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Diagnostic utility of sound naming in early Alzheimer's disease

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Abstract

While it is well known that picture naming (PN) is impaired in Alzheimer's disease (AD), sound naming (SN) has not been thoroughly investigated. We postulated that SN might be impaired more severely and earlier than PN, given the early involvement of the temporal cortex by AD-related pathology. SN and PN were assessed in 21 normal participants, 40 patients with mild cognitive impairment (MCI), and 27 patients in early stages of AD. Our results showed that SN accuracy and latency were more sensitive to advancing pathology in AD than PN accuracy and latency. SN was more useful and specific in distinguishing MCI patients from normal participants and therefore in potentially identifying the subset of MCI patients who already have impairment in more than one cognitive domain and may actually have incipient AD. These findings indicate a potential diagnostic utility of SN for early detection of the disease. Furthermore, even though most AD patients demonstrated more or less comparable impairment in both tasks, some were disproportionately impaired on SN and others were differentially impaired on PN. Future studies may be able to show that these discrepant groups correspond to patients with right and left hemisphere predominant AD, respectively. (*JINS*, 2009, *15*, 231–238).

Keywords: Dementia, Alzheimer's disease, Mild cognitive impairment, Sound naming, Picture naming, Response time

INTRODUCTION

Deficits on confrontation naming occur early in the course of Alzheimer's disease (AD) and exacerbate with time (Appell et al., 1982; Kirshner et al., 1984; Williams et al., 1989). The severity of dementia is correlated strongly and positively with the degree of anomia (Bayles, 1982; Kaszniak et al., 1986). Therefore, confrontation naming tests, such as the Boston Naming Test (BNT), have been commonly used to assist in the diagnosis of AD (Kaplan et al., 1983; Williams et al., 1989).

Whereas strong correlations have been demonstrated between the severity of dementia and the word-finding difficulty, there is some inconsistency across studies; a subgroup of AD patients was identified who had preserved ability in naming, despite significant deficits in other cognitive capacities (Martin et al., 1986). Naming disability in moderately demented AD patients was reported, but significant deficits were not present in mildly demented AD patients (Bayles & Tomoeda, 1983). When present in patients with mild AD, aphasia was characterized by impairments in comprehension and written expression, whereas naming ability was relatively preserved (Faber-Langendoen et al., 1988). These inconsistencies led some researchers to argue that BNT was useless in diagnosing and identifying early AD (Testa et al., 2004), while many clinicians and researchers still consider naming impairments a requisite deficit in AD (Sperling et al., 2003). Given the differing opinions in the literature, further investigation on the naming ability seems warranted.

Here, we postulated that utilizing the auditory as opposed to visual modality in the assessment of naming impairment might be more appropriate for the following reasons: according to the Braak and Braak staging (Braak & Braak, 1991), the temporal lobe was involved very early in AD patients as a group. Neurofibrillary tangles (NFT) and tau protein deposits develop first in the limbic structures and spread to the neighboring temporal cortex as the disease worsens (Braak et al., 1993). Histopathologic studies described abundant NFT and senile plaques within the auditory association cortex and the primary auditory cortex (Esiri et al., 1986).

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Substantial increases in the number of NFT have been found in auditory association cortex in AD compared with primary auditory cortex (Lewis et al., 1987). Pathologic changes became increasingly dense in primary, secondary, and tertiary auditory association cortices in AD patients, while areas 41 and 42 were least affected by NFT (Hyman et al., 1988). These studies suggest that the auditory system is involved very early in AD.

Given the differential vulnerability of auditory cortices, people have had growing interests in the central auditory processing in AD patients. Central auditory processing is defined as the auditory system mechanisms and processes responsible for the following behavioral phenomena: sound localization, auditory discrimination, auditory pattern recognition, temporal aspects of audition, and auditory performance decrements with competing and degraded acoustic signals (Hall & Antonelli, 2001). Central auditory function deficit may be early manifestation of AD, preceding the disease by a minimum of 5 and a maximum of 10 years (Hopper et al., 2001). There was also evidence of central auditory dysfunction in participants with even mild cases of AD, whereas peripheral auditory function was not different from normal group (Gates et al., 1995). These findings are consistent with our hypothesis that sound naming (SN) might be more impaired in earlier stages of the AD than picture naming (PN). To test our hypothesis, we administered SN and PN to normal participants and patients with mild cognitive impairment (MCI) and dementia of Alzheimer's type (AD). We measured not only accuracy but also response time (RT). Luce (1986) described in his extensive works that RT is "psychology's ubiquitous dependent variable" and RT measurements may allow inferences about mental processes involved in the task. While this has been applied quite extensively to studies using normal participants, less effort in this regard has been put in neuropsychological investigations of dementia. It is the hope of the authors that this study may contribute in filling the deficiency.

