



Connectivity analysis of normal and mild cognitive impairment patients based on FDG and PiB-PET images

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ABSTRACT

Connectivity analysis allows researchers to explore interregional correlations, and thus is well suited for analysis of complex networks such as the brain. We applied whole brain connectivity analysis to assess the progression of Alzheimer's disease (AD). To detect early AD progression, we focused on distinguishing between normal control (NC) subjects and subjects with mild cognitive impairment (MCI). Fludeoxyglucose (FDG) and Pittsburgh compound B (PiB)-positron emission tomography (PET) were acquired for 75 participants. A graph network was implemented using correlation matrices. Correlation matrices of FDG and PiB-PET were combined into one matrix using a novel method. Group-wise differences between NC and MCI patients were assessed using clustering coefficients, characteristic path lengths, and betweenness centrality using various correlation matrices. Using connectivity analysis, this study identified important regions differentially affected by AD progression.

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and has worldwide implications (Berchtold and Cotman, 1998; Brookmeyer, 1998; Hebert and Scherr, 2003). Many AD patients transition from a cognitively normal status to an intermediate stage called mild cognitive impairment (MCI), before finally converting to AD. There is no generally-accepted cure for far-progressed AD, and thus early detection of AD is important. Various imaging modalities, including magnetic resonance imaging (MRI), single photon emission tomography (SPECT), and positron emission tomography (PET) have been successfully applied to assess the progression of AD in patients (Greicius et al., 2004; Matsuda, 2007; Frapp et al., 2008; Frisoni et al., 2010; Mosconi et al., 2010a). The usage of PET has led to many discoveries in AD research as well (Klunk et al., 2004; Foster et al., 2007; Koivunen et al., 2008; Frapp et al., 2008; Mosconi et al., 2010a; Bohnen and Djang, 2012; Hatashita and Yamasaki, 2013). PET imaging provides contrast information derived from local radiotracer activity. PET imaging using fludeoxyglucose (FDG)

reflects local metabolism by region glucose uptake, which has been shown to be effective at distinguishing normal subjects from patients with AD (Foster et al., 2007; Mosconi et al., 2010a; Bohnen and Djang, 2012; Ishii, 2013). Pittsburgh compound B (PiB) is a radiotracer that binds to a well-established biomarker of AD known as beta-amyloid (Klunk et al., 2004; Koivunen et al., 2008; Frapp et al., 2008; Hatashita and Yamasaki, 2013). PET imaging using PiB (PiB-PET) provides contrast information based on local deposition of beta-amyloid, which has shown a high correlation with the progression of AD in patients (Klunk et al., 2004; Koivunen et al., 2008; Hatashita and Yamasaki, 2013). Many brain regions show decreased FDG-PET activity for AD patients compared to normal while the same regions show increased PiB-PET activity (Hatashita and Yamasaki, 2013; Klunk et al., 2004). A multi-modal PET study should exhibit this anti-proportional behavior of FDG and PiB PET.

Raw data from imaging modalities cannot be used directly for extracting relevant information for AD research. Imaging data are processed using various algorithms implemented in software packages for proper research (Friston and Holmes, 1994; Jenkinson et al., 2012). Many of these image-processing algorithms are intended to identify regions that reflect group-wise differences. Another type of algorithm, known as connectivity analysis, focuses on how activities in one region correlate with activities in another region of a complex network (Anwander et al., 2007; He et al., 2007; Bullmore and Sporns, 2009). Connectivity analysis allows observation of the

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¹ Data used in this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.

whole brain as a complex, connected network. Well-established theories and tools borrowed from network graphs can be applied to quantify the connectivity of any given brain (Bullmore and Sporns, 2009; He and Evans, 2010; Watts and Strogatz, 1998). Connectivity in our study refers to functional connectivity whose information is derived from functional imaging modalities such as fMRI or PET. The functional connectivity is primarily a statistical concept measured via correlation between distinct regions, which many studies adopted (Zalesky et al., 2012). It is different from structural connectivity where physical neuronal fibers connect two distinct regions. If two regions share a similar signal pattern, be it from blood-oxygen-level-dependent (BOLD) signal or some other relevant signal, the strength of functional connectivity is assumed to be high. Many studies successfully applied functional connectivity analysis to resting state fMRI and FDG-PET and the brain networks identified were large consistent with known brain circuitries (He and Evans, 2010; Seo et al., 2013; Wang et al., 2013; Zalesky et al., 2012). Some studies went further an adopted a morphological feature, cortical thickness, to compute connectivity (He et al., 2007; Wee et al., 2013; Wheeler et al., 2015). If two regions share a similar pattern of cortical thickness, the connectivity was assumed to be high. In the same vein, we applied functional connectivity analysis to patterns of amyloid deposition for PiB-PET. In this study, connectivity derived from PET reflects correlation between patterns of regional cerebral metabolism (FDG) or amyloid deposition (PiB). Connectivity analysis typically involves a matrix whose elements reflect some degree of correlation between two regions of interest (ROIs). The matrix, referred to as the correlation matrix, contains correlation values that are derived from underlying imaging modalities. More and more studies have adopted multi-modal approaches, thereby a single brain is described in two or more modalities. In such scenarios, more than two correlation matrices need to be combined properly for further analysis. Combining correlation matrices requires careful attention, because the matrices are derived from different modalities.

