Differences in Brain Metabolism Associated with Agitation and Depression in Alzheimer’s Disease
阿兹海默病的激越行为和抑郁与脑代谢的相关性

CF Tsai, CW Hung, JF Lirng, SJ Wang, JL Fuh

蔡佳芬、洪嘉蔚、凌憬峰、王署君、傅中玲

Abstract

Objective: Agitation and depression are among the commonest behavioural and psychological symptoms exhibited by Alzheimer’s disease patients. However, their pathophysiology remains unclear. We therefore investigated the relationship between the brain metabolism in the posterior cingulate gyrus and the dorsolateral prefrontal cortex, and agitation and depression in patients diagnosed with Alzheimer’s disease.

Methods: We recruited 26 patients (14 women and 12 men) with a mean age of 75 years and probable Alzheimer’s disease. All patients completed the Mini-Mental State Examination (MMSE), the Geriatric Depression Scale–Short Form (GDS) assessment, and the Cohen-Mansfield Agitation Inventory (CMAI) in order to evaluate cognition, depression, and agitation, respectively. All subjects underwent magnetic resonance imaging and 1H-magnetic resonance spectroscopy of the brain. The ratios of N-acetylaspartate (NAA), choline (Cho), and myo-inositol (mI) to creatine (Cr) in the posterior cingulate gyrus and the dorsolateral prefrontal cortex were measured and compared with neuropsychological test results.

Results: The MMSE scores correlated positively with the NAA/Cr ratio in the left posterior cingulate gyrus ($r = 0.56; p = 0.001$). The CMAI scores correlated negatively with the NAA/Cr ratio in the left posterior cingulate gyrus ($r = -0.46; p = 0.02$). The GDS scores correlated positively with the Cho/Cr ratio in the left dorsolateral prefrontal cortex ($r = 0.59; p = 0.01$), and mI/Cr in both left ($r = 0.47; p = 0.03$) and right ($r = 0.47; p = 0.03$) cingulate gyri.

Conclusions: Agitation and depression levels correlated with different neurochemical metabolites in specific brain areas. We conclude that various neuropsychiatric symptoms might have separate pathophysiologies.

Key words: Alzheimer disease; Dementia; Depression; Magnetic resonance spectroscopy; Psychomotor agitation

摘要

目的：激越行为和抑郁是阿兹海默病（AD）患者最常见的行为及心理症状。然而，有关的病理生理学机制仍不是很清楚。因此，本研究旨在检视AD患者其激越行为和抑郁与后扣带回和背外侧前额叶皮层脑代谢之间的关系。

方法：纳入26名可能有AD的患者（14名女性和12名男性），他们平均年龄为75岁。所有患者均透过简易精神状态量表（MMSE）、老年抑鬱量表简表（GDS），以及Cohen-Mansfield激越行为量表（CMAI）分别评估他们的认知、抑郁和激越行为。他们也接受脂共振和1H-磁共振波谱检查。研究也量度和比较后扣带回和背外侧前额叶皮层内N-乙酰天门冬氨酸（NAA）、胆硷（Cho）和肌醇（Ml）各自跟肌酸（Cr）的比值。

结果：MMSE比分与左后扣带回的NAA/Cr比值呈正相关（$r = 0.56; p = 0.001$）。CMAI比分则与左后扣带回的NAA/Cr比值呈负相关（$r = -0.46; p = 0.02$）。GDS比分与左背外侧前额叶皮层的Cho/Cr比值（$r = 0.59; p = 0.01$），以及与左、右扣带回的MI/Cr比值（分别为$r = 0.47; p = 0.03$和$r = 0.47; p = 0.03$）均呈正相关。

