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Low-dose CT for the spatial normalization of PET images: A validation procedure for amyloid-PET semi-quantification

Luca Presotto[a], Leonardo Iaccarino[b,c], Arianna Sala[b,c], Emilia G. Vanoli[a], Cristina Muscio[d], Anna Nigri[d], Maria Grazia Bruzzone[d], Fabrizio Tagliavini[d], Luigi Gianolli[a], Daniela Perani[a,b,c,*], Valentino Bettinardi[a]

[a] Nuclear Medicine Unit, IRCCS San Raffaele Hospital, Milan, Italy
[b] Vita-Salute San Raffaele University, Milan, Italy
[c] In vivo human molecular and structural neuroimaging Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy
[d] Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milano, Italy

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ABSTRACT

The reference standard for spatial normalization of brain positron emission tomography (PET) images involves structural Magnetic Resonance Imaging (MRI) data. However, the lack of such structural information is fairly common in clinical settings. This might lead to lack of proper image quantification and to evaluation based only on visual ratings, which does not allow research studies or clinical trials based on quantification.

PET/CT systems are widely available and CT normalization procedures need to be explored. Here we describe and validate a procedure for the spatial normalization of PET images based on the low-dose Computed Tomography (CT) images contextually acquired for attenuation correction in PET/CT systems. We included $N = 34$ subjects, spanning from cognitively normal to mild cognitive impairment and dementia, who underwent amyloid-PET/CT (^{18}F-Florbetaben) and structural MRI scans. The proposed pipeline is based on the SPM12 unified segmentation algorithm applied to low-dose CT images. The validation of the normalization pipeline focused on 1) statistical comparisons between regional and global ^{18}F-Florbetaben-PET/CT standardized uptake value ratios (SUVrs) estimated from both CT-based and MRI-based normalized PET images ($SUVr_{CT,}$ $SUVr_{MRI}$) and 2) estimation of the degrees of overlap between warped gray matter (GM) segmented maps derived from CT- and MRI-based spatial transformations.

We found negligible deviations between regional and global SUVrs in the two CT and MRI-based methods. $SUVr_{CT}$ and $SUVr_{MRI}$ global uptake scores showed negligible differences (mean ± sd 0.01 ± 0.03). Notably, the CT- and MRI-based warped GM maps showed excellent overlap (90% within 1 mm).

The proposed analysis pipeline, based on low-dose CT images, allows accurate spatial normalization and subsequent PET image quantification. A CT-based analytical pipeline could benefit both research and clinical practice, allowing the recruitment of larger samples and favoring clinical routine analysis.

1. Introduction

The evaluation of biomarkers for the early diagnosis of neurodegenerative conditions causing dementia has been increasingly recognized as of outmost importance in research and clinical practice (Ahmed et al., 2014; Albert et al., 2011; Armstrong et al., 2013; Dubois et al., 2014; Iaccarino et al., 2017; McKeith et al., 2017; McKhann et al., 2011a; Rascovsky et al., 2011; Sperling et al., 2011). As for Alzheimer's Disease (AD), the development of Positron Emission Tomography (PET) techniques to investigate brain amyloid accumulation (amyloid-PET) brought landmark changes in clinical neuroscience research (Villemagne, 2016). The reliability of PET tracers for in vivo amyloid assessment is supported by their correlation with post-mortem amyloid plaque measurement (Clark et al., 2012; Sabri et al., 2015; Wolk, 2011).

To date, their mandatory adoption in clinical trials and the great potential for diagnostic purposes is recognized, in particular to rule out AD pathology (Vandenberghe et al., 2013b; Vandenberghe et al., 2013a). Amyloid PET imaging plays a fundamental role for the inclusion and exclusion of subjects in clinical trials based on anti-amyloid treatments (Sperling et al., 2014a, 2014b), and it has been used as an

* Corresponding author at: Nuclear Medicine Unit, IRCCS San Raffaele Hospital, Milan, Italy.
E-mail address: perani.daniela@hsr.it (D. Perani).

