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Early Detection of Alzheimer's Disease with Cognitive Neuroscience Methods

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1. Introduction

Recently, the exploration of human brain function was examined in cognitive neuroscience and brain science. Along with the development of engineering technology, such as measurement technology, information technology, and artificial intelligence, we can record the brain activity on the timeframe of milliseconds or at the level of a single neuron to examine basic visual function or high level brain function (e.g., memory, language, or attention). In this chapter, we introduce a new research field that combines engineering and cognitive neuroscience, which was named "Neuromedical Engineering". We focused our research on five topics: 1. tactile perception and neurology (Yang et al., 2011a, 2011b, 2011c, 2010a, 2011; Wu et al., 2010a, 2011); 2. attention and cognitive brain function (Wu & Li, 2009) and multisensory integration (Li et al, 2009a, 2010a, 2010b; Touge et al., 2008; Wu & Kakura, 2010; Wu et al., 2009); 3. basic visual cognition (Li et al., 2009b; Wu et al., 2011; Yan et al., 2011); 4. language (Cai et al., 2007; Li et al., 2011a, 2011b; Wu et al., 2007); and 5. tactile perception and rehabilitation (Bai et al., 2010). Focusing on these five topics, we provide information on human brain function and neurology. Furthermore, using these cognitive and neurological methods, we are challenging the topic of "Early Detection of Alzheimer's Disease with Cognitive Neuroscience Methods".

The earliest symptoms of Alzheimer's disease (AD) involves learning, memory or planning problems. Currently, no medical tests are available to diagnose AD conclusively pre-mortem. However, several studies have used cognitive tasks (i.e., visuospatial tasks and language tasks) to discover preclinical cognitive markers of AD. These studies demonstrated that the cognitive deficits of AD can possibly be detected during a preclinical period that spans several years. In addition, numerous neuropathological, electrophysiological and neuroimaging studies support the hypothesis that cognitive deficits in AD are related to a possible disconnection between cortical areas. In this chapter, we describe current studies and possible future experiments on the early diagnosis method using cognitive and functional imaging testing to help with the clinical diagnosis of AD.

People with AD die an average of four to six years after diagnosis, but the duration of the disease can vary from three to 20 years. As shown in Fig. 1, the rate of cognitive decline in patients with AD was faster than healthy subjects after a specific point (before diagnosis). This specific point may be detectable using memory and planning tasks, such as visuospatial and language tasks. Recent studies have demonstrated that the cognitive deficits of AD can be detected using some simplex cognitive tests.

Previous studies have suggested that both amyloid plaques and neurofibrillary tangles are clearly visible in AD brains using microscopy. The plaques and tangles spread through the cortex in a predictable pattern as AD progresses (Fig. 2). First, during the earliest AD stage, the atrophy of brain cortices occurs in the hippocampus and the surrounding areas, and the changes may begin 20 years or more before diagnosis. Second, during the mild to moderate stages, the damage to the brain cortices is found in the temporal and parietal lobes and parts of the frontal cortex and cingulate gyrus. Finally, during the advanced AD stage, the degeneration of atrophy is found in the whole brain.

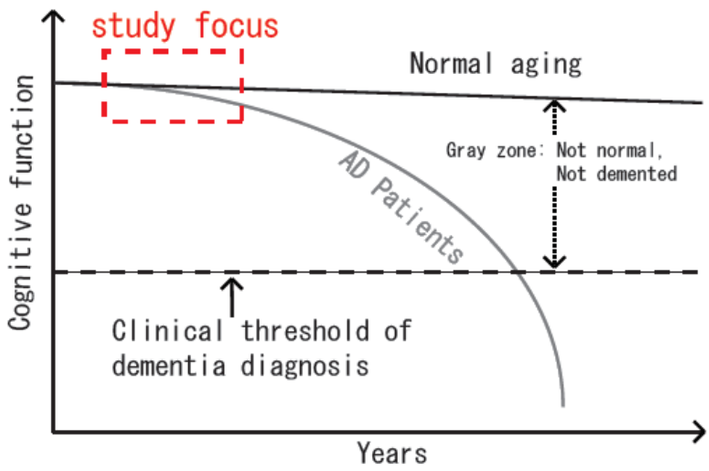

Fig. 1. The change of cognitive function deficiency model of aging healthy individuals and patients with AD.

Because the damage to the brain cortices occurs in the hippocampus, the early symptoms are mild memory loss. The first symptoms are often mistaken as related to aging or stress, but these early cognitive deficits can also be symptomatic of the early stages of AD and detected using long-term cognitive tests.

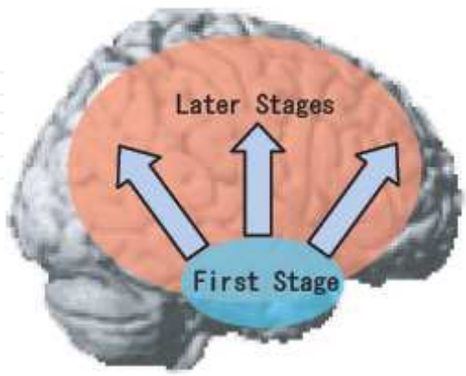

Fig. 2. The damaged cortex areas of AD patients during different stages.

Several studies have attempted to identify the preclinical cognitive markers of AD. Bäckman and Small (2007) used four episodic memory tasks on old non-dementia and incident AD subjects to investigate the cognitive deficit changes over three years. These tasks consisted of

free recall of rapidly presented random words, free recall of slowly presented random words, free recall of organisable words and cued recall of organisable words. The key finding from this study suggested that although the non-dementia subjects slightly declined across the three year retest interval, the incident AD subjects showed a significant performance deficit at baseline, which was further exacerbated long-term. These findings suggest that the time of AD diagnosis is characterised by a significant decline of episodic memory. In addition, this study also indicated that a combination of global and specific cognitive measures may optimise the identification of individuals in a preclinical phase of AD.