结论：激越行为和抑郁水平跟大脑不同的特定区域呈相关，结论是各种神经系统症状均可能有各自的病理生理机制。

关键词：阿兹海默病、老年痴呆症、抑郁、磁共振波谱、激越行为
Introduction

The behavioural and psychological symptoms of dementia (BPSD) are common in patients diagnosed with Alzheimer’s disease (AD) and responsible for substantial suffering endured by patients and caregivers. Although numerous studies have used neuroimaging techniques to investigate the relationship between BPSD and regional cerebral dysfunctions, no definite conclusions have been reached. H-magnetic resonance spectroscopy (MRS) is a unique neuroimaging technique that enables measurement of several metabolites within a single examination. The metabolite N-acetylaspartate–to-creatine (NAA/Cr) ratio is consistently lower in the MRS findings of patients with AD than in those of cognitively normal elderly people. In contrast, the myo-inositol–to-Cr (mI/Cr) level is higher. Agitation and depression are among the most common BPSD in AD patients. Agitation occurs in 60% of patients, whereas depression affects up to 50% of them. Moreover, depression is a risk factor for dementia. Lesion and imaging studies have suggested that frontal lobe dysfunction, particularly in the dorsolateral prefrontal cortex (DLPFC), is pathophysiologicaly linked to primary and secondary depression. The findings from neuroimaging and pathological studies have also demonstrated frontal lobe involvement in AD patients who suffer from agitation. The severity of agitation and aggression in AD patients was associated with an excessive atrophy of the frontal, insular, amygdala, cingulate, and hippocampal regions. However, whether these findings are caused by the pathological changes in patients suffering from AD or by an independent event remains unknown. In this study, we employed 1H-MRS with the objective of determining the relationship between the regional changes of brain metabolites and BPSD in AD patients, by using the cingulate gyrus and the DLPFC as sites of interest.

Methods

Subjects

We recruited 26 patients diagnosed with AD (14 women and 12 men; mean ± standard deviation [SD] age, 75 ± 9.3 years) from the memory clinic at the Taipei Veterans General Hospital. Diagnostic evaluation included a clinical interview, physical and neurological examinations, routine blood tests, an electroencephalogram, and a brain magnetic resonance imaging (MRI). All patients met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria for probable AD. The patients with substantial medical, neurological, and psychiatric diseases, but who were diagnosed as being free from AD were excluded from the study. The study protocol was approved by the Institutional Review Board of the Taipei Veterans General Hospital. After a complete description of the study to the patients or their legal guardians, all subjects provided written informed consent.

Neuropsychological Assessment

Cognitive function was evaluated using the Mini-Mental State Examination (MMSE). The severity levels of agitation and depression were assessed using the Cohen-Mansfield Agitation Inventory (CMAI) and the Geriatric Depression Scale–Short Form (GDS), respectively.

Cohen-Mansfield Agitation Inventory

The CMAI is composed of 29 descriptions of behavioural problems. Each item is scored according to the frequency of occurrence, ranging from 1 (never happens) to 7 (occurs several times in an hour). Scores on the scale, therefore, range from 29 to 203, with the higher scores representing increased frequency or numerous types of agitative behavioural problems.

Geriatric Depression Scale–Short Form

The GDS is a commonly used instrument for the assessment of depression, and consists of 15 questions, requiring “yes” or “no” answers. A higher score indicates more severe depression.

Magnetic Resonance Spectroscopy Study

Magnetic resonance image scans and spectroscopy were performed using a 1.5-T MR Imaging system (Signa Excite, GE Medical systems, Milwaukee [WI], US) with a standard head coil. Three-dimensional fast spoiled gradient-recalled acquisition in the steady state images in the axial plane were obtained for localising the 1H-MRS voxel (echo time [TE] = 6.90 ms, repetition time [TR] = 400 ms, 18 x 24 cm² field of view, slice thickness = 1.5 mm). The 1H-MRS was acquired through a proton brain exam (PROBE), according to the manufacturer’s automated MRI protocol, using a point-resolved spectroscopy sequence localisation (TE = 35 ms, TR = 1500 ms). The metabolite spectra that were suppressed using water were obtained from the average of 64 PROBE acquisitions and the water signal from the average of 8 PROBE acquisitions. The 1H-MRS data were acquired from 2 voxels (2.1 x 2.7 x 2.0 cm³) placed bilaterally over the posterior cingulate gyrus and 2 voxels (2.0 x 2.0 x 2.0 cm³) placed bilaterally over the DLPFC (Fig 1). The metabolite concentrations were calculated using the water signal of the brain tissue as a reference. The peak areas for NAA at 2.02 parts per million (ppm), Cr at 3.03 ppm, choline (Cho) at 3.22 ppm, and mI at 3.56 ppm were calculated using the Funtool (GE XVi, Milwaukee [WI], US) [Fig 2]. The peak integral values were expressed relative to the Cr peak. The
metabolite intensity ratios (NAA/Cr, Cho/Cr, and mI/Cr) were automatically calculated at the end of each single-voxel PROBE acquisition for comparisons.

