The use of an individual-based FDG-PET volume of interest approach in mild cognitive impairment: a multi-modality longitudinal follow-up study

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Research Article

Keywords: FDG-PET, MRI, MCI conversion

Posted Date: December 7th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2332093/v1

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Abstract

Background:

Based on a longitudinal cohort design, the aim of this study was to investigate whether individual-based \(^{18}\)F fluorodeoxyglucose positron emission tomography (\(^{18}\)F-FDG-PET) regional signals can predict dementia conversion in patients with mild cognitive impairment (MCI).

Methods:

We included 44 MCI converters (MCI-C), 38 non-converters (MCI-NC), 42 patients with amyloid-positive Alzheimer disease, and 40 cognitively normal controls. Data from annual cognitive measurements, 3D T1 magnetic resonance imaging (MRI) scans, and \(^{18}\)F-FDG-PET scans were used for outcome analysis. An individual-based FDG-PET approach was defined using seven volumes of interest (VOIs), Z transformed using a normal FDG-PET template. Hypometabolism was defined as a Z score < -2 of regional standard uptake value ratio. For the longitudinal cognitive test scores, generalized estimating equations were used. A linear mixed effect model was used to compare the time effect of cortical hypometabolism and cortical thickness degeneration.

Results

The clinical follow-up period was 6.6 ± 3.8 years (range 3.1 to 16.0 years). The cognitive decline trends could differentiate MCI-C from MCI-NC after 3 years of follow-up. In MCI at the first \(^{18}\)F-FDG-PET scan, medial temporal lobe (94.7% sensitivity, 80.5% specificity) and posterior cingulate cortex (89.5% sensitivity, 73.1% specificity) hypometabolism predicted conversion with high accuracy. \(^{18}\)F-FDG-PET hypometabolism preceded dementia conversion at an interval of 3.70 ± 1.68 years and was earlier than volumetric changes.

Conclusions

Our analysis support the use of individual-based \(^{18}\)F-FDG-PET analysis to predict MCI conversion. Changes in \(^{18}\)F-FDG-PET occurred 1 to 8 years prior to dementia conversion, and hypometabolism occurred 2 years before MRI findings.

Background

The diagnosis of Alzheimer’s disease (AD) includes positive findings of amyloid and tau biomarkers (1). Currently, AD can be diagnosed at the mild cognitive impairment (MCI) stage, however when patients at this stage will convert to dementia is unclear. One reason for the uncertainty is that MCI now represents a
clinical stage between a normal and dementia state, but the term is historically used in a heterogeneous context (2–6). Differences in case definition may affect the reported rate of MCI conversion, which ranges from 4–60% (7). Previously, “MCI progression to dementia” and “MCI conversion to AD” were used interchangeably. In 2011, Albert et al. published the core clinical criteria for the diagnosis of MCI due to AD (6). Using these core clinical criteria, researchers have an operational definition of MCI that aims to control the underlying pathology. Until 2018 (1), MCI stage transition and disease progression belonged to the same research concept in biomarker-validated AD. However, more data are still needed to understand the diagnostic or prognostic value of these criteria.

For MCI conversion, the observation time required for “conversion” is also unclear. Even in amyloid-positive AD, the conversion time may not be uniform. Similarly, not all MCI patients convert to dementia. In a 3-year follow-up study in Taiwan, the rate of MCI conversion to dementia was 18.2%/person-year (8). Whether more conversions from MCI to dementia would occur over a longer follow-up period or at an average time frame requires more data. Vemuri et al. (9) published a time-to-event follow-up study of MCI conversion, in which the conversion duration ranged from 1 to 6 years. Therefore, using a predefined time frame to construct a predictive model of MCI conversion may not be appropriate, since it is likely that those being classified as non-converters will convert at some point in the future.

Despite the importance of amyloid and tau biomarkers in the diagnosis of AD, neuronal injury biomarkers are still of great clinical importance, as they are more accessible and correlated more closely to the clinical features (10, 11). Therefore, constructing an individual-based model using neuronal injury biomarkers in MCI is rational. In amyloid-positive AD, the combined use of $^{18}$F fluorodeoxyglucose positron emission tomography (FDG-PET) and magnetic resonance imaging (MRI) has been shown to predict future cognitive decline more precisely than using amyloid scans only (12, 13). In addition, evidence has shown that the proper use of FDG-PET (14–18) or structural MRI (19) can also achieve a high diagnostic accuracy of AD.

In the past two decades, the use of FDG-PET or structural MRI as an adjuvant to predict dementia conversion has been widely investigated. In FDG-PET, regional hypometabolism of the temporoparietal cortex, posterior cingulate cortex (PCC), and precuneus has been associated with a higher likelihood of AD conversion (20–27). For structural MRI, decreased hippocampal or entorhinal volume is the most predictive factor (28–31). Since most previous studies have used a cross-sectional design, different inclusion criteria, and a relatively short follow-up period, it is possible that MCI conversion did not occur during the observational period or that the results were pointing to different diagnostic entities.

