Magnetic Resonance Hippocampal Subfield Volumetric Analysis for Differentiating among Healthy Older Adults and Older Adults with Mild Cognitive Impairment or Major Depressive Disorder

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ABSTRACT

Objective: Depression among older adults is frequently an early symptom of cognitive decline, and is believed to be a risk factor for Alzheimer's disease (AD). Hippocampal subfield volume loss is found in both mild cognitive impairment (MCI) and major depressive disorder (MDD). We aimed to investigate the potential of MR hippocampal subfield volumetry for discriminating among healthy older adults (HOA) and older adults with MCI or MDD.

Materials and Methods: Seventy age-matched subjects (29 non-depressed MCI, 12 MDD, and 29 HOA) underwent 3-Tesla MR imaging (MRI) with high-resolution 3D-T1W-TFE whole brain. Hippocampal subfield volumetric measurements were performed using FreeSurfer software to distinguish among MCI, MDD, and HOA. Subgroup analysis with amyloid PET result was also performed.

Results: Significantly smaller bilateral hippocampal tail volume was observed in MCI compared to HOA (p=0.004 and p=0.04 on the left and right side, respectively). The same comparative finding was observed at left HATA (hippocampus-amygdala-transition-area) of MCI (p=0.046). Other regions showed non-significantly smaller size in MCI than in HOA [left molecular layer HP (p=0.06), left whole hippocampus (p=0.06), and left CA1 (p=0.07)]. There was a non-significant trend toward smaller size in almost all 13 subfield hippocampal regions of MCI compared to MDD, even in subgroup analysis with amyloid PET result.

Conclusion: MR hippocampal subfield volumetry may have value in routine clinical practice for screening individuals with MCI, and may be a valuable adjunct to amyloid PET study for very early-stage diagnosis of AD.

Keywords: Magnetic resonance hippocampal subfield volumetric analysis, mild cognitive impairment (MCI), major depressive disorder (MDD), healthy older adults (HOA) (Siriraj Med J 2021; 73: 786-792)

INTRODUCTION

Mild cognitive impairment (MCI) is diagnosed when people have measurable changes in thinking ability noticed by the person affected, family members, or friends even though the observed impairment does not affect the individual's activities of daily living.[1] The 2011 recommendations from the National Institute on Aging-Alzheimer's Association diagnostic guideline for

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Alzheimer's disease (AD) working groups suggest that some MCI cases reflect the early stage of AD.[2] Depression, especially in older adults, frequently develops concomitantly with cognitive impairment, and it may be a psychological reaction or a risk factor for AD.[3]

One of the most mentioned structures in limbic system is hippocampus, which is known to involve in both neurodegenerative disease, especially AD, and emotional regulation.[4] Hippocampal atrophy is usually detected in late stage of AD. Previous study found that subfield hippocampal atrophy evidenced by magnetic resonance imaging (MRI) might be helpful for early detection of mild cognitive impairment who have converted to AD (MCI-c).[5]

Concerning mood regulation, a previous meta-analysis found more hippocampal volume loss in MDD than in the control; however, the impact of illness on hippocampal volume is probably related to duration and severity.[6]

To date, no study has compared subfield hippocampal volume between MCI and MDD in older adults. Accordingly, the aim of this study was to investigate the potential of MR hippocampal subfield volumetry for discriminating among older adults with non-depressed MCI, older adults with treatment-naïve MDD, and healthy older adults (HOA).

MATERIALS AND METHODS

Study population

This retrospective study reviewed the MRI DICOM files, clinical information, and neuropsychological test results of 72 subjects (30 MCI, 12 MDD, and 30 HOA) who were recruited at a single national tertiary referral center in Thailand during January 2016 to September 2020. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 1037/2020).

The 30 MCI and 30 HOA subjects, recruited from neurology and geriatric clinics at our center, were part from the SIRB-approved study (Si 137/2015). Clinical evaluation of MCI and HOA subjects was performed by a senior geriatric neurologist (WM) who specializes in dementia.

The 12 MDD subjects, first-diagnosed treatment-naïve patients, recruited from the psychiatric clinic at our center, were part from a different SIRB-approved study (Si 239/2016). Diagnosis and severity of depression were determined by a board-certified psychiatrist.