**Statistical Analysis**

To increase the reproducibility of the ¹H-MRS, the analysis was limited to measurements using a signal-to-noise ratio that exceeded 20. The sensitivity and specificity of the GDS in detecting clinical depression are low in people with MMSE scores of < 15, therefore patients with lower MMSE scores were excluded from the GDS and ¹H-MRS analyses. The relationships between the scores of the cognitive and neuropsychiatric scales and the metabolite ratios were assessed using Pearson correlation coefficients. A stepwise forward selection was used, and the criterion for entering adopted variables was $p < 0.05$. All tests were two-sided. A $p < 0.05$ was considered statistically significant.

**Results**

**Relationship between Cognitive and Neuropsychiatric Scales**

The mean (± SD) MMSE score of the subjects was $19 ± 5$ (range, 6-26). The mean CMAI and GDS scores were $38 ± 14$ (range, 29-82) and $5 ± 4$ (range, 0-14), respectively. Twenty-two patients had MMSE scores of $\geq 15$. Neither the MMSE nor the CMAI scores correlated with the GDS scores, and no correlation between MMSE and CMAI scores was observed (Table 1).

**Relationship between Brain Metabolites and Cognitive and Neuropsychiatric Scales**

As shown in Table 2, the MMSE scores correlated positively with the NAA/Cr ratio in the left posterior cingulate gyrus ($r = 0.56; p = 0.001$). The CMAI scores correlated negatively with the NAA/Cr ratio in the left posterior cingulate gyrus ($r = -0.46; p = 0.02$). The GDS scores correlated positively with mI/Cr over both left ($r = 0.47; p = 0.03$) and right cingulate gyri ($r = 0.47; p = 0.03$). The GDS scores also correlated positively with the Cho/Cr ratio in the left DLPFC ($r = 0.59; p = 0.01$) [Table 3]. The use of multivariate linear regressions after applying a forward stepwise selection (Table 4) showed that the MMSE scores (beta coefficient = 0.386; $p = 0.04$) and the CMAI scores (beta coefficient =
Magnetic Resonance Spectroscopy and Symptoms of Dementia

East Asian Arch Psychiatry 2013, Vol 23, No.3 89

Correlated negatively with the NAA/Cr ratio in the anterior cingulate gyrus, but not in the posterior cingulate gyrus. These distinct findings imply that different types of BPSD might be related to different brain areas.

Late-onset depression is often thought to differ from that at other stages of adulthood; it has been considered a risk factor, a prodrome phase, or a symptom of AD.20 Recently, numerous studies on biochemical abnormalities in late-life major depressive disorders have shown that mI/Cr and Cho/Cr ratios are significantly higher in the frontal white matter in those with major depression than in a comparison group.21-23 The mI is correlated with global cognitive function in late-onset depressed patients.18,21 The Cho peak in the 1H-MRS of the brain is thought to be composed of cytosolic glycerophosphocholine and phosphocholine, which are the products of membrane phosphatidylcholine breakdown, as well as precursors of Cho and acetylcholine synthesis. Most mI in the brain is present in the glial cells and an elevated level is thought to be associated with gliosis in AD.9 These studies imply that the frontal lobe,

Table 2. Relationship between the scores of cognitive and neuropsychiatric scales and brain metabolites in the posterior cingulate gyri.*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Left NAA/Cr</th>
<th>Left Cho/Cr</th>
<th>Left mI/Cr</th>
<th>Right NAA/Cr</th>
<th>Right Cho/Cr</th>
<th>Right mI/Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0.56†</td>
<td>0.30</td>
<td>-0.002</td>
<td>0.34</td>
<td>0.19</td>
<td>-0.19</td>
</tr>
<tr>
<td>CMAI</td>
<td>-0.46‡</td>
<td>0.18</td>
<td>0.19</td>
<td>-0.04</td>
<td>0.25</td>
<td>0.11</td>
</tr>
<tr>
<td>GDS</td>
<td>-0.01</td>
<td>0.39</td>
<td>0.47‡</td>
<td>0.23</td>
<td>0.26</td>
<td>0.47‡</td>
</tr>
</tbody>
</table>

Abbreviations: MMSE = Mini-Mental State Examination; CMAI = Cohen-Mansfield Agitation Inventory; GDS = Geriatric Depression Score–Short Form; NAA = N-acetylaspartate; Cr = creatine; Cho = choline; and mI = myo-inositol.

† p = 0.001.
‡ p < 0.05.

