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Research report

Brain single photon emission computed tomography findings in depressive pseudodementia patients

Maeng Je Cho^{a,*}, In Kyoon Lyoo^a, Dong Woo Lee^a, Jun Soo Kwon^a, Jae Sung Lee^b,
Dong Soo Lee^b, June Key Jung^b, Myung Chul Lee^b

^aDepartment of Neuropsychiatry, Clinical Research Institute, Seoul National University College of Medicine and Hospital,
28 Yongon-dong, Chongno-gu, Seoul, 110-744 South Korea

^bDepartment of Nuclear Medicine, Clinical Research Institute, Seoul National University College of Medicine and Hospital, Seoul,
South Korea

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Abstract

Background: Recently, there have been studies suggesting that depressive pseudodementia would include early-stage dementing disorder. Through the comparison of the ^{99m}Tc-HMPAO single photon emission computed tomography (SPECT) image of depressive pseudodementia subjects, healthy comparison subjects, depressed subjects free of cognitive impairment, and dementia of Alzheimer's type (DAT) subjects, we aimed to see part of pathophysiology of the depressive pseudodementia of elderly patients. **Methods:** Study subjects consisted of seven patients with depressive pseudodementia, seven healthy comparison subjects, seven patients with depression free of cognitive impairment, and eleven patients with DAT. Depression patients were diagnosed according to DSM-III-R. DAT patients were diagnosed by DSM III-R and NINCDS-ADRDA criteria of DAT. Other measures for assessment include Hamilton Rating Scale for Depression and Mini Mental State Exam. All underwent ^{99m}Tc-HMPAO SPECT scan. The images of each group were analyzed using statistical parametric mapping of Friston, which compares the images on voxel-by-voxel basis. **Results:** The results were as follows (1) The DAT group showed significant decreases of cerebral blood flow (CBF) in the right frontal, right temporal region, and both parietal regions as compared with control group ($P < 0.05$). (2) The depression group showed a significant decrease of CBF in the left frontal region as compared with control group ($P < 0.05$). (3) The depressive pseudodementia group showed significant decreases of CBF in both parietal regions as compared with control group ($P < 0.05$). (4) The depressive pseudodementia group showed significant decreases of CBF in the right temporal region and both parietal regions as compared with depression group ($P < 0.05$). (5) The DAT group showed significant decreases of CBF in the right temporal region, both frontal regions, and both parietal regions as compared with depressive pseudodementia group ($P < 0.05$). **Limitations:** The small number of subjects may make it difficult to generalize from our results. Because decreased CBF in depressive pseudodementia is found while the subjects were depressed, we cannot tell whether it is a state marker or a trait marker. **Conclusions:** The depressive pseudodementia group showed decreased CBF in the temporo-parietal region, similar to that of the DAT group and different from that of the depression group. © 2002 Elsevier Science B.V. All rights reserved.

*Corresponding author. Tel.: + 82-2-760-3155; fax: + 82-2-744-7241.

E-mail address: mjcho@plaza.snu.ac.kr (M.J. Cho).

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1. Introduction

A considerable proportion of geriatric depression patients show a cognitive decline which is comparable to primary degenerative dementia in severity. However, this condition is differentiated from primary dementia by its reversibility (Emery, 1988). This reversible dementia syndrome of geriatric depression has been called depressive pseudodementia (Brodaty et al., 1993).

The general trend in current clinical practice is to consider depressive pseudodementia as part of geriatric depression, differentiate it from degenerative dementia, and the clinical treatment of depressive pseudodementia follows the rule of depression. The term ‘pseudo-’ in depressive pseudodementia implies that it is not ‘real’ dementia, and there is no organic pathology underlying cognitive impairment.