METHODS

Subjects

Eighty-eight subjects (52 women, age ranged from 50 to 88 years, with $M = 73.8$ years and $SD = 6.37$ years) participated with an informed consent approved by the Seoul National University Hospital Review Board. The participants were categorized as normal participants (NM, $n = 21$), patients with MCI (MCI, $n = 40$), and patients with dementia of Alzheimer's type (AD, $n = 27$), according to the criteria described below. The patients were recruited from neurology outpatient clinics at Seoul National University Hospital. Spouses or guardians of the patients who had no neurological or psychiatric disorders also participated in this study as normal controls. All participants received behavioral neurological evaluations, including the Korean version of Mini-Mental State Examination (K-MMSE) (Kang et al., 1997) and the Korean version of expanded Clinical Dementia Rating Scale (K-CDR) (Choi et al., 2001). We used the norms of the K-MMSE of a population-based study (Han et al., 2007).

Normal participants were defined as the following (Hulette et al., 1998): (1) free of memory and cognitive disorders leading to corresponding functional impairments in everyday life; (2) live independently without difficulty; (3) absence of psychiatric and neurological illness; (4) absence of physical conditions that are known to compromise cognitive capacity such as hypertension or diabetes that could not be controlled by medication, thyroid disease, and loss of consciousness for more than 20 min; and (5) no severe hearing or vision problems that could significantly compromise the neuropsychological test results.

A diagnosis of MCI was made in accordance with the criteria established by Petersen et al., (1999): (1) subjective memory complaint (preferably corroborate by an informant); (2) normal activities of daily living: the patient should both keep the professional, social, and familial activities; (3) normal general cognitive function; and (4) abnormal memory for age. The working criteria of K-MMSE scores for detection of MCI were $\geq$ mean $-$ 2 *SD* (for age and educational level). Abnormal memory was determined as recall of fewer than three of three objects after 5 min on the K-MMSE. Exclusion criteria were as follows: (1) the presence of dementia, according to the *Diagnostic and Statistical Manual, 4th Edition* (DSM-IV) criteria (American Psychiatric Association, 1994), (2) clinical history, imaging or laboratory test indicating other neurological disorder; specifically, patients with a history of stroke or transient ischemic attack, presence of psychiatric disorders, namely patients with diagnosis of major depression according to the DSM-IV criteria (American Psychiatric Association, 1994); and (3) subjects with any condition with possible impact on cognition, like systemic disease, alcohol, or drug abuse.

The diagnosis of AD was based on the criteria of the National Institute of Neurological and Communications Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). The clinical diagnosis of probable AD was made if the patient met the following criteria: (1) dementia established by clinical examination and documented by the Mini-Mental Test or some similar examination and confirmed by neuropsychological tests; (2) deficits in two or more areas of cognition; (3) progressive worsening of memory and other cognitive functions; (4) no disturbance of consciousness; (5) onset between ages 40 and 90, most often after age 65; (6) absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition. Diagnostic accuracy for AD has been reported to be high (e.g., 96%, with AD confirmed in 102 of 106 consecutive autopsies in individuals with AD; Berg & Morris, 1994) when these criteria are used. All the MCI and AD patients in our study met these criteria. In Table 1, the age, sex, education, and the scores of K-MMSE and K-CDR are summarized for NM, MCI, and AD.

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Table 1. Initial demographic and neuropsychological characteristics

	NM		MCI		AD		
	M	*SD*	*M*	*SD*	*M*	*SD*	*p*
Age (years)	67.1	8.26	67.69	8.52	68.38	10.94	ns
n (%Male)	21 (43%)		40 (38%)		27 (48%)		ns
Education (years)	10.62	5.28	10.72	4.61	11.05	3.54	ns
K-MMSE	28.69	0.85	25.41	1.53	18.33	2.64	< .0001
K-CDR	0	0.2	0.5	0.35	2.0	0.4	< .0001

Note. Mean scores (*M*) and *SD* for age, years of education, K-MMSE, and K-CDR in NM, MCI, and patients with dementia of Alzheimer's type (AD).

