

# Basic MR sequence parameters systematically bias automated brain volume estimation

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## Synopsis

**Standard MR parameters, notably spatial resolution, contrast and image filtering, systematically bias results of automated brain MRI morphometry by up to 4.8%. This is in the same range as early disease-related brain volume alterations, for example in Alzheimer's disease. Automated brain segmentation software packages should therefore require strict MR parameter selection or include compensatory algorithms to avoid MR-parameter-related bias of brain morphometry results.**

## Introduction

Automated brain MRI morphometry, including hippocampal volumetry for Alzheimer's disease, is increasingly recognized as a biomarker. Consequently, a rapidly increasing number of software tools have become available. We tested whether modifications of MR protocol parameters which are often adapted in clinical routine systematically bias automated brain MRI segmentation results.

## Material and Methods

This study was approved by the local ethical committee and included 21 consecutive patients (13 females, mean age  $75.8 \pm 13.8$  years) undergoing clinical brain MRI for workup of cognitive decline. MR imaging was performed on a whole-body 1.5T clinical MR scanner (MAGNETOM Aera, Siemens Healthcare Ltd., Erlangen, Germany) using a 20-channel head coil. Three different 3D T1-weighted sagittal volumes (see Figure 1) were obtained using the magnetization-prepared rapid gradient-echo (MPRAGE) pulse sequences<sup>1,2</sup> employing the imaging parameter settings described in Figure 2.

Brain segmentation was performed by two different analysis tools, the MorphoBox prototype<sup>3,4</sup> and Freesurfer<sup>5</sup> using standard parameters. Estimated volumes of the following brain tissues and structures were analyzed with the R software package (version 3.1.1): total intracranial volume (TIV), grey matter (GM), cortical grey matter (cGM), white matter (WM), hippocampus, ventricles, and cerebellum.

In order to assess the presence of a potential systematic bias in the volumetric results, relative volume differences (RVD) between the reference protocol ( $V_r$ ) and each variant ( $V_v$ ) were computed for each structure as:

$$RVD(V_r, V_v) = 100 \frac{V_v - V_r}{(V_v + V_r)/2},$$

where  $RVD(V_r, V_v)$  is in the range [-200%, 200%].

ADNI-2 and LOCAL- protocols were used as the reference protocol ( $V_r$ ) in all subsequent analyses. Relative volume differences were averaged across the subjects. The statistical significance of the difference from the zero median in relative volumetric differences was tested using the Wilcoxon signed-rank test as the differences were not expected to be normally distributed. Bonferroni correction was used to correct for multiple comparisons.

It has been shown previously that the variance of volume differences does not significantly change across different systems (different field strength, different vendors), but systematic offsets in volumes may be present<sup>6</sup>. Therefore, to compare our results to previously reported scan-rescan reproducibility studies<sup>7,8,9,10</sup>, absolute relative volume differences (ARVD) between the reference protocol ( $V_r$ ) and each variant ( $V_v$ ) were recomputed for each structure as:

$$ARVD(V_r, V_v) = 100 \frac{|V_v - V_r|}{(V_v + V_r)/2},$$

where  $ARVD(V_r, V_v)$  is in the range [0%, 200%].

ADNI-2 and LOCAL- protocols were used as the reference protocol ( $V_r$ ) in all subsequent analysis. Absolute relative volume differences were averaged across the subjects.

## Results

### *Effect of spatial resolution - 1.2 versus 1.0 mm*

The comparison of ADNI2 versus LOCAL- protocols with the FreeSurfer segmentation tool revealed significant changes in TIV, GM, cGM, ventricles, and hippocampus volumes (see Figure 4A), even though they were hard to identify upon visual inspection (see Figure 3). The respective median RVDs were 2.42% ( $p < 0.01$ ), 3.14% ( $p < 0.001$ ), 4.52% ( $p < 0.001$ ), 2.40% ( $p < 0.001$ ), and -3.81% ( $p < 0.05$ ). For hippocampus volumes, the median ARVD was  $4.23 \pm 5.97$  %. Segmentation results obtained with the MorphoBox segmentation tool revealed significant changes in TIV and WM volumes (see Figure 4B); the respective median RVDs were 1.78% ( $p < 0.001$ ) and 1.60% ( $p < 0.01$ ). For hippocampus volumes, the median ARVD was  $4.55 \pm 4.68$  %. Note that the relative volume differences correspond to fixed offsets in segmentation results and do not represent scan-rescan variability of each protocol.