Two out of 72 subjects (1 MCI and 1 HOA) were excluded due to flaws in their MRI DICOM files. The remaining 70 subjects (29 MCI, 12 MDD, and 29 HOA) were included and analyzed. The amyloid PET result for all of the 29 MCI patients were recorded and subcategorized as PET positive MCI (PET+ve MCI; n=12) or PET negative MCI (PET-ve MCI; n=17) patients. Age, gender, education level, Thai Mental State Examination (TMSE)[7], Clinical Dementia Rating Scale (CDR), and Hamilton Rating Scale for Depression (HAM-D)[8] were also collected and recorded. Two years of clinical follow-up among the 29 MCI subjects was achieved by the end of September 2020.

Operational definitions

1. Criteria for mild cognitive impairment (MCI)

1) Age equal to or greater than 60 years

2) Subjective memory complaint by the patient, family member, or clinician with preserved activities of daily living (ADL)

3) CDR score of 0.5

4) Absence of dementia by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria

5) TMSE score from 24 to 30

6) No history of depressive symptom

2. Criteria for major depressive disorder (MDD)

1) Age equal to or greater than 60 years

2) First diagnosed approaching fulfillment of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for MDD[9]

3) Depression severity was measured by HAM-D

4) TMSE score from 24 and 30

5) No other psychiatric disorders, antidepressant drug use, currently unstable medical or neurological condition

3. Criteria for healthy older adults (HOA)

1) Age equal to or greater than 60 years

2) TMSE score from 24 to 30

3) CDR score of 0

4) No neurological or psychiatric illness, non-demented, and normal ADL

Magnetic resonance imaging (MRI) acquisition

All 70 enrolled subjects underwent 3T MRI scans (Ingenia, Philips Medical System, Best, the Netherlands) with a 32-channel head coil. The MRI protocol included a 3D high-resolution T1W-TFE sequence covering whole brain (field-of-view (FOV) 230×230×172 mm^3, matrix size 352x352, voxel size 0.72×0.72×0.65 mm^3, echo time

(TE)/repetition time (TR) 4.8/9.8 ms, flip angle 8°, scan time 6 min). All MRI DICOM files were transferred to hippocampal subfield segmentation process.

Hippocampal subfield segmentation

The FreeSurfer image analysis pipeline (version 6.0)[10] was used for automated hippocampal subfield segmentation. The validated ultra-high resolution 13 subfield hippocampal regions (Fig 1) were, as follows: presubiculum, subiculum, parasubiculum, cornu ammonis (CA)1, CA2/3, CA4, molecular layer hippocampus (HP), GC-ML-DG (granule cell layer and molecular layer of dentate gyrus), HATA (hippocampus-amygdala-transition-area), hippocampal tail, fimbria, hippocampal fissure, and the whole hippocampus, bilaterally.

The raw volume data each of subfield was displayed and then normalized according to each subject's intracranial volume (ICV) derived from FreeSurfer software via this following formula: volume normalized = volume raw data x 1,000/ICV in cm^3.[10,11]

[18F] Florbetapir PET/CT to detect cerebral amyloid deposition

All 29 MCI patients also underwent amyloid positron emission tomography (PET) study with administration of our proprietary [18F] florbetapir biomarker[12] shortly before or after MRI scan. Our specific PET/CT scan (Discovery STE; GE Healthcare, Chicago, IL, USA) acquisition and image protocols are described in ADNI GO[13] and ADNI 2.[14] In the present study, two nuclear medicine physicians who were blinded to patient clinical information reached a consensus decision regarding who was amyloid positive and who was amyloid negative according to the published criteria.[15] (Fig 2)

