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Functional Near-Infrared Spectroscopy Analysis of the Cognitive Functions of Elderly Patients With Hearing Loss

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Background and Objectives: Age-related hearing loss is a modifiable risk factor for mild cognitive impairment (MCI); however, the potential mechanisms linking these conditions remain unclear. Therefore, in this study, we analyzed the cognitive function profiles of elderly patients with hearing loss via functional near-infrared spectroscopy (fNIRS) to determine the cortical activity differences between patients at risk of MCI and those with normal cognition. **Materials and Methods**: Sixty-three elderly patients with bilateral, moderate, or severe hearing loss were prospectively recruited for this study. Their demographic information was obtained, and audiological evaluations and cognitive function tests were performed. Various instruments were used to assess the cognitive and depression domains. Additionally, fNIRS was used to image the brains of the normal group and group at risk of MCI. **Results**: fNIRS analysis of individual cognitive task data revealed that the normal group exhibited significantly higher oxygenated hemoglobin (HbO_2) levels in all cognitive function tasks, except the Stroop color and word test, than the group at risk of MCI. Detailed comparisons of the Brodmann areas revealed that, compared to the group at risk of MCI, normal group exhibited significantly higher HbO_2 levels in the right and left dorsolateral prefrontal cortices, ventrolateral prefrontal cortex, frontopolar cortex, and orbitofrontal cortex in the J1 task, right ventrolateral prefrontal cortex in the J2 task, and right orbitofrontal cortex in the J6 task. **Conclusions**: Measurement of fNIRS signals in the frontal lobes revealed different HbO_2 signals between the normal group and group at risk of MCI during minimal hearing loss. Future studies should explore the causal link between hearing loss and cognitive impairment by analyzing the changes in cognitive function after auditory rehabilitation.

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Keywords: Hearing loss; Cognitive dysfunction; Dementia; Hearing aids; Near-infrared spectroscopy.

Introduction

Dementia is defined as a disorder in which occupational and social functions are severely impaired by a decline in cognition. The prevalence of dementia is estimated to be up to 7% in individuals aged >65 years, but it is higher in developed countries (8%–10%) because of their longer life spans [1]. Aging, certain genetic profiles, and systemic vascular disease are major risk factors for the development of dementia [2]. During the course of cognitive decline, mild cognitive impairment (MCI) can occur, an intermediate condition between age-related forgetfulness and dementia which is defined by subjective changes in cognition, impairment of at least one cognitive domain, preservation of independent functional activities, and the absence of dementia. People with MCI can autonomously engage in the activities of daily life, whereas people with dementia cannot. More than half of all patients with MCI progress to dementia within 5 years [3].

The incidence of hearing loss also increases with age. Approximately one-third of adults aged >65 years experience age-related hearing loss. A previous cohort study demonstrated that age-related hearing loss preceded the onset of clinical dementia by 5–10 years and proposed that age-related hearing loss might serve as a valuable noninvasive clinical biomarker of a future diagnosis of dementia [4].

Evidence that dementia and hearing loss are related has been accumulating. Brain imaging tools such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are widely used to detect functional changes associated with early-stage cognitive decline. Of these methods, functional near-infrared spectroscopy (fNIRS), which monitors cerebral hemodynamic changes evoked by neural activity, yields valuable neuroradiological insights into cognitive domains. fNIRS exploits the fact that biological tissues are relatively transparent to near-infrared light (700–1,000 nm) [5]. When neurons are activated, they consume oxygen delivered by oxyhemoglobin in the adjacent bloodstream, associated with an immediate (albeit slight) decrease in the concentration of oxy-hemoglobin (oxy-Hb) and an increase in the level of deoxyhemoglobin (deoxy-Hb). To compensate for an inadequate oxygen supply, neurovascular coupling increases perfusion in regions of neuronal activity [6]. The enhanced supply of oxygen-rich blood significantly increases oxy-Hb levels and significantly reduces deoxy-Hb concentrations in the local bloodstream.