The primary aim of this study was to understand the interval between changes in FDG-PET volumes of interest (VOIs) and the occurrence of dementia in a group of patients who met the MCI due to AD clinical core criteria (6). Amyloid-positive AD cases and cognitively unimpaired controls were enrolled to compare cognitive performance and image findings. The FDG-PET regions used for feature extraction were assessed with predefined VOIs based on the literature (14–18). We then developed and applied an individual-based Z-transformed VOI score using FDG-PET in four groups of participants, and reported the
sensitivity and specificity of the score to predict conversion. In group analysis, data of repeated neuropsychological measurements and single or multiple neuronal injury biomarkers (FDG-PET and structural MRI) were used. Longitudinal MRI analysis using a linear mixed effects model was conducted to contrast temporal and spatial differences in FDG-PET. The follow-up data were used in head-to-head comparisons of the two neuronal injury biomarkers, which revealed the time sequence of their occurrence and the temporal relationships with MCI conversion.

Methods

Standard Protocol Approval, Registration And Patient Consent

We selected controls, patients with MCI due to AD (6) and AD (1) from the database of our institute. The Institutional Review Board of our institute approved this study, and written informed consent was obtained from all participants or legally authorized representatives in the cases with cognitive impairment.

Inclusion And Exclusion Criteria

Subjects were eligible if they had available brain MRI, FDG-PET, and at least 3 years of follow-up data. Neuropsychological assessments including the Mini-Mental State Examination (MMSE) (32) Cognitive Ability Screening Instrument (CASI) (33), and Clinical Dementia Rating (CDR) (34) were evaluated annually. The MCI cases fulfilled the core clinical criteria of MCI due to AD (6), and their FDG-PET scans should not contradict the clinical diagnosis. The MCI cases were divided into converter (MCI-C) or non-converter (MCI-NC) groups according to: (1) losing more than 3 points between the first and last MMSE assessments, or (2) progression to a demented state during multi-year follow-up. The MCI group had a mean clinical follow-up period of 6.6 ± 3.8 years (from 3.1 to 16.0 years). Research criteria-based AD patients (1) were also enrolled for statistical comparisons, with the diagnosis confirmed by positive amyloid PET findings rating by two independent raters. The normal cognitive control group had an MMSE score of > 25, a CASI total score of > 50 percentile, and a CDR score of 0.

The exclusion criteria were degenerative brain diseases other than AD, lesions on T2-weighted MRI indicating stroke or severe white matter diseases, clinically unmanaged diabetes, or clinical evidence of depression. Based on the inclusion and exclusion criteria, 11 patients were excluded according to FDG-PET and MRI findings: five with frontotemporal dementia, four with Lewy body dementia, and two with vascular dementia.

MRI Acquisition And Preprocessing Steps

Three-dimensional (3D) T1 MR images were obtained using a 3T GE Discovery 750 (GE Medical Systems, Milwaukee, WI, USA) and acquired using a T1-weighted, inversion-recovery-prepared, 3D, gradient-recalled
acquisition in a steady-state sequence [repetition time (TR) = 12.24 msec; echo time (TE) = 5.18 msec; field of view (FOV) = 256 × 256; matrix size = 256 × 256; number of excitations (NEX) = 1; inversion time (TI) = 450 msec; flip angle = 15] with a 1-mm slice sagittal thickness and a resolution of 0.5 × 0.5 × 1 mm³. Details of the preprocessing pipeline are shown in the Supplementary file.

**Pet Acquisition And Preprocessing Steps**

FDG-PET images were acquired using GE scanners (Discovery ST or MI PET/CT scanner; GE Healthcare, Waukesha, WI). The subjects received 5 mCi of FDG intravenously, and a low dose CT scan was acquired for attenuation correction. Thirty minutes after the injection, the subjects underwent a 30-minute dynamic PET scan with six 5-minute frames. Scans were acquired in 3D mode and reconstructed using an ordered subset expectation maximization algorithm, with 16 subsets and four iterations, yielding a 128 × 128 matrix with a pixel size of 1.56 mm. The images from the dynamic frames were averaged to create a single static image.

At the individual PET level, standard uptake value ratio (SUVr) images were calculated using a mid-pontine 16x16 mm box as the reference region. The FDG-PET images of the patients and controls were normalized to an optimized FDG-PET template (35) using Statistical Parametric Mapping (SPM12) (https://www.fil.ion.ucl.ac.uk/spm/), according to the validated pipeline (36, 37).

**Individualized Voi Scale And Definition Of Abnormality In Each Subject**

For VOI analysis, seven signet regions were selected according to previous studies on FDG-PET brain scans (14–18) to evaluate the prognostic values of conversion, including frontal lobe, parietal lobe, medial temporal lobe (MTL), lateral temporal lobe, posterior cingulate cortex (PCC), precuneus, and occipital lobe (38). SUVr values of seven VOIs were transformed into Z scores, with a Z score below −2 considered a hypometabolism state for qualitative analysis. The analysis included age, sex, and years of education as confounding variables.

**Group Preprocessing Of Pet**

We used PETSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki/PetSurfer) to register a PET scan to its corresponding time point MRI with output tables of PET values in each atlas region (39). Details of the preprocessing pipeline are shown in the Supplementary file.

**Statistical Analysis Of Clinical Data**

Statistical analyses were performed in SPSS version 25 (IBM, Armonk, NY), and parameters were described as mean ± standard deviation. Differences among the four diagnostic groups (AD, MCI-C, MCI-
NC, controls) were assessed using the chi-square test for categorical variables and Kruskal-Wallis test with Bonferroni correction for continuous variables. Pearson correlation analysis was used to explore the relationships between continuous variables. For longitudinal data, a generalized estimating equation (GEE) model was used, since it does not require the assumption of multivariate normal distribution of the data. Variables were retrieved from demographic data and imaging biomarkers of significance. Results were considered as significant at $p < 0.05$.