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outcome measure as well (Salloway et al., 2014; Sevigny et al., 2016). The positivity of an amyloid-PET scan is commonly assessed qualitatively through a visual evaluation of the PET radiotracer distribution, in accordance to tracer-specific guidelines (Rowe and Villemagne, 2013).

A correct and reliable quantification of regional amyloid burden with PET, however, is considered mandatory to avoid the limitations of the operator-dependent visual classification, especially in longitudinal studies (Perani et al., 2014a,b). The most commonly adopted semi-quantification techniques involve tracer-specific approaches to estimate regional amyloid burden based on Standardized Uptake Value Ratio (SUVr) measurements. SUVrs are obtained by comparing tracer uptake in target regions to a reference area devoid of specific uptake. By comparing SUVrs in AD patients with SUVrs obtained in healthy volunteers, previous studies derived cut-off thresholds that could discriminate between amyloid positive and amyloid negative individuals (Barthel et al., 2011; Chiotis et al., 2015; Fleisher, 2011; Nordberg et al., 2013; Oh et al., 2015; Ong et al., 2015; Vandenberghe et al., 2010). Semi-quantitative amyloid burden is generally estimated on average (composite) SUVr based on neocortical regions, usually including frontal, parietal, temporal and cingulate regions (Clark et al., 2012; Fleisher, 2011). The adopted reference regions for amyloid PET SUVr can vary and may include the whole cerebellum, the cerebellar gray matter (GM) and/or specific portions of the white matter (WM) (Brendel et al., 2015; Schmidt et al., 2015). Of note, the implementation of semi-quantification techniques can also introduce variability, especially with respect to differences in analysis procedures and scan protocols. All these factors can heavily impact the classification of amyloid burden, with considerable effects in research studies and consequences in clinical trials (e.g. inclusion/exclusion of subjects). Among the most important factors there are: i) the selection of regions of interest (ROIs); ii) the selection of reference regions and iii) the choice of running quantifications in either native or standard space, with the latter being strongly influenced by the spatial normalization algorithms.

In an ideal setting, structural Magnetic Resonance Imaging (MRI) scans are available for each subject, allowing high precision spatial normalization and ROIs definition. Conveying the PET images to standard space can offer the use of standardized, published atlases with regions of interest, such as Automatic Anatomical Labeling: AAL (Tzourio-Mazoyer et al., 2002), Talairach Daemon: TD (Lancaster et al., 2000; Lancaster et al., 1997), Individual Brain Atlas: IBA (Aleman-Gomez et al., 2006), allowing for the definition of ROIs and to estimate regional SUVrs. In a routine diagnostic setting, however, MRI data are not always available, thus preventing an MRI-based spatial normalization of the amyloid-PET images to a standard space. For many centers, the lack of an MRI-based normalization pipeline prevents any further quantification.

To overcome this limitation, several PET-only pipelines for spatial normalization have been developed, based on custom or simulated PET templates (Hutton et al., 2015; Lundqvist et al., 2013; Saint-Aubert et al., 2014). These templates enable an accurate PET image warping and semi-quantification, but they are tracer-specific, limiting their utilization to radioligands with similar radioactivity distributions. Furthermore, to perform an appropriate PET-based normalization, the tracer uptake should define brain anatomy in sufficient details, which is not always the case for PET molecular imaging radiotracers. Finally, the spatial distribution of the tracer should be reasonably similar across subjects, to prevent bias in registration. This is not the case for amyloid tracers, where tracer distribution varies markedly across individuals, depending on the degree of amyloid burden: while in positive cases GM uptake is on par with WM uptake, amyloid-negative subjects display high contrast between the two.