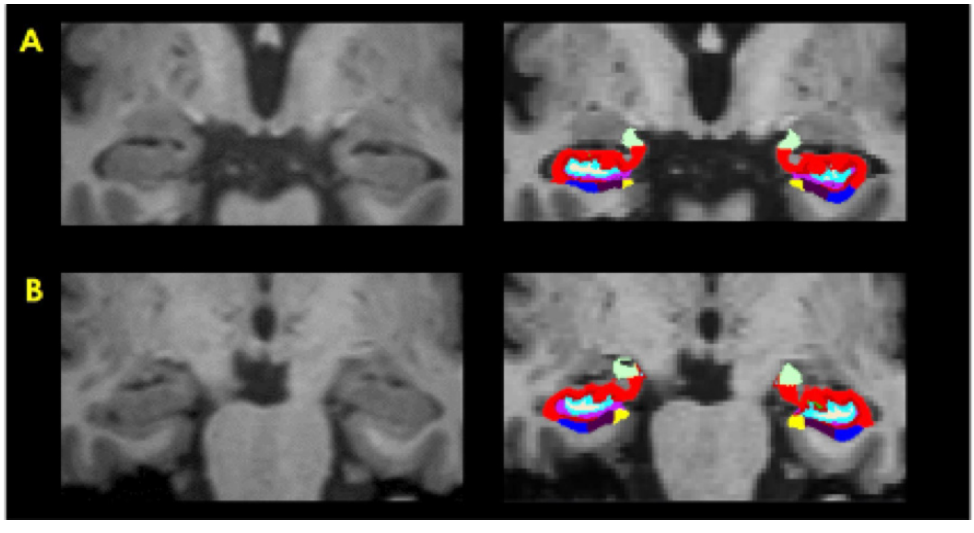

Fig 1. Coronal view MRI bilateral hippocampi of a 72-year-old male with mild cognitive impairment (amyloid PET positive) (A), and a 68-year-old male with first diagnosis treatment-naïve MDD (B) shown in T1-weighted image (left), and T1-weighted image with subfield hippocampal segmentations (right).

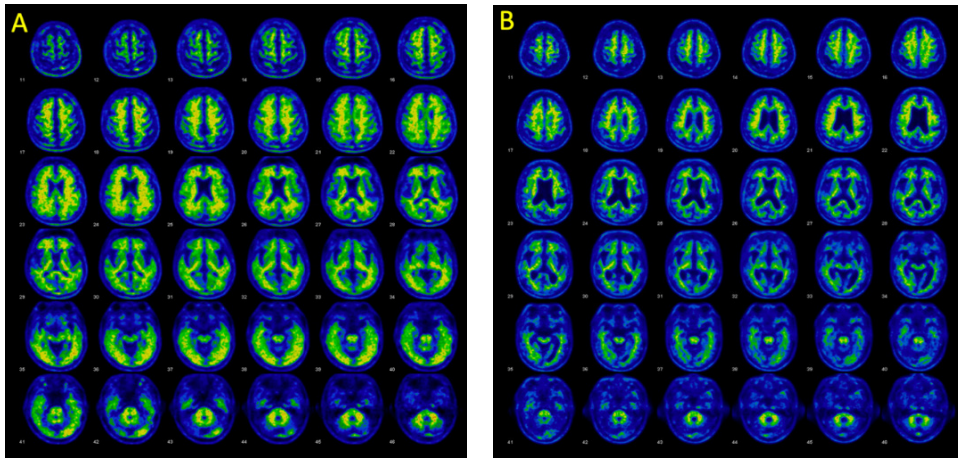

Fig 2. The transaxial images of [F-18] florbetapir PET brain study in two different patients with mild cognitive impairment (MCI) showing positive brain amyloid deposition due to mildly increased radiotracer uptake at bilateral temporal cerebral cortices (A), and negative amyloid deposition due to clear gray-white matter discrimination without abnormal cortical uptake (B).

Statistical analysis

All statistical analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were analyzed by analysis of variance (ANOVA) with Bonferroni post hoc comparisons, and the categorical variables were analyzed by chi-square test. A *p*-value <0.05 was considered to be statistically significant.

RESULTS

1. Demographics, clinical and neuropsychological data

Seventy age-matched subjects were included in this study (MCI=29, MDD=12, HOA=29). The mean ± SD age of these 3 groups was 68.1±4.3, 70.8±6.0, and 68.7±4.8 years, respectively. As expected, there were no statistically significant differences in TMSE score among the 3 study groups (Table 1). Six of the 29 MCI patients had clinically proven AD-converted MCI by the end of the 2-year follow-up, and all 6 of those patients had an initial amyloid PET result that was positive.