**Time Effect Of MRI And FDG-PET**

A linear mixed effects (LME) model was performed in MATLAB 2019b (The Mathworks Inc., Natick, MA, USA) for postprocessing FDG-PET and MRI data and to assess changes in cortical metabolism (FDG-PET) and cortical thickness (structural MRI). The time effect on cortical hypometabolism and cortical thickness degeneration was assessed, using age, sex and years of education as covariates for both imaging modalities, and additionally estimated total intracranial volume for MRI. The time effect was modeled by dividing data into two stages: 1) data within the first 2-year follow-up period representing the early disease stage; and 2) data pooled from the entire follow-up period (mean: $6.6 \pm 3.8$ years) representing the disease progression stage. With cluster-wise correction computed with parametric Gaussian-based simulations to calculate the false positive rate of 0.05, we used a vertex-wise threshold of 3.0 (40).

**Results**

**Demographic data and FDG-PET**

A total of 164 subjects were enrolled, including 44 MCI converters (MCI-C), 38 non-converters (MCI-NC), 42 patients with amyloid-positive AD, and 40 cognitively normal controls, all of whom had at least one FDG-PET scan (Table 1), while 37 patients in the MCI group had two or more FDG-PET scans (MCI-C: 24, MCI-NC: 13). The interval from the first FDG-PET scan to the diagnosis of dementia in the MCI-C group and the observation intervals in the MCI-NC group are shown in Fig. 1. FDG-PET hypometabolism preceded conversion to dementia after an average of $3.70 \pm 1.68$ years (range, 1 year to 8 years). The mean observation duration after the first FDG-PET in the MCI-NC group was $4.34 \pm 1.26$ years (range, 2 years to 7 years).
Table 1
Demographic data of four groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-converter</td>
<td>Converter</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>40</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>Age at first visit FDG-PET</td>
<td>62.6 ± 11.6</td>
<td>72.1 ± 7.60*</td>
<td>74.7 ± 7.04*</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>23/17</td>
<td>15/23*</td>
<td>19/25*</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.6 ± 3.7</td>
<td>6.9 ± 5.0*</td>
<td>7.1 ± 4.9*</td>
</tr>
<tr>
<td>APOE 4 carriers</td>
<td>23.8%</td>
<td>37.8%*</td>
<td>60.9%* §</td>
</tr>
<tr>
<td>First time MMSE</td>
<td>28.1 ± 2.1</td>
<td>23.5 ± 4.36*</td>
<td>21.8 ± 3.7*</td>
</tr>
<tr>
<td>Baseline Cognitive ability Screening Instrument</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total scores (100)</td>
<td>92.6 ± 6.1</td>
<td>77.84 ± 13.9*</td>
<td>74.9 ± 12.2*</td>
</tr>
<tr>
<td>Long term memory (10)</td>
<td>9.88 ± 0.7</td>
<td>9.2 ± 1.8*</td>
<td>9.1 ± 2.6*</td>
</tr>
<tr>
<td>Short term memory (12)</td>
<td>10.5 ± 1.7</td>
<td>7.1 ± 3.6*</td>
<td>4.1 ± 4.0* §</td>
</tr>
<tr>
<td>Attention (8)</td>
<td>7.3 ± 0.8</td>
<td>6.8 ± 1.2*</td>
<td>6.7 ± 1.4*</td>
</tr>
<tr>
<td>Mental manipulation (10)</td>
<td>8.8 ± 1.8</td>
<td>6.3 ± 2.9*</td>
<td>7.0 ± 3.2*</td>
</tr>
<tr>
<td>Orientation (18)</td>
<td>17.7 ± 1.0</td>
<td>15.0 ± 4.0*</td>
<td>11.7 ± 5.1* §</td>
</tr>
<tr>
<td>Drawing (10)</td>
<td>9.8 ± 0.5</td>
<td>8.3 ± 2.3*</td>
<td>8.1 ± 2.9*</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation.

* p < 0.05 with control; § p < 0.05 with MCI non-converter; # p < 0.05 with MCI converter.

