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Short communication

# Volume transition analysis: A new approach to resolve reclassification of brain tissue in repeated MRI scans

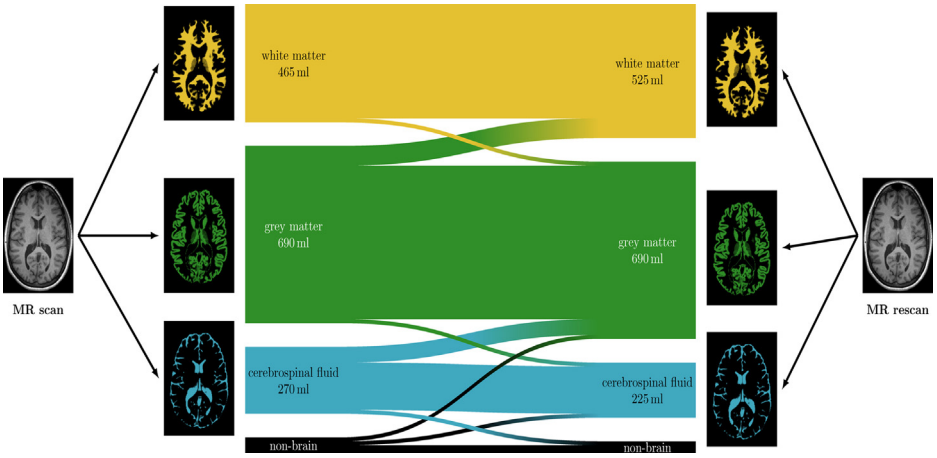
Anja Teuber[a,*], Jan-Gerd Tenberge[b], Harald Kugel[c], Michael Deppe[b], Klaus Berger[a], Heike Wersching[a]

[a] Institute of Epidemiology and Social Medicine, University of Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany
[b] Department of Neurology, University Hospital Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany
[c] Department of Clinical Radiology, University Hospital Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany

## HIGHLIGHTS

- Brain tissue segmentations of repeated cerebral MRI scans are compared.
- A new approach to resolve tissue type reclassifications is introduced.
- Voxel inflows from and outflows towards adjacent tissue volumes are quantified.
- Three scan–rescan scenarios imitate data basis of various applications.
- Monodirectional net flows increase with longer timespan and scanner switch.

## GRAPHICAL ABSTRACT

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## ABSTRACT

*Background:* Variability in brain tissue volumes derived from magnetic resonance images is attributable to various sources. In quantitative comparisons it is therefore crucial to distinguish between biologically and methodically conditioned variance and to take spatial accordance into account.
*New method:* We introduce volume transition analysis as a method that not only provides details on numerical and spatial accordance of tissue volumes in repeated scans but also on voxel shifts between tissue types. Based on brain tissue probability maps, mono- and bidirectional voxel shifts can be examined by explicitly separating volume transitions into source and target. We apply the approach to a set of subject data from repeated intra-scanner (one week and 30 month interval) as well as inter-scanner measurements.
*Results:* In all measurement scenarios, we found similar inter-class transitions of 9.9–15.9% of intracranial volume. The percentage of monodirectional net volume transition however increases from 0.3% in short term intra-scanner to 1.6% in long term intra-scanner and 9.3% in inter-scanner comparisons.

*Abbreviations:* MRI, magnetic resonance imaging; GM, grey matter; WM, white matter; CSF, cerebrospinal fluid; ICV, intracranial volume; DoM, distance over mean; DC, Dice's coefficient; VOI, volume of interest; OLS, ordinary least square; MAD, median absolute deviation.

* Corresponding author. Tel.: +49 251 83 56086; fax: +49 251 83 55300.
*E-mail address:* anja.teuber@uni-muenster.de (A. Teuber).

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*Comparison with existing methods:* Unlike most routinely used variability measures volume transition analysis is able to monitor reclassifications and thus to quantify not only balanced flows but also the amount of monodirectional net flows between tissue classes. The approach is independent from group analysis and can thus be applied in as few as two images.
*Conclusions:* The proposed method is an easily applicable tool that is useful in discovering intra-individual brain changes and assists in separating biological from technical variance in structural brain measures.


## 1. Introduction

Magnetic resonance imaging (MRI) of the brain is used in medical research and increasingly in epidemiologic studies with assumedly healthy community-dwelling individuals examined repeatedly over large periods of time. Image-derived structural brain measures thereby serve as outcomes, mediators or surrogate markers for various physiological processes, such as maturation or ageing, as well as for pathological processes particularly in degenerative and neuropsychiatric diseases. Accordingly, the precise classification and quantification of brain tissue volumes – consisting of brain parenchyma, which is subdivided into grey matter (GM) and white matter (WM), and cerebrospinal fluid (CSF) – from MR data is a non-negligible core task of medical image analysis.

