Impact of ventricular enlargement on the measurement of metabolic activity in spatially normalized PET

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In pathologic brains with morphological alterations, the process of spatial normalization, as performed by SPM methods, may introduce a confounding effect in the measurement of metabolic activity data. To investigate the effect of the spatial normalization of PET images, we analyzed MRI and PET studies of 20 schizophrenic patients and 18 controls. Using a Talairach-based segmentation procedure and manual segmentation, we measured regional metabolic activity in the untransformed brains and after their spatial normalization. The effect of spatial normalization seems minimal for large ROIs like the main brain lobes, even in brains showing pronounced morphological abnormalities. However, the caudate nucleus shows a considerable change in metabolic activity values after normalization. This normalization effect is much larger in patients than in controls, and leads to artifactual differences between them. We obtained incorrect results (SPM analysis) regarding functional differences between patients and controls in the caudate due to this bias introduced by the spatial normalization. There was a significant correlation between the size of the lateral ventricles and the underestimation of metabolic activity of the caudate. Normalization bias seems to arise from a misalignment of the caudate in the normalized space, pixel overlap between the normalized caudate, and the caudate of the template being on average lower than 50% in both groups. Spatial normalization of the PET images of pathologic brains may introduce a potential source of error that should be taken into account in the analysis of functional data, in particular, in the study of small brain nuclei like the caudate.
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Introduction

This paper addresses a common problem in quantitative studies involving multi-subject analysis of functional images: the requirement for a spatial normalization step to provide a standardized reference space for all images included in the study. Among the procedures for analysis of functional data, Statistical Parametric Mapping (SPM, Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, UK) has become one of the most widely used for locating differences in brain activation patterns in PET studies (Frackowiak et al., 1997). Prior to the main statistical analysis, SPM methods perform a spatial normalization by means of a nonlinear registration of PET images onto a reference PET template (generally, the standard template provided with SPM software). After this geometric transformation, multi-subject PET scans are in a common neuroanatomical space that enables voxelwise statistical analysis, direct inter-subject analysis of voxel data, and the possibility of testing a wide variety of functional designs. One of the main consequences of this spatial normalization is that the particular brain morphology of each subject becomes warped to match the shape and size of the PET template, thus eliminating the individual anatomical characteristics which differ from the template.

The repeatability and accuracy of spatial normalization are hampered by the enormous morphological variability of the human brain (Narr et al., 2004), introducing an undetermined amount of error in inter-subject comparison studies (Bookstein, 2001). In addition to natural variability, morphological heterogeneity can be greatly increased in neurodegenerative diseases by the existence of pathological processes.

The possible bias resulting from the spatial normalization of brain anatomy has been investigated with two main focuses: anatomical accuracy and reliability of the various methods for spatial normalization, and its effect on the results obtained from the analysis of functional images.

The anatomical accuracy of the spatial normalization performed by the SPM95 package was analyzed by Sugiura et al. (1999), who examined the anatomical accuracy of the geometric transformations required to normalize PET images by applying the same geometric transformations to MRI images of the same subjects, which were then compared anatomically. They concluded that the normalization of PET images obtained by SPM95 produced a fairly accurate anatomical correspondence (Sugiura et al., 1999).