NeuroImage 146 (2017) 589–599

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Data-driven identification of intensity normalization region based on longitudinal coherency of ^{18}F-FDG metabolism in the healthy brain

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ARTICLE INFO

Keywords:
Positron emission tomography
^{18}F-fluorodeoxyglucose
intensity normalization

ABSTRACT

Objectives: In brain ^{18}F-FDG PET data intensity normalization is usually applied to control for unwanted factors confounding brain metabolism. However, it can be difficult to determine a proper intensity normalization region as a reference for the identification of abnormal metabolism in diseased brains. In neurodegenerative disorders, differentiating disease-related changes in brain metabolism from age-associated natural changes remains challenging. This study proposes a new data-driven method to identify proper intensity normalization regions in order to improve separation of age-associated natural changes from disease related changes in brain metabolism.

Methods: 127 female and 128 male healthy subjects (age: 20 to 79) with brain ^{18}F-FDG PET/CT in the course of a whole body cancer screening were included. Brain PET images were processed using SPM8 and were parcellated into 116 anatomical regions according to the AAL template. It is assumed that normal brain ^{18}F-FDG metabolism has longitudinal coherency and this coherency leads to better model fitting. The coefficient of determination R^2 was proposed as the coherence coefficient, and the total coherence coefficient (overall fitting quality) was employed as an index to assess proper intensity normalization strategies on single subjects and age-cohort averaged data. Age-associated longitudinal changes of normal subjects were derived using the identified intensity normalization method correspondingly. In addition, 15 subjects with clinically diagnosed Parkinson's disease were assessed to evaluate the clinical potential of the proposed new method.

Results: Intensity normalizations by paracentral lobule and cerebellar tonsil, both regions derived from the new data-driven coherency method, showed significantly better coherence coefficients than other intensity normalization regions, and especially better than the most widely used global mean normalization. Intensity normalization by paracentral lobule was the most consistent method within both analysis strategies (subject-based and age-cohort averaging). In addition, the proposed new intensity normalization method using the paracentral lobule generates significantly higher differentiation from the age-associated changes than other intensity normalization methods.

Conclusion: Proper intensity normalization can enhance the longitudinal coherency of normal brain glucose metabolism. The paracentral lobule followed by the cerebellar tonsil are shown to be the two most stable intensity normalization regions concerning age-dependent brain metabolism. This may provide the potential to better differentiate disease-related changes from age-related changes in brain metabolism, which is of relevance in the diagnosis of neurodegenerative disorders.

Abbreviations: ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET, Positron emission tomography; SMC, sensorimotor cortex; PD, Parkinson's disease; AAL, Automated Anatomical Labeling; STDN, standard deviation of normal subjects; 3D-SSP, 3-dimensional stereotactic surface projection; PVC, partial volume correction

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http://dx.doi.org/10.1016/j.neuroimage.2016.09.031
Received 6 May 2016; Accepted 13 September 2016
Available online 28 September 2016

1. Introduction

^{18}F-fluorodeoxyglucose (^{18}F-FDG) Positron emission tomography (PET) is an established method for imaging brain glucose metabolism. For many years it has been widely applied in the diagnosis of neurodegenerative disorders including Alzheimer's disease (Yakushev et al., 2008; Kuntzelmann et al., 2013), frontotemporal lobar degeneration (Dukart et al., 2013), dementia with Lewy bodies (Bohnen et al., 2012), Parkinson's disease (Ma et al., 2007; Borghammer et al., 2009b) and Huntington's disease (Lee et al., 2012). The brain^{18}F-FDG PET method is based on the assessment of absolute or relative changes in brain metabolism (Carson, 1991). Although it has been demonstrated to be effective in the diagnosis and differentiation of neurodegenerative disorders, the method can be influenced by physiological differences in brain metabolism between subjects, i.e. such as age and gender (Loessner et al., 1995; De Santi et al., 1995; Moeller et al., 1996; Perneczky et al., 2007), and by other factors of no direct neurological relevance. Disease-unrelated physiological influences may especially become relevant in the early diagnosis, i.e. of younger patients with different gender and suspicious dementia symptoms (Mosconi, 2013; Perneczky et al., 2007), or in the longitudinal investigation of neurodegenerative patients, as there may be expected only slight disease related changes in brain metabolism which could be masked by physiological variance. As soon as disease-modifying treatments become available, the demand in early diagnosis and treatment monitoring brain FDG-PET scans will increase dramatically. To this end, optimized control for unwanted factors confounding ^{18}F-FDG brain metabolism seems to be of increasing importance as these factors may mask detection especially of subtle disease-related changes in brain metabolism.

