Use of T1-weighted/T2-weighted magnetic resonance ratio to elucidate changes due to amyloid β accumulation in cognitively normal subjects

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ABSTRACT

The ratio of signal intensity in T1-weighted (T1w) and T2-weighted (T2w) magnetic resonance imaging (MRI) was recently proposed to enhance the sensitivity of detecting changes in disease-related signal intensity. The objective of this study was to test the effectiveness of T1w/T2w image ratios as an easily accessible biomarker for amyloid beta (Aβ) accumulation. We performed the T1w/T2w analysis in cognitively normal elderly individuals. We applied [^{11}C] Pittsburgh Compound B (PiB)-PET to the same individuals, and Aβ deposition was quantified by its binding potential (PiB-BP$_{ND}$). The subjects were divided into low and high PiB-BP$_{ND}$ groups, and group differences in regional T1w/T2w values were evaluated. In the regions where we found a significant group difference, we conducted a correlation analysis between regional T1w/T2w values and PiB-BP$_{ND}$. Subjects with high global cortical PiB-BP$_{ND}$ showed a significantly higher regional T1w/T2w ratio in the frontal cortex and anterior cingulate cortex. We found a significant positive relationship between the regional T1w/T2w ratio and Aβ accumulation. Moreover, with a T1w/T2w ratio of 0.55 in the medial frontal regions, we correctly discriminated subjects with high PiB-BP$_{ND}$ from the entire subject population with a sensitivity of 84.6% and specificity of 80.0%. Our results indicate that early Aβ-induced pathological changes can be detected using the T1w/T2w ratio on MRI. We believe that the T1w/T2w ratio is a prospective stable biological marker of early Aβ accumulation in cognitively normal individuals. The availability of such an accessible marker would improve the efficiency of clinical trials focusing on the initial disease stages by reducing the number of subjects who require screening by Aβ-PET scan or lumbar puncture.

1. Introduction

The amyloid beta (Aβ) cascade is currently the most convincing hypothesis for the pathogenesis of Alzheimer's disease (AD), suggesting that the formation of senile plaques followed by the deposition of Aβ

are the earliest pathological changes in the disease (Hardy and Selkoe, 2002; Hardy and Higgins, 1992). Recent evidence has shown that amyloid pathology occurs >20 years before the clinical onset of AD (Bateman et al., 2012; Jack et al., 2013). Therefore, biomarker-based detection of the initial Aβ pathology is important for better clinical management of AD, potentially providing the opportunity to start disease-modifying therapies before the progression stages of AD.

The accumulation of brain Aβ can be assessed by measurement of the Aβ concentration in the cerebrospinal fluid (CSF) or by molecular imaging techniques such as positron emission tomography (PET) using a specific radioligand for Aβ. However, lumbar puncture, needed for the collection of a CSF sample, is associated with the risk of a clinically noxious event and thus is unsuitable as a mass screening tool.

Neuroimaging has the merit of being less invasive. However, PET is relatively expensive, and its availability is limited. Furthermore, PET leads to cumulative radiation exposure of subjects (Tosun et al., 2014).

Magnetic resonance imaging (MRI) is an appealing candidate for the inexpensive and noninvasive identification of surrogate biomarkers for altered brain anomalies in neurological and psychiatric diseases. The ratio of the signal intensities of T1-weighted (T1w) and T2-weighted (T2w) MRI was recently proposed to enhance the sensitivity of detecting changes in signal intensity associated with diseases (Glasser and Van Essen, 2011). Signal intensity changes may be a particularly sensitive measurement, as exhibited by findings in various brain diseases (e.g., infarction and multiple sclerosis), and measuring the signal intensity ratio of T1w and T2w images has conceivable advantages over standard volume/size measurements (Iwatani et al., 2015).

Recently, improved methods have been developed that use the ratio of T1w/T2w MRI images (Ganzetti et al., 2014; Shafee et al., 2015). We hypothesized that the T1w/T2w ratio analysis may also be helpful to detect signal intensity changes due to Aβ accumulation within subjects at pre-clinical stage of AD. To test this hypothesis, we examined the effectiveness of T1w/T2w ratio imaging as an easily accessible biomarker for Aβ accumulation. We applied the T1w/T2w analysis workflow (Ganzetti et al., 2014) to structural MRI data collected in cognitively normal elderly individuals. For comparison to standard PET techniques, we performed [11C] Pittsburgh Compound B (PiB)-PET in the same individuals, and Aβ deposition was quantified by cortical binding potential (PiB-BP$_{ND}$). The main purpose of this study was to develop a new method for screening patients for high accumulation of Aβ deposits by using the ratio of the signal intensities in T1w and T2w images.

2. Materials and methods

2.1. Participants

Thirty-eight cognitively normal older participants were recruited from the local area by poster advertisements. The inclusion criteria were an age of 55–85 years, a mini-mental state examination score of 27 or higher, independent living in the community, and no major structural abnormalities or signs of major vascular pathology on MRI. The exclusion criteria included major neurological, psychiatric, or medical illnesses; the use of medications that affect cognition; and MRI contraindications. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study was approved by the institutional review boards of all of the participating institutions, and all participants gave written informed consent.