In addition, numerous neuropathological and neuroimaging studies have suggested that the cognitive deficits in AD were related to a possible disconnection between cortical areas. The tactile and visual objects cognition are the major manual learning and memory skills of humans, which also require extensive connections between cortical areas. Thus, preclinical alterations in AD are not restricted to language tasks. There are many studies that have attempted to find cognitive markers of AD using visual, auditory or tactile tasks. This review suggested that the preclinical cognitive deficit markers of incident AD may be detectable using a combination of multisensory cognitive or functional MRI tasks.

In this chapter, we first introduce a normal study on visual and auditory orienting attention using functional magnetic resonance imaging (fMRI). Secondly, a unique tactile angle discrimination experiment was introduced, which found significant behavioural cognitive differences between normal aging and dementia.

2. Pilot fMRI study on spatial and temporal attention cognition of normal, young subjects

2.1 Introduction

The human brain is a highly efficient information processing system capable of handling a large amount of information rapidly and simultaneously. If we were able to elucidate the sophisticated mechanisms of the brain accurately, we could construct flexible, efficient, humanlike artificial systems. We would also have the capacity to assess the most relevant ways to present information and in the most appropriate manner.

Previously, we studied the human visual and auditory systems, which convey almost all external information, with an emphasis on the parallel processing of visual and auditory data. In human information processing systems, attention plays an important role in selecting and integrating information. Previous studies on attention have proposed various psychological models, which are supported by a variety of psychological and physiological evidence. The neuronal substrate of the human attention system has also been investigated using positron emission tomography (PET) and fMRI to examine visual and auditory attention in humans using audiovisual stimuli. However, the common and unique networks used by the visual and auditory attention systems remains poorly understood. Furthermore, attention to time has not been studied sufficiently compared to space, and little research has compared the differences between the visual and auditory systems regarding spatial and temporal attention.

In this study, we analysed spatial and temporal attention using both visual and auditory stimuli. To evaluate these processes behaviourally, we conducted psychological experiments where we measured the reaction times (RTs) for each task. To reveal the neuronal networks related to these attention systems, we measured the haemodynamics using fMRI.

2.2 Method

2.2.1 Subjects

The subjects were 16 healthy, right-handed students aged 21–32 years. Informed consent was obtained from each participant following a detailed explanation of the study. During fMRI scanning, visual and auditory stimuli were generated on a personal computer and presented to the subjects via a projector-screen–mirror system and headphones, respectively.

2.2.2 Experimental stimuli

The visual stimulus consisted of a target ("X") with a diameter of 1° eccentricity that was shown for 50 ms, 7° to the right or left of the central point on a screen located 130 cm in front of the subjects. The auditory stimulus was the sound of a 1,000 Hz sine wave presented to either ear for 50 ms. Visual and auditory experiments included space tasks (S), time tasks (T), and control tasks (N). The tasks were designed in a factorial format and are shown in Table 1.

	Modality	
Task	Visual	Auditory
spatial	VS	AS
temporal	VT	AT
neutral	VN	AN

Table 1. Experimental tasks

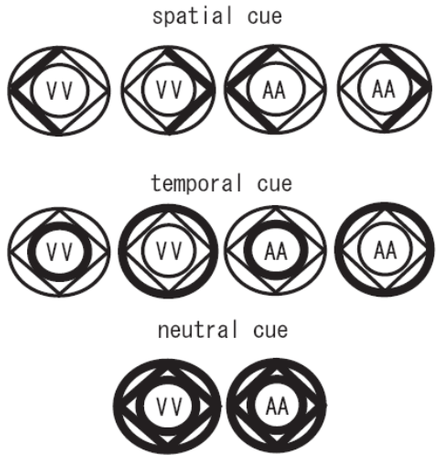

Fig. 3. Central cues used in the experimental task. The spatial cue was used in the spatial attention tasks. For the stimulus, the right or left half of the cube was lit to give the subjects information on the target location (right or left). The temporal cue was used in the temporal attention tasks. When the target came within a short cue–target interval, the inside circle was lit; and when it came after a long cue–target interval, the outside circle was lit. The neutral cue was used in the control task and gave neither spatial nor temporal information. A double 'V' in the centre of the cue indicated a visual experiment, whereas a double 'A' indicated an auditory target.

Cue stimuli (shown in fig. 3) were used to direct the subjects' attention to a particular target location or onset time. The neutral cue provided neither spatial nor temporal information; the spatial (space) cue directed the subjects' attention to the left or right; and the temporal (time) cue directed their attention to a short or long stimulus onset time. The flow chart of one trial is shown in Fig. 4. The time from the end of stimulus presentation to the onset of the next stimulus was defined as the interval of the stimuli (IOS) and was either 2,200 or 3,700 ms. We recorded the RT, the time from the presentation of a stimulus to a response indicated by a reaction key. The subjects responded to a right stimulus using the middle finger of their right hand and to a left stimulus with the forefinger of their right hand. The subjects performed 60 trials under each condition.

2.2.3 fMRI scanning

We used a Philips 1.5 Tesla Magnetom Vision whole-body MRI system to measure the brain activation using a head coil. The imaging area consisted of 32 functional gradient-echo planar imaging (EPI) axial slices (voxel size 3x3x4 mm^3, TR=3,000 ms, TE=50 ms, FA=90°, 64x64 matrix) that were used to obtain T2*-weighted fMRI images in the axial plane. The EPI imaged the entire cortex. For each task, we obtained 124 functional volumes. Before the EPI scan, a T2-weighted volume was acquired for anatomical alignment (TR=3,500 ms, TE=100 ms, FA=90°, 256x256 matrix, voxel size=0.75x0.75x4 mm^3). The T2 image acquisition used the same slices as the functional image acquisition.

2.2.4 Data analysis

Reaction times were used as the behavioural data. The RT data during the fMRI experiment were analysed using repeated measures analysis of variance (ANOVA; SPSS 12.0j for Windows). For each task, 60 RTs were acquired from each subject. We used the average of the RT data for the ANOVA, except for error trials (all subjects reacted with an accuracy above 90%). Therefore, we had 16 RT data for each task. Six tasks were presented in this experiment, and we compared the visual and auditory tasks separately. Between the modalities (visual and auditory), we compared VS and AS, VT and AT, and VN and AN.