Age- and gender-related changes in regional cerebral glucose metabolism have been investigated for decades (Kuhl et al., 1982; Hawkins et al., 1983; Loessner et al., 1995; Moeller et al., 1996; Willis et al., 2002; Fujimoto et al., 2008; Yoshizawa et al., 2014). Although age-associated ^{18}F-FDG hypometabolism has been confirmed, age-dependent changes in ^{18}F-FDG metabolism are usually slight (Moeller et al., 1996). In contrast, the biological variability as well as the noise caused by the PET measurement and the data analysis may influence the corresponding hypometabolic changes (Carson, 1991). Thus, characterizing the changes in regional brain metabolism due to the normal aging process remains very challenging. From a methodological point of view several approaches have been applied to characterize physiological brain metabolism in healthy subjects. The scaled subprofile model has been developed to separate region-specific from region-independent metabolic contributions, and was applied in the investigation of age-associated hypometabolism (Moeller et al., 1996). Regression models have been applied to extract the age-associated tendencies from longitudinal scatter plots of regional metabolic values with age (Willis et al., 2002; Fujimoto et al., 2008). These longitudinal plots are relatively scattered and present different distributions by different quantification methods of regional glucose metabolism. Thus, the analysis of healthy subjects is sensitive to quantification methods, and the regression on data using different quantifications may lead to different age-associated interpretations (Willis et al., 2002). It is still not clear what kind of quantification method may best uncover the metabolic changes of normal brain aging. In contrast to complex mathematical modeling, intensity normalizations, such as standard uptake value (SUV), global mean normalization or normalization to an anatomical reference region, have been usually considered and are easily available for clinical applications. They can significantly reduce inter-subject variation due to confounding factors unrelated to the investigated pathophysiology (Borghammer et al., 2008; Yakushev et al., 2008; Grunder, 2009). Global mean scaling (intensity normalization to the global mean value in the whole brain) is the default recommendation within the SPM framework and is widely employed in neuroimaging studies (Minoshima et al., 1995; Ma et al., 2007). Cerebellum is another commonly used reference region for intensity normalization i.e.in patients with Alzheimer's Disease and its advantages have been reported repeatedly (Bittner et al., 2005; Kim et al., 2005). The advantages of normalization by primary sensorimotor cortex (SMC) have also been revealed in several studies (Sakamoto et al., 2002; Yakushev et al., 2008). In contrast to the preselected reference regions, data-driven methods have been proposed to identify individualized intensity normalization regions, i.e. regions which are not affected by regional brain hypometabolism in comparison to a healthy reference group, an approach that was shown to improve the diagnostic accuracy in the clinical diagnosis and differential diagnosis of patients with neurodegenerative diseases (Borghammer et al., 2009a; Yakushev et al., 2009; Andersson, 1997).

However, it is still not clear how intensity normalization performs to better uncover age-associated physiological metabolic changes. The normal brain aging process is characterized by degeneration of the neural system and this process is usually irreversible (Mosconi, 2013). The study assumed that age-associated neuronal loss leads to consistent metabolic decline. A representative quantification of brain metabolism in the course of normal aging is expected to preserve such consistent metabolic changes and to be less influenced by non-age related biological variability. In normal, healthy subjects the longitudinal distribution of brain metabolism data (in the course of normal aging) is expected to conform to a certain tendency with less scattering of data distribution.

To this end, we propose the conformance to a tendency of longitudinal normal aging as *longitudinal coherency* in this study, and we introduce a proper intensity normalization strategy for normal aging, based on brain FDG-PET data from a large cohort of healthy normal subjects that will enhance this longitudinal coherency. Specifically, we employed the fitting quality of certain mathematical models for the normal aging brain FDG-PET data to quantitatively represent the longitudinal coherency, and proposed a data-driven method to explore proper normalization methods to maximize the longitudinal coherency of ^{18}F-FDG metabolism in normal brain. Normalizations by global mean and by different anatomical brain regions were also investigated. The proposed concept was further preliminarily tested on patients with Parkinson's disease (PD).

2. Materials and methods

This study was approved by the medical ethics committee of Huashan Hospital, Fudan University, Shanghai, China. All the subjects signed agreements to participate in this study. 127 female and 128 male healthy subjects (age: 20–79) (Table 1 and Fig. 1) receiving a cancer-screening whole-body ^{18}F-FDG PET, including brain ^{18}F-FDG PET, were included in this study. Only those subjects, who had no current axis I psychiatric disorder, no psychotropic medication use or hormone use within the prior 6 months, and no history of neurological disease, head injury, or alcohol abuse, were included. No occult ^{18}F-FDG-avid carcinoma was determined for all the included subjects based on the whole-body PET/CT examination. The blood glucose level was monitored prior to ^{18}F-FDG injection (5.5 ± 0.8 mM for males and

Table 1
Distribution of subjects and corresponding blood glucose level (mM) by age.

Age (years)	Male	Blood Glucose Level	Female	Blood Glucose Level	Total
20–29	19	5.0 ± 0.5	23	5.0 ± 0.4	42
30–39	20	5.3 ± 0.6	21	5.1 ± 0.5	41
40–49	22	5.6 ± 0.9	22	5.2 ± 0.9	44
50–59	22	5.8 ± 0.6	22	5.5 ± 0.7	44
60–69	28	5.8 ± 0.9	24	5.4 ± 1.1	52
70–79	17	5.4 ± 1.1	14	5.7 ± 1.2	31
Total	128	5.5 ± 0.8	127	5.3 ± 0.9	255