NeuroImage 87 (2014) 170–182

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Impact of image acquisition on voxel-based-morphometry investigations of age-related structural brain changes

Daniel-Paolo Streitbürger [a,d,*], André Pampel [a], Gunnar Krueger [b], Jöran Lepsien [a], Matthias L. Schroeter [a,c], Karsten Mueller [a,1], Harald E. Möller [a,*,1]

[a] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[b] Siemens Schweiz AG, Healthcare Sector IM & WS, Renens, Switzerland
[c] Clinic for Cognitive Neurology, University of Leipzig, Leipzig, Germany
[d] Leipzig Research Center for Civilization Diseases, University of Leipzig, Leipzig, Germany

ARTICLE INFO

Article history:
Accepted 24 October 2013
Available online 2 November 2013

Keywords:
Aging
Imaging pulse sequence
Radiofrequency coil
Voxel size
Voxel-based morphometry

ABSTRACT

A growing number of magnetic resonance imaging studies employ voxel-based morphometry (VBM) to assess structural brain changes. Recent reports have shown that image acquisition parameters may influence VBM results. For systematic evaluation, gray-matter-density (GMD) changes associated with aging were investigated by VBM employing acquisitions with different radiofrequency head coils (12-channel matrix coil vs. 32-channel array), different pulse sequences (MP-RAGE vs. MP2RAGE), and different voxel dimensions (1 mm vs. 0.8 mm). Thirty-six healthy subjects, classified as young, middle-aged, or elderly, participated in the study. Two-sample and paired *t*-tests revealed significant effects of acquisition parameters (coil, pulse sequence, and resolution) on the estimated age-related GMD changes in cortical and subcortical regions. Potential advantages in tissue classification and segmentation were obtained for MP2RAGE. The 32-channel coil generally outperformed the 12-channel coil, with more benefit for MP2RAGE. Further improvement can be expected from higher resolution if the loss in SNR is accounted for. Use of inconsistent acquisition parameters in VBM analyses is likely to introduce systematic bias. Overall, acquisition and protocol changes require careful adaptations of the VBM analysis strategy before generalized conclusion can be drawn.

Introduction

Over the past decade, an increasing number of studies have used voxel-based morphometry (VBM) for assessing structural brain changes (Draganski et al., 2011; Ferreira et al., 2011; Good et al., 2001; Hutton et al., 2009). VBM is a whole-brain technique to investigate so-called local tissue-density changes, typically employing three-dimensional (3D) T_1-weighted magnetic resonance imaging (MRI) data sets. Recent developments led to an increased accuracy of segmentation (Ashburner and Friston, 2005) and registration (Ashburner, 2007; Ashburner and Friston, 2005; Klein et al., 2010) and, thereby, to improved statistical assessment. Besides sophisticated image processing, the quality of the input images is also relevant in VBM, for example, a sufficient signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR), and minimal image artifacts are of critical importance. Naturally, input quality does not just impact VBM but image (pre-)processing methods in general. In this context, it is noteworthy that volume-based pre-processing is also employed in surface-based approaches, for instance FreeSurfer uses 'non-parametric non-uniform intensity normalization', N3, (Sled et al., 1998) and 'constrained Laplacian anatomic segmentation using proximity', CLASP, (Kim et al., 2005) for bias correction and segmentation, respectively. However, only some studies have systematically investigated the impact of image acquisition parameters, including the employed pulse sequence, on VBM and whole-brain measures (Acosta-Cabronero et al., 2008; Bach Cuadra et al., 2013; Helms et al., 2009; Klauschen et al., 2009; Krueger et al., 2012; Pereira et al., 2008; Shuter et al., 2008; Stonnington et al., 2008; Tardif et al., 2009, 2010).