For the functional images, we used MRIcro to change the DICOM files into MRIimg and MRIhdr files. In each task, the functional images of the first four volumes were not used for the data analysis. The DICOM files from the 5th through 124th scan were exported as MRIima and MRIhdr files. In addition, the DICOM files for the T2 images were exported as MRIimg and MRIhdr files.

The functional images were analysed using statistical parametric mapping (SPM5, Wellcome Department of Cognitive Neurology, London, UK). The functional images from each task were realigned using the first scan as a reference. The T2-weighted anatomical images were co-registered to the first scan in the functional images. Then, the co-registered T2-weighted anatomical images were normalised to standard T2 template images as defined by the Montreal Neurological Institute. Finally, these spatially normalised functional images were smoothed using an isotopic Gaussian kernel of 8 mm.

Statistical analyses identified the brain areas shared by visual (VS, VT) and auditory (AS, AT) attention and the brain areas that were selectively engaged by each task. To eliminate the brain activation caused by finger motion, we told the subjects to click the reaction key ten times during every rest. As a control task, we used VN for the visual attention task and AN for the auditory attention task.

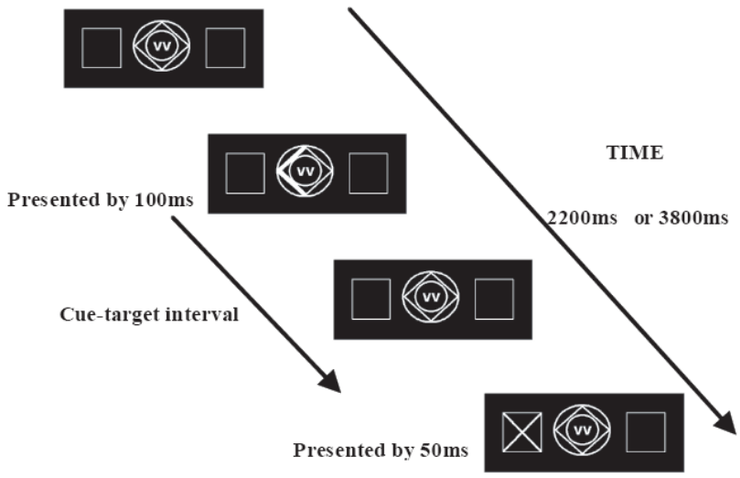

Fig. 4. Flow of a trial. The visual spatial cue indicated spatial information but provided no information about the cue–target interval. The cue was lit for 100 ms, and after the cue–target interval (300 or 1,800 ms), the target was illuminated for 50 ms.

Task	Mean reaction time (ms)
VS	364 (72.9)
VT	373 (58.6)
VN	390 (62.5)
AS	394 (82.4)
AT	448 (93.1)
AN	460 (86.2)

Table 2. Reaction time during each task (±SD)

2.3 Results

2.3.1 Behavioural data

Behavioural data were derived from the performance during the fMRI experiment. The reaction time for each task (Table 2) was computed from the data for the 16 subjects (the average of 16×55=880 trials).

2.3.2 fMRI data

From the imaging results comparing the visual tasks with the other tasks, all of the visual tasks activated the bilateral visual association cortex (BA18/19, Brodmann area). In VN, significant activation occurred only in the visual association cortex (BA18/19). From the imaging results comparing the auditory tasks with the other tasks, all of the auditory tasks activated the bilateral visual association cortex (BA18/19) because in the auditory tasks, the cues were visual as they were in the visual tasks. In addition, all of the auditory tasks activated the bilateral primary and auditory association cortex (BA41/42). In AN, significant activation occurred only in BA18/19/41/42. Therefore, as a baseline, we used VN for the visual tasks and AN for the auditory tasks.

This study focused on visual spatial attention, visual temporal attention, auditory spatial attention, and auditory temporal attention. Fig. 3 compares the activation in VS–VN, VT–VN, AS–AN, and AT–AN.

VS–VN

The areas of significant activation are shown in Fig. 5, and the right frontal cortex had more activations than the left. In the parietal cortex, BA7/40 was activated bilaterally, and the visual cortex had more activations on the left.

VT–VN

In this comparison, significant activation occurred only in the bilateral parietal cortex. In a previous study (Coull & Nobre, 1998), the medial premotor (BA6) cortex had significant activation bilaterally when the visual temporal task was compared to baseline.

AS–AN

More activation occurred in the left premotor (BA6) and left parietal (BA40) cortices.

AT–AN

Right STG was observed in this comparison.

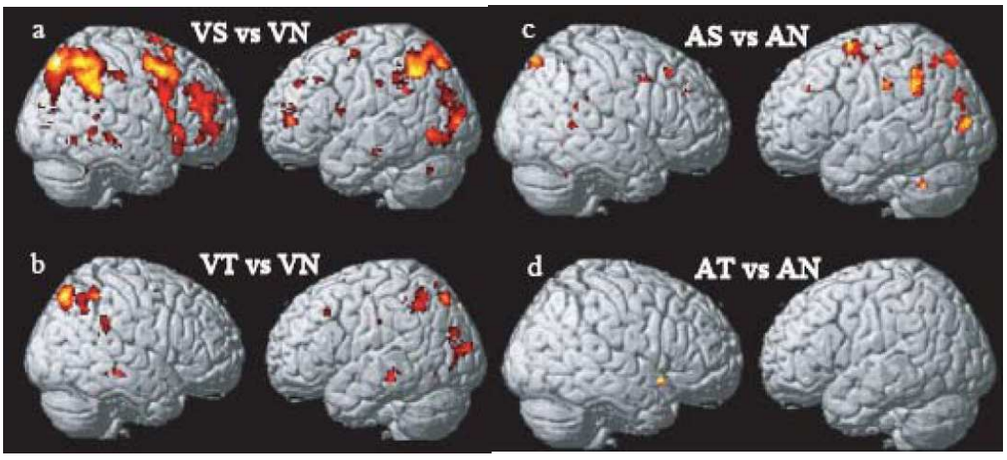

Fig. 5. Activations in visual attention and auditory attention (p=0.001, voxel=0). Left sides are right hemispheres in a-b, respectively.

