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# The Association Between Distinct Delusional Ideations and Depressive Symptoms in Alzheimer's Disease: A Re-Analysis of CATIE-AD

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**Abstract**.
**Background:** Delusional ideations, one of neuropsychiatric symptoms (NPSs), are frequently shown in the long-term progression of Alzheimer's disease (AD), and comorbid with other NPSs including depression or agitation. Despite various types of delusional ideations, the comorbidity between each delusional ideation and depressive symptoms has not been discussed.
**Objective:** The present cross-sectional study is aimed at testing the hypothetical mechanism of comorbid pattern in AD.
**Methods:** Among 421 patients with AD, we analyzed the dataset of the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease to compare age, sex, racial type, Mini-Mental State Examination (MMSE) scores, and Neuropsychiatric Inventory (NPI) depression score of between the presence and absence of each delusional ideation (delusion of persecution, theft, jealousy, abandonment, phantom boarder, Capgras syndrome, misidentification of place, or television sign). Next, with the stratification based on MMSE score of $<$ or $>=$ 15 points, we further explored association between delusional ideation and depressive symptom that was found significances in the primary analysis
**Results:** Among eight subtypes of delusional ideations, depression score was higher in those with persecution delusion or Capgras syndrome. Moreover, the Capgras syndrome was associated with presence of depression in severer global cognitive impairment status.
**Conclusions:** As comorbid NPSs of delusional ideation in AD, depressive severity is associated with specific delusional subtype: persecution delusion and Capgras syndrome. Capgras syndrome may be attributable to severe cognitive impairment in addition to depressive symptom. The consideration of pathogenetic differences in the distinct delusional ideations may be helpful for clinicians to select the treatment strategy.

Keywords: Alzheimer's disease, delusion, depression, misidentification, paranoid

## INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive impairments, which progressively impairs activities of daily living (ADL).[1] In the long-term course of the disease progression, non-cognitive neuropsychiatric symptoms (NPSs) (e.g., delusional ideation, hallucination, agitation, depression, disinhibition, aberrant motor behavior, sleep problem, eating problem, and apathy) emerge in patients with AD. These NPSs increase the risk of excess mortality, and neuropsychiatric hospital stays, institutionalization, or healthcare utilization.[2,3] Among them, psychosis

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(delusional ideations or hallucinations), agitation, and depression tend to be more urgent or severe, leading to self-harm or violence, which may need pharmacological treatments.[2,3]

The effectiveness of antipsychotics for delusional ideations and hallucinations have been investigated in randomized control trials (RCTs) or meta-analyses since 1980 s.[4] However, the effectiveness of antipsychotics for delusional ideations has been obscure, and it has been noted that the antipsychotic intake increases mortality and adverse effects, leading to safety concerns in these 20 years.[4–6] Thus, the more careful usage of antipsychotics for delusional ideations in patients with dementia has been recommended in the practical coping strategy of clinicians, as a next engagement for non-pharmacological treatment-resistant NPSs.[2,7] To develop alternative strategy as replacement for pharmacological treatments, the investigation of relevant factors in delusional ideation and the elucidation of its mechanism is needed.[2,3]

Some cross-sectional studies have reported that female sex, non-Caucasian race, and lower cognitive function are as critical demographic factors of delusional ideation in AD, and that depressive symptom or agitation are representative comorbid affective symptom.[8–11] In a longitudinal study, there was a significant relationship between progressive cognitive impairments and the occurrences of delusion ideations in patients with AD,[12] while the relevance of depressive symptom has not been warranted. The inconclusive relationship of delusional ideation and depressive symptoms in AD may be influenced by distinct delusional subtypes and its complicated pathogenetic mechanism.[9–12]

