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# Cholinesterase inhibitors are compatible with psychosocial intervention for Alzheimer disease patients suggested by neuroimaging findings

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ABSTRACT

We previously reported that the frontal lobe was stimulated by psychosocial intervention for dementia patients, and that the parietal lobe was associated with logical judgment. We hypothesized that the combined therapeutic approach with symptomatic drug treatment can directly stimulate not only attention function but also judgment function indirectly to observing other participants' behaviors. Fifty-two patients with Alzheimer disease underwent the group reminiscence approach with reality orientation, as well as the donepezil treatment. The cerebral blood flow (CBF) was assessed with $^{99\,m}$Tc-ECD SPECT. Two analyses were performed: Analysis 1 was to compare Responders vs. Non-responders as shown by MMSE scores, whereas Analysis 2 was to compare Good vs. Poor reminders of the intervention content. We found that the CBF in the frontal lobe was significantly higher in Responders (vs. Non-responders). The CBF in the parietal lobe, especially the left side, was significantly higher in the Good reminders (vs. Poor reminders). The donepezil stimulated the areas similar to where the psychosocial intervention was previously found to be stimulated directly, thus the drug was thought to be compatible for psychosocial intervention. The parietal lobe was stimulated indirectly, suggesting that the indirect effect of the intervention may be based on logical judgment function.

## 1. Introduction

Since no curable drugs are available for patients with dementia, psychosocial intervention is thought to be necessarily for maintaining their quality of life (QOL). Among the interventions, the reminiscence approach is usually performed on the concept of "life review as a naturally occurring, universal mental process" (Butler, 1963). It consists of recollections and discussions of past events in one's life with the aid of materials that remind of one's memories, and is classified into two methods: individual reminiscence and group reminiscence approach (GRA) (Wang, 2007). Reality orientation (RO) (Taulbee and Holsom, 1966) is another intervention aimed for reinforced recognition of orientation. Some researchers reported (Baines et al., 1987; Goldwasser et al., 1987; Tadaka et al., 2000; Tadaka and Kanagawa, 2004; Akanuma et al., 2006) that the GRA with RO exhibited synergistic effects, and a combined approach has been widely practiced.

To reveal the direct effect of the GRA with RO without a symptomatic drug treatment using cholinesterase inhibitors (ChEI), such as donepezil, we previously recruited patients with vascular dementia (VaD) who were not indicated for the administration of such drugs. Using the fluorodeoxy glucose (FDG) method and positron emission tomography (PET), we noted (Akanuma et al., 2011) that the cerebral glucose metabolism in the anterior cingulate was increased after the GRA with RO with an association of their increased activities of social interaction (Fig. 1).

Regarding patients with Alzheimer's disease (AD), ChEI treatment is indicated for delaying progression of the disease (Homma et al., 2000), and a combination of psychosocial interventions remains the main therapeutic strategy (Onder et al., 2005; Meguro et al., 2009a). We previously reported (Meguro and Meguro, 2009b) a case with advanced AD who showed QOL improvement associated with an increase of cerebral glucose metabolism in the thalamus and medial frontal lobes after the combined approach of ChEI and psychosocial intervention. A further comparative study (Meguro et al., 2008) between the group with only drug treatment and that of combined therapy disclosed that the latter showed an increase in the QOL scores despite no change of the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) scores.

Several studies using single-photon emission CT (SPECT) have reported a positive clinical effect of ChEI on cerebral blood flow (CBF) for AD patients. The stimulated areas reported were the frontal, limbic, lower temporal lobes, and cingulate (Shimizu et al., 2006), the frontal and parietal lobes, and the basal ganglia (Yoshida et al., 2007), and the

SPM5 p<0.001, uncorrected
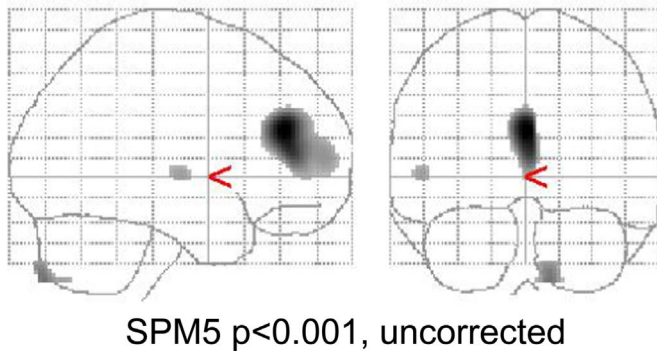
**Fig. 1. Direct effect of psychosocial intervention.** We previously noted that the cerebral glucose metabolism in the anterior cingulate cortex was increased after psychosocial intervention with an association of their increased activities of social interaction. (Akanuma et al. Psychiatry Res: Neuroimag 2011.).

left callosomarginal, bilateral pericallosal and basal ganglia (Tateno et al., 2008). Although the region activated by ChEI may be influenced by the participants, all might be related to the neuronal network associated with the frontal lobe. All studies also manifested that their psychomotor speed and attention function increased after the drug treatment. However, a combined effect of the ChEI and psychosocial intervention on CBF has not been fully investigated.