We used SPSS for the paired t-test. The comparison of RTs across visual tasks showed a significant difference between VN and VS ($t(15)=2.53$, $p<0.05$) and between VN and VT ($t(15)=2.82$, $p<0.05$). AS and AT ($t(15)=4.86$, $p<0.001$) and AN and AS ($t(15)=6.19$, $p<0.001$) differed significantly, whereas AN and AT did not.

2.4 Discussion

2.4.1 Baseline: At rest or during the neutral task

A previous study (Coull & Nobre, 1998) used the resting state as the baseline to be consistent with previous reports using visual fixation controls (Corbetta et al., 1993). In addition, the neutral condition engages attention and orients attention between two spatial locations and two temporal intervals.

In this study, we focused on the activation without finger movement by asking the subjects to click the reaction key ten times during rest. We compared the activation in each task with the resting state. With the exception of the visual and auditory cortices, no significant activation occurred in the N task. Therefore, we used the N task as the baseline to examine

the activation that resulted from spatial or temporal cues. The activation in VS–VN in the frontal (BA4/6/47) and parietal (BA7/40) cortices was similar to previous studies (Coull & Nobre, 1998; Nobre et al., 2000). The VT–VN revealed bilateral activation in the parietal cortex (BA7) (Coull et al., 2000).

The right hemisphere bias for spatial orientation in this study was consistent with a previous report (Coull & Nobre, 1998). Therefore, we conclude that visual orienting attention uses a frontal–parietal neutral network for visual spatial orienting attention but uses the parietal cortex for visual temporal attention.

2.4.2 The cue used in the auditory orienting attention task

We used a visual cue in the auditory orienting attention tasks, whereas no cue was used in previous studies (Zatorre et al., 1999; Degerman et al., 2006). When comparing the activation in those studies, we found common areas in both the parietal (BA7) and frontal (BA6) cortices. In this study, the prefrontal cortex showed less activation than in previous studies (Zatorre et al., 1999; Degerman et al., 2006), and when examining the RT in the auditory orienting attention task that revealed a slow reaction, we noted that the magnetic resonance machine made a sound that drew the subjects' attention. Therefore, the AT–AN showed no activation for the same problem. One study (Schubotz et al., 2003) mentioned an auditory temporal attention task, with activation of the inferior temporal gyrus (BA20) and fusiform gyrus (BA37). In that study, only one temporal interval was used, which was different than this study.

Some studies (Loose et al., 2003; Johnson & Zatorre, 2006) used both visual and auditory stimuli to measure the attention to the stimuli feature and divided attention. Although no spatial or temporal attention task was applied using a similar task, they revealed similarities between the activation in response to visual and auditory tasks. We postulate that if the proper auditory stimulus was used in the auditory orienting attention task, neutral network activation and visual orienting attention might be demonstrated.

3. Tactile angle cognitive ability for distinguishing normal aging and dementia

3.1 Introduction

As described above, AD is a progressive neurodegenerative disease that is characterised by a loss of neurons and synapses in the cerebral cortex. Currently, many pathophysiological and molecular neurological studies (Francis et al., 1999) have focused on the cause of AD to find its clinical biomarkers, such as phosphorylated tau. In recent decades, researchers have also used PET (Huang et al., 2010) and fMRI (Delbeuck et al., 2003; Johnson et al., 2006) to assess brain functional deficits and disconnections between cerebral areas in patients with mild cognitive impairment (MCI) and AD. These studies have shown that AD brains may have different activity and connectivity patterns compared to normal brains. A few recent neuropsychological studies (Baddeley et al., 1991) have also explored the effects of disconnection between cerebral areas on cognitive functioning.

The altered cognitive symptoms in the earliest stages of AD include mild problems in learning, memory and planning (Förstl & Kurz, 1999). Unlike normally aged controls, profound impairments in working memory, episodic memory and spatial discrimination are found in patients with AD (McKhann et al., 1984). Eventually, most AD patients in the

severe stages of the disease lose their ability to perform the simplest of tasks encountered in their daily routine. Mild cognitive impairment is a clinical disorder that afflicts elderly individuals and is characterised by memory impairment that does not interfere significantly with their daily living (Petersen et al., 1999). In addition, MCI is a major risk factor in the development of AD (Petersen, 2004). Currently, the mini-mental state examination (MMSE) (Folstein et al., 1975) and the clinical dementia rating (CDR) system (Morris, 1993) are used as references to help a physician determine whether a person diagnosed with memory problems has AD.

The somatosensory system is a diverse sensory system comprising the receptors and processing centres to produce the sensory modalities. Tactile spatial discrimination is one of the major manual learning and memory skills of humans. Tactile spatial acuity at the fingertips varies significantly with age (Stevens & Patterson, 1995). Previous studies have suggested two possible effects of this variation on tactile spatial discrimination: (a) differences in the central pathways of the brain leading to tactile perception and (b) differences in afferent innervation density between younger and older subjects. However, the differences in the ability to discriminate tactile angles between healthy older individuals and patients with MCI and AD has not been reported.

To differentiate two different objects by touch, humans need to store the spatial information of the first object in their working memory and then compare the spatial construction of the first object to that of the second. This procedure activates a diverse cerebral network that primarily includes areas involved with the initial processing of skin indentations (i.e., primary and secondary somatosensory cortex) (Blatow et al., 2007), the high-class areas for computation and elaborate reconstruction of shapes (i.e., part of the intraparietal sulcus) and the prefrontal cortex (Bodegård et al., 2001), which is activated for tactile working memory processing. We hypothesise that having abnormal somatosensory information processing contributes to the functional decline of tactile shape discrimination in patients with MCI and AD compared to NC individuals.

In this section from our recent study (Yang et al., 2010), we characterised tactile shape discrimination deficits in patients with MCI and AD and assessed whether tactile shape discrimination impairment could distinguish patients with MCI and AD from NC individuals. To allow a controlled study of shape, we used a restricted working definition of shape that can be applied to any object with angles (Wu et al., 2010) and to examine the ability to identify differences in raised angles in MCI and AD patients and the NC individuals. The results indicated that the decline in tactile angle discrimination in patients with MCI and AD compared to the NC group was significant.