The delusional ideations have conventionally been classified into main two subtypes: paranoid type (e.g., delusion of persecution, theft, jealousy, and abandonment) and misidentification type (e.g., phantom boarder, Capgras syndrome, misidentification of place, and television sign), and the two types have been associated with quantitative severity or characteristic kind (e.g., executive dysfunction, attention deficits) of cognitive impairments in AD.[10,13] Paranoid types in AD have been shown in the comparatively earlier phase of disease, and may be relevant to neurochemical and neuropathological changes in frontal-subcortical neurocircuits, which may cause a vulnerability of executive impairments.[10,14,15] In contrast, misidentification types in AD are associated with severer global cognitive impairment and progressive limbic neuropathological degenerative changes.[14,15] The effectiveness of antipsychotics for distinct delusional ideations in AD have been limited compared with other psychotic symptoms, and it proves that the delusional ideations in AD may be different from typical bizarre delusions like schizophrenia with interactive auditory hallucinations, in the neuropharmacological viewpoints relating to monoaminergic or cholinergic neuronal loss.[4,15–17] Moreover, the symptomatic mechanism of different delusional subtypes may be associated with aforementioned comorbid affective symptoms including depressive symptoms or agitation, which may cause treatment-resistant delusions in the course of treatment, in addition to neuropathological and neurocognitive viewpoints.[8,11,12,17] The coincident association between delusional ideations and depression may be facilitated by following two syndromic mechanisms, one is that delusional ideations are symptoms of psychotic depression, or the other is that depressive symptoms is secondary to the delusional ideations.[8] However, the association between each delusional subtype and depressive symptoms has not been investigated in AD, yet.

Herein, the aim of the present study was to examine the association between each delusional subtype and depressive symptoms in patients with AD and explore this relationship with the stratification based on cognitive status to elucidate such a hypothetical mechanism of ideational patterns and affective problems among various NPSs in AD.

## METHODS

### *The enrolled participants in the present study*

In the present study, the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer disease (CATIE-AD) (ClinicalTrials.gov identifier: NCT00015548) dataset has been used, and includes detailed background information concerning to patients with AD among clinic/research-based population.[16,17] The CATIE-AD study has enrolled ambulatory outpatients ($n = 421$) with psychosis or aggressive symptoms who needed administration of atypical antipsychotics (AAPs) as a pharmacological intervention to sustain their daily life at-home, not nursing home.[16] The pharmacological trial has been performed at the 45 sites in the United States to investigate the safety and effectiveness in AAPs for patients with AD.[16] All patients have been diagnosed as a people with dementia of the Alzheimer's type with using the Diagnostic and Statistical Manual

of Mental Disorders (DSM-4) or National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for possible or probable AD, which was defined based on the information of the past history, physical examination, and results of structural brain imaging.[16] All participants ($n = 421$) gave written informed consent to participate in the protocols approved by the local institutional review boards.[16] Concerning a reward of study entry, participants and their caregivers were performed all evaluation with no cost to maintain fairness of the study.[16]

*The evaluation of delusion subtypes and depressive severity*

Of enrolled subjects, the present study has used the only baseline data of CATIE-AD Phase 1, the severity of NPSs was evaluated with the Neuropsychiatric Inventory (NPI) composed of 12 sub-items at initial point.[16,18] Among the sub-items, we used the subquestion of delusions to investigate each presence of detailed eight subtypes (delusion of persecution, theft, jealousy, abandonment, phantom boarder, Capgras syndrome, misidentification of place, or television sign).[18] And, to evaluate the severity of depressive symptoms, we used the scores in depression/dysphoria (the scores range from 0 to 12) among the sub-item.[18]

*Other interactive demographic factors for each delusional subtype*

According to our previous study with using CATIE-AD dataset, the presence in psychotic symptoms including delusional ideations and hallucinations has been significantly associated with several demographic factors: female sex, non-Caucasian race, and lower Mini-Mental State Examination (MMSE) (scores range from 0 to 30) reflecting cognitive function.[9,19] In addition to the such 3 critical factors, age (years) of subjects was also used to know the orthodox interactive factors for each delusional subtype according to previous studies.[8–13]

*The screening for significant delusional ideation associated with depressive symptoms or other factors, in preliminary analyses*

In the preliminary analyses, to choose significant variables in above factors (age, sex, racial type, MMSE scores, and NPI depression scores), we compared the 5 variables between presence and absence of each delusional ideation (delusion of persecution, theft, jealousy, abandonment, phantom boarder, Capgras syndrome, misidentification of place, or television sign).