Basic visual and auditory functions were tested to rule out lower level deficits in vision and audition. Visual fields, visual acuity, and auditory thresholds were assessed in all patients during initial neurological examinations at the clinic. Any difficulty in audiovisual functions was monitored during neuropsychological testing sessions as well. Patients with serious impairments in vision or audition were excluded from the current study.

Stimuli

A set of 80 objects was chosen that could be named by the sound as well as by the appearance. This set was administered to 20 neurologically and psychiatrically normal individuals, and we selected the objects to which at least 18 of 20 people provided the same response. The resulting set of stimuli consisted of 50 objects. The sounds for use in SN represented a wide variety of different acoustic events, such as those produced by animals (e.g., tiger, dog), people (e.g., crying, coughing), musical instruments (e.g., piano, trumpet), tools (e.g., hammering), transportation (e.g., car, train), signals (e.g., telephone, doorbell), liquids (e.g., water dripping, ocean waves), and so on. We considered each of these to be an "environmental sound" that might be defined as a nonspeech sound representing "… any potentially audible acoustic event which is caused by motions in the human environment" (Vanderveer, 1979). Stimuli for PN were line drawings of the objects used in SN. Some of them were selected from those used in BNT (Snodgrass & Vanderwart, 1980), and the others were drawn by a painter. Since vocabulary knowledge, which is of concern in the assessment of naming (Morton, 1969), may vary across participants, items were selected such that the names were mid- to high-frequency Korean words. Word frequency is measured as the number of occurrences of a word within a given corpus of written and/or spoken items according to the frequency counts in the Korean word frequency database (Suh, 1998). High-frequency words had a frequency count greater than 60 per million, and mid-frequency words had frequencies more than 20 and less than 60 per million.

Test Procedure

All the participants performed SN, PN, K-MMSE, and K-CDR in one session. Before the start of session, they were given detailed instructions on the naming tasks with five example trials in both SN and PN, respectively. The example trials were not included in the analysis. The order of naming tasks was counterbalanced across participants within the normal and patient groups.

In SN, the task was to name the stimulus presented through a headphone by speaking at a microphone. The participant was instructed to respond as soon as he or she could (even while the sound was still playing), with cautions that they needed to speak loudly, avoid making extraneous sounds, and guess when unsure. In PN, participants named a line drawing picture stimulus presented to a computer monitor, still answering by voice. Each stimulus was presented for 7 s for both naming tasks. We concurred with Fabiani et al. (1996) in that short stimuli in SN tasks are perhaps equivalent to naming picture fragments rather than naming the whole pictures. Therefore, participants were given enough duration to respond in both tasks. Concerned that sound stimuli that were transient might place more demands on working memory than picture stimuli, which remained in the participant's view, we continuously repeated a sound stimulus for the duration of the presentation. When the participants provided an incorrect response, they were encouraged to think more and to correct the answer. If the subject managed to provide the correct response within the time limit of 7 s, the trial was counted as a correct answer. A fixation mark was shown for 1 s before the next trial began.

Every response from SN and PN was saved as a WAV file and analyzed utilizing SoundForge 7.0 by Sony Media Software (Madison, WI). A correct verbal response was identified in recorded sound tracks trial by trial, and the RT was measured as the interval from the onset of the stimulus to the beginning of the response.

RESULTS

The mean scores of RT and percent correct in SN and PN are shown in Figure 1 for NM, MCI, and AD. Results of repeated-measures, group by modality analysis of variance indicated significant main effects of both group [percent correct: $F(2,170) = 23.6$, $p < .001$; RT: $F(2,170) = 40.8$, $p < .001$] and modality [percent correct: $F(1,170) = 80.3$, $p < .001$; RT: $F(1,170) = 718.01$, $p < .001$]. There was a significant interaction between group and modality in RT [$F(2,170) = 18.4$, $p < .001$] but not in percent correct [$F(2,170) = 1.17$, $p = .313$]. Results of planned comparison *t* test indicated that the