3.2 Methods

3.2.1 Subjects

Three groups of right-handed subjects (i.e., NC, MCI and AD) consented to participate in the study. Handedness was confirmed with the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). All MCI and AD patients were recruited from the Okayama University Hospital, Japan, and all subjects had no deficits in motor and sensory systems and deep tendon reflexes. They also reported no loss of tactile sensation or any unusual experiences with haptic input. All subjects signed informed consent forms, and the experiments were performed in accordance with a protocol approved by the Okayama University.

The NC group consisted of 14 subjects between the ages of 67 and 79, with a mean age of 71.5±3.7 years. The NC individuals were designated as "cognitively normal" when they presented no cognitively based limitations in daily living activities, and the NC was defined by an MMSE score (Folstein et al., 1975) of 27 or greater and a CDR (Hughes et al., 1982) of 0. No NC subjects had a history of neurological or psychiatric disease, and no subjects were taking any medications that affected the central nervous system at the time of testing.
The MCI group consisted of 10 subjects between the ages of 56 and 85, with a mean age of 71.3±9.4 years. Patients with amnestic MCI were diagnosed using the Petersen criteria (Petersen et al., 1999). In addition, all patients with amnestic MCI had MMSE scores of 27 or greater and CDR scale scores of 0.5. These individuals underwent magnetic resonance imaging (MRI) of the brain to confirm that they did not have a focal lesion that affected memory sensitive substrates. As assessed by the Consortium to Establish a Registry for Alzheimer's Disease cognitive battery (Morris et al., 1989), MCI patients typically show a memory performance that was 1.5 reference deviations below the age-adjusted average, which includes verbal learning, recognition and recall tests, global cognitive function and activities of daily living impairment.
The AD group consisted of 13 subjects between the ages of 57 and 83, with a mean age of 73.4±7.7 years. The diagnosis of AD was made in accordance with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) Alzheimer's Disease and Related Disorders Association (ADRDA) criteria (Morris et al., 1989). All patients with AD had MMSE scores between 15 and 26 and a CDR score of 1 or 2, corresponding to what is known as mild to moderate AD.
In addition, all MCI and AD patients were confirmed based on a Rosen modified Hachinski ischemic score that was at least 4 (Rosen et al., 1980), and they did not show any atrophy of the somatosensory cortex on MRI. Patients were excluded if they had clinically significant neurological diseases other than MCI and AD or had a major psychiatric disorder. Psychiatric co-morbidity was excluded by history, clinical examination, and a Composite International Diagnostic Interview (Robins et al., 1988).

3.2.2 Apparatus and stimuli

One reference angle and eight comparison angles were used in this study. During each trial, one pair of angles consisting of the reference angle, and a comparison angle was presented to the subject. Fig. 6(a) is an illustration of the angles. In this experiment, the apex of the angles was always pointing to the right. All angles were mounted so the two arms were symmetrically placed above and below an imaginary bisector. The size of the reference angle was 60° with the eight comparison angles being larger than the reference angle by 4°, 8°, 12°, 16°, 20°, 24°, 32° and 50°. The raised angles consisted of custom-built plastic shapes that were raised 0.5 mm (Fig. 6(b)) over a 40.0 mm square base. Varying in two spatial dimensions, the angles were formed by two raised lines (i.e., the arms of the angles) at the centre of the 40.0 mm square base with an accuracy of ± 0.1°. The arms were 8.0 mm long and 1.5 mm wide.
As shown in Fig. 6(c), the two angles were clamped horizontally in the apparatus. Subjects were blindfolded and seated at a table. The right hand of the subject was fixed with tape to an immobile plastic plate with only the right index finger making contact with the angles. The apparatus consisted of an electric slide that moved the angles along the horizontal axis in the transverse plane.

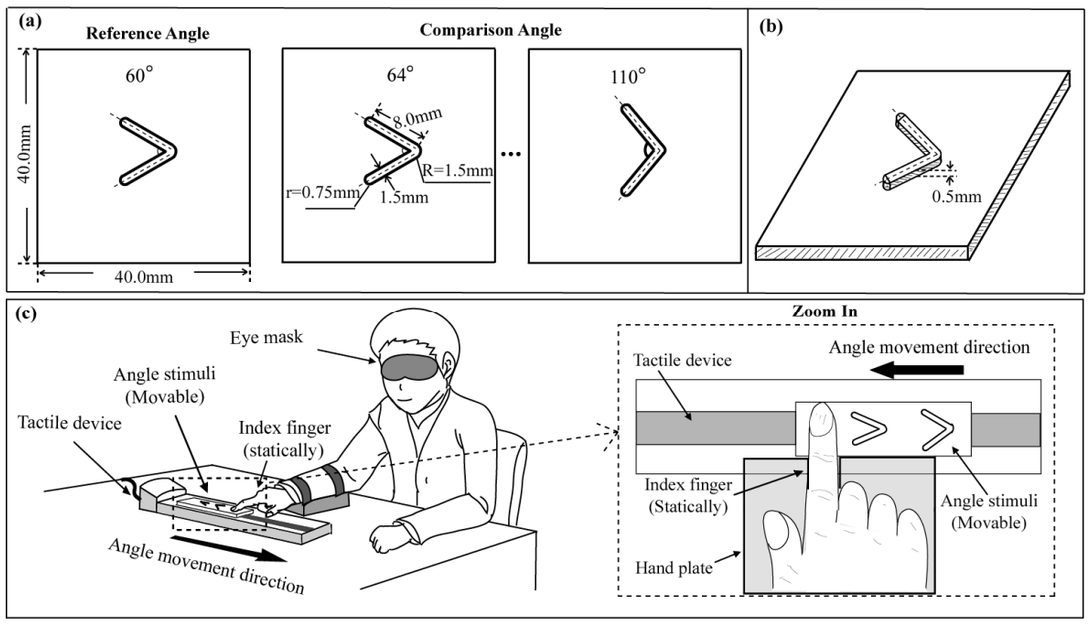

Fig. 6. Example of angle stimuli and position of subject's finger. (a) An illustration of the reference angle (60°) and two of eight comparison angles (64° and 110°) used in this experiment. (b) Three-dimensional view of an example of angle. (c) The angle movement apparatus and the subject's finger position. The reference angle and one comparison angle of a typical trial were clamped on the apparatus. These angles were moved by an electric slide on the tactile apparatus from right to left in a horizontal direction. The subject's right hand was fixed on the plate and kept static during each discrimination trial.