*The occurrence associations between each delusional ideation and depression presence or severer cognitive impairment in the secondary analysis*

The previous studies have reported that the degree in global cognitive impairments was significantly different between paranoid and misidentification in AD, and the latter was severer than former.[11–13] Moreover, the interaction of the neurocognitive reductions may influence the depressive symptoms, when both significant differences of depressive severity are shown between presence and absence in each delusion.[13] Therefore, if the significant association between any delusional ideation and depressive symptoms in the preliminary analyses is found, the re-examinations of associations between depression and delusional ideation with using stratification are needed to correct the interaction of cognitive reduction to occurrence of delusional ideations in the secondary analysis. The MMSE score has been used conventionally as a neuropsychological tool to evaluate the global cognitive impairments, and the cut off score was regarded as 23/24 points to differentiate between people with dementia and non-dementia.[11–13,19] A previous report also examined the scores in MMSE between paranoid and misidentification, and the mean score was respectively $16.9 \pm 4.9$ and $13.4 \pm 5.4$.[13] In the CATIE-AD trial, the mean score in enrolled subjects with AD was shown to be $15.0 \pm 5.8$ at baseline point.[17] Taken together, in the present study, it was defined as a subject with severer cognitive impairment when the MMSE score is $< 15$ points. Likewise, the presence of depression was defined when depression score in a subject is $> 0$ point, we examined the association between depression presence or severer cognitive impairment and delusional ideation, finally.

*Statistical analysis*

In the primary analyses, demographic factors and depression sub-scores of the NPI were compared based on the presence and absence in each delusional subtype. The *t*-tests were used when the factors were continuous variables (age year, baseline scores on the MMSE, and depression sub-scores),

whereas the $\chi^2$ tests with Yates' continuity correction were used to examine the independencies or associations strictly when the factors were categorical variables (sex and race). A Bonferroni-corrected $p$ value ($<0.05/8 = 0.00625$) was considered statistically significant for these analyses because of multiple comparisons of 8 delusional subtypes to avoid the type I errors. In a secondary analysis, when significant associations between delusional ideation and depression were found by the primary analyses, $\chi^2$ tests with Yates' continuity correction were used to test the independency of occurrences between presence of each delusional ideation (delusion of persecution and Capgras syndrome) and depression (presence was $>0$ point [$n = 251$], or absence was 0 point [$n = 163$]), after stratification into two cognitive status based on MMSE score ('severer cognitive impairment' was 0–14 points [$n = 190$], or 'milder cognitive impairment' was 15–30 points [$n = 220$]). A $p$ value ($< 0.05$) was considered statistically significant for the secondary analysis. The IBM SPSS Statistics Version 22.0 (Armonk, NY: IBM Corp.) was used for the statistical analyses.

## RESULTS

### *Patient characteristics*

Four hundred and twenty-one patients with AD (235 females [55.8%]; age = 77.9 ± 7.5 years; 331 Caucasians [79.0%]; MMSE score = 15.0 ± 5.8) were included in this analysis. Baseline demographic characteristics are summarized in the Table 1. The mean depression sub-score in NPI was 2.7 ± 3.2 ($n = 414$), and the 8 subtypes of delusional ideations were classified into two main subtypes (paranoid and misidentification) according to the sub-question of delusions, each paranoid type: delusion of persecution ($n = 107$; 25.8%); theft ($n = 229$; 55.2%); jealousy($n = 66$; 15.9%); abandonment ($n = 101$; 24.3%), and each misidentification type: phantom boarder ($n = 137$; 33.0%); Capgras syndrome ($n = 124$; 29.9%); misidentification of place ($n = 158$; $n = 38.1\%$); television sign ($n = 49$; 11.8%).

### *The comparisons of depression sub-score and demographic variables between presence and absence of each delusional subtype*

The depression sub-scores were higher in the following groups of delusional ideations: delusion of persecution ($p = 0.003$) and Capgras syndrome ($p = 0.003$), than absence groups (Table 2). The MMSE scores were lower in the following groups of delusional ideations: misidentification of place ($p < 0.001$) and television sign ($p < 0.001$) than absence groups (Table 2). The ratio of female was higher in presence group of place misidentification ($p = 0.002$); the age years was higher in presence group of place misidentification ($p = 0.003$), than absence (Table 2).