Several researchers have shown that fNIRS is useful to evaluate changes in cerebral hemodynamics associated with cognitive decline in patients with specific psychopathological diseases, such as MCI and dementia. Katzorke, et al. [7] reported that frontotemporal hemodynamic decreases during the performance of verbal frequency tasks were suggestive of MCI. Lee, et al. [8] aimed to evaluate the hemodynamic activities between the individuals with MCI and subjective memory complaints with fNIRS and showed significantly lower oxy-Hb levels in amnestic type MCI, but not in non-amnestic MCI type, compared to the normal control group. However, no study has compared hemodynamic changes between elderly patients with MCI and those exhibiting normal cognition in the context of moderate-to-severe hearing loss. Herein, we used fNIRS to analyze and compare the cortical activities of patients with hearing loss to clarify whether fNIRS signals can serve as potential neural biomarkers reflecting different hemodynamic changes between subjects at risk of MCI and those with normal cognition. In addition, considering that the prefrontal areas are closely related with memory functions [7,8], we have also analyzed the different hemodynamic activities of prefrontal cortical areas between the normal and MCI at risk group. Evaluating the different hemodynamic changes through fNIRS would provide insight into the novel neuroradiological diagnostic assessments for those with early state of dementia (i.e., MCI) and normal cognition.

Materials and Methods

Participants

We prospectively recruited adult patients >50 years of age who visited the outpatient clinic of a tertiary medical center. At the initial visit, thorough otoendoscopic examinations followed by pure-tone audiogram (PTA) and speech audiometry were performed in all patients. Patients with conductive or mixed hearing loss, chronic otitis media, otosclerosis, Meniere's disease, vestibular schwannoma, and/or other neurological diseases were excluded. The average pure-tone threshold was calculated across the frequencies of 0.5, 1, 2, and 4 kHz. The speech discrimination score was determined using monosyllabic words that were phonetically balanced and presented at 30 dB above the speech recognition threshold. In total, 100 patients (35 males and 65 females) who met the diagnostic criteria for bilateral moderate or severe sensorineural hearing loss (average pure tone thresholds >40 dB HL) were recruited. This prospective single-center study was approved by the Seoul National University Hospital Institutional Review Board (IRB) (no. 2105-073-1218). All participants gave written informed consent in accordance with the Declaration of Helsinki before participating in the study.

Clinical diagnosis of mild cognitive impairment

After the initial clinical and audiological evaluations, all participants were screened in terms of MCI status using the Clinical Dementia Rating (CDR) and the Global Deterioration Scale (GDS) [9]. Both staging examinations were published in 1982 and are currently used by clinicians to assess dementia independent of patient educational levels. The CDR evaluates three domains of cognition (memory, orientation, and judgment/problem solving) and three domains of function (community affairs, home/hobbies, and personal care). Using a 5-point scale (rescaled to 0–3), the CDR rates dementia status (0=no dementia; 0.5=questionable dementia or MCI; 1=mild dementia; 2=moderate dementia; 3=severe dementia). Individuals with CDR scores of 0.5 exhibit mild but consistent forgetfulness and slight impairments in independent functioning in the occupational, shopping, business, and financial affairs domains. The GDS, which is similar to the CDR, provides a rapid clinical rating of dementia severity and has also been used extensively in trials of medications for dementia. The GDS divides dementia into seven stages (1, as-

ymptomatic; 7, late dementia) and thus facilitates detailed evaluation of subjective cognitive impairment. The GDS 2 explores age-associated memory impairment, and the GDS 3 is principally concerned with MCI status [10].

Although both the CDR and GDS scales can identify patients in various stages of cognitive impairment, neither score is closely associated with clinically relevant conditions, i.e., normal aging, MCI, or mild Alzheimer's disease (AD). However, previous researches established a significant relationship between the CDR and GDS scores via cross-sectional regression analysis [11]. Petersen, et al. [12] considered that a CDR score of 0.5 combined with a GDS score of 3 might distinguish groups with MCI and mild AD. A similar study by Choi, et al. [11] suggested that MCI patients with initial CDR scores of 0.5 might include some subjects with GDS scores of 2–4. Given these diverse MCI diagnostic criteria, we broadly defined patients at risk of MCI (hereafter, MCI patients) as those with CDR scores of 0.5 or 1 and/or GDS scores of 2 or 3. Using these diagnostic criteria, all participants were divided into normal and MCI groups.