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's disease; APOE, Apolipoprotein E; MMSE, mini-mental state examination; FDG-PET, fluorodeoxyglucose positron emission tomography; SUVr, standard uptake value ratio.
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract thinking (12)</td>
<td>10.8 ± 1.2</td>
<td>8.5 ± 2.3*</td>
<td>8.3 ± 2.7*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.5 ± 2.7*§#</td>
</tr>
<tr>
<td>Verbal fluency (10)</td>
<td>8.2 ± 2.1</td>
<td>5.7 ± 2.3*</td>
<td>5.8 ± 2.8*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.8 ± 1.8*§#</td>
</tr>
<tr>
<td>Language (10)</td>
<td>9.8 ± 0.8</td>
<td>9.0 ± 1.5*</td>
<td>8.7 ± 2.1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.9 ± 2.1*§#</td>
</tr>
<tr>
<td>First visit FDG-PET SUVr</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Frontal lobe</td>
<td>1.41 ± 0.10</td>
<td>1.45 ± 0.04</td>
<td>1.35 ± 0.06* §</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.30 ± 0.07*§#</td>
</tr>
<tr>
<td>Medial temporal lobe</td>
<td>1.10 ± 0.07</td>
<td>1.06 ± 0.05</td>
<td>0.91 ± 0.07 *§</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.86 ± 0.02 *§#</td>
</tr>
<tr>
<td>Lateral temporal lobe</td>
<td>1.40 ± 0.12</td>
<td>1.38 ± 0.04</td>
<td>1.23 ± 0.08* §</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.19 ± 0.11 *§#</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>1.61 ± 0.13</td>
<td>1.60 ± 0.20</td>
<td>1.37 ± 0.14 *§</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.20 ± 0.07 *§#</td>
</tr>
<tr>
<td>Precuneus</td>
<td>1.61 ± 0.12</td>
<td>1.61 ± 0.05</td>
<td>1.48 ± 0.09* §</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.31 ± 0.08 *§#</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>1.50 ± 0.10</td>
<td>1.49 ± 0.04</td>
<td>1.36 ± 0.08 *§</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.21 ± 0.06 *§#</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>1.60 ± 0.11</td>
<td>1.59 ± 0.05</td>
<td>1.56 ± 0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.39 ± 0.12 *§#</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>4.4 ± 1.8</td>
<td>6.4 ± 3.8*</td>
<td>6.7 ± 3.6*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.6 ± 3.2*</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation.

* $p < 0.05$ with control; § $p < 0.05$ with MCI non-converter; # $p < 0.05$ with MCI converter.

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's disease; APOE, Apolipoprotein E; MMSE, mini-mental state examination; FDG-PET, fluorodeoxyglucose positron emission tomography; SUVr, standard uptake value ratio.

For the first FDG-PET scan, there was no significant difference in mean age between the two MCI groups ($p = 0.156$). However, the SUVr of seven preselected VOIs, but not the occipital lobe, were significantly
lower in the MCI-C group (p < 0.05) (Table 1). The cognitive test scores and SUVr of all VOIs were lowest in the patients with AD.

The percentages of hypometabolism in the MCI-C group were significantly higher than those in the MCI-NC group. For the MCI-C group, the percentages of hypometabolism in the PCC, MTL, precuneus, frontal, parietal, and lateral temporal lobe were 75.2%, 70.0%, 41.2%, 40.0%, 36.7%, and 32.0%, respectively, compared to 12.8%, 5.2%, 8.1%, 5.0%, 5.2%, and 5.0% in the MCI-NC group (Supplementary Fig. 1).

In the two MCI groups and the first FDG-PET, MTL hypometabolism predicted future conversion with 94.7% sensitivity and 80.5% specificity, followed by the PCC (89.5% sensitivity and 73.1% specificity). Thirty-four cases (of 82 MCI cases) were categorized as having normal metabolism status in MTL and PCC areas; all of these cases were in the MCI-NC group. Of note, three cases with MCI showed MTL and PCC hypometabolism but remained cognitively stable (no-conversion) during follow-up.

**First Fdg-pet Topography And Its Relationship With Cognitive Performance**

The correlation between first FDG-PET Z scores and corresponding MMSE scores, adjusted for years of education, best fit in the AD group (Fig. 2). Among the preselected VOIs, six had significant correlations with MMSE scores in the AD group.

The same analysis was conducted with the CASI and its subdomains to clarify whether hypometabolism in different brain regions was associated with cognitive impairment of different domains (Supplementary results and Supplementary Table 1).

**Longitudinal Cognitive Trajectory**

Based on the median follow-up duration, we represented the first six consecutive measurements of MMSE or CASI total scores in the four groups (Fig. 3). The MCI-C and AD groups had similar progression trajectories, showing a continuous decline in MMSE and CASI scores as the number of measurements increased. In contrast, the trends of cognitive decline in the MCI-NC and control groups were less obvious. Data of the cognitive features of the two MCI groups are listed in the Supplementary results and Supplementary Table 2.

**Evolutional pattern of cortical hypometabolism & cortical atrophy**

**-individual Level**

A representative example of an MCI-C individual depicting the evolutional pattern of three consecutive FDG-PET scans is shown in Fig. 4. Hypometabolism (Z score < -2) started in the MTL and inferior frontal
region, followed by lateral temporal, PCC, parietal and frontal cortex regions years before the cognitive changes.

**-group Level**

The group-level FDG-PET hypometabolism evolution and cortical thickness degeneration in the MCI-C, MCI-NC and AD groups are shown in Fig. 5. According to the predefined time frame, the time effect of FDG-PET hypometabolism and MRI cortical thickness degeneration was divided into early disease stage (Fig. 5A) and disease progression stage (Fig. 5B).

