SOURCE BASED MORPHOMETRY USING STRUCTURAL MRI PHASE IMAGES TO IDENTIFY SOURCES OF GRAY MATTER AND WHITE MATTER RELATIVE DIFFERENCES IN SCHIZOPHRENIA VERSUS CONTROLS

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ABSTRACT

We present a novel multivariate approach called source based morphometry (SBM) to study the novel structural MRI phase images and get sources of relative gray matter and white matter differences between patients and healthy controls. SBM considers the information cross brain voxels and provides spatially maximal independent sources about localization of changes. The structural MRI phase images efficiently summarize the relationship that exists between the gray and white matter without having to increase the dimensionality of the problem. SBM was then applied to the phase images. Results identified patient versus control differences in gray matter and white matter for visual-motor cortex as well as other areas. These interesting findings show that SBM is a useful multivariate approach for studying the brain. Moreover, the use of structural MRI phase images to joint gray and white matter together provides a significant advantage.

Index Terms— Source based morphometry, gray matter, white matter, phase, schizophrenia

1. INTRODUCTION

Structural magnetic resonance imaging (sMRI) is a useful tool for detecting differences in brain morphometry. It has been used widely to study various mental illnesses such as schizophrenia and Alzheimer's disease. One common approach to study changes in brain structure using sMRI is to compute volume differences of the regions of interest (ROI) between groups; Another common approach is voxel-based morphometry (VBM) which identifies voxelwise group differences throughout the brain [1]. In order to automatically detect whole brain structure and use the information across the different voxels, we propose a multivariate data-driven approach named source-based morphometry (SBM) (see Fig. 1). SBM hypothesizes that a small number of sources in the brain will show differences between patients and healthy controls. Under this assumption, SBM combines independent component analysis (ICA) and VBM in order to identify spatially independent sources from the preprocessed sMRI images, and perform a statistical analysis to identify which sources distinguish patients from healthy controls. SBM takes advantage of VBM by using its preprocessing steps to make the whole approach automatic. What's more, a multivariate approach utilizes the spatial information between voxels to identify multiple grouped sources in a natural manner. These maximally spatially independent sources reveal regions of covariation that occur in sMRI images and can be tested to identify sources that show differences in patients versus controls.

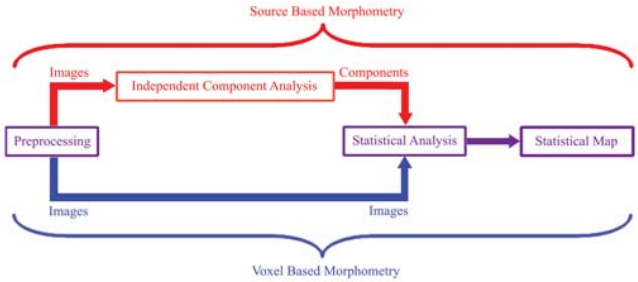

Figure 1. Source Based Morphometry

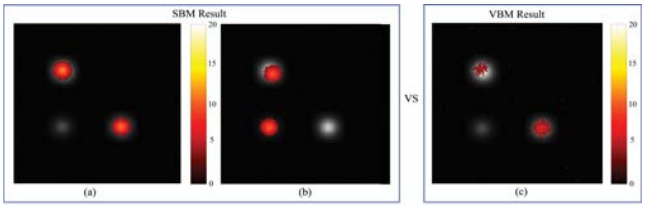

Figure 2. SBM vs. VBM

The advantage of SBM can also be showed via a simple example (See Figure 2). SBM found nearly all the regions of the ground truth (the white dots) and grouped the regions into two different sources (one with group differences (2b), one without (2a)); while VBM was unable to detect overlapping regions and those without group differences.

Schizophrenia is a well studied mental illness in which many abnormal brain regions have been identified [2, 3]. However, it is not clear how the different brain regions

might be subdivided into naturally grouped circuits. What's more, as far as we know, few studies have concentrated on changes in both gray matter and white matter in schizophrenia. Within these few studies the ROI or VBM approaches were used to study the gray matter and white matter separately (the relative changes between the gray matter and white matter tissues are not considered). In order to efficiently discover the relative changes of both gray matter and white matter, we constructed a complex variable whose real part is the gray matter intensity and the imaginary part is the white matter intensity. The phase part of the complex variable then offers the relative partition information of the gray matter and white matter of certain brain volume. We then apply SBM to the brain phase images and expect to find the sources circuits which represent the relative changes of the gray matter and white matter.

In this paper, we first introduce our method and show an application to real data. Then we present the results followed by discussion and conclusion.

2. METHODS

SMRI images:

One hundred and twenty structural MRI images of schizophrenia patients (51 females, mean age = 42.1, SD = 12.9, range 20-81) and 120 images of healthy controls (65 females, mean age = 42.7, SD = 16.59, range 18-78) were scanned at Johns Hopkins University.