Table 1
Demographics of Patients with AD (n = 421)

| | |
|---|---|
| **Age, y ($n = 421$)** | 77.9 ± 7.5 (range: 51–103) |
| **Sex ($n = 421$)** | *n* (%) |
| female / male | 235 (55.8) /186 (44.2) |
| **MMSE total score ($n = 416$)** | 15.0 ± 5.8 (range: 4–29) |
| **Race ($n = 419$)** | n (%) |
| Caucasian / non-Caucasian | 331(79.0) / 88(21.0) |
| **Depression sub-score of NPI ($n = 414$)** | 2.4 ± 3.2 (range: 0–12) |
| **Paranoid type ($n = 415$)** | *n* (%) |
| ① Delusion of persecution | 107 (25.8) |
| ② Delusion of theft | 229 (55.2) |
| ③ Delusion of jealousy | 66 (15.9) |
| ④ Delusion of abandonment | 101 (24.3) |
| **Misidentification type ($n = 415$)** | *n* (%) |
| ⑤ Phantom boarder | 137 (33.0) |
| ⑥ Capgras syndrome | 124 (29.9) |
| ⑦ Misidentification of place | 158 (38.1) |
| ⑧ Television sign | 49 (11.8) |

AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory.

### *The occurrence association between depression and delusional ideation in each cognitive status based on stratification by MMSE score (over: 15–30 or under: 0–14 points)*

In the primary analyses, the delusion of persecution and Capgras syndrome were associated with depression (Table 2). We then divided the subjects into the severer cognitive impairment group and milder cognitive impairment one and examined the association between each delusion subtype (delusion of persecution and Capgras syndrome) and depression in each cognitive status. The mean MMSE score in enrolled subjects with AD was about 15 points (Table 1), which was regarded as a valid classification of cognitive status into the two groups. Delusion of persecution and depression was not significantly associated in either two cognitive status (Table 3A). On the other hand, Capgras syndrome was significantly associated with depression in the severer cognitive impairment group ($p = 0.033$) while not in the milder impairment group (Table 3B).

Table 2
The comparison of depression score of NPI subitems in each delusion subtype

| | Mean±SD or number (%) | | *t*-score or $\chi^2$ score | *p* |
|---|---|---|---|---|
| 1. *Delusion of persecution* | Yes ($n=107$) | No ($n=308$) | | |
| Age | 78.7 ± 7.9 | 77.6 ± 7.2 | 1.3 | 0.207 |
| Sex (female) | 60 (56.1%) | 170 (55.2%) | 0.0 | 0.964 |
| Race (Caucasian) | 87 (81.3%) | 241 (78.5%) | 0.2 | 0.633 |
| MMSE score | 13.8 ± 5.6 | 15.3 ± 5.8 | –2.4 | 0.019* |
| **Depression score** | **3.5 ± 3.6** | **2.4 ± 3.0** | **3.0** | **0.003**¶ |
| 2. *Delusion of theft* | Yes ($n=229$) | No ($n=186$) | | |
| Age | 78.5 ± 7.2 | 77.2 ± 7.6 | 1.8 | 0.083 |
| Sex (female) | 127 (55.5%) | 103 (55.4%) | 0.0 | 1.000 |
| Race (Caucasian) | 171 (75.0%) | 157 (84.4%) | 5.0 | 0.026* |
| MMSE score | 14.7 ± 5.5 | 15.3 ± 6.1 | –1.0 | 0.297 |
| Depression score | 2.9 ± 3.3 | 2.3 ± 3.1 | 2.0 | 0.047* |
| 3. *Delusion of jealousy* | Yes ($n=66$) | No ($n=349$) | | |
| Age | 77.6 ± 7.2 | 78.0 ± 7.5 | –0.4 | 0.700 |
| Sex (female) | 35 (53.0%) | 195 (55.9%) | 0.1 | 0.771 |
| Race (Caucasian) | 52 (78.8%) | 276 (79.3%) | 0.0 | 1.000 |
| MMSE score | 15.3 ± 5.3 | 14.9 ± 5.9 | 0.5 | 0.638 |
| Depression score | 3.4 ± 3.4 | 2.5 ± 3.2 | 2.2 | 0.031* |
| 4. *Delusion of abandonment* | Yes ($n=101$) | No ($n=314$) | | |
| Age | 78.1 ± 8.0 | 77.9 ± 7.2 | 0.3 | 0.796 |
| Sex (female) | 67 (66.3%) | 163 (51.9%) | 5.9 | 0.015* |
| Race (Caucasian) | 85 (85.0%) | 243 (77.4%) | 2.2 | 0.136 |
| MMSE score | 14.5 ± 5.6 | 15.1 ± 5.8 | –0.8 | 0.430 |
| Depression score | 3.5 ± 3.7 | 2.4 ± 3.0 | 2.7 | 0.007** |
| 5. *Phantom boarder* | Yes ($n=137$) | No ($n=278$) | | |
| Age | 77.5 ± 7.8 | 78.1 ± 7.2 | –0.8 | 0.429 |
| Sex (female) | 74 (54.0%) | 156 (56.1%) | 0.1 | 0.764 |
| Race (Caucasian) | 105 (76.6%) | 223 (80.5%) | 0.6 | 0.434 |
| MMSE score | 14.3 ± 5.4 | 15.3 ± 5.9 | –1.6 | 0.109 |
| Depression score | 2.7 ± 3.2 | 2.6 ± 3.3 | 0.3 | 0.781 |
| 6. *Capgras syndrome* | Yes ($n=124$) | No ($n=291$) | | |
| Age | 78.6 ± 6.8 | 77.6 ± 7.6 | 1.2 | 0.231 |
| Sex (female) | 76 (61.3%) | 154 (52.9%) | 2.1 | 0.144 |
| Race (Caucasian) | 101 (82.1%) | 227 (78.0%) | 0.7 | 0.419 |
| MMSE score | 13.8 ± 5.3 | 15.4 ± 5.9 | –2.6 | 0.011* |
| **Depression score** | **3.4 ± 3.6** | **2.3 ± 3.0** | **3.1** | **0.003**¶ |
| 7. *Misidentification of place* | Yes ($n=158$) | No ($n=257$) | | |
| **Age** | **79.3 ± 7.0** | **77.1 ± 7.5** | **3.0** | **0.003**¶ |
| **Sex (female)** | **103 (65.2%)** | **127 (49.4)** | **9.2** | **0.002**¶ |
| Race (Caucasian) | 126 (80.3%) | 202 (78.6%) | 0.1 | 0.781 |
| **MMSE score** | **13.5 ± 5.1** | **15.8 ± 6.0** | **–4.2** | $p<$**0.001**¶ |
| Depression score | 2.9 ± 3.6 | 2.5 ± 3.0 | 1.3 | 0.198 |
| 8. *Television sign* | Yes ($n=49$) | No ($n=366$) | | |
| Age | 77.1 ± 7.2 | 78.0 ± 7.4 | –0.9 | 0.392 |
| Sex (female) | 32 (65.3%) | 198 (54.1%) | 1.8 | 0.184 |
| Race (Caucasian) | 41 (83.7%) | 287 (78.6%) | 0.4 | 0.529 |
| **MMSE score** | **11.6 ± 4.8** | **15.4 ± 5.8** | **–4.4** | $p<$**0.001**¶ |
| Depression score | 2.5 ± 3.3 | 2.7 ± 3.2 | –0.5 | 0.641 |