3.2.3 Procedure

We measured angle discrimination thresholds based on each subject's ability to judge the relative sizes of the reference angle and the comparison angles. All subjects were asked to place their right index fingers at the initial starting point of the plate (Fig. 6(c)). To hold the right index finger and arm in the vertical direction, the right hand was fixed to the plate, and the forearm was fixed to an immobile support stand. The subjects wore an eye mask during the task to prevent visual feedback. Moreover, all subjects were asked to keep their right hand immobile and perceive the angles passively. For AD patients, the experimenter intermittently reminded the patients of this requirement to ensure compliance with the instructions to differentiate the size of the two angles.

As shown in Fig. 6(c), the experimenter first clamped the reference angle and one of eight comparison angles on the apparatus. Then, the angles were moved under the subject's right index finger for the subject to perceive the size of the angle by following the imaginary bisector. Moreover, all angles were moved from the end points towards the apex. Each angle was scanned in succession, once per trial. The contact force was restricted, and the movement speed of the angles was maintained at 5.0 mm/s. The subject was then asked to verbally identify the larger angle in each pair of angles (2AFC: two-alternative forced choice). A pseudorandom order was used to present the reference angle and comparison angle to the subject. The reference angle was either the first or the second angle in each pair presented to the subjects who were not informed about the change in the order of angles.

Each subject underwent at least 10 practice trials prior to the start of the experiment. After the training, each pair of angles was presented 10 times in a pseudorandom order. Each subject completed 80 angle discrimination trials.

3.2.4 Data processing and analysis

In this study, the 2AFC technique was used to measure the angle discrimination threshold. Subjects were forced to make a choice of what they perceived was the larger of two angles even if they could not detect a difference. The logistic curve is the most common sigmoid curve used extensively in cognitive psychological experiments for measuring thresholds (Voisin et al., 2002a,b). Here, the accuracy data were applied to the following logistic function (1) (adapted from Wu et al., 2010):

$$Accuracy = \frac{1}{1 + e^{d|RA-CA|}} \tag{1}$$

In this equation, d represents the unique degree of freedom of the logistic curve, which was adjusted to fit the accuracy data. RA and CA represent the degree values of the reference and comparison angles, respectively.

The discrimination threshold was defined as the angle difference at an accuracy rate of 75%. Fig. 7 shows the 2AFC results of one NC subject. The discrimination threshold is indicated where the accuracy line and the 75% line (dashed line) intersect. The discrimination threshold (DT) was computed from the logistic function (2) as follows (X = 75% accuracy):

$$DT = d^{-1}Ln(\frac{1-X}{X}) \tag{2}$$

The data were incorporated into logistic functions (1) and (2). The same analyses were applied to all of the data in this experiment.

3.2.5 Statistics

To calculate angle discrimination thresholds, regression analysis with logistic function was performed. Differences in the accuracy and discrimination thresholds of the three subject groups were analysed using separate one-way analysis of variance (ANOVA). The level of significance was fixed at $P < 0.05$. The Bonferroni test ($\alpha = 0.05$) was performed to detect the difference between each subject group. Finally, to compare the sensitivity of angle discrimination accuracy and the MMSE score, a receiver operator characteristic (ROC) analysis was used. All analyses were performed using SPSS version 12.0j (SPSS, Tokyo, Japan).

3.3 Results

3.3.1 Accuracy

To investigate the differences in the accuracy of angle discrimination for different angle pairs, we calculated the mean accuracy for each pair of reference and comparison angles in different subject groups. The accuracy rate was defined as the number of correct trials divided by the total number of trials for each angle pair. As described above (Fig. 7), the accuracy increased with an increase in the difference between the reference angle and the comparison angle in this experiment. The regression analysis of the mean accuracy yielded

significant r^2 values of 0.98, 0.98, and 0.67 for the NC, MCI and AD groups, respectively [NC: $F(1,6) = 323.95$, $P < 0.001$; MCI: $F(1,6) = 473.76$, $P < 0.001$; AD: $F(1,6) = 12.16$, $P = 0.013$]. The mean angle discrimination accuracy for the NC (82.1% ± 2.2%), MCI (78.6% ± 1.8%) and AD (67.9% ± 2.5%) groups is shown in Fig. 8(a). We performed a one-way ANOVA on the mean accuracy. The mean accuracy of the angle discrimination differed significantly between the three groups [$F(2,34) = 8.01$, $P = 0.001$]. A multiple comparison using the Bonferroni correction ($\alpha = 0.05$) revealed that the mean accuracy of patients with AD was significantly lower than patients with MCI ($P = 0.04$) and the NC subjects ($P = 0.001$). However, the difference in accuracy between patients with MCI and NC subjects was not significant ($P = 0.93$).

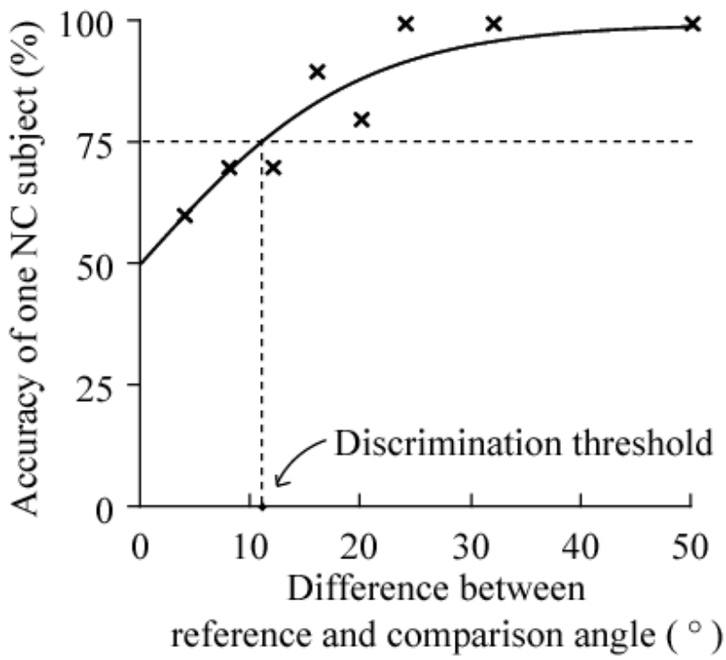

Fig. 7. Calculation method of the angle discrimination threshold. Accuracy of one NC subject is plotted as a function of the angular difference between the comparison (62°–110°) and the reference angle (60°). The solid line represents the logistic curve for threshold calculation. The horizontal dashed line indicates accuracy at 75%. The horizontal axis value of the intersection between the 75% line and logistic curve is defined as the angle discrimination threshold. For this NC subject, the threshold is 10.7°.