Image Preprocessing:

The images were preprocessed using the preprocessing steps used for a voxel-based morphometry (VBM) approach [1, 4, 5] employing the Matlab program SPM5 (Statistical Parametric Mapping, developed by the Welcome Institute, London, UK). Images were first spatially normalized to the 152 average T_1 MNI (Montreal Neurological Institute) template. Normalized images were then interpolated to voxel dimensions of 1.5x1.5x1.5 mm and segmented into gray, white and cerebrospinal fluid (CSF) compartments using a modified mixture model cluster analysis technique with a correction for image intensity nonuniformity [5]. The gray matter images and white matter images were then smoothed with 12-mm full width at half-maximum (FWHM) Gaussian kernel. Each voxel in a smoothed image contains the averaged partial volume of gray/white matter from around and within the selected voxel, which contains gray/white matter concentration, a value ranging from 0 to 1. The size of every processed image is 121x145x121.

Structural MRI Phase image generation:

Let us assume that each voxel value in one gray matter image is g_i and the corresponding voxel value in the white matter image is w_i, i=1,…,121x145x121. The phase part of the complex variable g_i+jw_i is $\varphi_i(g_i,w_i)=\arctan(w_i/g_i)$. We can generate a phase image of the brain using $\varphi_i(g_i,w_i)$, which represents the relative partition of the gray matter and white matter (See Fig. 3).

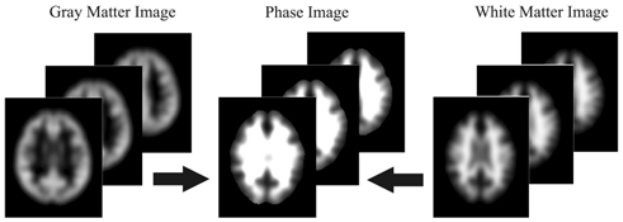

Figure 3. Structural MRI Phase Image Generation

Independent Component Analysis:

Akaike's information criterion (AIC) [6, 7] modified to improve the estimation performance for medical images [6, 7] was used to estimate the number of components, *k*, from the 240 phase images [8]. Next, every phase image was converted to a one-dimensional vector. The 120 phase image vectors of schizophrenia patients and 120 phase image vectors of healthy controls were then arrayed into one 240 row subject-by-phase matter data matrix. This matrix was decomposed into a mixing matrix and source matrix using spatial ICA [8] (See Fig. 4). The mixing matrix expresses the relationship between 240 subjects and *k* components. The rows of the matrix are scores that indicate to what degree each of the *k* components contribute to a given subject. The columns of the matrix indicate how one component contributes to each of the 240 subjects. In contrast, the source matrix expresses the relationship between the *k* components and the voxels within the brain. The rows of the matrix indicate how one component contributes to different brain voxels and the columns of the matrix are scores that indicate how one voxel contributes to each of the components.

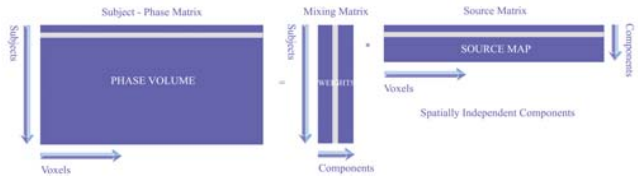

Figure 4. ICA

Statistical Analysis:

A two sample t-test was used on each column of the mixing matrix, which tested the identical between healthy control and schizophrenia with respect to the k components. A corrected threshold of $p<0.05$ which controls for the false discovery rate (FDR) was used to determine the most significant components/sources [9].

The effects of age and sex on the sources can also be determined. We regressed the columns of the mixing matrix separately on age and sex using a threshold of $p<0.05$ to determine the sources that were significantly affected by age and sex. We also did the two sample t-test on the residual of the regression to verify the group differences of the sources after removing the effect of age and sex.

3. RESULTS

The number of components was estimated to be twenty using the modified AIC approach. The mixing matrix and source matrix were determined using Infomax ICA[10]. We then analyzed the mixing matrix using a two-sample t-test for patients versus controls. Six sources whose loading scores differed significantly between controls and patients were identified. Here we list the two most interesting sources.

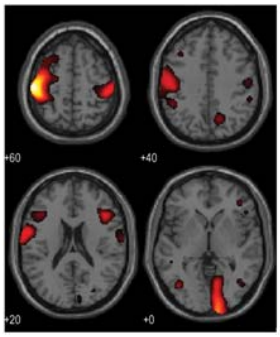

Figure 5. Source 1

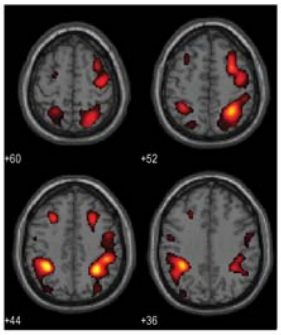

Figure 6. Source 2

Source 1: Visual-Motor Source (See Fig. 5). Within this source the partition of white matter increases while the partition of gray matter decreases in the schizophrenia patients. The source areas include the precentral gyrus, postcentral gyrus, inferior frontal gyrus, middle frontal gyrus, cuneus, middle occipital gyrus and lingual gyrus.

Source 2: Frontal-Temporal-Parietal Source (See Fig. 6). This source consisted of the inferior parietal lobule, superior parietal lobule, middle frontal gyrus, medial frontal gyrus, superior temporal gyrus and middle temporal gyrus. The healthy controls had more gray matter partition and less white matter partition than schizophrenia patients in this source.