### *Effect of image filtering*

The comparison of LOCAL- versus LOCAL+ protocols with the FreeSurfer segmentation software revealed a significant change in WM and ventricle volumes. The respective RVDs for WM and ventricle volumes were: -1.82% ( $p < 0.05$ ), and -0.98% ( $p < 0.05$ ). The median ARVD of the hippocampus volumes was  $2.99 \pm 7.70$  % (see Figure 5A). Using the MorphoBox segmentation tool, significant changes in TIV and WM volumes were observed. The respective RVDs of TIV and WM volumes were: -0.28% ( $p < 0.05$ ), and -4.84% ( $p < 0.05$ ). The median ARVD of the hippocampus volumes was  $3.39 \pm 3.91$  % (see Figure 5B).

## Discussion

A simple change of MR parameters, notably spatial resolution, contrast and image filtering, may systematically bias results of automated brain MRI morphometry by up to 4.8%. This is in the same range as early disease-related brain volume alterations, for example in Alzheimer's Disease<sup>11</sup>. Automated brain segmentation software packages should therefore require strict MR parameter selection or include compensatory algorithms<sup>12</sup> to avoid MR-parameter-related bias of brain morphometry results.

## Acknowledgements

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## Figures

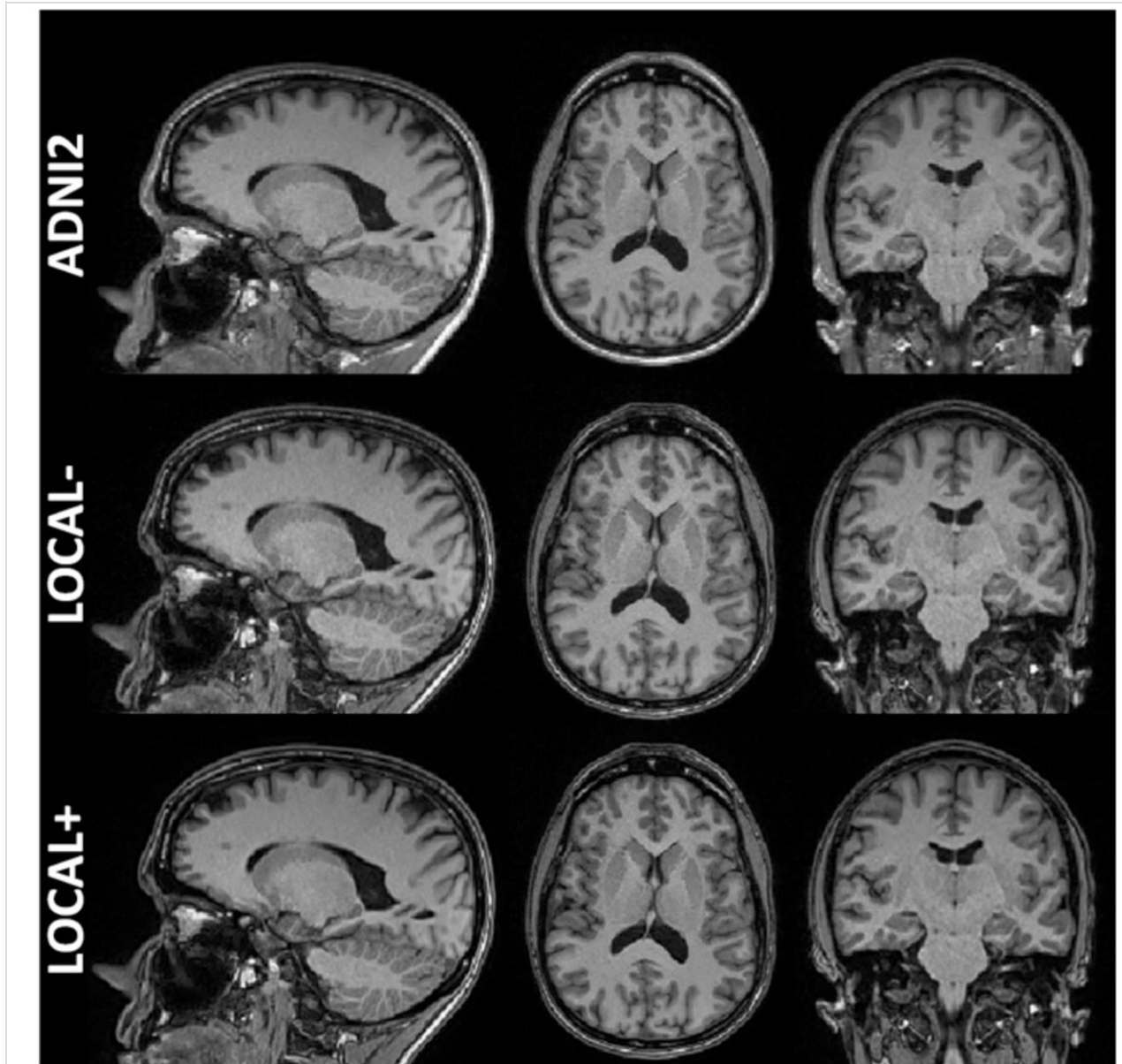


Figure 1. Example of the three different parameter settings for the MPRAGE sequences in coronal, sagittal, and axial slices

	ADNI2	LOCAL-	LOCAL+
Voxel size (mm <sup>3</sup> )	1.25 x 1.25 x 1.2	0.97 x 0.97 x 1	0.97 x 0.97 x 1
TR (ms)	2400	2200	2200
TI (ms)	1000	900	900
Bandwidth (hz/px)	180	150	150
FOV read/phase (mm)	240/240	250/240	250/240
Edge enhancement filter	OFF	OFF	ON

Figure 2. Overview of the essential parameters of the three different MPRAGE protocols.