However, some recent reports contradict these conventional concepts. After a follow-up of 57 elderly patients with depression for 33.8 months, Alexopoulos et al. (1993) reported that irreversible dementia developed significantly more frequently in the depressed group with reversible dementia (43%) than in the group with depression alone (12%). From this result, Alexopoulos et al. (1993) suggested that geriatric depression with reversible dementia would be a clinical entity that includes a group of patients with early-stage dementing disorders. After comparing studies of depressive pseudodementia with different duration of follow-up, Emery and Oxman (1992) reported that the incidence of degenerative dementia was higher in the group with longer duration of follow-up. Pearlson et al. (1989) reported that depressive pseudodementia patients are differentiated from depression patients by the higher incidence of delusion, more severe anxiety and more severe atrophy in neuroimaging findings. In a study of 30 depressive patients with cognitive impairment, Kony and Stassen (1995) reported that a considerable number of patients with a significant reduction of depressive symptomatology at hospital discharge still suffered

from severe cognitive dysfunctions. From this result, they suggested that cognitive impairment in depressive patients encompasses two dichotomous entities: a core entity of long-persisting, treatment-resistant impairment and an entity of reversible impairment with a prompt onset of improvement.

Structural brain imaging studies using computed tomography (CT) or magnetic resonance imaging (MRI) suggested that geriatric depression had similar findings and possibly common pathophysiology with degenerative dementia. Previous CT or MRI studies reported that there were large differences between early-onset depression and late-onset depression, and the findings of late-onset depression were similar to those of degenerative dementia (Jacoby and Levy, 1980; Coffey et al., 1990; Alexopoulos et al., 1992). Coffey et al. (1993) suggested that late-onset depression might be a part of degenerative dementia with the possible abnormalities of frontal-subcortical circuit.

Functional imaging studies such as single photon emission computed tomography (SPECT) or positron emission tomography (PET) have shown contrasting patterns of abnormalities between the patients with DAT and patients with depression. In contrast to DAT patients who are characterized by a decreased blood flow or metabolism in temporal and parietal lobes (Hoffman et al., 1989; Mayberg, 1994), depressed patients show blood flow or metabolism abnormalities in dorsolateral prefrontal cortex (DLPFC; Baxter et al., 1989; Martinot et al., 1990). So, comparing the SPECT findings of depressive pseudodementia with those of depression without cognitive impairment and degenerative dementia will contribute to elucidating whether the state of depressive pseudodementia is functionally close either to depression or to degenerative dementia.

As far as we know, there has been only one functional imaging study performed with depressive pseudodementia patients. Dolan et al. (1992) performed a PET study which showed that depressive pseudodementia patients showed a decreased blood

flow in left anterior medial frontal lobe whereas non-cognitively impaired depressed patients showed decreased blood flow in left anterior lateral prefrontal areas. However, the depressive pseudodementia patients of their study had a mean age of 53.2 years, who were much younger than DAT patients in other studies (Benson et al., 1983; Curran et al., 1993; mean age (S.D.), 70 (10.6), 73.5 (11.6), respectively). We report a SPECT study on depressive pseudodementia patients whose mean age was older than 65.

In this study, we aimed to examine whether the depressive pseudodementia patients would show cerebral blood flow (CBF) abnormalities more similar to those of DAT patients or they would show CBF abnormalities more similar to those of depression patients without cognitive impairment.

2. Methods

2.1. Subjects and diagnostic procedures

The subjects consisted of seven patients with depressive pseudodementia, seven healthy comparison subjects, seven patients with depression free of cognitive impairment, and eleven patients with DAT.

The patient groups were selected from men and women over 55 years who visited the geriatric psychiatry clinic of Seoul National University Hospital. Depression patients underwent a routine clinical interview by a psychiatrist and a structured clinical interview using the Korean version of Diagnostic

Interview Schedule-III-R (DIS-III-R) by another psychiatrist, and were diagnosed according to DSM-III-R criteria of major depression (American Psychiatric Association, 1987). MMSE-K score 24 (Park and Kwon, 1989) was used as a reference point in differentiating depressed patients with and without cognitive impairment. DAT patients were diagnosed by the consensus diagnosis between two psychiatrists according to the DSM III-R criteria of DAT and the NINCDS-ADRDA criteria of probable Alzheimer's disease (McKhann et al., 1984). DAT patients who also met the diagnosis of depression by DIS-III-R were excluded from this study. Control subjects were selected from physically and psychologically healthy men and women over 55 years without history of mental illness. Control subjects were diagnosed and rated by the same methods.