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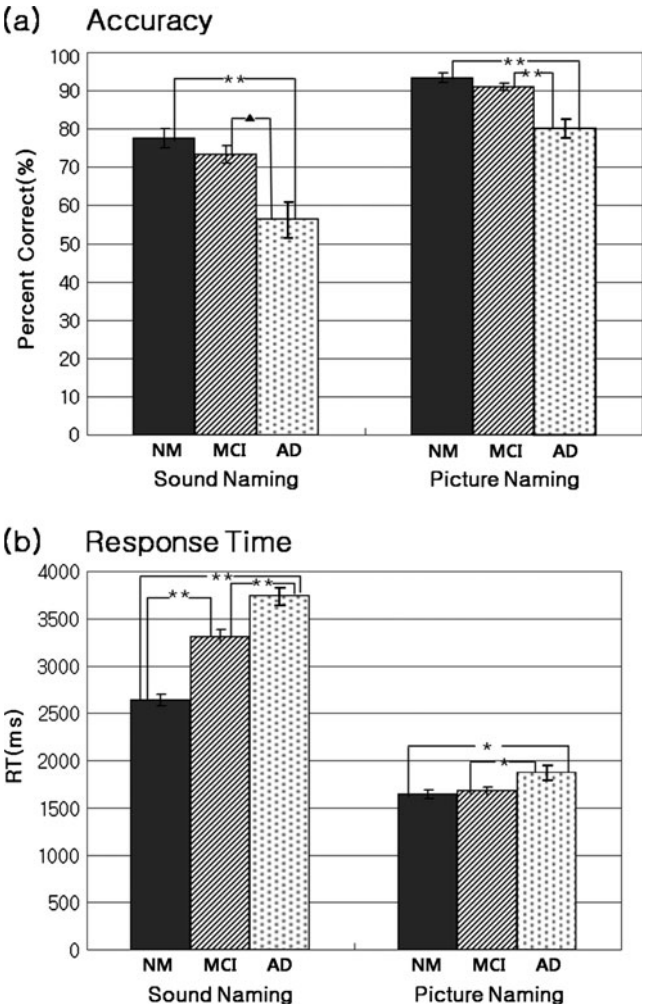

Fig. 1. Mean performance of NM, patients with MCI, and patients with dementia of Alzheimer's type (AD) for (a) accuracy (percent correct) and (b) RT. Error bars indicate the standard error of the mean. $^{**}p < .001$, $^{*}p < .05$, ▲$p < .01$.

AD group obtained significantly lower accuracy and longer RT compared with the MCI group in both PN and SN, PN [percent correct: $t(65) = 4.617$, $p < .001$; RT: $t(65) = -2.476$, $p < .05$] and SN [percent correct: $t(65) = 3.645$, $p < .01$; RT: $t(65) = -3.86$, $p < .001$]. The same pattern of performance was shown between NM and AD groups, PN [percent correct: $t(46) = 4.383$, $p < .001$; RT: $t(46) = -2.513$, $p < .05$] and SN [percent correct: $t(46) = 3.84$, $p < .001$; RT: $t(46) = -10.110$, $p < .001$]. In the comparison of NM and MCI, however, only in RT of SN task did MCI show slower latency than NM [$t(59) = -6.16$, $p < .001$], while they did not differ from each other in the percent correct in PN/SN [PN: $t(59) = 1.392$, not significant (ns); SN: $t(59) = 1.166$, ns] and RT in PN [$t(59) = -0.52$, ns]. RT in SN yielded statistically significant differences between the NM, MCI, and AD groups.

Figure 1b shows that there is a difference between NM and MCI in RTs in SN but not in PN. Therefore, in Figure 2, we provided a two-column scatter plot of RTs in SN, one column for the NM, one for the MCI, in order to examine to

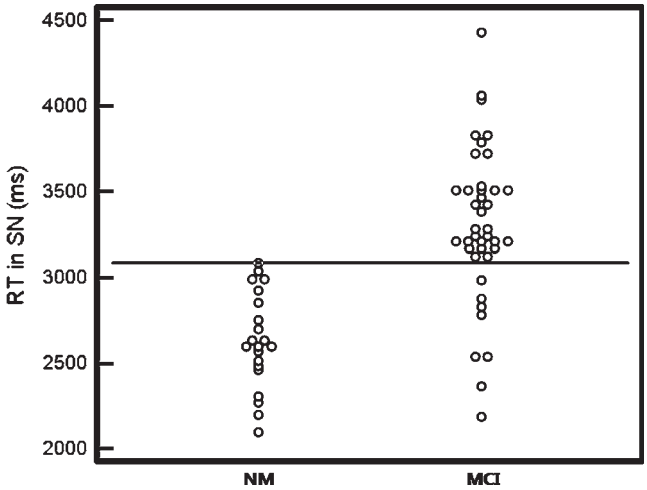

Fig. 2. The scatter plot of the RTs in SN for the NM and patients with MCI. A cutoff latency depicted as the horizontal line was 3089 ms, which had a sensitivity of 80% and a specificity of 95.2%.

what extent prolonged SN latency serves to discriminate between the two groups. The corresponding statistical test is explained in Figure 1. The sensitivity to discriminate MCI patients from normal participants was 80% at a specificity of 95.2%. The cutoff latency was 3089 ms.

