Automated imaging classification based on volumetric analysis: application on primary progressive aphasia

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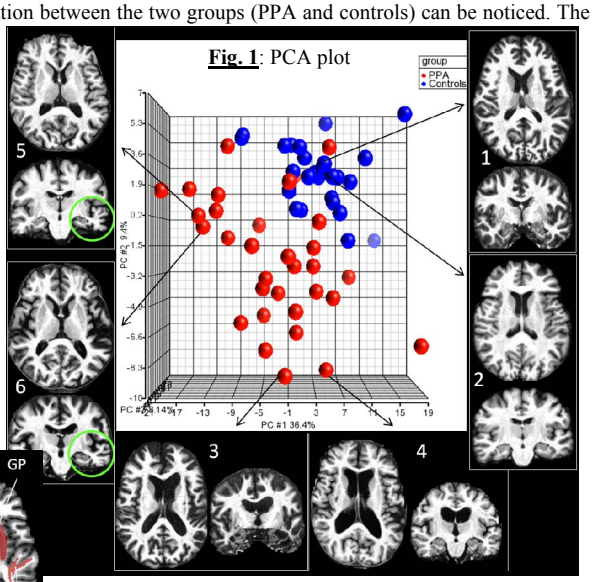
Introduction: Although the atrophy patterns associated with Primary Progressive Aphasia (PPA) have been described, because of the anatomic variability within the population, qualitative examination of the structural imaging has not always been useful to diagnose individual cases[1]. A quantitative image analysis could allow the objective assessment of the atrophy, assisting the diagnosis and classifications. One of the most widely used quantitative analyses, normalization-based whole brain analysis, is largely dependent on the accuracy of the image transformation, which is a significant issue for PPA subjects that exhibit a large and variable degree of brain atrophy. To overcome these challenges, we used a state-of-the-art non-linear normalization method (large-deformation diffeomorphic metric mapping, LDDMM[2]) and an automated 3D whole brain segmentation based on our brain atlas that contains detailed parcellation of 211 structures[3].

Methods: The altas-based brain segmentation using LDDMM was applied to 32 PPA patients and 27 age-matched normal controls. PPA patients were diagnosed by a cognitive neurology on the basis of a history of selective deterioration of language for at least two years, extensive language testing and a neuropsychological battery, MRI, and PET or SPECT imaging. All variants of PPA (semantic, logopenic, nonfluent) were included. The dual contrast LDDMM, based on T1-weighted MRIs and cerebrospinal fluid maps, were performed using the software DiffeoMap (www.mristudio.org). In a exploratory analysis to find the most correlated participants in terms of anatomical features, we used Principal Component Analysis (PCA) where the variables are the volumes of each of the 211 parcels defined by our Atlas in each individual. Then, we created and tested predictive models to classify participants as control or as PPA based on this volumetric data.

Results and Discussion: In the PCA plot of the three first principal components (Fig. 1), a segregation between the two groups (PPA and controls) can be noticed. The exploratory analysis of individual data shows that participants closer in this plot have similar anatomical features. For instance: participants #1 and #2 (controls) have no noticeable abnormalities and their images could be qualitatively classified as normal for the age; #3 and #4 (PPAs) have a global parenchyma atrophy and a marked ventricle enlargement while #5 and #6 (PPAs), although having more discrete abnormalities, are similar to each other due to regional specific features such as left temporal atrophy (green circle). This indicates that the quantitative analysis is able to capture anatomical features that can be visually confirmed.



Using ANOVA for feature selection and *k*-nearest neighbor algorithm to predictive modeling, we created a model that correctly classifies PPA and controls 83% of times, both after two-level cross-validation and testing with external dataset (table 1). Figure 2 shows the selected variables for this model: amygdales (Amy), uncinates (Unc), left hippocampus (Hippo), putamenes (Put), left globus pallidum (GP), left fusiform (Fus), left sagital striatum and inferior longitudinal fasciculus (SS, ILF), left cerebral peduncle (CP), left inferior, medium, and superior temporal (I,M,ST), and right medium temporal (MT). Not surprisingly, temporal, limbic system structures, and regions involved in language process (such as inferior longitudinal fasciculus, fusiform and uncinate), particularly in the left hemisphere, are areas previously and repetitively described as involved in the pathogenesis, evolution and clinical symptoms of PPA.