Exclusion criteria applied to all subjects were a past or present history of neurological disorders, drug or alcohol abuse or any significant past medical illnesses including hypertension, diabetes mellitus, renal or endocrine disorders.

All subjects underwent physical examination including a neurological examination. They also underwent a complete blood count, liver function test, blood urea nitrogen, creatinine, thyroid function test, vitamin B₁₂, folate tests, to rule out medical disorders which can cause dementia. All were rated on Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) and the Korean version of Mini Mental State Exam (MMSE-K; Kwon and Park, 1989). The demographic profiles and scale scores of each group were suggested in Table 1.

Table 1
Demographic characteristics

Demographic variables	DAT ^a (n = 11) Mean ± S.D.	Depression ^b (n = 7) Mean ± S.D.	Pseudodementia ^c (n = 7) Mean ± S.D.	Control ^d (n = 7) Mean ± S.D.
Age (years)	69.8 ± 9.3	67.4 ± 8.3	65.3 ± 9.1	73.5 ± 6.4
Gender (M/F)	6/5	1/6	3/4	2/5
Mean score of HAM-D	10.1 ± 8.0	20.0 ± 4.4	21.3 ± 5.8	3.3 ± 2.0
Mean score of MMSE-K	19.0 ± 5.0	27.4 ± 2.4	21.6 ± 5.6	28.3 ± 1.5

^a Dementia of Alzheimer's type.

^b Depression without cognitive impairment.

^c Depressive pseudodementia.

^d Control: normal control.

2.2. Brain SPECT imaging

All subjects underwent ^{99m}Tc -HMPAO SPECT scan within 2 weeks of clinical evaluation. They were lying in supine position, with their eyes closed, in a quiet room with dimmed lights. SPECT scanings were performed for 15 min on each subject with intravenous injection of 30 mCi ^{99m}Tc HMPAO using triple head gamma camera (Prism 3000, Picker, spatial resolution: 12.5 mm). LEHR (low energy high resolution) parallel hole collimator was used. Transaxial images were reconstructed as 64×64 matrixes and filtered with Metz filter ($\chi = 1.5$ – 2.0). All images were corrected for attenuation by means of the method of Chang (1978). Finally, 40–50 images from the top of cerebral cortex to the bottom of cerebellum perpendicular to orbitomeatal line were reconstructed.

2.3. SPECT image analysis

All images were transferred to a UNIX workstation, Indigo 2 (Silicon Graphics, USA), where all data analyses were performed. Image data were analyzed using statistical parametric mapping 96 (SPM 96) implemented in MATLAB (Mathworks, USA). Statistical parametric mapping (SPM) of Friston et al. (1991) has some advantages over the traditional region of interest (ROI) method. SPECT image files were converted to ANALYZE format used in SPM.

Prior to statistical analysis, all images were normalized using linear transformation (translation, rotation and scaling) on the standard atlas to remove the intersubject anatomical variability. As a final preprocessing, all images were smoothed using Gaussian kernel with 16 mm full width half maximum (FWHM). The aim of smoothing is to increase signal-to-ratio and account for the variations in subtle anatomical structures. Scans were analyzed according to a model in which regional changes in CBF are assumed to be independent of global changes. Global changes in CBF across subjects were removed on a voxel-by-voxel basis using an analysis of covariance (ANCOVA). Significant differences of mean value of CBF between control group and each patient group were estimated at every voxel, using the t -statistic. In this way, the t value was computed on every voxel level. For the sake of easy interpretation, the t values were transformed to the standard Gaussian distribution (Z score). The level of significance was set to a threshold of $P < 0.05$. Significant voxels were projected in the form of SPM. Difference between depression patient group and depressive pseudodementia patient group was estimated in the same way.