We hypothesized that the combined therapeutic approach of ChEI and the psychosocial intervention could stimulate not only psychomotor speed and attention function associated with general cognitive function, but also to improve judgment function related to reminding of the intervention content and to observing other participants' behaviors of the same psychosocial intervention group. The two possible neurological backgrounds were expected to be demonstrated using SPECT.

## 2. Methods

### 2.1. Patients

From among eighty-four consecutive outpatients with dementia during January 2015 to June 2015, fifty-two patients with AD with the moderate degree of dementia fulfilling the following inclusion and exclusion criteria were recruited at the memory clinic of the Tajiri SKIP center.

A study design was illustrated in Fig. 2.

Inclusion criteria:

1) Probable AD according to the diagnostic criteria for the NINCDS-ADRDA (McKhann et al., 1984).
2) The MMSE scores were 10 or more for understanding the instruction.
3) Undergoing treatment with 5 mg/day of donepezil.
4) Participating in the psychosocial interventions (see below).
5) Exclusion criteria:

1) Concomitant cerebrovascular diseases (CVD) as shown by magnetic resonance imaging (MRI)
2) Decreased daily activities that could prevent participation in the psychosocial interventions

For the ChEI, only donepezil was analyzed since we could only use donepezil from 1999 to 2010 in Japan.

Written informed consent was obtained from all patients and from family members according to the Declaration of Helsinki. The study protocol was approved by the Ethical Committees of Tohoku University School of Medicine and the Osaki-Tajiri SKIP Center.
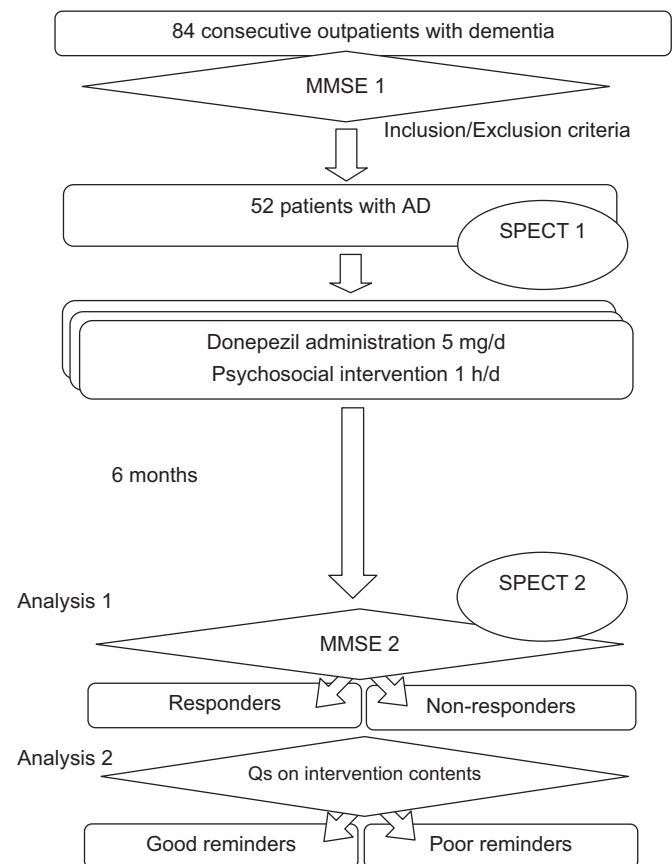


**Fig. 2. An illustration of the study design.** See the text. MMSE=Mini-Mental State Examination, AD=Alzheimer's disease, SPECT=single photon emission CT, Qs=questions.

### 2.2. Study design (see Fig. 2)

All participants were received SPECT with the $^{99m}$Tc-ethyl cysteinate dimer ($^{99m}$Tc- ECD, see below) twice, i.e., at the baseline and after the combined intervention of donepezil and psychosocial intervention for three months.

For **Analysis 1** (Responders vs. Non-responders by MMSE), the 52 participants were classified into two groups, i.e., Responders and Non-responders. Responders were defined as those exhibiting an increase of three points or greater (Kasuya et al., 2012) on the MMSE scores after donepezil treatment.

For **Analysis 2** (Good vs. poor reminder of the intervention content), the same 52 participants were re-classified into two groups, i.e., Good reminders and Poor reminders, independent of the previous groups for Analysis 1. We asked the patients to describe the content of the interventions; i.e., 1) the place, 2) the topics, and 3) the members. We also asked the patients how they observed the other members of the group: and 4) the reason why the members were joining the group and if and how they enjoyed the activities. Good reminders were operationally classified as they responded correctly to 3 or more questions, whereas the remaining patients were classified as Poor reminders.

SPM5 was used to compare voxel-based differences between the two groups for each analysis above. The uncorrected significance level was set at < 0.001.

### 2.3. Psychosocial intervention

There are four apparent seasons in Japan, and traditionally the following festivals are commonly performed in the community: *Oshogatsu* (New Year) in January, *Sestubun* (Bean Throwing Night) in February, *Hinamatsuri* (Girls' Festival) in March, *Hanami* (cherry