To examine whether the patients with MCI and AD showed any decline in angle discrimination, we further examined the angle discrimination threshold. We performed a one-way ANOVA and a multiple comparison using the Bonferroni correction ($\alpha = 0.05$) on the mean discrimination threshold. As shown in Fig. 8(b), differences in the mean discrimination thresholds among patients with AD (25.2°±4.2°) or MCI (13.8°±2.7°) and NC subjects (8.7±0.8°) were significant [$F(2,34) = 9.45$, $P < 0.001$], with a larger threshold in patients with AD compared to patients with MCI ($P = 0.036$) and NC ($P < 0.001$). In addition, the threshold in patients with MCI was also significantly larger compared to NC ($P = 0.049$). These results indicated that the decline in the ability to discriminate tactile angles in patients with MCI and AD was significant compared to the NC group.

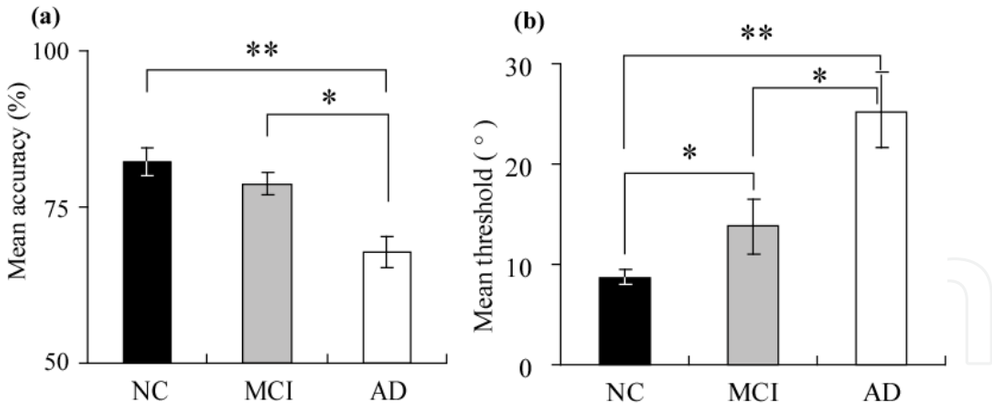

Fig. 8. Mean accuracy and discrimination threshold of MCI and AD compared to NC. (a) The mean accuracy of the three groups (NC: 82.1% ± 2.2%, MCI: 78.6% ± 1.8%, AD: 67.9% ± 2.5%). (b) The mean discrimination thresholds for the three groups are shown (NC: 8.7° ± 0.8°, MCI: 13.8° ± 2.7°, AD: 25.2° ± 4.2°). Vertical error bars represent standard error of the mean. *P < 0.05, **P < 0.001.

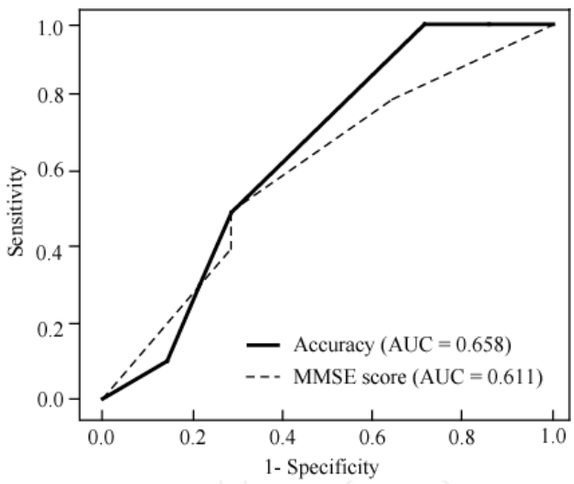

Fig. 9. Receiver operating characteristic (ROC) curves for the angle discrimination accuracy and MMSE score showing discrimination between the NC and MCI groups. The solid line represents the ROC curve of angle discrimination accuracy, and the dashed line represents the ROC curve of MMSE score. The area under the curve (AUC) of angle discrimination accuracy is larger than that of MMSE score.

3.3.2 Comparison between angle discrimination accuracy and MMSE score

ROC analysis is a useful tool for evaluating the performance of diagnostic tests (Mendiondo et al., 2003; Zou et al., 2007). We used a ROC analysis to compare the sensitivity of angle discrimination accuracy to that of the MMSE scores. The fundamental measures of diagnostic accuracy are sensitivity (i.e., true positive rate) and specificity (i.e., true negative rate). As described in the Subjects section, all NC and MCI patients were defined by an MMSE score of 27 or greater and the CDR score of 0 and 0.5. In contrast, all AD patients had MMSE scores between 15 and 26. Therefore, only the ROC curves for angle discrimination

accuracy and MMSE score of NC and MCI subjects were compared and are presented in Fig. 8. The area under the curve (AUC, is an overall summary of diagnostic accuracy) values for the angle discrimination accuracy was 0.658, and the MMSE score was 0.611. As shown in Fig. 8, we found that the AUC of the angle discrimination accuracy was higher than the MMSE score.

3.4 Discussion

The present study demonstrated that patients with MCI or AD have an impaired ability to discriminate tactile angles compared to age-matched healthy subjects. The current study compared the performance of angle discrimination in three different subject groups (i.e., NC, MCI and AD). The results of this study indicated that there were significant group differences in the ability to discriminate tactile angles (NC > MCI > AD). Both the mean accuracy and threshold of angle discrimination of AD patients were significantly decreased compared to NC individuals and MCI patients. In contrast, although the mean threshold of angle discrimination of patients with MCI was significantly higher than NC individuals, the mean accuracy of the MCI group was similar to the NC group.