Student or Welch's t-tests were used to compare continuous variables. $\chi^2$ tests with Yates' continuity correction were used to compare categorical variables. MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; ***$p<0.001$, **$p<0.01$, *$p<0.05$, ¶$p<0.00625$. Values in bold font are significant results at each Bonferroni correction.

Table 3A
The occurrence associations between delusion of persecution and depression in each cognitive status

| | Number (%) | | $\chi^2$ score | $p$ |
|---|---|---|---|---|
| **Milder cognitive impairment ($n = 220$)** | | | | |
| Delusion of persecution | Yes ($n = 50$) | No ($n = 170$) | | |
| Depression (presence) | 36 (72.0%) | 96 (56.5%) | 3.3 | 0.071 |
| **Severer cognitive impairment ($n = 190$)** | | | | |
| Delusion of persecution | Yes ($n = 56$) | No ($n = 134$) | | |
| Depression (presence) | 39 (69.6%) | 79 (59.0%) | 1.5 | 0.222 |

$\chi^2$ tests with Yates' continuity correction were used to compare categorical variables. MMSE, Mini-Mental State Examination; *$p < 0.05$.

Table 3B
The occurrence associations between Capgras syndrome and depression in each cognitive status

| | Number (%) | | $\chi^2$ score | $p$ |
|---|---|---|---|---|
| **Milder cognitive impairment ($n = 220$)** | | | | |
| Capgras syndrome | Yes ($n = 59$) | No ($n = 161$) | | |
| Depression (presence) | 39 (66.1%) | 93 (57.8%) | 0.9 | 0.336 |
| **Severer cognitive impairment ($n = 190$)** | | | | |
| Capgras syndrome | Yes ($n = 64$) | No ($n = 126$) | | |
| **Depression (presence)** | **47 (73.4%)** | **71 (56.3%)** | **4.6** | **0.033*** |

$\chi^2$ tests with Yates' continuity correction were used to compare categorical variables. MMSE, Mini-Mental State Examination; *$p < 0.05$. Values in bold font are a significant result.