2.4. Statistical analysis

Group differences in demographic variables involving continuous data (age, HAM-D, and MMSE-

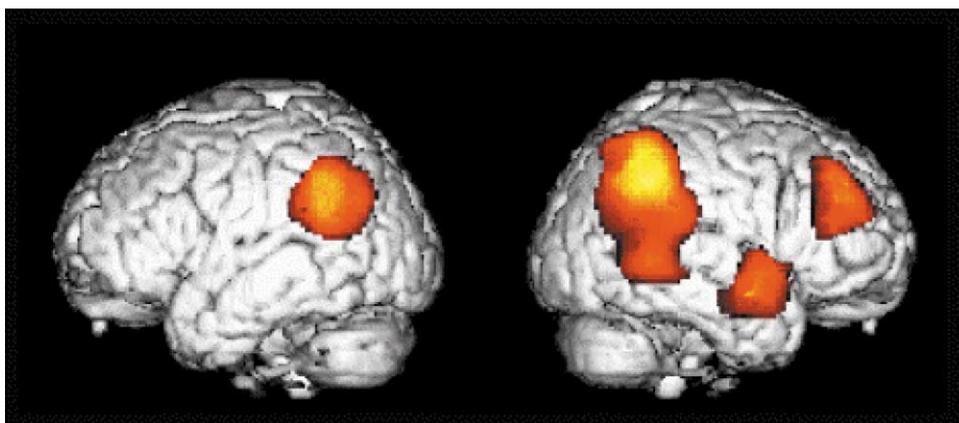


Fig. 1. DAT group showed significant decreases of CBF in the right frontal, right temporal and both parietal regions compared with controls ($P < 0.05$).

K) were computed using one-way ANOVA for continuous variables. Between-group comparison involving categorical data (gender) was assessed using Fischer's exact test.

3. Results

SPECT imaging analysis showed the following results; (1) the DAT group showed significant decreases of CBF in the right frontal, right temporal region and both parietal regions compared with controls (Fig. 1, $P < 0.05$). (2) The depression group

showed a significant decrease of CBF in the left frontal region compared with controls (Fig. 2, $P < 0.05$). (3) The depressive pseudodementia group showed significant decreases of CBF in both parietal regions compared with controls (Fig. 3, $P < 0.05$). (4) The depressive pseudodementia group showed significant decreases of CBF in the right temporal region and both parietal regions compared with depression group (Fig. 4, $P < 0.05$). (5) The DAT group showed significant decreases of CBF in the right temporal region, both frontal regions, and both parietal regions compared with the depressive pseudodementia group (Fig. 5, $P < 0.05$).

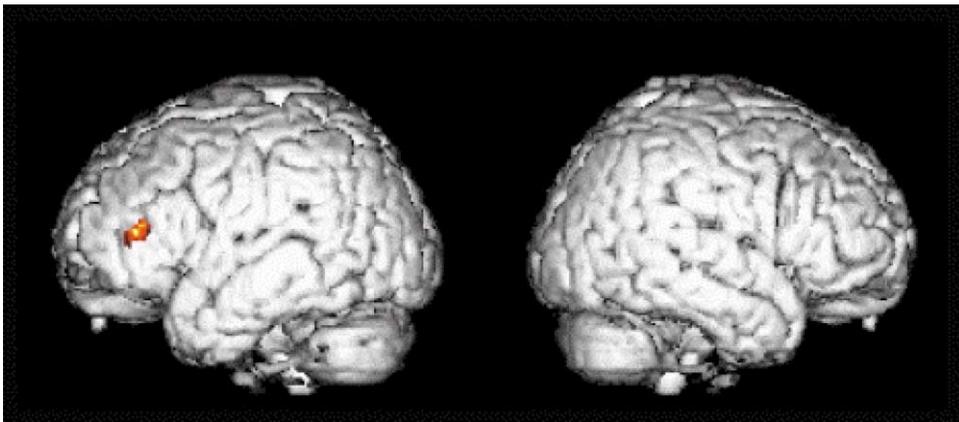


Fig. 2. Major depression group showed a significant decrease of CBF in the left frontal region compared with controls ($P < 0.05$).

