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Intracranial volume normalization methods: Considerations when investigating gender differences in regional brain volume

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ABSTRACT

Intracranial volume (ICV) normalization of regional brain volumes (v) is common practice in volumetric studies of the aging brain. Multiple normalization methods exist and this study aimed to investigate when each method is appropriate to use in gender dimorphism studies and how differences in v are affected by the choice of method. A new method based on weighted ICV matching is also presented. Theoretical reasoning and simulated experiments were followed by an evaluation using real data comprising 400 subjects, all 75 years old, whose ICV was segmented with a gold standard method. The presented method allows good visualization of volume relation between gender groups. A different gender dimorphism in volume was found depending on the normalization method used for both simulated and real data. Method performance was also seen to depend on the slope (B) and intercept (m) from the linear relation between v and ICV ($v = B \cdot \text{ICV} + m$) as well as gender distribution in the cohort. A suggested work-flow for selecting ICV normalization method when investigating gender related differences in regional brain volume is presented.

1. Introduction

Volumetric assessment of human regional brain volume is important for understanding diseases associated with brain morphology, and volumetry is increasingly used for diagnostic purposes, for example hippocampal volume in Alzheimer's disease. The assessment of gender specific differences in regional brain volume may further add to the understanding of a disease and be important for setting gender specific normal cut off ranges.

In regional brain volumetric studies, intracranial volume (ICV) normalization is an important step (Barnes et al., 2010). It has been used to compensate for gender differences (Scahill, 2003; Whitwell et al., 2001) and inter-subject variations in head size (Free et al., 1995; Whitwell et al., 2001). ICV can also be used as a measure of premorbid brain size (Davis and Wright, 1977).

Since ICV is typically larger in males than in females (Gur et al., 1999; Nordenskjöld et al., 2013), and many regional brain volumes are associated with ICV, ICV normalization is needed before any inter-gender comparisons of these regional brain volumes are performed.

There are multiple approaches for ICV normalization in regional brain volumetric studies investigating gender differences. The proportion method aims to express a regional brain volume as the proportion of the entire cranial cavity it occupies. The residual method aims to remove the variation in the regional brain volume associated with ICV (Jack et al., 1989). A third method uses ICV as a covariate in a linear regression model. Finally, the need for ICV compensation can be removed by ICV matching where only inter-gender pairs having similar ICV are used.

In previous studies investigating gender associated differences in regional brain volume, different normalization methods have been used. In Sullivan et al. (2001) gender differences in corpus callosum (CC) volume were investigated using the proportion, residual, and covariate methods. Additional analysis was conducted on a subset of males and females where the subjects were matched on age, ICV mean, and ICV range between genders. Raw CC volumes were found to be larger in males. With the exception of one test using the proportion method, males were found to have larger CC than females. Ardekani et al. (2013) found females to have larger CC volume than males both when using the covariate method on the entire cohort, and

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when using a subset of males and females matched by ICV and approximately by age.

Gray matter (GM) and white matter (WM) differences between genders have been investigated by Gur et al. (1999). Using the covariate method as well as ICV matching, females were found to have larger GM volume than males, while males had larger WM volumes than females. In Greenberg et al. (2008) no difference in hippocampal volume was found between genders when using the proportion or covariate methods. Gender differences in GM and WM volumes ($p < 0.05$) were consistent with the findings by Gur et al. (1999) when using either of the methods. Murphy et al. (1996) found that age related volume loss in hippocamus was greater in females than in males when using the proportion method.

The proportion, covariate, and a residual method based on one group to normalize the entire cohort using total brain volume were compared by O'Brien et al. (2011). The theoretical background to each method was followed by a volumetric analysis where the results were found to differ between the methods. The authors concluded that visual representation of data should be used to aid selection of the best method. The residual method used in that study utilized a control group to normalize both the control and disease groups (Mathalon et al., 1993). They reasoned that if the covariate method is appropriate, it will give superior results compared to the residual method due to the entire cohort being used. In the case of gender comparisons, however, it is unclear which gender to select as the control.

There are, to the authors' knowledge, no prior studies that give an in-depth explanation of the cause of differences between methods, what bias to expect, and when each method is appropriate for use in studies investigating sexual dimorphism using ICV normalized volumes.

The aim of this study was threefold. Firstly, we aimed to present a theoretical background for different ICV normalization procedures and evaluate how the procedures handle gender differences in regional brain volume using simulated data. Secondly, we aimed to apply the normalization methods to real data comprising 400 elderly subjects, all of the same age. Thirdly, we aimed to determine if and when the different methods are appropriate for analyzing gender associated regional brain volume differences.