## DISCUSSION

In the present study, the severer depressive symptoms were found in subjects with delusion of persecution and Capgras syndrome. In contrast, significant differences in MMSE scores were detected in subjects with two misidentification types (misidentification of place and television sign). Moreover, the association between Capgras syndrome and depression was shown in the much severer cognitive impairment group in particular.

Previous studies have reported association between depressive symptoms and delusions, but the associations have not been investigated in each delusional subtype, yet.[8–13] The association between cognitive status and delusional subtypes has been investigated previously, and subjects with misidentification type were much severer cognitive impairment than paranoid type.[12,13] In the present study, similar results were shown in two misidentification types (misidentification of place and television sign), which supports above previous studies. Among other demographics factors, age years and sex type (female) were also associated with misidentification of place in the present study, and with paranoid types more robustly in the previous studies.[20–23] The sex difference of delusion occurrence has been discussed in the previous studies, which have revealed the divergence of findings until the present.[9,20–23] The sex difference may be relevant to various psychosocial factors including the education durations, marital status, residence type, income status, and the kind of cohabitants, which causes statistical interactive effects for results.[9,20–23] Previously, Inamura et al. found the severity of delusions in only female people with mild AD was relevant to the status of global cognitive function reflecting MMSE scores and ADL in the comparison study after classifying into two sex groups.[23] In subjects with misidentification of place, the differences of age years and sex type were also shown, such results may be caused by older people linking to severer cognitive impairments including disorientation of place like a previous our study.[9]

In the present study, while delusion of persecution and Capgras syndrome were associated with depressive symptoms, two misidentification types were associated with severe cognitive impairments, which supports the three different pathogenetic hypothesis of paranoid, Capgras syndrome, and misidentification in the previous reviews.[14,15] In the comparison of MMSE scores between the pres-

ence and absence in persecution delusion, the mildly significant difference of MMSE scores was shown ($p < 0.05$) (Table 2). When the stratification based on cognitive impairment, the significant contribution of depression for persecution delusion was not detected (Table 3A). Thus, the persecution delusion in AD may be associated with distinct any cognitive domain including working memory, attention, recent memory, or visuospatial function like previous studies.[10,14,15] Capgras syndrome is conventionally defined as a delusional misidentification characterized by 'a belief that a known person is replaced by an imposter or unknown people'.[24] The occurrence in Capgras syndrome in AD was associated with depressive symptoms in especially much severer cognitive impairment (Table 3B). The result implicates that when occurrence of depressive symptoms in addition to severer global cognitive impairment accelerates the reduction of the known familiarity linking to identification of person as a result of so-called 'psychotic depression'.[24] Otherwise, the Capgras syndrome relevant to antecedent disorientation of person in the neurocognitive deterioration course may cause any confusional feeling related to the affective problems including anxiety or depressive symptoms as secondary results of severer cognitive impairments.[25] While the causal relations between depression and neurocognitive impairments are still controversial, the Capgras syndrome may be different from paranoids and other misidentification having more close relation to global cognitive impairments, from viewpoints of etiopathogenesis.[24–27] On the other hand, phantom boarder in AD was neither associated with depressive symptoms or severer cognitive impairment like a previous study, which implies the influence of unknown causative factors including psychosocial or neurobiological factors (Table 2).[28]

As viewpoints of neural basis of two delusional ideations, a previous report showed that eight delusional ideations of NPI sub-items in patients with AD were statistically classified into representative three groups based on principal component analysis, and investigated their neural correlates to regional cerebral blood flow (rCBF) by using single-photon emission computed tomography (SPECT) data.[29] In the study, a group including delusion of persecution was related to hypo-perfusion in the precuneus and hyper-perfusion in the insula and thalamus.[29] On other hand, Capgras syndrome in patients with AD was related to hypometabolism in posterior cingulate/precuneus cortex and dorsomedial prefrontal cortex in the positron emission tomography (PET) study.[30] The two research on brain metabolism in AD implies that the 'precuneus' is a most common brain region within default mode network relevant to self-reference, and its poor activity linking to impaired self-correction may be caused by functional alterations based on antecedent depressive symptoms or pessimistic feelings in patients with AD.[31,32] The depressive symptoms in the elderly people also associate with lower structural and functional integrity in a front-limbic network as another core connectivity region of delusional ideations, and may cause more refractory outcomes in the course of conventional pharmacological treatments (usage of antipsychotics), in comparison to schizophrenia.[2,4,17,31–33] Thus, such an assumption of comorbid neural network between delusional ideation and depressive symptom may highlight the possibility of neuroplasticity modified by neuromodulation including transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT) for treatment (usage of psychotropics or hospitalization in intensive high care unit for behavioral symptoms)-resistant or much harmful symptoms in the future.[34,35]