Table 1: Predictive Modelling

			% Correct classification
2-level cross validation			83
Test with external data			83
1-level cross validation			88.14
Confusion Matrix	PPA	controls	78
PPA (diagnosis)	25	7	
controls (diagnosis)	0	27	100

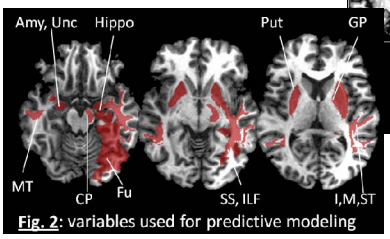
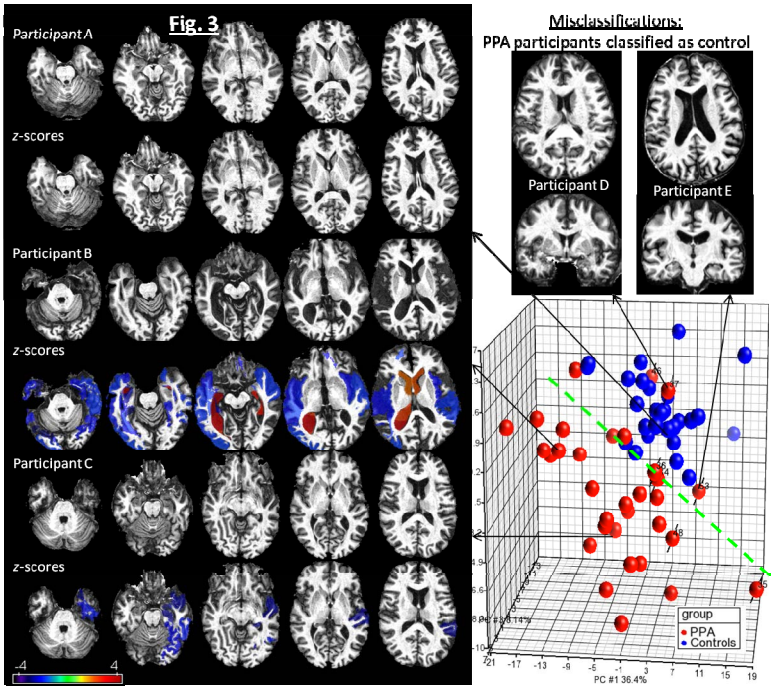


Fig. 2: variables used for predictive modeling

Despite the fact that visual analysis confirms that subjects with small left temporal, for example, were classified as PPA, it is difficult to quantify their degree of abnormality based on visual inspection only. The representation of the z-scores in which the amounts of deviations from the normal values are color-coded in each individual allows the quantitative evaluation of their anatomy at a glance and can be an interesting solution for combining qualitative and quantitative information.



This is shown in the left panel of Fig. 3, where areas with volumes above or below 2 standard deviations from the controls average are colored-coded. As suspected by visual analysis, participant A (control) has no volumetric "abnormalities" while B (PPA) has cortical atrophy particularly in temporal (z-score<2, blue), and ventricles enlarged (z-score>2, red). Quantitative analysis could help in cases as participant C (PPA) where the visual analysis can be dubious but the quantitative analysis is effective on detecting atrophy in specific areas that characterize PPA group (such as left temporal).

Figure 3 also shows that PPA participants misclassified by our model had either brain image compatible with normal controls (participant D) or, although having some atrophy, lacked the "anatomical signatures" (areas shown in fig. 2) used in our predictive model. This is the case of participant E and other subjects positioned in the "uncertainty" area close to the imaginary plane that segregates the groups (green dashed line).

Conclusion: Based on LDDMM normalization and Atlas-based analysis, we developed a method to capture the anatomical features and classifying PPA patients. The ability to generalize this approach to an automated method for individual classification that could be applied to routine clinical practice has a great potential to assist the diagnosis of many other diseases.

Bibliography: 1. Wilson SM, et al. 2009. *NeuroImage*, 47(4):1558-67;
2. Miller MI, et al. 2005. *PNAS*, 102(27):9685-690; 3. Oishi K, et al. *NeuroImage*, 46(2):486-99. Acknowledges: NIH grants F05NS059230, RO1DC05375,RO1AG20012, R21AG033774, P41RR15241, P50AG05146