All subjects were asked to passively perceive the angles moved under their right index fingers and discriminate the largest of each angle pair, which consisted of a reference angle and a comparison angle. The current angle discrimination task is a commonly used procedure of tactile passive shape discrimination. The sensory feedback, which is critical for shape discrimination by passive touch, is generated by the four mechanoreceptive afferent systems (Johnson, 2001) located in the skin. Moreover, previous studies (Goodwin et al., 1997; Johnson, 2001) have suggested that tactile shape perception can be defined as the sum of the functions of cutaneous mechanoreceptors. However, there are numerous anatomical and morphological changes that develop with age and affect the hand and fingers. The density of mechanoreceptors in the skin was decreased (Wollard, 1936; Bruce, 1980), and the conduction velocity of peripheral nerves was significantly reduced with age (Peters, 2002). A decreased touch sensitivity in elderly individuals can cause many problems (Stevens & Choo, 1996; Vega-Bermudez & Johnson, 2002), including the inability to recognise objects by touch and an impaired ability to detect an object that has come into contact with the skin. Consequently, the ability of normal, older subjects to discriminate angles will be reduced compared to normal, young subjects. For example, the mean threshold of young subjects was 3.7° in our previous angle discrimination study (Wu et al., 2010), and the mean threshold of NC subjects in the present study was 8.7°, which was more than twice the previous value. However, the results of the present study indicated that the older subjects, as well as patients with MCI and AD, were able to complete the angle discrimination task. All subjects in the current experiment were able to perceive the change in size of the angle stimuli.

However, a significant deficit in angle discrimination was observed in MCI and AD patients in this study. One of the earliest symptoms of AD is impaired working memory (Baddeley et al., 1991; Bäckman & Small, 2007). In addition, previous studies have observed that patients with MCI also show impairments in memory processing compared to healthy aging subjects (Siedenberg et al., 1996; Petersen et al., 1999). In this study, all subjects were instructed to discriminate the larger of two angles by passive touch. To perform this task, the subject had to remember the composing feature of the first angle

and then compare it with the second angle to make a judgment. The working memory contributed to the performance of the somatosensory discrimination (Bodegård et al., 2001; Kitada et al., 2006). Therefore, the present study suggests that the impaired working memory of MCI and AD patients is one factor that contributes to the decline of angle discrimination performance.

Moreover, we found that the mean accuracy of AD patients was significantly lower than the accuracy of the MCI and NC groups, and the mean threshold of AD patients was also reduced compared to the other two groups. Specifically, the mean threshold of AD patients was almost double the threshold of the MCI patients. However, we also found that there was a significant difference in the mean threshold between the MCI patients and the NC group, whereas the mean accuracy of the MCI patients and the NC group remained unchanged. There are two possible reasons to explain this phenomenon. First, AD is a neurodegenerative brain disease. Unlike patients with MCI, AD patients have more severe working memory impairments (Blatow et al., 2005). Second, the isolated memory impairment found in patients with MCI is more severe than the impairment observed in healthy aging individuals, whereas other cognitive functions remain normal. In contrast, AD patients have further deficits in spatial learning and memory and planning and problem solving (Kalman et al., 1995; Förstl & Kurz, 1999). These profound cognitive impairments of AD patients may explain the more severe deficits in angle discrimination found in patients with AD.

In addition, the tactile spatial discrimination procedure activates a diverse cerebral network (Bodegård et al., 2001; Kitada et al., 2006; Wu et al., 2010). The results from these neuroimaging studies also support our findings. For example, the intraparietal sulcus (located on the lateral surface of the parietal lobe) is engaged in multisensory spatial processing during the classification of grating and shape, and it has been shown that the intraparietal sulcus is a high-class area for computations and elaborates shape reconstructions (Bodegård et al., 2001). Neuroimaging studies (Delbeuck et al., 2003; Dickerson & Sperling, 2009; Huang et al., 2010) have demonstrated that abnormalities in the frontal, temporal, and parietal cortices contribute to the functional deficits in AD patients. Consequently, our results suggest that both the impairment of working memory and spatial discrimination of AD patients contribute to the lowest angle that is discernible compared to the MCI patients and the NC group.

The MMSE is a brief mental status examination designed to quantify the cognitive status in adults (Folstein et al., 1975). Recently, MMSE has been commonly used to test for complaints of memory problems or when a diagnosis of dementia is being considered. We plotted the ROC curves for the angle discrimination accuracy and MMSE score. We found that used the angle discrimination accuracy was better anbe to differentiate the MCI patients from older individuals than the MMSE score because the MMSE also has limitations. For example, previous studies (Anthony et al., 1982; Galasko et al., 1990) have suggested that the sensitivity of the MMSE has been rated at approximately 80%. Thus, the MMSE score may not represent the cognitive function deficits of all individuals. In contrast, we specifically focused on the difference in tactile angle discrimination in MCI and AD patients compared to the NC group. Although the present angle discrimination experiment examined working memory, spatial discrimination and problem-solving processes, there were limitations to this study. Despite these limitations, we have found a significant decline in tactile angle

discrimination between the MCI patients and the NC group using the present tactile discrimination system. These findings may improve the sensitivity of the previous mental tests for AD diagnosis and treatment.

4. Conclusion

Audiovisual spatial and temporal orienting attention studies were examined in our study to further our understanding of neuroimaging studies for early detection of dementia. By using another method to compare the cognitive ability of tactile angle discrimination, we initially found that at the early stages of Alzheimer's disease, the behavioural cognition was decreased. These basic data that obtained from our studies, we consider that they are able to apply for a clinical diagnosis method of dementia early detection after enough confirm experiments.

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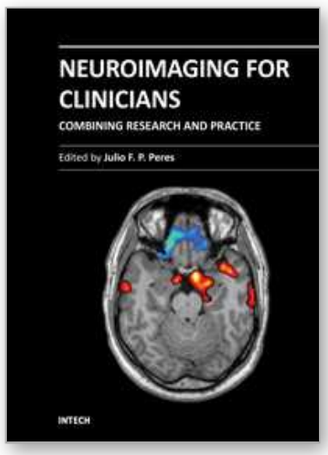

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