Well-known biological factors that influence brain tissue volumes are sex and age. Women generally show smaller brain tissue volumes, although their brain parenchymal fraction (i.e. the ratio of brain parenchymal volume to total intracranial volume) is higher than in men (Littmann et al., 2006). Regarding age, a continuous decline in parenchyma volume is assumed after the age of 35 years, starting with a decrease of about 0.2% per year and accelerating gradually to an annual brain volume loss of 0.5% and more in people over 60 years of age (Fotenos et al., 2005; Hedman et al., 2012; Good et al., 2001). Even independent from sex and age, brain tissue volumes also underly a large inter-individual physiologic variability of about 10% (coefficient of variation) (Courchesne et al., 2000). Further sources of variability are present at all levels of image acquisition and processing. They arise from the subject (e.g. movements during scan, including breathing and pulsation of the CSF, or hydration status (Duning et al., 2005)), the scanner (field strength, gradients or hardware instability (Jovicich et al., 2009; Shuter et al., 2008; Lüders et al., 2002)) and analysis (segmentation algorithm (de Boer et al., 2010; Eggert et al., 2012; Klauschen et al., 2009) and normalisation method (O'Brien et al., 2011, 2006)).

In order to quantify and provide valid interpretations of subtle inter-individual differences or intra-individual changes over time, high reproducibility and accuracy in acquisition and analysis of brain volumes are crucial. Regarding image processing, MR image segmentation methods are being continuously improved, with recently developed algorithms for brain tissue segmentation yielding generally low variability in brain volume measures (de Boer et al., 2010).

However, low variability does not necessarily correspond to good reliability as numerically small variances can mask considerable systematic voxel shifts among separated tissue classes. Settings with repeated measurements of the same subject – like longitudinal data assessment in the course of a study, follow-up examinations of patients, or reliability tests – provide the opportunity to keep track of these voxel shifts and separate biological from technical variance. We here suggest an easily applicable method (*volume transition analysis*) that provides information on differences as well as similarities in brain tissue volumes obtained from spatial tissue probability maps as returned by every commonly used segmentation software. We illustrate the benefit of this approach in subjects repeatedly examined for a reliability check prior to a large-scale neuroimaging study (Teismann et al., 2014).

## 2. Theory

Commonly used software packages for tissue segmentation take a grey-value image $\mathbf{G} \in \mathbb{R}^{n_x \times n_y \times n_z}$ of the brain as input and return spatial probability maps $\mathbf{P}_t \in \mathbb{R}^{n_x \times n_y \times n_z}$ for each tissue class, i.e. the probability $(p_t)_{xyz} \in [0, 1]$ of belonging to the particular tissue class $t$ is assigned to every voxel/matrix element of the image. By default, the considered tissue classes are GM ($t$ = g), WM ($t$ = w) and CSF ($t$ = f). The overall tissue volume $V_t$ is calculated as sum over all voxels

$$V_t = V_{\text{vox}} \cdot \sum_{x,y,z} (p_t)_{xyz},$$

$V_{\text{vox}}$ being the voxel's volume.

The comparison of brain tissue volumes in repeated measurements $\mathbf{G}^{(1)}$ and $\mathbf{G}^{(2)}$ can be done in various ways. The aim in each case is to calculate parameters that quantify similarities as well as differences rather than to spatially present variances, since voxel based statistics is not meaningful when comparing as few as two images.

*Variation measures* of overall tissue volumes $V_t^{(1)}$ and $V_t^{(2)}$ like the distance over mean (DoM)

$$DoM_t = \frac{2 \cdot |V_t^{(1)} - V_t^{(2)}|}{V_t^{(1)} + V_t^{(2)}}$$

do not contain any spatial information and therefore carry the risk of concealing considerable differences between images $\mathbf{G}^{(1)}$ and $\mathbf{G}^{(2)}$. If, for example, the amount of tissue is similar in both scans whereas the contributing voxels in the tissue probability maps have a poor spatial overlap, the DoM will be low in spite of the fact that many of the voxels accounting for the total volume are of different spatial origin.

*Similarity measures* of tissue probability maps $\mathbf{P}_t^{(1)}$ and $\mathbf{P}_t^{(2)}$ like the Dice's coefficient (DC) (Dice, 1945; Sorensen, 1948)

$$\text{DC}_t = \frac{2 \cdot \sum_{x,y,z} \min((p_t)_{xyz}^{(1)}, (p_t)_{xyz}^{(2)})}{\sum_{x,y,z} [(p_t)_{xyz}^{(1)} + (p_t)_{xyz}^{(2)}]}$$

take spatial overlap into account, but results depend on the size of the intersection as well as on the variation of overall tissue volumes.

DoM and DC analysis is beneficial in confirming good reliability since a low $\text{DoM}_t$ accompanied by a high $\text{DC}_t$ is indicative of close similarity of the amount and spatial distribution of the corresponding tissue $t$. In case of non-negligible technically or biologically conditioned changes, however, this analysis does not directly allow for a meaningful interpretation of the observed change in one particular tissue volume. In order to accomplish this, the knowledge of changes in the remaining tissue volumes is required. In other words, DoM and DC analysis considers each tissue class individually, i.e. the initial algorithmic work step of the evaluation