Grouping the participants was based on the clinical diagnosis, which was designed to provide the information of categorical classification of NM, MCI, and AD. Since such a gross categorical classification may not reflect the disease severity properly, we used the MMSE score instead in examining the correlation between the behavioral measures (i.e., percent correct and RT) and the disease severity in individual patients. Figure 3 shows the scattergram for the Pearson's correlation between behavioral performances and MMSE scores in SN and PN in all groups of participants (Figure 3).

The scatter plot of SN and PN accuracy with AD patients is shown in Figure 4. SN and PN accuracy was normalized so that the solid diagonal drawn from the lower left quadrant through the (0,0) point to the upper right quadrant represented equal impairment of both naming tasks. For a substantial portion of our AD population, those within the two dashed lines, there was fairly comparable impairment in SN and PN naming accuracy. However, for the participants in the area of the upper left corner (beyond the dashed line), PN accuracy was >1 *SD* better than SN accuracy, and for all participants in the lower right corner (beyond the other dashed line), SN accuracy was >1 *SD* better than PN accuracy.

DISCUSSION

The primary purpose of the current study was to compare SN and PN in normal participants and in patients with MCI and AD. Although a few investigators have explored naming abilities based on modalities other than vision, for instance, by touch or verbal description (Hamberger & Seidel, 2003), no published study, to the best of our knowledge, has examined environmental SN in dementia patients.

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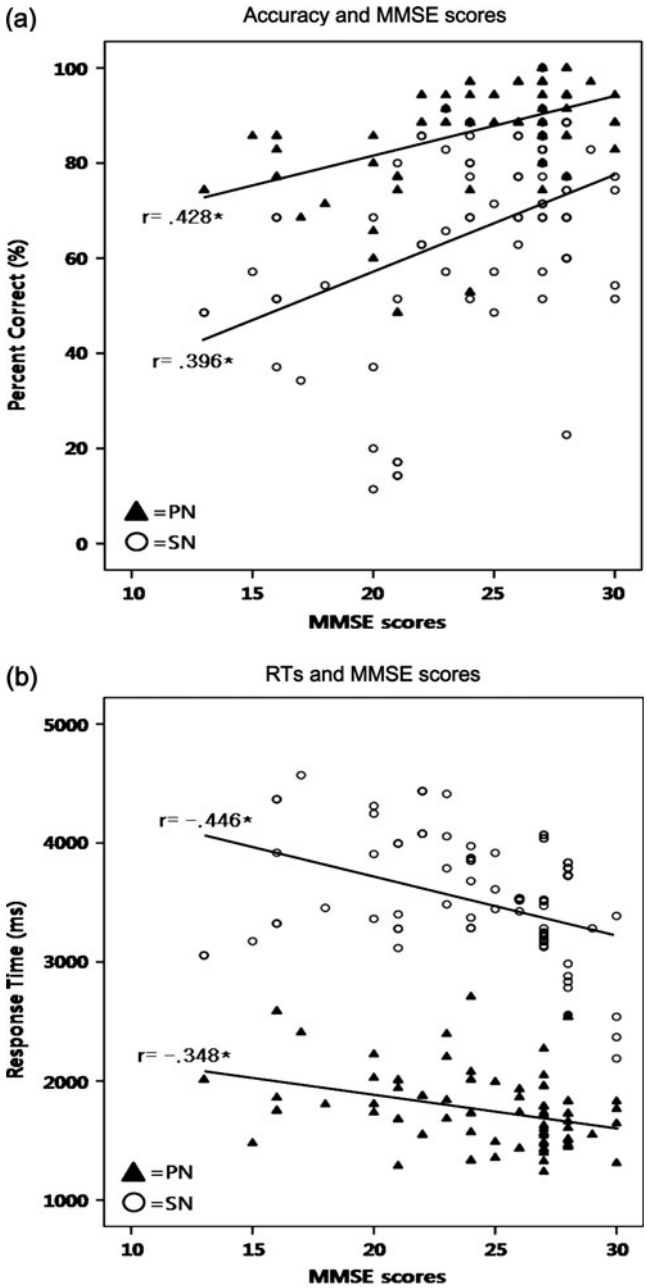

Fig. 3. Pearson's correlation between MMSE score and accuracy/RT in both SN and PN. Data points included all participants (NM, MCI, and AD). The statistical results denoted correlation coefficient. *$p < .05$.

