Table 2. FAB subtest scores (mean ± SD)

SUBTEST	MILD ATROPHY (MEAN ± SD)	MODERATE ATROPHY (MEAN ± SD)	SEVERE ATROPHY (MEAN ± SD)	*F SCORE*	*P* VALUE
Similarities	2.05 ± 0.86	1.76 ± 1.11	1.79 ± 1.04	0.602	0.55
Lexical fluency	1.81 ± 0.93	1.93 ± 0.99	1.79 ± 0.74	0.303	0.739
Motor series	2.52 ± 0.87	2.16 ± 0.98	2.26 ± 0.95	1.085	0.342
Conflicting instructions	2.86 ± 0.65	2.60 ± 0.84	2.68 ± 0.66	0.86	0.426
Go/no-go[a]	2.10 ± 0.94	1.67 ± 1.09	1.29 ± 1.16	3.795	**0.026***
Prehension behavior	2.57 ± 0.93	2.73 ± 0.65	2.79 ± 0.58	0.685	0.506

[a]Tukey post-hoc test: mild atrophy vs. severe atrophy: $P < 0.05$ ($P = 0.021$).
*$P < 0.05$.

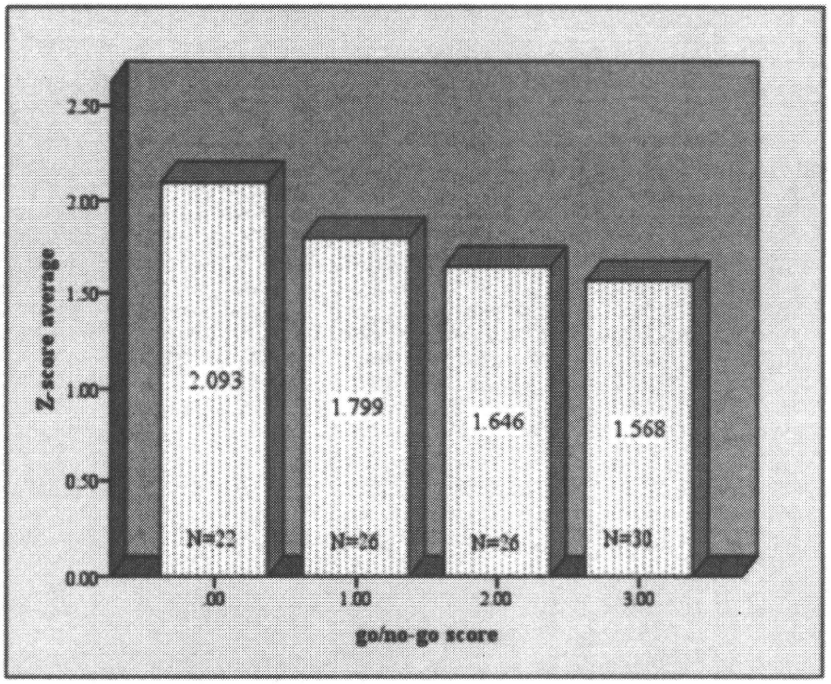

Figure 1. Bar graph showing the average Z-score for each go/no-go score. The go/no-go score and the Z-score were almost significantly correlated (r = −0.259, P = 0.008). The statistical analysis was performed using the Spearman correlation coefficient.

Association of go/no-go score with hippocampal atrophy and diagnosis (AD or A-MCI)

A generalized linear model examined (one variable) whether the severity of hippocampal atrophy (mild, moderate or severe) and diagnosis (AD or A-MCI) were associated with the go/no-go scores. As a result, we found that the go/no-go scores were significantly associated with the severity of hippocampal atrophy ($F = 3.312$; $df = 2$; $P = 0.041$) but not with the diagnosis ($F = 3.025$; $df = 1$; $P = 0.085$) (Table 3). A significant interaction between the severity of hippocampal atrophy and diagnosis ($F = 0.841$; $df = 2$; $P = 0.435$) was not detected.

Discussion

The present results suggested that atrophy of the entorhinal cortex and parahippocampal gyrus in patients with early AD or A-MCI might influence one of the executive functions – the go/no-go task of the FAB – independently of the diagnosis (A-MCI or early AD). In addition to memory cognitive impairments, the subjects with A-MCI also exhibited executive dysfunction, similar to previously reported patients with AD (Baudic *et al.*, 2006; Traykov *et al.*, 2007; Hanyu *et al.*, 2009). To eliminate the influence of atrophy or disruption in other cerebral areas and cognitive impairments (attention deficits and memory disorders) other than executive dysfunction during the course of

Table 3. Association between go/no-go, the severity of hippocampus atrophy and diagnosis

STATISTICAL COMPARISON	*df*	MEAN SQUARES	*F* SCORE	*P* VALUE
Hippocampus atrophy severity (range: 1–3)	2	3.771	3.312	**0.041***
Diagnosis (A-MCI or AD)	1	3.443	3.025	0.085
Hippocampus atrophy severity × diagnosis	2	0.957	0.841	0.435

Generalized linear models were used to investigate whether the severity of hippocampus atrophy and the diagnosis (A-MCI or AD) were associated with the go/no-go scores.
*$P < 0.05$; $R^2 = 0.133$.

the disease, this study enrolled AD patients with a comparatively early stage of dementia (CDR of 0.5 or 1.0 and MMSE score of 15 or more points) and mild atrophy in the total brain. As a result, we were able to compare subjects with a homogeneous condition, other than executive function, in each of the hippocampal atrophy groups. Moreover, a significant influential interaction between the severity of hippocampal atrophy and the diagnosis (A-MCI or AD) could not be shown.