2. Hippocampal subfields

2.1 Comparison between MCI and HOA (Table 2)

The bilateral hippocampal tails showed significantly smaller volume in the MCI group compared to the HOA group (p=0.004 and p=0.04 on the left and right side, respectively), as well as at the left HATA (hippocampus-amygdala-transition-area) (p=0.046). We also observed a trend towards significantly smaller size in the MCI group compared to the HOA group for left molecular layer HP (p=0.06), left whole hippocampus (p=0.06), and left CA1 (p=0.07).

2.2 Comparison between MCI and MDD (Tables 2, 3)

There was a non-significant trend toward smaller size in almost all of the 13 subfield hippocampal regions when compared between MCI and MDD subjects – even in subgroup analysis (MCI PET+ve and MCI PET-ve).

2.3 Comparison between MDD and HOA (Table 2)

There was no significant difference between the MDD and HOA groups for any subfield hippocampal regions.

2.4 Comparison between MCI PET+ve and HOA (Table 3)

In subgroup analysis combined with amyloid PET result, we found that the bilateral hippocampal tails showed a significantly smaller volume in the MCI PET+ve group than in the HOA group (p=0.002 and p=0.02 on the left and right side, respectively). The left whole hippocampus (p=0.05), left molecular layer HP (p=0.07), and left subiculum (p=0.07) all demonstrated smaller volume among MCI PET+ve subjects compared to HOA subjects.

2.5 Comparison between MCI PET-ve and HOA (Table 3)

No statistically significant difference in hippocampal subfield volumes was observed between these two groups.

TABLE 1. Demographic, clinical and neuropsychological data of MCI, MDD, and HOA subjects.

Subject data	MCI (n=29)	MDD (n=12)	HOA (n=29)	*p*
Gender (male/female), n	15/14	5/7	10/19	0.41
Age (years), (mean±SD)	68.1±4.3	70.8±6.0	68.7±4.8	0.26
Education, n (%)				***<0.0001***
- High school or lower	2 (6.9%)	8 (66.7%)	16 (55.2%)	
- Higher than high school	27 (93.1%)	4 (33.3%)	13 (44.8%)	
TMSE (mean±SD)	27.3±1.6	26.8±2.0	27.9±1.9	0.17
HAM-D (mean±SD)	NA	24.5±4.3	NA	NA

A *p*-value<0.05 indicates statistical significance

Abbreviations: MCI, mild cognitive impairment; MDD, major depressive disorder; HOA, healthy older adults; SD, standard deviation; TMSE, Thai Mental State Examination, HAM-D; Hamilton Rating Scale for Depression; NA, not applicable

TABLE 2. Normalized hippocampal subfield volume compared among MCI, MDD, and HOA subjects.

Parameters	MCI (n=29)	MDD (n=12)	HOA (n=29)	*P* (MCI vs HOA)
Left hippocampal tail	323.4±67.2	342.4±70.2	383.0±67.5	***0.004***[a]
Right hippocampal tail	345.3±78.2	368.0±54.0	392.4±70.1	***0.04***[a]
Left HATA	37.4±7.5	43.7±13.9	42.3±7.4	***0.046***[a]
Left molecular layer HP	352.1±67.7	385.6±88.0	394.1±58.2	0.06
Left whole hippocampus	2,151.5±376.2	2,338.6±521.6	2,396.6±337.1	0.06
Left CA1	394.4±79.9	435.0±88.3	440.8±68.5	0.07

[a] Statistically significant difference ($p<0.05$) between the MCI and HOA groups
Abbreviations: MCI, mild cognitive impairment; MDD, major depressive disorder; HOA, healthy older adults; HATA, hippocampus-amygdala-transition-area; HP, hippocampus; CA1, cornu ammonis 1

TABLE 3. Hippocampal subfield volume compared among MCI PET +ve, MCI PET -ve, MDD, and HOA subjects.