To study the influence of resolution, Pereira et al. (2008) used different interpolated voxel sizes comparing patients with Alzheimer's disease and patients with semantic dementia to healthy controls. They showed that interpolation effects are highly dependent on the acquired image volume itself and have to be treated carefully. In two studies, Tardif et al. (2009, 2010) investigated the impact of different acquisition protocols on VBM results. In particular, three MRI sequences—the 'fast low-angle shot' technique, FLASH, (Frahm et al., 1986); the 'magnetization-prepared rapid gradient echo' imaging, MP-RAGE, (Mugler and Brookeman, 1990; Mugler et al., 1992); and the 'modified driven equilibrium Fourier transform' approach, MDEFT, (Lee et al., 1995)—were compared at 3 T and 1.5 T. Each protocol yielded a distinct regional sensitivity pattern to morphometric gray-matter

* Corresponding authors at: Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstraße 1a, 04103 Leipzig, Germany. Fax: +49 341 9940 2448.
E-mail addresses: paolo@cbs.mpg.de (D.-P. Streitbürger), moeller@cbs.mpg.de (H.E. Möller).
[1] These authors contributed equally.

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.10.051

density (GMD) changes. Results from power analyses showed that MP-RAGE required more subjects than FLASH to detect GMD changes but offered higher CNR and improved tissue classification. The MDEFT protocol, which is currently used only in research settings, yielded the highest CNR and the smallest GMD variability. A limitation of both studies was the small number of subjects ($\leq$9). Similarly, Helms et al. (2009) suggested by means of VBM that the segmentation of deep gray-matter (GM) structures is improved when using acquisition protocols that allow the computation of magnetization-transfer maps compared to optimized T_1-weighted MRI protocols. In those former studies paired *t*-tests showed the effect of mixing two different imaging parameters into one VBM analysis. However, this analysis does not provide direct information on altered detectability of structural brain changes due to the variation of the parameters. In principle, such changes can be assessed by statistical interaction analysis of two experimental factors, where one of the factors is a well-established structural process. Note, however, that the VBM analysis is only an indirect assessment of brain structure as it interprets GMD measures, which are estimated using a-priori template and model information.

To expand the scope of previous findings, the objective of the current work was to evaluate the impact of acquisition parameters in detecting age-related structural brain changes causing atrophy and reduction in the GMD. Previous research showed GMD changes across the whole cortex (Good et al., 2001), which provides excellent conditions to study distinct sensitivity profiles of different imaging parameters employing interaction analyses. Besides interaction tests, paired *t*-tests were utilized to detect artificially introduced differences in GMD estimates due to variation of acquisition parameters.

Following similar motivation as discussed by Tardif et al. (2009, 2010), the MP-RAGE technique was employed as one of the most popular anatomical sequences in morphometric studies. Due to ubiquitous availability, good GM/white matter (WM) contrast, and relatively short scan times, the MP-RAGE sequence has been frequently used in investigations of neurodegenerative diseases (Camicioli et al., 2009; Feldmann et al., 2008) including multicenter trials of the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Jack et al., 2008; Mueller et al., 2005). Briefly, MP-RAGE consists of an initial preparation of the magnetization by an adiabatic inversion pulse, followed by a relaxation delay (inversion time, TI) and a segmented acquisition period employing a snapshot FLASH sequence (Haase, 1990). Typically, the FLASH readout proceeds through the entire partition-encoding loop during each segment (i.e., during each repetition time, TR, of the inversion pulse), and the phase-encoding gradient is incremented from segment to segment (i.e., with every TR) (Deichmann et al., 2000; Mugler and Brookeman, 1990; Mugler et al., 1992).

Additional imaging with the recently published 'magnetization-prepared 2 rapid gradient echoes' sequence, MP2RAGE, (Marques et al., 2010) was included for a comparison of acquisition techniques. It is a variation of the MP-RAGE sequence, in which two FLASH readouts are quasi-simultaneously acquired at different TI. The images can be combined by computing the product of the (complex) signal intensities divided by the sum of the squared intensities to obtain so-called 'uniform images' with T_1 contrast, which are largely free of both the radiofrequency (RF) reception bias field and RF transmit-field inhomogeneity. Although the SNR might be reduced on the 'uniform images' due to noise propagation, contrast is improved as unwanted proton-density contrast and residual T_2^* contrast are removed by the image combination as well. We thus hypothesize that MP2RAGE offers potential advantages of (*i*) an intrinsic bias correction based on a well-defined physical concept of signal generation and (*ii*) improved contrast between GM, WM, and cerebro-spinal fluid (CSF) that might lead to better tissue classification and segmentation.