The FAB consists of six main cognitive components that are reportedly associated with different anatomical frontal regions (Dubois *et al.*, 2000). Of the six components, the go/no-go is known as "inhibition control" – i.e. conduct which inhibits inappropriate responses and regulates impulsions (Drewe *et al.*, 1975; Dubois *et al.*, 2000). Some previous studies have reported that the go/no-go task was impaired in patients with an early stage of AD or A-MCI (Amieva *et al.*, 2004; Hanyu *et al*, 2009). Some authors have suggested that this phenomenon is associated with selective attention deficit and psychomotor speed decrement, rather than errors in inhibition control (Langley *et al.*, 1998; Amieva *et al.*, 2004). Collette *et al.* (2009) implied that impaired performance on suppression tasks in patients with AD might represent a directed forgetting among working memory processes, rather than a specific alteration of some inhibitory resolving system. In the present study, however, the go/no-go score was not correlated with the MMSE subtest score reflecting attention deficits and memory impairment. If another neuropsychological test reflecting attention deficits or memory impairment had been used in the present study, a significant association might have been observed, possibly supporting the findings and hypotheses of these previous reports.

In neuroimaging studies using functional MRI (fMRI) and enrolling healthy controls, the inhibition control task was associated with the activation of the right orbitofrontal cortex and the inferior frontal cortex (Chikazoe *et al.*, 2009). While some studies reported that patients with AD and MCI had impaired executive function since an early stage (Baudic *et al.*, 2006; Traykov *et al.*, 2007), several PET studies have shown that executive function is associated not only with the frontal lobe, but also with the tempo-parietal lobe or cingulate gyrus (Kessler *et al.*, 2000; Collette *et al.*, 2002). Moreover, in the neuroimaging studies researching inhibition tasks in patients with AD, some reports have presented a negative viewpoint in which the dysfunction is localized in the frontal lobe (Kessler *et al.*, 2000; Collette *et al.*, 2002). A previous neurophysiological study and a review also stated that the disruption of neural networks between the anterior and posterior cerebral areas, known as disconnection syndrome, during the initial stage of AD causes executive dysfunction, including inhibition control (Leuchter *et al.*, 1992; Delbeuck *et al.*, 2003).

From a neuropathological view, the entorhinal cortex includes both afferent and efferent linkages between the hippocampus and the neocortical areas, respectively, and plays conjunctive roles (Leuchter *et al.*, 1992; Gómez-Isla *et al.*, 1996; Mega *et al.*, 1997). Delbeuck *et al.* (2003) stated that the deposition of neurofibrillary tangles (NFTs) in the entorhinal cortex may disrupt neural networks and cause disconnection syndrome in patients with early-stage AD. Thus, whether such neuropathological backgrounds indirectly or directly influence executive dysfunctions, including the go/no-go task, should be investigated in the future.

The present study had some limitations. First, we used only the FAB to confirm the patients' executive dysfunction in this study. Many other neuropsychological test batteries for evaluating executive functions exist, and these test batteries might have provided useful information. However, the FAB is one of the easiest tests to administer and can be completed at bedside without requiring any tools or instruments; we believe that the simplicity of this test makes it a valuable tool. Although some previous studies have reported that hippocampal atrophy was associated with memory disorders, the present study did not observe such an association between hippocampal atrophy and the MMSE

subtest scores. Therefore, the Wechsler Memory Scale or the Rivermead Behavioral Memory Test might have been more useful, especially for the evaluation of memory disorder, rather than only using the MMSE subtests in the present study. Secondly, no associations between the other five FAB subscores and the severity of hippocampal atrophy was observed, although this result might represent a type II error because of the relatively small sample size in this study. Thirdly, the VSRAD system was developed to measure the total atrophy in the bilateral parahippocampal gyrus and entorhinal cortex. Ferreira *et al.* (2009) reported that in a VBM study enrolling subjects with A-MCI, the reduction in the gray matter volume of the left parahippocampal gyrus was the most consistent neuroanatomical biomarker for predicting the conversion from A-MCI to AD. Schroeter *et al.* (2009) indicated that the bilateral hippocampus volume was significantly reduced in patients with AD, compared with normal controls, in a quantitative meta-analysis study. Thus, the association between executive function and both or each hippocampal volume reduction should be investigated in the future. Finally, while memory disorder and executive dysfunction are frequently observed in patients with early AD, apraxia symptoms as focal signs should be quantitatively assessed, as subjects with severe ideational apraxia cannot carry out sequences of action to achieve an intended purpose in the correct order.

In conclusion, to investigate the cognitive significance of hippocampal atrophy (including the entorhinal cortex and parahippocampal gyrus) in patients with early AD, we focused on the impairment of executive functions as a non-memory function, which is a core symptom of early AD. Accordingly, we found a significant association between go/no-go (inhibition control) and hippocampal atrophy in the present study. An association between hippocampal volume and executive function has not been previously reported, and our results may contribute to a better understanding of the actual pathogenesis of this disease. Furthermore, elucidating the neural network connecting the posterior and anterior areas in patients with AD will be an important task in the future.

Conflict of interest

None.

Description of authors' roles

Tomoyuki Nagata designed this study, examined the subjects, and wrote the paper. Shunichiro Shinagawa gave advice, including the analysis method, and reviewed the paper. Yusuke Ochiai, Ryo Aoki and Hiroo Kasahara examined the patients with AD at the Jikei University School of Medicine, Kashiwa Hospital. Kazutaka Nukariya, and Kazuhiko Nakayama reviewed and commented on the final paper.

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