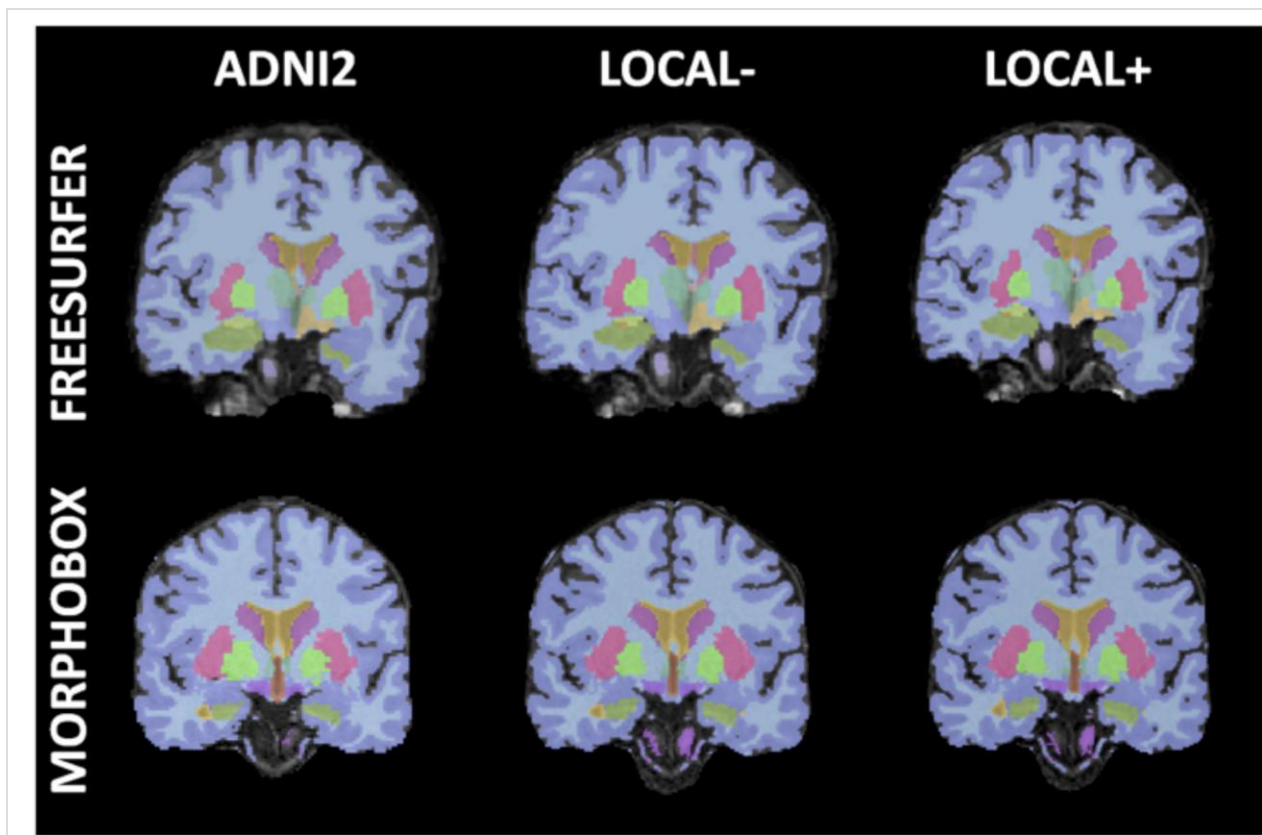


Figure 3. Example of coronal T1V extraction and segmentation obtained with Freesurfer and Morphobox for the three MPRAGE parameter settings