Table 3. Relationship between the scores of cognitive and neuropsychiatric scales and brain metabolites in the dorsolateral prefrontal cortex.*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Left NAA/Cr</th>
<th>Left Cho/Cr</th>
<th>Left mI/Cr</th>
<th>Right NAA/Cr</th>
<th>Right Cho/Cr</th>
<th>Right mI/Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0.35</td>
<td>-0.22</td>
<td>-0.31</td>
<td>0.28</td>
<td>0.07</td>
<td>-0.39</td>
</tr>
<tr>
<td>CMAI</td>
<td>-0.40</td>
<td>0.08</td>
<td>0.41</td>
<td>-0.26</td>
<td>0.20</td>
<td>0.27</td>
</tr>
<tr>
<td>GDS</td>
<td>0.01</td>
<td>0.59†</td>
<td>-0.17</td>
<td>-0.05</td>
<td>0.41</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Abbreviations: MMSE = Mini-Mental State Examination; CMAI = Cohen-Mansfield Agitation Inventory; GDS = Geriatric Depression Score–Short Form; NAA = N-acetylaspartate; Cr = creatine; Cho = choline; and mI = myo-inositol.

† p < 0.05.

Table 4. Linear regression coefficients and standard error (SE).

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>NAA/Cr of left cingulate gyrus (R² = 0.464)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β coefficient</td>
<td>SE</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.386</td>
</tr>
<tr>
<td>CMAI</td>
<td>-0.442</td>
</tr>
</tbody>
</table>

Abbreviations: MMSE = Mini-Mental State Examination; CMAI = Cohen-Mansfield Agitation Inventory; NAA = N-acetylaspartate; and Cr = creatine.

Discussion

We demonstrated a relationship between regional ratio levels of brain metabolites and the severity of cognitive impairment, agitation, and depression in patients with AD. Agitation scores were negatively correlated with the NAA/Cr ratio over the left posterior cingulate gyrus, whereas the depression scores were positively correlated with the Cho/Cr ratio over the left DLPFC and positively with the mI/Cr ratio over both cingulate gyri. The relationship persisted even after controlling for other factors, including age, gender, and education. In patients with mild cognitive impairment and AD, structural frontolimbic atrophy, including that affecting the posterior cingulate gyrus, has been shown to associate with agitation and aggression.14

Our findings, which consider the level of brain metabolism, provide additional support to these findings. Notably, NAA is related to the metabolic state and the activity of neurons and has been considered a marker of neuronal density because it is primarily localised in neurons. Evidence has shown that an NAA decrease in the posterior cingulate gyrus is involved in cognitive impairment in AD patients.4 Our results might suggest not only cognitive impairment, but also agitation in association with a reduced NAA/Cr ratio in the posterior cingulate area. However, the findings of another study2 revealed that the scores obtained during delusional thought and activity disturbance categories of the Behavioral Pathology in Alzheimer’s Disease Scale

-0.442; p = 0.02) were independently associated with the NAA/Cr ratio in the left posterior cingulate gyrus, even after adjusting for age, gender, and education.
particularly the DLPFC, is involved in depression. The cholinergic system might constitute the connection between AD and depression. However, this putative relationship requires further investigation. Depressive symptoms in AD had biochemical manifestations similar to those of late-life depression, suggesting that they might share a common pathway at the biochemical level. In addition, we did not find a correlation between cognition and BPSD, which is in contrast to the findings of others. Whereas certain studies have shown that psychosis is associated with more severe cognitive impairment, others have not. The patients in this study developed AD at an early stage, and led to conjectures that the severity of the BPSD might not be correlated with cognitive decline in early AD, whereas severe cognitive decline might be associated with an increased prevalence of psychosis.

One limitation of our study was that our results were obtained only from patients with dementia; comparison with healthy controls is required and must be interpreted with caution. Second, because only the effects of agitation and depression were studied, this study cannot provide a comprehensive assessment of behavioural symptoms. Third, using various neuropsychological testing instruments to evaluate the cognitive function and the severity of the BPSD in AD patients complicated the comparison with previous reports. Because the sample size used for the cross-sectional research design was small, the direction of causality cannot be inferred from our analysis. Our study only enrolled patients with AD, which might limit its application to other types of dementia. Beyond our region of interests, other cortical locations might also be related to BPSD in patients with AD. Further studies are required to elucidate these hypothetical relationships.

Conclusions

Our data emphasise the critical role of the posterior cingulate gyrus and the frontal cortex in the manifestations of agitation and depression in AD patients. In particular, neural degeneration in the frontal cortex and poor neuronal function, second messenger system dysfunction, or glial dysfunction in the post-cingulate region are considered to be associated with the BPSD in these patients. Different pathophysiological findings for agitation and depression in AD suggest that BPSD is a heterogeneous symptom in AD.

References