In the present study, there are following some limitations that: 1) the overlapped eight delusional ideations were not assessed by clustering or factorial analysis statistically, 2) the sample was not population -or community-based, and needed the pharmacological treatments, which may cause the sampling bias generally, 3) severer cognitive impairment was defined based on cut off score in 14/15 points of MMSE score to classify into only two groups, but the sample may need to be classified into three or four groups more detailed with referring to interquartile range,[36] 4) confounding effects by other affective symptoms (e.g., anxiety, irritability, agitation, and apathy) among NPI sub-items was not investigated, 5) the evaluation of depression was defined with using only NPI sub-item: depression/dysphoria scores range from 0 to 12 points, 6) the delusional ideations were classified into the limited eight types with using detailed sub-questions of NPI, but the present study did not examine other subtypes defined as conventional delusional ideations shown frequently in the elderly people: e.g., Fregoli syndrome, mirror sign, nurturing syndrome, reduplicative paramnesia, feeling of presence, intermetamorphosis, delusional parasitosis, and Cotard syndromes, 7) the specific biomarkers reflecting hallmark protein (amyloid-$\beta$ or tau) have not been

examined in the CATIE-AD dataset, and 8) diagnostic biomarkers reflecting neuropathological overlaps of other dementia in advanced stage of AD should be investigated in the future, because the characteristic misidentifications (Capgras syndrome, Phantom boarder, and television sign) often are shown in DLB also.[25–28,37] Thus, the present results should be viewed as preliminarily pilot findings, which warrant a further prospective clinical study to confirm our observations in the future studies.

In spite of above limitations, the present study investigated co-occurrence relationships between each delusional subtype and depression as common-usual affective symptoms with interactive effects of global cognitive status in subjects with AD. Traditional eight delusional subtypes in dementia have been often defined in the structured interview of NPI sub-items until now, however, the pathogenesis of each delusional ideations may be different, and may be influenced by various related factors. As a perspective of scope in the present study, the featured delusional ideations in the long-term course of AD may actually co-occur with other various NPS sub-symptoms including affective symptoms, diurnal rhythm problems, or autonomic nerve (neurovegetative aspects) related symptoms as comorbid symptoms relevant to its etiopathogenesis, which cause a necessity of re-consideration in symptomatic combination of each NPSs symptoms and re-constructure of traditional syndromic ideations as result. As a next step, future research is warranted to examine the response rate of AAPs for the distinct delusional types with each comorbid symptom including affective symptoms, diurnal rhythm problems, or autonomic nerve related symptoms, which is helpful for clinicians to predict the outcomes in the course of treatment for AD with NPSs. Further, discovery of such etiopathogenetic diversity from viewpoints of bio-psycho-sociology may contribute to novel personalized treatment strategy including non-pharmacological approach, pharmacological replacement including combination therapies with antidepressants or mood stabilizer, and neuromodulation approach (TMS or ECT) as third way.

## AUTHOR CONTRIBUTIONS

Tomoyuki Nagata (Conceptualization; Formal analysis; Investigation; Project administration; Writing – original draft); Shinichiro Nakajima (Conceptualization; Project administration; Supervision; Writing – review & editing); Shinsuke Kito (Supervision; Writing – review & editing); Shunichiro Shinagawa (Conceptualization; Project administration; Writing – review & editing).

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## CONFLICT OF INTEREST

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## DATA AVAILABILITY

In the present re-analysis study, the CATIE-AD (ClinicalTrials.gov identifier: NCT00015548) dataset has been used, and the version of the dataset used was one. The data used in the preparation of this article were obtained from the limited access datasets distributed from the CATIE-AD trial established by NIMH.

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