The FDG-PET hypometabolic time effect in the AD group suggested a greater spatial extent of hypometabolism (over the medial prefrontal, lateral temporal, temporal-parietal and precuneus regions; Fig. 5A) in the early disease stage compared to the corresponding cortical thickness degenerative trajectory (only over the hippocampus). As the disease progressed, the cortical thickness degenerative pattern became more consistent with the hypometabolic pattern (Fig. 5B). In the MCI-C group, the evolitional pattern of hypometabolism in the early disease stage (Fig. 5A) was similar to the AD group, but with a relatively sparse distribution. As the disease progressed, the hypometabolism pattern mimicked that of AD (Fig. 5B). One exception was the time effect on the dorsolateral prefrontal cortex (DLFC), which showed progressive hypometabolic changes in the MCI-C group (observed at the disease progression stage) but not in the AD group (in either the early stage or progression stage); instead, in the AD group, cortical atrophy over the DLFC was observed. Hypometabolism or cortical atrophy in the MCI-NC group was inconspicuous at the early stage; however, as the follow-up duration increased, cortical atrophy over the hippocampus and lateral temporal lobe was noted. Of note, there was no signal change in the hippocampus in the FDG-PET time effect model at either the early disease stage or disease progression stage among the three groups. In fact, hippocampal hypometabolism, defined as a Z score < -2, was noted from the first FDG-PET scan in both the MCI-C (70%) and AD (81%) groups.

**Distinct Fdg-pet Topographies Of Mci Converters And Non-converters**

Repeated-measures analysis was conducted in the MCI subjects who received two FDG-PET scans (MCI-C: 24, MCI-NC: 13). The preselected seven VOIs between the two MCI groups and the two scans were compared (Table 2). There was no significant difference in the mean age at the second FDG-PET scan between the two groups. In the first scan, the MCI-C group had significantly lower frontal, PCC, precuneus, lateral temporal, and MTL Z scores. During follow-up, the Z scores of all VOIs became significantly lower in the MCI-C group. Figure 6 shows the distinct differences in the cortical hypometabolic pattern of FDG-PET in the MCI-C and MCI-NC groups (Fig. 6A, B). The difference could be observed from the first FDG scan and became more evident during follow-up (Fig. 6C, D).
Table 2
Difference of FDG-PET Z scores of two scans between MCI-C (n = 24) and MCI-NC (n = 13)

<table>
<thead>
<tr>
<th>MCI-C compares to MCI-NC</th>
<th>$\beta$</th>
<th>SE</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal$^1$</td>
<td>-0.650</td>
<td>0.311</td>
<td>0.044*</td>
</tr>
<tr>
<td>Frontal$^2$</td>
<td>-0.952</td>
<td>0.337</td>
<td>0.008**</td>
</tr>
<tr>
<td>PCC$^1$</td>
<td>-1.467</td>
<td>0.319</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>PCC$^2$</td>
<td>-1.636</td>
<td>0.308</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>Precuneus$^1$</td>
<td>-0.969</td>
<td>0.342</td>
<td>0.008**</td>
</tr>
<tr>
<td>Precuneus$^2$</td>
<td>-1.094</td>
<td>0.360</td>
<td>0.004**</td>
</tr>
<tr>
<td>Parietal$^1$</td>
<td>-0.696</td>
<td>0.358</td>
<td>0.060</td>
</tr>
<tr>
<td>Parietal$^2$</td>
<td>-0.966</td>
<td>0.374</td>
<td>0.014*</td>
</tr>
<tr>
<td>Occipital$^1$</td>
<td>-0.527</td>
<td>0.334</td>
<td>0.123</td>
</tr>
<tr>
<td>Occipital$^2$</td>
<td>-0.888</td>
<td>0.334</td>
<td>0.014*</td>
</tr>
<tr>
<td>Lat. temporal$^1$</td>
<td>-1.211</td>
<td>0.345</td>
<td>0.001**</td>
</tr>
<tr>
<td>Lat. temporal$^2$</td>
<td>-1.577</td>
<td>0.328</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>Med. temporal$^1$</td>
<td>-1.757</td>
<td>0.310</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>Med. temporal$^2$</td>
<td>-2.018</td>
<td>0.331</td>
<td>&lt; 0.001***</td>
</tr>
</tbody>
</table>

Superscript 1 indicates the first scan of FDG-PET; 2 indicates the second scan of FDG-PET. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Abbreviations: MCI-NC, non-converter of mild cognitive impairment; MCI-C, converter of mild cognitive impairment; PCC, posterior cingulate cortex; Lat. temporal, lateral temporal; Med. temporal, medial temporal.

Generalized Estimating Equation Model Revealed The Factors Correlated With Cognitive Decline

To better understand which factors affected cognitive change, a generalized estimating equation model was used for the longitudinal data. As shown in Table 3, the FDG-PET PCC, precuneus and lateral temporal lobe Z scores were inversely correlated with MMSE scores, of which the lateral temporal lobe
had the most significant effect. In contrast, the Z scores of the frontal lobe had a positive effect on the MMSE scores. Similar findings were seen when using CASI total scores as the dependent variable.
### Table 3
The coefficient of covariates in generalized estimating equation model for MMSE & CASI