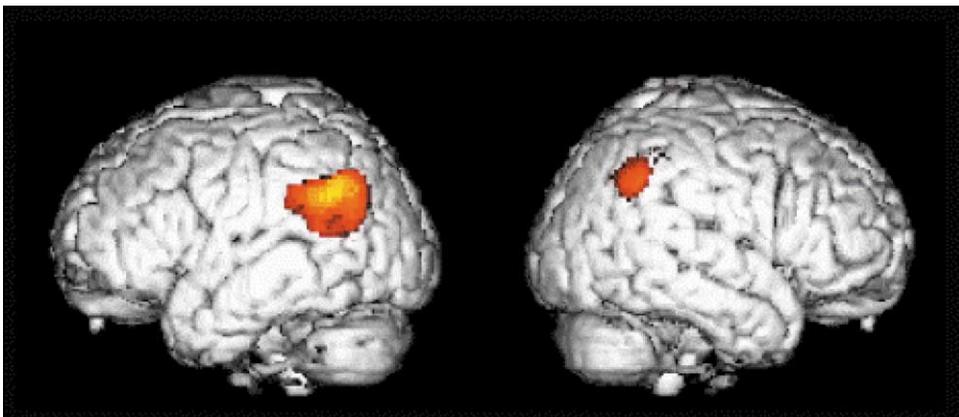


Fig. 3. Depressive pseudodementia group showed significant decreases of CBF in both parietal regions compared with controls ($P < 0.05$).

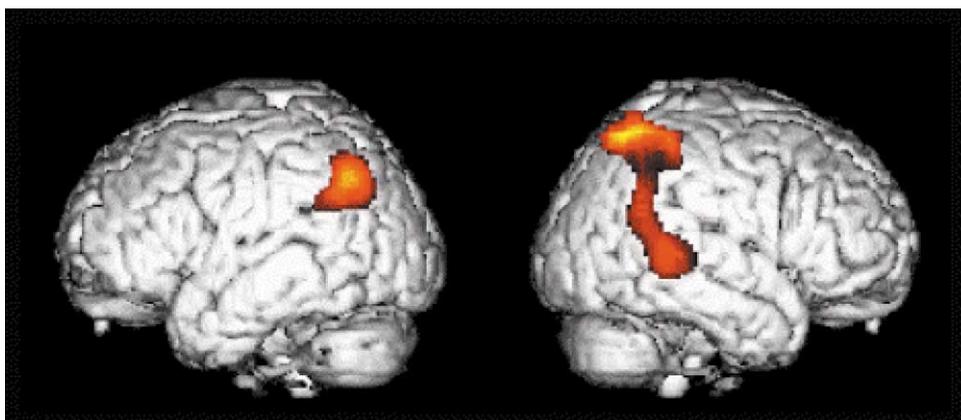


Fig. 4. Depressive pseudodementia group showed significant decreases of CBF in right temporal and both parietal regions compared with depression group ($P < 0.05$).

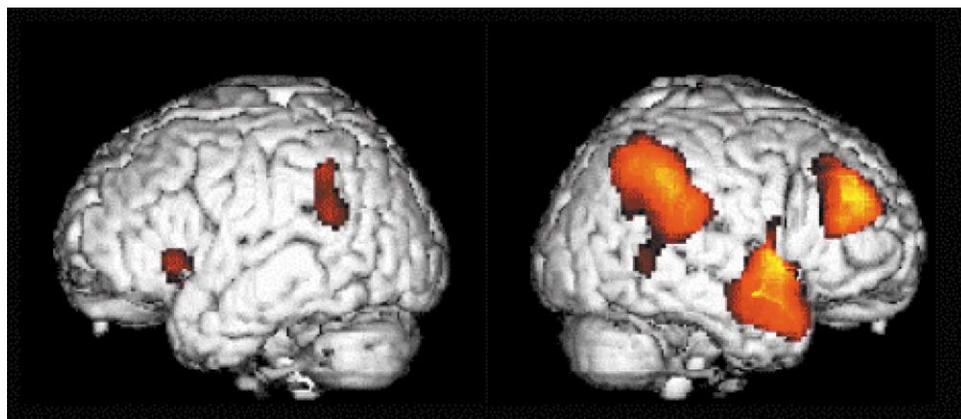


Fig. 5. DAT group showed significant decreases of CBF in the right temporal region, both frontal regions, and both parietal regions compared with depressive pseudodementia group ($P < 0.05$).