For further comparisons, acquisitions were performed with both a 12-channel coil and a 32-channel coil to study the influence of imaging hardware, and with two different voxel dimensions to study the effect of image resolution and/or interpolation.

Subjects and methods

Subjects

Thirty-six healthy Caucasian adults grouped into 12 young (6 females, mean age plus/minus one standard deviation: 22.3 $\pm$ 1.1 years), 12 middle-aged (6 females, 46.6 $\pm$ 1.4 years), and 12 elderly (6 females, 71.8 $\pm$ 1.9 years) subjects participated in the study. All participants gave written consent after being informed about the possible risks and discomforts of the experimental procedure. Subjects also completed a health history questionnaire to assess their suitability for undergoing MRI scanning. Exclusion criteria comprised known contraindications to MRI, a history of neuropsychiatric diseases, and abnormalities on T_1-weighted and on 'fluid-attenuated inversion recovery' (FLAIR) (Hajnal et al., 1992) head scans (both acquired in preceding scanning session).

Image acquisition

All acquisitions were performed at 3 T on a single MAGNETOM Verio scanner (Siemens, Erlangen, Germany). The body coil was used for transmission, and two commercial head coil arrays, a 12-channel matrix coil and a 32-channel array were used for signal reception. The inner diameter of the 32-channel coil is approximately 3–5 cm smaller than that of the 12-channel coil and fits the subject's head as a helmet. A total of six different T_1-weighted 3D data sets were acquired from each subject in a single session lasting approximately 1 h (i.e., $6 \times 36 = 216$ image volumes in total). In particular, data with nominal voxel size of $1 \times 1 \times 1$ mm^3 were acquired with both RF coils and with both MP-RAGE and MP2RAGE (Table 1; protocols 1, 2, 4, and 5). Additionally, data sets with nominal voxel size of $0.8 \times 0.8 \times 0.8$ mm^3 were acquired with the 32-channel array and with MP-RAGE and MP2RAGE (Table 1; protocols 3 and 6). The order of the six acquisition protocols was pseudo-randomly changed across subjects to avoid any systematic confound. Except for the image resolution, acquisition parameters used with MP-RAGE and MP2RAGE were consistent with those employed in the ADNI study (Jack et al., 2008) and by Marques et al. (2010), respectively. The 3D data sets stored from each MP2RAGE experiment included two series of inversion-contrast image volumes acquired at the two inversion times, TI_1 and TI_2, and the computed 'uniform images'.

Defaced data sets derived from the original images will be made available upon request (e-mail to the corresponding authors).

Masking of MP2RAGE images

Initial pre-processing of MP2RAGE data included a masking step to eliminate the artificially enhanced background noise on the computed 'uniform images' (see below) and ensure optimal performance of the VBM algorithms. In both inversion-contrast image volumes, voxel values less than 10% of the maximum signal were set to zero. Both image volumes were then combined using a logic OR-operator and binarized to obtain a brain mask. Subsequently, hole filling and a morphological closing filter as offered in Matlab 7.11.0 (R2010b, MathWorks, Natick, MA) were applied. Finally, the T_1-weighted 'uniform image' data were multiplied with the resulting binary mask. The masking step preserved the signal from the brain and non-brain tissue.

Pre-processing for VBM

Both MP-RAGE and masked MP2RAGE image volumes were segmented with the function '*segment*' implemented in SPM12b (Wellcome Trust Centre for Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). The algorithm bias corrects, segments, and spatially normalizes the image data by estimating the generative model parameters in a parallel fashion (Ashburner and Friston, 2005). Thereby, it