<table>
<thead>
<tr>
<th></th>
<th>MMSE</th>
<th></th>
<th>CASI</th>
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</tr>
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<tr>
<td></td>
<td>$\beta$</td>
<td>SE</td>
<td>$p$ value</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.198</td>
<td>0</td>
<td>.025*</td>
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<tr>
<td>Education year</td>
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<td>0.074</td>
<td>&lt;0.001***</td>
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<tr>
<td>FDG-PET Z score</td>
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<td></td>
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<tr>
<td>Frontal</td>
<td>-2.289</td>
<td>0.496</td>
<td>&lt;0.001***</td>
<td>-9.620</td>
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<tr>
<td>PCC</td>
<td>1.637</td>
<td>0.497</td>
<td>0.001**</td>
<td>4.676</td>
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<tr>
<td>Precuneus</td>
<td>1.434</td>
<td>0.657</td>
<td>0.029*</td>
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<td>Parietal</td>
<td>-0.968</td>
<td>0.660</td>
<td>0.143</td>
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<tr>
<td>Occipital</td>
<td>-0.244</td>
<td>0.587</td>
<td>0.667</td>
<td>-1.582</td>
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<tr>
<td>Lat. temporal</td>
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<td>0.547</td>
<td>0.001**</td>
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<td>Med. temporal</td>
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<td>-0.574</td>
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<tr>
<td>Measurement number, AD</td>
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<td></td>
</tr>
<tr>
<td>2nd time</td>
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<td>0.632</td>
<td>0.180</td>
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<tr>
<td>3rd time</td>
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<td>0.765</td>
<td>0.182</td>
<td>-3.177</td>
</tr>
<tr>
<td>4th time</td>
<td>-2.256</td>
<td>1.123</td>
<td>0.045*</td>
<td>-8.341</td>
</tr>
<tr>
<td>5th time</td>
<td>-3.004</td>
<td>1.227</td>
<td>0.014*</td>
<td>-15.092</td>
</tr>
<tr>
<td>6th time</td>
<td>-5.325</td>
<td>2.154</td>
<td>0.013*</td>
<td>-21.842</td>
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<tr>
<td>Measurement number, MCI-C</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd time</td>
<td>-0.339</td>
<td>0.590</td>
<td>0.565</td>
<td>-1.260</td>
</tr>
<tr>
<td>3rd time</td>
<td>-0.888</td>
<td>0.719</td>
<td>0.217</td>
<td>-2.628</td>
</tr>
</tbody>
</table>

* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Abbreviations: MCI-NC, non-converter of mild cognitive impairment; MCI-C, converter of mild cognitive impairment; AD, Alzheimer’s disease; MMSE, mini-mental state examination; CASI, cognitive ability screening instrument total score; FDG-PET, fluorodeoxyglucose positron emission tomography; PCC, posterior cingulate cortex; Lat. temporal, lateral temporal; Med. temporal, medial temporal; SE, standard error.
Furthermore, using time as a categorical variable, we found negative interactions between the number of measurements and cognitive test scores in the AD and MCI-C groups but not in the MCI-NC group. In addition, the interactions became significant after the third measurement. Interestingly, the MCI-NC group showed some improvement in cognitive test performance during follow-up; for example, the third MMSE scores increased by 0.557 points from baseline, and the third CASI total scores increased by 4.204 points. Nevertheless, the performance worsened from the fourth measurement. The trends in cognitive decline were most prominent in the AD and MCI-C groups.

**Discussion**

**Major Findings**

In this study, we assessed longitudinal neuropsychological tests (MMSE and CASI), FDG-PET and structural MRI in subjects with MCI-C and MCI-NC, and constructed cognitive, cortical hypometabolism, and cortical degeneration features to predict conversion. There were three significant findings. First, the best applicable model to predict MCI conversion was based on the individual-based VOI approach using...
one FDG-PET scan at the MCI stage. Hypometabolism of the MTL and PCC (Z<-2) reached the highest specificity at the subject level, while the predictive abnormalities could be detected at 3.70 ± 1.68 years prior to conversion, although we also observed an 8-year interval between the FDG-PET scan and the occurrence of dementia. Second, we assessed the relationships between the evolution of two neuronal injury biomarkers with related cognitive decline patterns. We found that the subjects with MCI-C and AD followed similar degenerative trajectories, supporting the clinical significance of the core clinical criteria of MCI due to AD (6) with the neuronal injury biomarkers in the MCI predictive model. Finally, we explored longitudinal data, and found that decreased glucose metabolism over the PCC, precuneus and lateral temporal lobe could reflect cognitive decline. Moreover, comparing cortical hypometabolism and cortical atrophy at different disease stages suggested that FDG-PET had higher sensitivity in detecting regional abnormalities.

**Fdg-pet As A Biomarker Of Mci Conversion**

Both FDG-PET and MRI represent neuronal injury biomarkers in AD (10). Hypometabolism of temporoparietal and PCC regions in FDG-PET has been shown to be a typical feature of AD (41), and it has been reported as early as the preclinical or prodromal stage (42). To predict MCI conversion using FDG-PET, hypometabolism over the PCC, precuneus or temporoparietal cortex has frequently been reported (20, 22–26, 43–52). However, the application of a subject-level-based VOI approach in MCI conversion is novel. We found that the PCC was a conversion predictor, however, changes in the PCC may have been less specific than in the MTL based on the relatively higher proportion of hypometabolism in the PCC than in the MTL (12.8% vs. 5.2%) in the MCI-NC group. The role of MTL as a predictor for MCI conversion has rarely been reported; this may be related to the temporal course of the disease, as the evolutional pattern of glucose metabolic abnormalities has been shown to occur relatively early in the hippocampus compared to the temporoparietal and PCC in MCI (53). This evolutional pattern was also observed in our FDG-PET time effect analysis; as illustrated in Fig. 5A, the time effect of SUVr change over the hippocampus was limited compared to the PCC, even at the early disease stage of MCI-C or AD. We propose that hypometabolism over the MTL reached a signal valley at the very early stage of disease. Since our follow-up duration was longer than in most previous studies, the hypometabolism in the MTL may be an earlier indicator of MCI conversion than PCC.