4. Discussion

The depressive pseudodementia group showed significant decreases of CBF compared with controls in both parietal regions. This pattern was similar to temporo-parietal decrease pattern of DAT, rather than the frontal decrease pattern of depression.

The DAT group showed significant decreases of CBF compared with controls in the right frontal, right temporal region and both parietal regions. Hoffman et al. (1989) and Mayberg (1994) reported decreased CBF in temporo-parietal area. There are studies that reported parietal CBF decrease in mild DAT patients. Haxby et al. (1986) reported that mild

DAT patients with MMSE scores over 22 showed decreased CBF in the parietal lobes, and that they showed normal blood flow in the temporal lobes. Duara et al. (1986) reported that mild DAT patients with MMSE scores over 21 showed decreased CBF in both superior parietal lobes, and that moderate DAT patients with MMSE scores between 10 and 21 showed decreased CBF in the right superior temporal lobes and left midfrontal gyrus in addition to both superior parietal lobes. Small et al. (1995) reported a lower glucose metabolism in the left parietal cortex in subjects with apoE e4 and at risk for DAT as compared with subjects at risk without apoE e4. This suggests that decreased CBF in the parietal lobe,

when found in subjects without dementia, is a potential marker for early DAT group or a subgroup of people with at risk for DAT. Our finding supports the suggestion of Alexopoulos et al. (1993) that depressive pseudodementia may include a group of patients with early-stage dementing disorders.

There are contradictory findings about frontal CBF decrease in DAT patients. Whereas Foster et al. (1984) reported that there were no frontal lobe abnormalities even in severe DAT patients, Duara et al. (1986) reported decreased blood flow in left midfrontal gyrus in moderate DAT patients.

Left frontal CBF decrease in depression group coincides with the previously cited results of Baxter et al. (1989) and Martinot et al. (1990). Although frontal hypometabolism or CBF decrease is a consistent finding in functional imaging studies of depression, many studies have reported not only decrease of CBF in frontal lobe but also decreases of CBF in temporal lobe (Curran et al., 1993; Mayberg et al., 1994), or temporo-parietal lobes (Sackeim et al., 1990; Upadhyaya et al., 1990; Austin et al., 1992). However, the majority of these studies were performed on a heterogeneous group, without subtyping the subjects according to cognitive function. In addition, when we compared the regional cerebral blood flow of depressive pseudodementia patients with that of depressed patients without cognitive impairment, we found that depressive pseudodementia group showed significant decreases of CBF compared with depression group in the right temporal region and both parietal regions, which were wider than the areas of Fig. 3. This suggests that the frontal hypometabolism, the most consistent finding in previous studies, was caused by the depression per se, and that the parietal hypometabolism in some of these studies was caused by either comorbid cognitive decline or depressive pseudodementia patients contained in the subjects of these studies.

The DAT group showed significant decreases of CBF compared with the depressive pseudodementia group in the right temporal region, both frontal regions, and both parietal regions. This result may be in line with the fact that cognitive impairment of DAT is more severe than that of depressive pseudodementia.

Previous functional imaging study by Dolan et al.

(1992) proposed left anterior medial prefrontal abnormality as the main abnormality of depressive pseudodementia patients. The difference between our result and that of Dolan et al. (1992) might have resulted from the difference in age of the study subjects and difference in scanning modalities.

In conclusion, our results indicate that subjects with depressive pseudodementia have cerebral blood flow patterns similar to the DAT group rather than the depression group.

There are some limitations in our study. First of all, because of small number of subjects, it is difficult to generalize from our results. Second, because the decreased CBF in depressive pseudodementia was found while the subjects were depressed, we cannot tell whether it is a state marker or a trait marker. Third, the 2-week interval between the SPECT scan and the clinical evaluation was relatively long since MMSE in subjects with depressive pseudodementia may change during that period.

Additional studies would be needed to show the replication of parietal blood flow decrease in larger number of subjects with pseudodementia. A study of the parietal blood flow abnormality before and after the recovery of depression is also needed.

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