Building on these premises, there is a need for validated methods to perform reliable spatial normalization of PET amyloid images. In this view, and considering that most PET clinical studies are nowadays performed using PET/Computed Tomography (CT) systems, we tested and validated a method for a high precision spatial normalization and SUVr computation using the low-dose CT image acquired for attenuation correction (AC). The inclusion of a CT-based analytical pipeline for PET quantification would allow a net benefit in terms of both research and clinical practice, allowing the recruitment of larger samples and favoring clinical routine analysis.

2. Materials and methods

2.1. Participants

Subjects were retrieved from the Ricerca Finalizzata Progetto di Rete Nazionale AD (AD-NETWORK/RETEAD) database. RETEAD is a large Italian multicenter study that aims at developing and validating operational research criteria for diagnosis of AD in the preclinical/predementia phase and early recognition of atypical forms, based on a multi-factorial protocol that integrates molecular, imaging, neuropsychological and clinical profiles. The study conformed to the ethical standards of the Declaration of Helsinki for protection of human subjects. Each subject provided written informed consent as approved by the Local Ethical Committees.

Thirty four subjects (age = 69.58 ± 6.63 (range:50–80) years; M/F = 16/18) were recruited at Fondazione IRCCS Istituto Neurologico Besta, Milan. The sample consisted of subjects in preclinical and prodromal dementia phases and patients with overt dementia, thus covering a wide spectrum of cases, from normal cognition to dementia. In detail, the sample included 4 subjects with subjective cognitive complaints (Jessen et al., 2014), 12 subjects with pre-mild cognitive impairment (pre-MCI) (Storandt et al., 2006), 14 subjects with MCI (8 single-domain MCI and 6 multi-domain MCI) (McKhann et al., 2011b) and 4 patients with a diagnosis of probable AD dementia (McKhann et al., 2011a). Each subject underwent brain structural imaging, including an MRI scan at Fondazione IRCCS Istituto Neurologico Besta, Milan and an amyloid PET/CT scan at the Nuclear Medicine Unit of San Raffaele Hospital, Milan. Inter-scan interval was no longer than six months for MRI and amyloid PET scans.

2.2. Image acquisition

2.2.1. ^{18}F-Florbetaben PET/CT

Each subject received an intravenous injection of 300 ± − 37 MBq of ^{18}F-Florbetaben (Neuraceq, Piramal). The dose was administered as a single bolus injection followed by 20 cc of saline flush. All PET acquisition were performed using a hybrid PET/CT Discovery-690 system (General Electric Medical Systems Milwaukee, WI, USA) (Bettinardi et al., 2011). After positioning, a low dose CT scan (kVp: 140 kV, current: 40 mA, rotation time: 0.8 s, slice thickness: 3.75 mm, pitch: 1.375:1) was acquired to be used for attenuation correction of PET data. Images were reconstructed using the “standard” kernel, a 30 cm reconstruction field of view, and 3.27 mm slice interval, for a resulting voxel size of 0.59 × 0.59 × 3.27 mm^3. A 3D-PET acquisition (list mode) was started about 90 min after the injection of the tracer and lasted for 20 min. Image reconstruction was performed by using a 3D Ordered Subsets Expectation Maximization (OSEM) algorithm with the following parameters: Image matrix = 128, Field Of View = 250 mm, Subsets = 24, Iterations = 3, Post Filter (Gaussian) = 3 mm FWHM, Attenuation Correction = CT-based. The resulting voxel size was 1.95 × 1.95 × 3.27 mm^3.

2.2.2. MRI

The MRI imaging data were acquired in Neurological Institute “C. Besta”, using an Achieva 3 T MR scanner (Philips Healthcare BV, Best, NL) equipped with a 32-channel head coil. A volumetric turbo field echo (TFE) T1-weighted structural sequence (180 sagittal slices, TR = 8.3 ms, TE = 3.9 ms, FOV = 240 × 240 mm, voxel size = 1x1x1 mm^3, flip angle = 8°) was acquired for each subject. Other structural, diffusion and functional magnetic imaging data were also