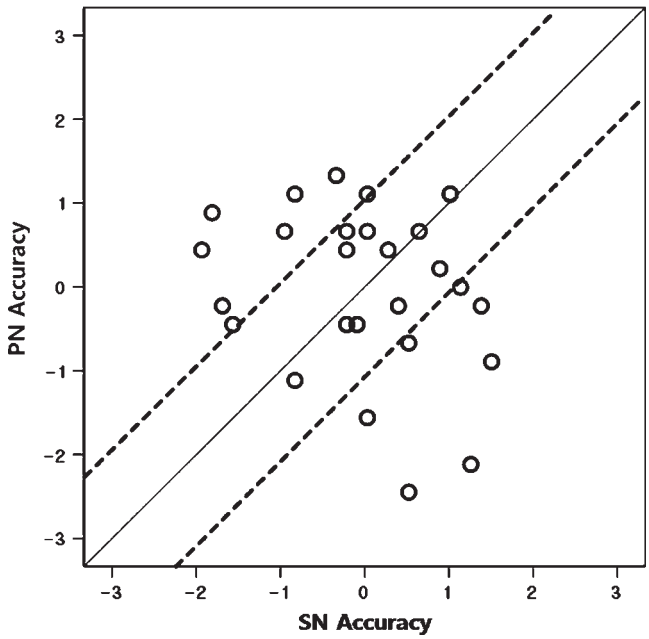

Fig. 4. The scatter plot of the AD group with accuracy in SN (SN accuracy) on *X*-axis and accuracy in PN (PN accuracy) on the *Y*-axis. The accuracy data were normalized by replacing raw scores with *Z* scores relative to the AD means. The solid line represented equal impairment of SN and PN, and the two dashed lines were set at a solid line ±1 *SD*.

We found that the performance differences across NM, MCI, and AD groups were larger in SN than in PN. In particular, PN accuracy was not significantly different between normal participants and MCI patients, indicating that PN may not be a sensitive measure in these populations. Some may argue that PN in our study was not directly compared with BNT. We, however, feel that the two are very similar since many items used in PN were originated from BNT. In fact, the accuracy measure in the PN test discriminated AD from the normal group as expected from previous experiences with BNT.

SN differentiated NM and MCI groups better. We found that at the early stages of the disease, the RT reflected the disease severity better than the accuracy, especially in SN. The significant degradation of RT in SN is likely related to one of the earliest changes in AD brains, namely, a reduction in functional activation in the auditory cortex (Kato et al., 2001). As suggested in the introduction, increases in the number of NFT and senile plaques within the auditory cortex may be one of the reasons for the deficit in naming environmental sounds in MCI patients. Moreover, our results supported the findings that early AD or MCI patients showed central auditory dysfunction even without the peripheral auditory function deficit (Gates et al., 1995). Thus, these pathologic changes in the temporal lobe of early AD may be the predictor of poor naming performance in SN. This further raises the diagnostic potential of an SN test for detecting an early abnormality in MCI patients who may later develop AD (Small et al., 2003).

We have taken the MMSE scores as an index of dementia severity across the spectrum of participants tested in our study. The MMSE was originally developed as a simple screening test at the bedside of patients at increased risk for dementia (Folstein et al., 1975), and it has served this purpose well, particularly when age and education are adjusted (Petersen et al., 2001). However, it has some limitations; it is insensitive to frontal–executive dysfunction and visuospatial deficits. In fact, it relies heavily on verbal response (Bak & Mioshi, 2007), which likely explains in large part that there has been a highly significant correlation between the scores

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of MMSE and BNT (Calero et al., 2002; Larrain & Cimino, 1998). This statement is still a source of debate; as we already mentioned in the introduction, people have often failed in finding a relation between PN deficit and dementia severity. Unfortunately, the current study cannot provide a clear explanation about the low correlation between the MMSE scores and PN.