## EFFECT OF SPATIAL FILTER: LOCAL+ vs LOCAL-

**FreeSurfer**

**MorphoBox**

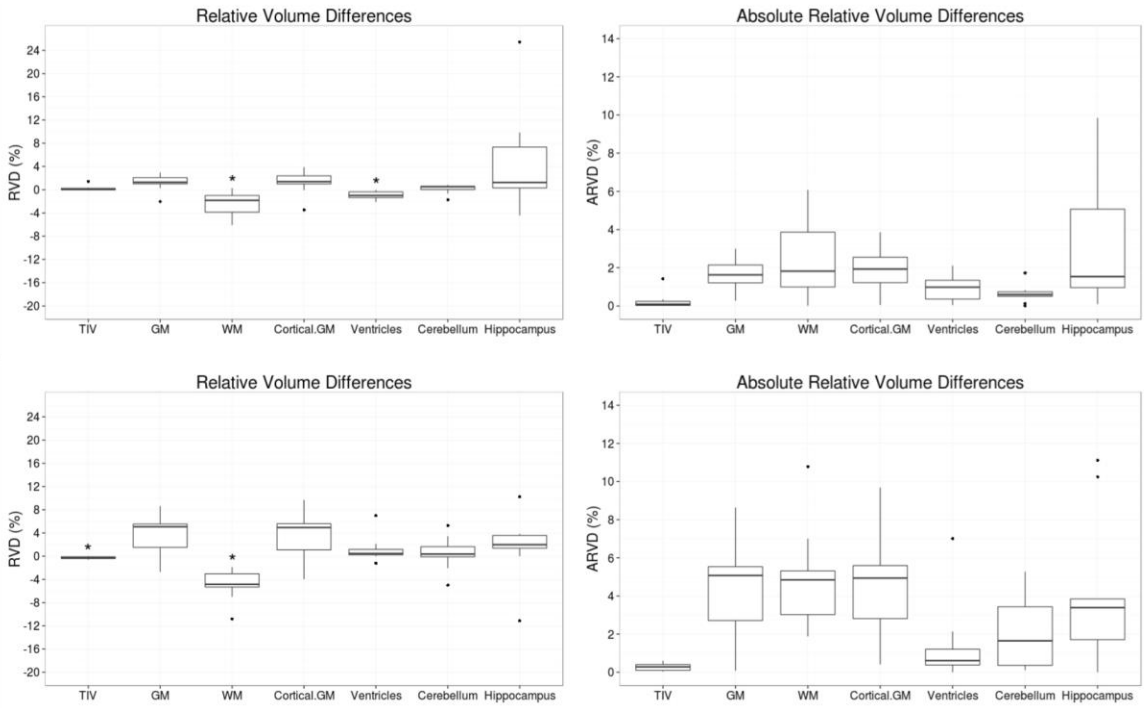


Figure 5. Variability of the brain segmentation results for the effect of spatial resolution and contrast by the comparison of ADNI2 versus LOCAL-. Note that the RVDs correspond to fixed offsets in segmentation results and do not represent scan-rescan variability of each protocol. TIV: total intracranial volume, GM: total grey matter, WM white matter, Cortical GM: only cortical grey matter. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$  - corrected for multiple comparisons

## SPATIAL RESOLUTION / CONTRAST: ADNI2 vs LOCAL-

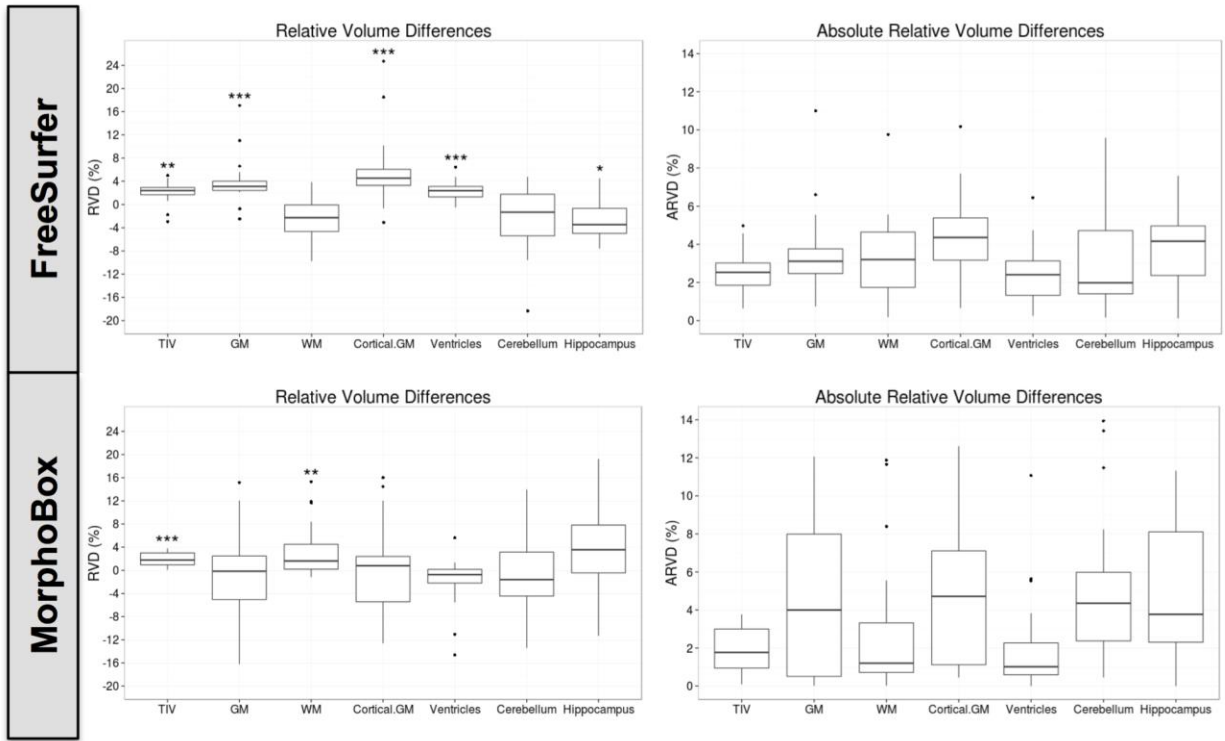


Figure 4. Variability of the brain segmentation results for the effect of image filtering (present versus absent filter) by the comparison of LOCAL- versus LOCAL+. Abbreviations equivalent to Figure 5

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