The focus of this study is to assess information regarding MCI in patients showing AD progression. We attempt to distinguish MCI from normal cognitive aging in an effort to detect AD progression early on. Unlike many studies that utilize various methods of MRI to investigate AD, we utilized PET imaging. We obtained FDG-PET and PiB-PET imaging from the Alzheimer's Disease Neuroimaging Initiative (ADNI), an extensive research database on the topic (Carrillo et al., 2012). For our purposes, connectivity analysis was applied to PET images of normal control (NC) and MCI patients. Each imaging modality resulted in a separate correlation matrix, which we later combined using pseudo-logical operations. Group-wise differences (i.e., differences between MCI and NC subjects) were assessed using clustering coefficients, characteristic path lengths, and betweenness centrality. The goals of this study are (1) to apply connectivity analysis to two types of PET imaging, FDG-PET and PiB-PET, and (2) to combine the results of the connectivity analyses of both types of PET imaging in a novel way. As a brief preview of the findings, we were able to combine different correlation matrices and to replicate important known ROIs for AD progression.

2. Materials and methods

2.1. Subjects and PET images

We collected two types of PET imaging, PiB and FDG imaging, from the ADNI database (Carrillo et al., 2012). For FDG-PET, the following imaging parameters were used on a Siemens scanner. Image matrix = 128×128 ; number of slices = 63; pixel resolution = $2 \text{ mm} \times 2 \text{ mm}$; slice thickness = 2.4 mm; radiopharmaceutical = ^{18}F -FDG, reconstruction method = iterative. For PiB-PET,

Table 1

Demographic information for NC and MCI groups. Mean and standard deviation values are reported.

PET tracer	Information	NC (n = 20)	MCI (n = 20)	p-Value
FDG	Gender (M:F)	12:8	14:7	0.6673
	Age	76.34 (6.41)	78.49 (7.19)	0.3245
	MMSE score	30 (0)	22.9 (1.74)	<0.001
	CDR score	0 (0)	0.5 (0)	0
PET tracer	Information	NC (n = 15)	MCI (n = 20)	p-Value
PiB	Gender (M:F)	9:6	12:8	1
	Age	77.78 (6.23)	76.07 (6.68)	0.4445
	MMSE score	29 (1)	23.65 (1.87)	<0.001
	CDR score	0 (0)	0.5 (0)	0

the following imaging parameters were used on a Siemens scanner. Image matrix = 128×128 ; number of slices = 63; pixel resolution = $2 \text{ mm} \times 2 \text{ mm}$; slice thickness = 2.4 mm; radiopharmaceutical = ^{11}C -PiB, reconstruction method = iterative. In patients, MCI can be associated with non-AD type dementias such as vascular or Lewy body dementia, which we excluded in this study (Hansen and Samuel, 1997; Braak et al., 1999; Lee et al., 2009). We focused on the type of MCI that is an early stage of AD known as "MCI due to AD." Seventy-five patients were divided into NC (n = 20) and MCI (n = 20) sub-groups for the FDG group, and NC (n = 15) and MCI (n = 20) sub-groups for the PiB group. Patients in the NC group had global clinical dementia rating (CDR) scores of 0 and mini-mental state examination (MMSE) scores between 27 and 30. Patients in the MCI group had global CDR scores of 0.5 and MMSE scores between 20 and 26 (Folstein et al., 1975; Morris, 1993). Details regarding the patient groups, including age and sex ratios, are provided in Table 1. There were no significant differences (p-value > 0.05) between the groups in age or sex ratio.

2.2. Image pre-processing and ROIs

The PET images in the ADNI database were standardized from different systems using a system of pre-processing steps. First, each extracted frame of PET is co-registered to the first extracted frame of the raw image file (frame acquired at 30–35 min post-injection). The base frame image and the five co-registered frames (or all the co-registered frames for quantitative studies) are recombined into a co-registered dynamic image set. Second, the co-registered dynamic image set is averaged to create a single 30-minute PET image, which averages six 5-min frames (or the last six frames for quantitative studies). Third, each subject's co-registered, averaged image from their baseline PET scan is then reoriented into a standard $160 \times 160 \times 96$ grid, having 1.5-mm cubic voxels. This image grid is oriented in such a way that the anterior–posterior axis of the subject is parallel to the anterior–posterior commissure (AC-PC) line. Fourth, each image obtained from the third step is filtered with a scanner-specific filter function to produce images of a uniform isotropic resolution of 8-mm full width half maximum (FWHM), the approximate resolution of the lowest resolution scanners used in the ADNI database. The standardized uptake value (SUV) of PET is normalized by the mean SUV of the cerebellar region.

Connectivity analysis requires specifying ROIs in order for any correlations among them to be investigated. ROIs can be specified manually or by automatic methods. We used an automatic method to propagate ROIs from a pre-defined atlas onto the standard space. A well-known atlas with 90 labeled ROIs is available as a result of previous research (Tzourio-Mazoyer et al., 2002). We applied an image registration software based on C/C++ to register the atlas with the standard space of PET using mutual information cost function and affine geometric transform (Meyer et al., 1997). Once the

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