All participant groups appeared to experience more difficulty with SN, with lower accuracy and slower naming latency in SN than in PN. The performance difference between the two tasks may reflect the difference in cognitive demand for the tasks. Naming a picture needs complex stages that involve a number of mental representations and cognitive processes: (1) visual object recognition, (2) access to the meaning of the stimulus (semantic system), (3) access to the phonological word form, and (4) motor programming and planning of articulation (Indefrey and Levelt, 2004). As for SN, the processing demands of audition differ from those of vision because sounds evolve over time, which potentially places different demands on the nature of auditory "memory" (Handel, 1988). According to Griffiths and Warren (2004), we require both delicate and non-verbalizable analysis of sound sequences for sound recognition. In the auditory domain, sound can be represented in the temporal or spectral (frequency) dimensions, and these two-dimensional temporal frequency representation of a sound contains information that is not available in the time or frequency domain representation alone. As a result, SN requires more sequential and greater association processing than PN.

The difference in task difficulty in SN and PN may tap the function of different hemispheres, and the test results may reflect asymmetric distribution of AD pathology in individual patients. It is well documented that subgroups of AD patients exhibit disproportionate impairments in spatial abilities relative to verbal skills, or vice versa (Albert et al., 1990; Becker et al., 1988; Haxby et al., 1985; Martin et al., 1986; Massman & Doody, 1996; Naugle et al., 1985; Ober et al., 1991). Isolated impairments in either spatial or verbal functions have been reported in a few studies (Crystal et al., 1982; Mesulam, 1983; Pogacar & Williams, 1984). From the different patterns of impairment on traditional clinical tests, we can predict AD patients' performances on experimental cognitive procedures (Delis et al., 1992; Massman et al., 1993). For example, high spatial AD subgroup who showed greater impairment on a verbal test (i.e., confrontation naming) than on a spatial test (i.e., block construction) had difficulty reproducing the local forms (Navon figures; Navon, 1977), a pattern found previously in patients with focal left hemisphere damage (Delis et al., 1988). On the other hand, the high verbal AD patients exhibited a marked deficit in analyzing global forms relative to local forms, a pattern shown previously in patients with focal right hemisphere damage (Delis et al., 1988). Consequently, the distinct dissociations in verbal or spatial ability in AD patients are related in asymmetrical cerebral pathology.

Most AD patients demonstrated more or less comparable impairment in SN and PN accuracy. However, some patients (data points in the upper left corner of the graph in Figure 4) were impaired in SN, a process that might depend substantially on right hemisphere resources. Other patients were disproportionately impaired in PN, a process possibly more related to the function of left hemisphere. Even though a clear distinction between right and left hemispheric difference is still controversial, some evidence shows that the right hemisphere appears to be implicated in naming environmental sound (Eustache et al., 1990; Fujii et al., 1990; Griffiths et al., 1997; Spreen et al., 1965). For example, auditory agnosia—a neurological disorder characterized by a relatively isolated deficit in auditory comprehension despite normal hearing (Vignolo, 1982)—is often termed nonverbal auditory agnosia when the deficit is in recognizing environmental sounds (Albert et al., 1972). Much literature has addressed the questions about the relation of nonverbal auditory agnosia to the hemispheric locus of the lesion and discovered that right hemisphere is deeply involved in processing environmental sounds [see for an extensive review of Clarke et al. (1996) and Griffiths et al. (1999)]. Unfortunately, the issue of correlation between hemispheric asymmetry in AD and the sensory modality in naming tests could not be resolved in the current study because neuropsychological data detailed enough to determine the laterality of cognitive impairments were not available for all patients. This issue is definitely worth further investigation in the future.

In conclusion, this study suggests that naming by auditory features is impaired in AD sooner than that by visual features. Also, SN appears to reflect the severity of the disease better than PN. Collectively, these results suggest that SN tests may prove more useful in early detection and clinical monitoring of AD progression. The establishment of methods to accurately detect early signs of AD becomes increasingly important as techniques for prevention or delay of dementia are being pursued. The SN test will add much to clinicians' armamentarium for detecting early signs of AD and monitoring the progression. Furthermore, we discovered that SN and PN could subtype our AD patients into three groups: those with greater deficits in SN than in PN, those with greater deficits in PN than in SN, and those with equivalent levels of deficits in SN and PN. Future investigation will be required to test our conjecture that SN may efficiently differentiate right hemisphere predominant AD patients from left hemisphere predominant AD patients.

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