Moreover, an important aspect of FDG-PET in MCI is its exclusionary role. In our series, 34 MCI patients did not demonstrate hypometabolism in FDG-PET and 33 did not show progression. The high specificity (93.7%) and negative predictive value (93.7%) can be extremely useful to rule out progression in MCI. A normal FDG-PET scan at the MCI stage has been shown to be a reliable indicator of non-progression or for reconsidering the diagnosis of neurodegenerative disease (54, 55).

**Cognitive Decline Trajectory Still Reflected Mci Conversion At Year 3**
Although previous studies on the use of neuropsychological tests to predict MCI conversion have commonly focused on the predictive value of single memory tests (56, 57), our outcome measures focused on the longitudinal changes and interval to conversion to dementia. We found similar declining trends of MMSE and CASI scores in the MCI-C and AD groups, but not in the MCI-NC group. In addition, the differences became significant after the third year of follow-up. As both patients with MCI-C and MCI-NC were enrolled based on the MCI due to AD criteria, the declining trend in MCI-C suggests that at least 3 years of follow-up is required for patients with MCI to predict the prognosis. Moreover, the declining patterns in the MCI-C and AD groups were similar, meaning that the longitudinal follow-up of MCI could still reveal possible neuronal injury similar to AD.

**Multi-modal Model For MCI Conversion**

Structural MRI is considered to be of equal value to FDG-PET as a neuronal injury biomarker (1). The use of MRI in assisting the prediction of MCI conversion has also been widely investigated (28–31, 58–61). The issue of whether MRI is superior to FDG-PET is still under debate, which could be related to the variety of selected metrics when evaluating the two imaging modalities and the study populations (62). In our time effect analysis of the two imaging modalities, FDG-PET revealed more widespread abnormalities at the early stage of MCI compared with MRI, which is consistent with the temporal order of biomarkers in AD (10). Meanwhile, we also observed that group FDG-PET signal reduction reached a plateau in both the MCI-C and AD groups at the early stage of disease. In contrast, MRI abnormalities were restricted mainly to the hippocampus at the early stage; however, with disease progression, more extended atrophy was noted compared to the time effect on FDG-PET. In line with other studies (48, 63), we suggest that FDG-PET has a higher predictive value than MRI, especially in the early disease stage of MCI; whereas in the late stage of MCI, MRI has an important role in monitoring disease progression. Since there was no definition of the severity of MCI, and the enrolled time-point of each MCI case could not be the same among different studies, it is very likely that the sampled MCI cases had different stages, therefore resulting in inconsistent findings in multi-modal comparative studies. With advances in the diagnosis and interventions for AD at the prodromal stage, constructing a uniform scale to evaluate the stage or severity of MCI could be of clinical and research importance.

**Evolution In Fdg-pet Reflected Cognitive Decline**

Instead of hypometabolism, increased SUVr over the frontal lobe was found in the patients with cognitive decline in our longitudinal data. In early AD, activation over the DLFC and parietal-temporal border has been reported to be higher than in the general population in FDG-PET when performing verbal episodic memory tasks (64). Similarly, in an MCI functional MRI study, increased activation over frontal regions was found when performing memory-related tasks (65). We speculate that the increase in frontal FDG-PET signal could be a compensatory mechanism during the loss of cognitive function. As shown in Fig. 5, we found cortical hypometabolism over the DLFC in the disease progression stage but not in the
early stage of MCI-C, and cortical atrophy over the DLFC in the patients with AD. This suggests that failure of DLFC compensation could be an indicator of AD conversion.

Limitations And Strength

This study had two limitations. First, the underlying neuropathology of MCI was not assessed; therefore, the definite diagnosis of MCI could still be heterogeneous. As our MCI patients were enrolled based on the core clinical criteria of MCI due to AD, and as the MCI-C patients showed a similar degenerative trajectory to the amyloid-positive AD patients, it is very likely that the majority of the MCI-C group had AD pathophysiology. Second, because this was a retrospective analysis, not all MCI cases had a second FDG-PET scan, and the interval between two scans was not arranged in the same time frame. However, the randomly scattered time points of FDG-PET with an individualized prediction model may enhance its clinical application. For the follow-up FDG-PET scans, we used a GEE model to construct the longitudinal changes in SUVr signals, and their correlations with cognitive decline were not significant. This suggests that cross-sectional FDG-PET was adequate to build the model, and that the non-fixed time frame of FDG-PET scans could be considered a real-world situation.

Conclusion

In conclusion, our results showed that FDG-PET tailored to individual MCI cases with a VOI approach could assist in the prediction of future progression. Reduced FDG-PET signals in the MTL and PCC were strongly associated with future cognitive decline in the MCI-C group. The average interval between changes in FDG-PET signal and dementia conversion was 3 years (range, 1 to 8 years). Hypometabolism preceded corresponding cortical thickness degeneration in those with dementia conversion if the FDG-PET was arranged at the MCI stage.