One important point to emphasize is that these sources reflect the relative changes of gray matter and white matter in schizophrenia patients, not the relative volume changes in gray matter or white matter separately.

The effect of age on sources 1 and 2 was significant with p values less than 10^{-7}. The correlation plots for age versus ICA weights for sources 1 and 2 are presented in Figure 7. The ICA weight (The partition of white matter concentration) increased as age increased. The slope value of the controls was slightly lower than that of the patients, although there was not a significant group difference in the slopes. The effect of sex was significant only on source 2 as presented in Figure 8 with p = 0.0001. The mean of the ICA weight of males is large than that of females for both healthy controls and patients. The overall mean of the patients was slightly larger than that of the healthy controls. The relationship of the means for males (M), females (F), healthy controls (HC) and patients (SZ) is M_SZ(0.0162)>F_SZ(0.0153)≈M_HC(0.0154)>F_HC(0.0138). After removing the effect of age and sex, the group differences in the sources remained unchanged.

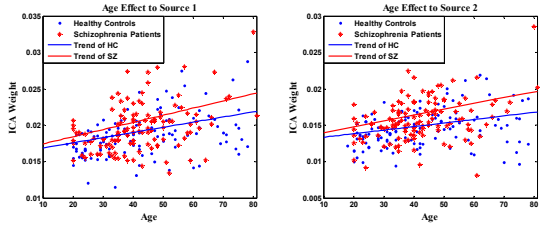

Figure 7. Age Effect

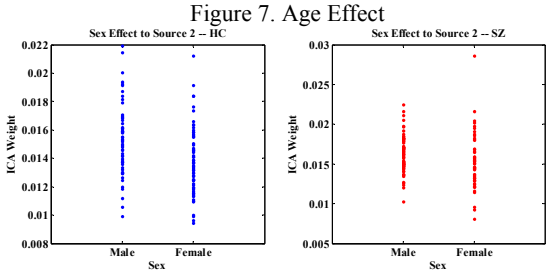

Figure 8. Sex Effect

4. DISCUSSION

We have presented SBM approach in which we decompose the structural MRI phase images into natural groups showing similar covariation between subjects. This systemic approach was applied to detect relative gray matter and white matter differences between 120 healthy controls and 120 patients with schizophrenia. The results identify a structural network in which the relative changes of gray matter and white matter is significantly different between healthy controls and schizophrenia patients.

Source 1 is consistent with previous findings [11, 12]. The regions identified in source 1 are primarily within visual and motor cortex. Interestingly, the source pattern looks similar to a functional MRI image which suggests that structural brain information underlying functional areas may be identified with our approach. Our findings suggest that the relative partition changes of gray matter and white matter may underlie visual-motor disturbances in schizophrenia patients.

Source 2 is consistent with previous findings [2, 13-16]. Our findings suggested that in addition the precuneus, which has not been well studied, might also be a key area in the regional brain abnormalities which underlie the disease. The inter-correlations of frontal and temporal volumes is also consistent with previous finding [17].

We found significant age effects on both sources. The positive slopes of the correlations between ICA weights and age of both the healthy control and schizophrenia for these 2 sources reveals the white matter partition increased with the age in both diagnostic groups. The value of the slope of healthy controls was lower than patients implies the partition of white matter in patients increase at an early age and keep increasing with age. The significant sex effect was only on source 2. The mean difference between male and female for both healthy controls and patients implies the partition of white matter of male is greater than that of

female. The mean difference between healthy controls and patients suggests the white matter partition increase for patients.

In summary, these interesting results support the efficaciousness of the SBM approach and also the joint analysis of gray and white matter via structural phase images. An advantage of the SBM approach is it incorporates the additional information about the grouping of the regions within several distinct, anatomically consistent sources. It is well-suited for capturing natural groupings in the structural brain imaging data. The phase image effectively fuses the gray matter and white matter into one image without adding computing dimensionality. The use of SBM applied to gray/white phase images is thus a suitable approach for studying the relative changes occurring between gray matter and white matter.

5. CONCLUSION

In this study, we present a multivariate approach for analyzing brain structure called source based morphometry. What's more, we constructed a structural gray/white matter phase image in order to emphasize the partition between gray and white matter and avoid the typically approach of separately analyzing gray and white matter.

The use of SBM allows us to identify structural brain networks showing significant differences between schizophrenia and healthy controls. SBM is a multivariate method that takes the interrelationship among voxels into account. Each identified source represents a distinct set of regions derived from the dataset. The mixing matrix captures the covariation of specific sources among individuals and can also be used to identify sources that exhibit group differences or particular relationships with other variables of interest (e.g., age and sex). The usage of structural brain phase images allows us to study the relative changes of gray matter and white matter. The utilization of the complex model effectively fuses the gray matter and white matter without increasing the dimensionality. The application of SBM to structural brain phase images thus creates new opportunities to identify distinct brain source networks of the relative partitions of gray matter and white matter between groups.

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6. REFERENCES

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