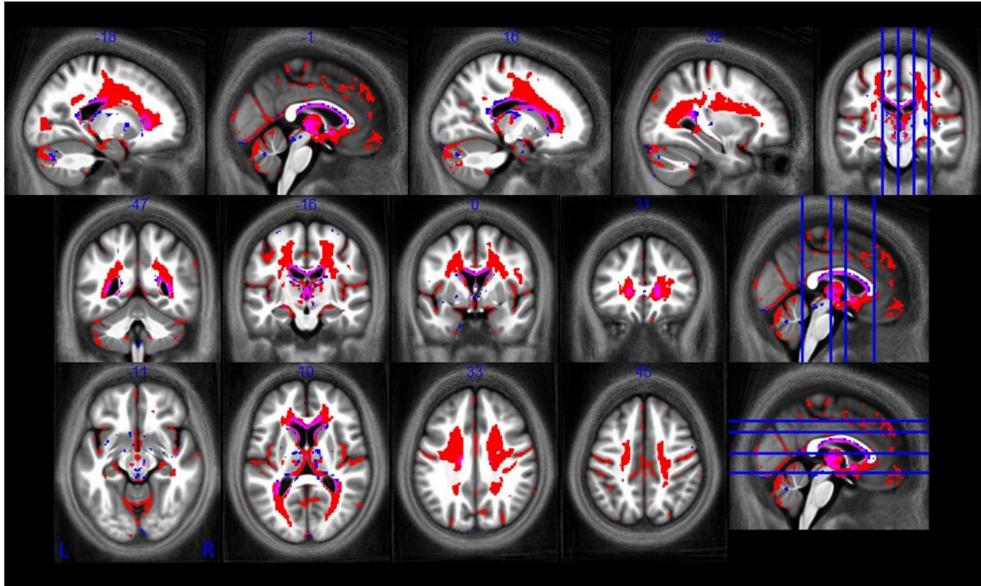


Figure 3: Age regression, in GM & WM, for multiple and single subject $R2^*$ map