2. Materials and methods

In this section a comprehensive introduction to ICV normalization is given. First, the basic principles and assumptions of ICV normalization are presented. This is followed by a description and theory of different normalization methods, as well as the presentation of a new method for matching females and males in terms of ICV. After this, experiments using simulated and real data are presented. In the theoretical parts of this section, the data is assumed to be perfectly linear for simplified reasoning and illustration purposes. In real data this is naturally not the case. The section concludes by summarizing the ICV normalization methods presented.

2.1. Normalization pre-requirements

A goal of ICV normalization is to enable comparison between subjects with differently sized cranial cavities, which can be achieved by expressing regional brain volume as a percentage of ICV or to determine regional brain volumes that are not associated with ICV (i.e. all variation in a regional brain volume associated with ICV has been removed).

Most methods for ICV normalization rely on an assumption that the association between regional brain volume (v) and ICV is linear. A linear equation

$$v = B \cdot \text{ICV} + m, \tag{1}$$

where B is the slope and m is the intercept, can be used to express this association.

In real data, this linear association will almost certainly not be perfect. Therefore, an error term equal to the residual of the linear fit should be added to all equations below when considering real data.

2.2. Proportion method

The aim of this method is to express a regional brain volume as the proportion of the cranial cavity it occupies. The normalized volume ($\check{v}$) is calculated as

$$\check{v} = v/\text{ICV} \tag{2}$$

If a linear relation between v and ICV is assumed, substituting v in Eq. (2) with Eq. (1) gives

$$\check{v} = \frac{(1)}{\text{ICV}} = B + m/\text{ICV} \tag{3}$$

This shows that the normalized volume is still dependent on ICV. It also shows that the error will be introduced differently depending on the sign of m. When using this method one does therefore typically not *correct* or *compensate* for ICV, but rather extract a measure that can be used to investigate if regional volume ratios differ between compared groups.

Note that this method normalizes each subjects regional volume without considering other subjects in the study cohort.

2.3. Residual method

This method estimates the linear association between v and ICV, and transforms v so that this association is removed according to Eq. (4) (Jack et al., 1989):

$$\check{v} = v - B(\text{ICV} - \overline{\text{ICV}}) \tag{4}$$

where B is the slope of the linear association between v and ICV, and $\overline{\text{ICV}}$ is the mean of all ICV measures included in the calculation of B. Multiple subjects are needed to approximate the normalization parameters, and as the number of

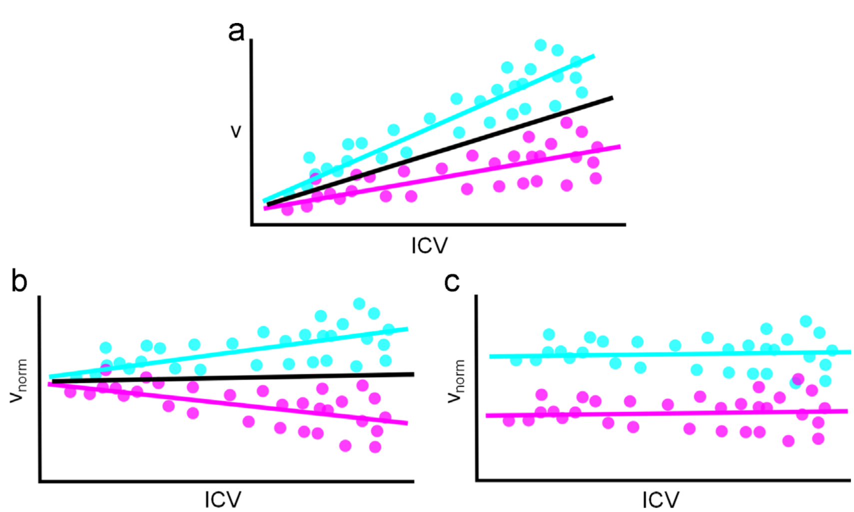

Fig. 1. Theoretical example of residual method normalization. Cyan and magenta dots represent different groups, each having their linear fit between regional brain volume (v) and intracranial volume (ICV) shown as a line having the same color. Cohort linear fit is represented by a black line. (a) Raw values. (b) Normalized using linear fit based on the entire cohort. (c) Normalized using gender specific linear fit. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)