Abbreviations

AD
Alzheimer's disease
MCI
mild cognitive impairment
\(^{18}\text{F-FDG-PET}\)
\(^{18}\text{F fluorodeoxyglucose positron emission tomography}\)
MRI
magnetic resonance imaging
VOI
volumes of interest
MMSE
Mini-Mental State Examination
Declarations

Ethics approval and consent to participate

Ethics committee approval of the baseline and follow-up plan protocol was obtained at Chang Gung Memorial Hospital, Kaohsiung with the following IRB numbers: 200700077B0, 200903596A3C501, 200901852A0, 201104249A3C101, 201201074A0, 201407770A3, 201504890A0C101, 201901949A0, 201901949A0. Written Informed consent was obtained from all participants and legally authorized representatives in the cases with cognitive impairment.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.
Competing interests

The authors declare that they have no competing interests.

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Funding

This research was funded by Chang Gung Memorial Hospital, grants number CMRPG8J0524, CMRPG8J0843, CMRPG8K1533, and Ministry of Science and Technology (MOST), Taiwan, grants number 111-2314-B-182A-143 to C.C.C. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Authors' contributions

Shu-Hua Huang, conception and design, FDG-PET data acquisition, and drafting of the manuscript; Wen-Chiu Hsiao, conception and design, drafting of the manuscript; Chi-Wei Huang, contributions to FDG-PET statistical analysis; Hsin-I Chang, LME model design; Mi-Chia Ma, statistical analysis; Shih-Wei Hsu, MRI acquisition and interpretation of data; Chen-Chang Lee, MRI acquisition and interpretation; Hong-Jie Chen, acquisition of data and interpretation of data; Ching-Heng Lin, surface analysis, image preprocessing and statistical model design; and Chiung-Chih Chang, funding and study design and critical revision.

Acknowledgements

Not applicable.

References


Figures

![Bar chart showing duration from first visit FDG-PET scan to conversion, n = 44](image1)

![Bar chart showing observation duration after first visit FDG-PET scan of non-converter, n = 38](image2)

Figure 1
Intervals of MCI conversion to AD after the first visit FDG-PET scan (A) and observation intervals of MCI non-converter after the first visit FDG-PET scan (B). Bars represent the follow-up years of each case.

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer’s disease.

Figure 2

Scatter plot of the correlations between the first visit FDG-PET Z scores from six volume-of-interests and MMSE scores, adjusted for years of education (A-F). Dots represent each participant in this study; the linear relationships are shown in lines. Solid lines indicate a significant correlation. $r =$ correlation coefficient; * $p < 0.05$; ** $p < 0.01$.

Abbreviations: MCI-NC, non-converter of mild cognitive impairment; MCI-C, converter of mild cognitive impairment; AD, Alzheimer’s disease; MMSE, mini-mental state examination.
Figure 3

Cognitive test scores of the first six consecutive MMSE (A) and CASI (B) measurements. The progression trajectories of the MCI-C group were similar to the AD group. In contrast, the declining trend of the MCI-NC group was not as conspicuous as the AD or MCI-C group. The difference became significant since the third time measurement of MMSE and CASI. The average interval between each measurement was one year. ** indicates p < 0.05 comparing the MCI-C to MCI-NC groups.

Abbreviations: MCI-NC, non-converter of mild cognitive impairment; MCI-C, converter of mild cognitive impairment; AD, Alzheimer’s disease; MMSE, mini-mental state examination; CASI: cognitive ability screening instrument total scores.
Figure 4

FDG-PET Z score map in a female patient showed conversion in three scans. At the baseline, decreased uptake was noted in the medial temporal lobe and inferior frontal cortex (MMSE = 24; 4 years before dementia). 2.5 years later, hypometabolism was noted in the lateral temporal lobe, posterior cingulate cortex and dorsolateral prefrontal cortex (MMSE = 24; 1.5 years before dementia). Five years after the first visit FDG-PET scan, hypometabolism was more widely spread with a pattern similar to the default mode network (MMSE = 11). Only regions showing a Z score < -2 were displayed.

Abbreviations: MMSE, mini-mental state examination.
Figure 5

Time effect of cortical hypometabolism (FDG-PET) and cortical thickness degeneration (volumetric MRI) in the AD, MCI-C and MCI-NC groups. (A) Data from the first two years of follow-up represents the early disease stage. (B) Pooling data from the entire follow-up (mean: 6.6 ± 3.8 years) represents the disease progression stage. The circle indicates the dorsolateral prefrontal cortex. Significance was set at a vertex-wise threshold of 3.0.

Abbreviation: MCI-NC, non-converter of mild cognitive impairment; MCI-C, converter of mild cognitive impairment; AD, Alzheimer’s disease; MRI, magnetic resonance imaging.
Figure 6

FDG-PET topography of the preselected seven volume-of-interests. The MCI-C group showed prominent hypometabolism in the medial temporal lobe and PCC, and the FDG-PET uptakes over all regions decreased in the second scan (A). In contrast, the MCI-NC group seemed to have a relatively hypometabolic change in PCC in the first scan; however, the condition was not noted in the second scan, and there was no significant declining trend over all regions (B). The difference between the two groups could be pointed out in the first scan and became more robust in the second scan (C, D). Numbers on the chart indicate the Z score of FDG-PET.

Abbreviation: MCI-NC, non-converter of mild cognitive impairment; MCI-C, converter of mild cognitive impairment; PCC, posterior cingulate cortex; Med. temporal, medial temporal; Lat. temporal, lateral temporal.

Supplementary Files

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