2.2. PET and MRI scans

PET and MRI examination methods have been described in detail previously (Yasuno et al., 2016). PET examinations were performed with a Biograph mCT (Siemens, Knoxville Healthcare/Molecular Imaging, TN, USA). [11C]PiB (645 ± 30 MBq) was intravenously injected with 50 mL of saline. A sequence of 33 scans was acquired during the

70 min (4 × 15 s, 8 × 30 s, 9 × 1 min, 2 × 3 min, and 10 × 5 min) after the [11C]PiB injection. All MRI examinations were performed using a 3.0-Tesla whole-body scanner (Signa Excite HD V12M4; GE Healthcare, Milwaukee, WI, USA) with an 8-channel phased-array brain coil. High-resolution three-dimensional T1-weighted images were acquired using a spoiled gradient-recalled sequence (TR = 12.8 ms, TE = 2.6 ms, flip angle = 8°, FOV, 256 mm; 188 sections in the sagittal plane; acquisition matrix, 256 × 256; acquired resolution, 1 × 1 × 1 mm). T2-weighted images were obtained using a fast-spin echo sequence (TR = 4800 ms; TE = 101 ms; echo train length (ETL) = 8; FOV = 256 mm; 74 slices in the transverse plane; acquisition matrix, 160 × 160, acquired resolution, 1 × 1 × 2 mm).

2.3. PET data analysis

PET data analysis has been previously described in detail (Yasuno et al., 2016). [11C]PiB-PET data were corrected for partial volume effects using an algorithm introduced by Muller-Gartner et al. (1992) that was implemented in the PMOD software package (PMOD V.3.3; PMOD Technologies GmbH, Adliswil, Switzerland). The radioactivity levels in six brain regions (the prefrontal cortex, lateral temporal cortex, parietal cortex, anterior cingulate cortex, posterior cingulate cortex, and cerebellum) were obtained with a template-based method for defining volumes of interest (VOI) (Yasuno et al., 2002). Regional time-activity data were analyzed from 35 to 70 min of PET data with the Logan graphical method (Logan et al., 1996). This method yields BP estimates relative to non-displaceable (ND) binding, which is denoted by BP$_{ND}$ (Innis et al., 2007). Global cortical mean PiB-BP$_{ND}$ was evaluated from the measured brain regions.

2.4. MRI data analysis of T1w/T2w images

T1w and T2w images were preprocessed and combined using a dedicated workflow as described in the previous papers by Ganzetti et al. (2014, 2015). This includes bias correction and intensity calibration on

Table 1
Demographic statistics of low and high PiB-BP$_{ND}$ groups.

Characteristic/test	Low PiB-BP$_{ND}$ (BP < 0.20)	High PiB-BP$_{ND}$ (BP ≥ 0.20)	t or χ^2	p
No.	25	13		
Global cortical mean PiB-BP$_{ND}$	0.10 ± 0.07	0.40 ± 0.26	4.06	0.001[a]
Age, years	70.2 ± 6.9	70.8 ± 7.0	0.24	0.810
Sex M/F	19/6	4/9	7.32	0.007[a]
Education, years	14.4 ± 2.5	11.7 ± 2.3	3.27	0.002[a]
Mini-mental state examination	29.3 ± 0.9	29.5 ± 1.1	0.54	0.590

Data are represented as mean ± sd.
[a] p < 0.05.

Table 2
Differences in regional T1w/T2w ratio between low and high PiB-BP$_{ND}$ groups.

Regions	T1w/T2w ratio		t-Test[a]	
	Low PiB-BP$_{ND}$ (N = 25) (BP < 0.20)	High PiB-BP$_{ND}$ (N = 13) (BP ≥ 0.20)	t (1, 31)	p
Orbital frontal cortex	0.78 ± 0.06	0.84 ± 0.08	2.54	0.02[b]
Lateral prefrontal cortex	0.70 ± 0.06	0.74 ± 0.05	2.10	0.04[b]
Medial prefrontal cortex	0.64 ± 0.05	0.68 ± 0.04	2.63	0.01[b]
Lateral temporal cortex	0.76 ± 0.05	0.79 ± 0.04	1.69	0.10
Medial temporal cortex	0.70 ± 0.05	0.73 ± 0.03	1.72	0.09
Parietal cortex	0.71 ± 0.05	0.70 ± 0.06	0.05	0.96
Occipital cortex	0.76 ± 0.06	0.77 ± 0.05	0.50	0.62
Striatum	0.90 ± 0.06	0.93 ± 0.05	1.38	0.18
Anterior cingulate cortex	0.63 ± 0.04	0.66 ± 0.04	2.48	0.02[b]
Posterior cingulate cortex	0.69 ± 0.04	0.72 ± 0.05	1.96	0.06

[a] Repeated measures of analysis of variance revealed a significant interaction of regions × groups of low/high PiB-BP$_{ND}$ (regions, F = 235.4, df = 3.6, 128.2, p < 0.01, regions × groups of low/high PiB-BP$_{ND}$; F = 2.54, df = 3.6, 128.2, p = 0.05, groups of low/high PiB-BP$_{ND}$; F = 3.87, df = 1, 36, p = 0.06).
[b] p < 0.05.

Table 3
Correlation between T1w/T2w ratio and PiB-BP$_{ND}$ in measured regions.

	Spearman's ρ (p)
Orbital frontal cortex	0.21 (0.21)
Lateral prefrontal cortex	0.24 (0.14)
Medial prefrontal cortex	0.54 (0.0005)[a]
Anterior cingulate cortex	0.25 (0.13)
Combination of the above regions	0.45 (0.005)[a]

[a] Significant with consideration to the multiple comparisons with p < 0.01 (0.05/5).