Parameters	MCI PET+ve (n=12)	MCI PET-ve (n=17)	MDD (n=12)	HOA (n=29)	*P* (MCI PET+ve vs HOA)
Left hippocampal tail	297.5±79.1	341.7±52.4	342.4±70.2	383.0±67.5	***0.002***[a]
Right hippocampal tail	318.2±87.5	364.4±67.0	368.0±54.0	392.4±70.1	***0.02***[a]
Left whole hippocampus	2,035.4±380.4	2,233.5±361.8	2,338.6±521.6	2,396.6±337.1	0.05
Left molecular layer HP	334.3±66.8	364.6±67.5	385.6±88.0	394.1±58.2	0.07
Left subiculum	261.9±56.5	292.6±50.6	310.1±78.2	311.6±48.4	0.07

[a] Statistically significant difference ($p<0.05$) between the MCI PET+ve and HOA groups
Abbreviations: MCI, mild cognitive impairment; MDD, major depressive disorder; HOA, healthy older adults; HP, hippocampus

DISCUSSION

Interestingly, the significantly smaller volume of the bilateral hippocampal tails in the MCI compared to the HOA group, as well as in subgroup analysis, was observed in the MCI PET+ve, but not in the MCI PET-ve group. Previous study[16,17] reported some differences in functionality between the ventral (anterior) and the dorsal (posterior) hippocampus in which the posterior part primarily performs cognitive functions, such as learning and memory, whereas the anterior part is more related to stress and emotion. Our 2-year clinical follow-up data showed that about 20% of our MCI patients (6/29 subjects) converted to clinically diagnosed Alzheimer's disease (AD). More importantly, all 6 of those AD-converted MCI patients (MCI-c) also had an initial amyloid PET result that was positive. We propose that the structural change of the hippocampus demonstrated by MRI volumetric analysis, especially the small size of the hippocampal tail, might be a predictor of conversion to AD among MCI patients.

The relatively smaller volume of the left molecular layer HP, left CA1, left subiculum, and left whole hippocampus in the MCI group (especially MCI PET+ve) compared to HOA subjects suggests that other hippocampal

subfield regions might also be affected in the early stage of neurodegenerative disease. Scharfman, *et al*. reported that neurons in the entorhinal cortex, especially the superficial layer, were believed to be particularly vulnerable to adverse effect in the early stage of Alzheimer's disease (AD)[18] and have been found interconnecting to axons within the hippocampal formation.

From neuroanatomy, the subiculum is the grey structure that is located above the parahippocampal gyrus, which is part of the entorhinal cortex, and it superolaterally connects to the CA1 region. We postulate that the change in the entorhinal cortex in early AD might also propagate effect to the subiculum and CA1, as well as to the molecular layer HP adhering to both subiculum and CA1.

In older adults, depression often develops concomitantly with cognitive impairment. This is likely a psychological reaction to cognitive decline, so it may manifest as an early symptom in early-stage dementia patients. However, recent data suggests that depression, particularly late-life depression, can also be a risk factor for AD.[3]

Two prior studies[19,20] reported significant volume change in some subfield hippocampal regions in MDD patients with some specific conditions, such as recurrent episode of depressive symptom (decreased volume as the number of prior episodes increased)[19], or continuous remission of drug-naive disease (increased volume in MDD patients who were in remission at least 6 months). Concerning our result, there was no statistically significant difference in volumetric analysis compared between first-diagnosed and untreated MDD and either MCI or HOA subjects. This may suggest that the hippocampus has some plasticity, especially relative to volumetric change in depressive condition, but not in early or late-stage neurodegenerative disease, which known to be associated with progressive permanent neuronal loss.

Strengths and limitations

The strengths of our study were: 1) Clinical evaluation of MCI and HOA subjects was performed by a senior geriatric neurologist (WM) who specializes in dementia; 2) Amyloid-PET result was available for all MCI patients; and, 3) All MDD patients had first-diagnosed and untreated status without any confounding factors, such as repeated episode of depressive symptom or treatment-related issues.

Limitations of the present study include 1) A lack of data specific to depressive illness duration, which may affect hippocampal subfield volume change as found from prior study[21]; 2) The fact that our MDD patients had only mild to moderate depressive severity, which may not clearly demonstrate alteration of hippocampal volume; 3) Our study's single-center retrospective design; and, 4) our overall small size and small group sample sizes may have limited the statistical power of our study to identify all significant differences between and among groups.

CONCLUSION

MR hippocampal subfield volumetry may have value in routine clinical practice for screening individuals with MCI, and may be a valuable adjunct to amyloid PET study for very early-stage diagnosis of AD. Future study in subfield hippocampal volumetry compared between MCI patients with and without codepressive symptoms will further clarify the influence of depression on hippocampal atrophy, especially in some specific subfield regions. This information will improve our understanding of the underlying pathophysiology, and will help us to better guide disease management in the future.

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