Assessment of cognitive functions

One of our primary outcome measures was cognitive functioning. To compare this between the normal and MCI groups, we employed various cognitive assessment tools including the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Battery (CERAD-K), the Korean version of the Montreal Cognitive Assessment (MoCA-K), and the Korean version of the Instrumental Activities of Daily Living (K-IADL).

The CERAD-K is a standardized clinical and neuropsychological evaluation battery for assessing AD [13]. The CERAD-K comprises 10 tests: verbal fluency (J1), the Boston Naming Test (J2), the Korean version of the Mini-Mental State Examination (MMSE-KC; J3), a word list memory test (J4), a constructional praxis test (J5), a word list recall test (J6), a word list recognition test (J7), a constructional praxis recall test (J8), the Trail-Making Test (J9), and a STROOP word and color test. Of these tests, the J1, J2, J4, J6, and STROOP word and color tests were utilized in the present study.

The MoCA-K was introduced by Lee, et al. [14] and is based on the original English version of the MoCA (version 7.1); this test rapidly screens those with suspected MCI. Similar to the CERAD-K, the MoCA-K evaluates eight cognitive domains: 1) attention and concentration, 2) executive functioning, 3) memory, 4) language, 5) visuo-constructional skills, 6) conceptual thinking, 7) calculations, and 8) orientation. One point is added if a participant reports at least 6 years of education. The total possible score is 30 points, and a score of ≤22 is considered indicative of cognitive impairment.

The K-IADL also assesses impairment in daily living activities such as using the telephone, housekeeping, using public transportation, shopping, doing laundry, and watching television [15]. The K-IADL has a 4-point scale: independent/normal=0; a need for some help/mild impairment=1; a need for a lot of help/moderate impairment=2; and impossible=3. The total score ranges from 10 to 33, with higher scores indicating greater dependency on other people in daily living.

Identification of anxiety and depression symptoms

Anxiety and depression symptoms were explored using the Patient Health Questionnaire-9 (PHQ-9), which comprises nine questionnaire modules and is used to screen for depression in clinics. Previous studies demonstrated that patients with amnestic MCI were more likely to develop depression compared to those with normal cognitive function, and subjects with both MCI and depression exhibited poorer executive function, flexibility, and lexico-semantic function than MCI patients without depression [16]. The PHQ-9 rates nine items from "0" (not at all) to "3" (nearly every day), and the answers to all questions are summed to determine the overall severity of depressive symptoms (range: 0–27). Typically, PHQ-9 scores ≥10 indicate the existence of depressive symptoms.

fNIRS data measurement and hemodynamic feature quality

Raw fNIRS data were recorded at a sampling rate of 8.138 Hz as a time series of light intensity values for each channel using a commercial, wireless, continuous-wave high-density near-infrared spectroscopic system (NIRSIT; OBELAB Inc.). The fNIRS system features 24 laser diode sources emitting at two wavelengths (780/850 nm) and 32 photodetectors; the system covers the bilateral frontal lobes (eight Brodmann areas). We compared all eight Brodmann areas in the bilateral dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), frontopolar prefrontal cortex, and orbitofrontal cortex (OFC) [17]. A schematic illustration of the task processes is also depicted in Fig. 1.

Cognitive tasks were performed as fNIRS recordings proceeded. Five tasks were semi-randomized between subjects. Task J1 (a verbal frequency task) evaluates semantic word fluency; as many descriptive words as possible (i.e., for animals) are generated within 30 seconds. The control task involves simply reading letters on a computer monitor. Task J2 measures the naming of figures shown on the monitor; the corresponding control task simply involves the reading of letters. Task J4 evaluates working memory capacity; 20 everyday word items are conveyed via a loudspeaker (female voice) at

60–65 dB SPL, and the subjects report all words that they can remember within a 30-s period, without any feedback. Task J6 measures delayed memory retrieval after 5 minutes. The STROOP task measures cognitive control of executive function; the colors of letters written in red, blue, pink, green, yellow, or black are recorded within 30 seconds. The control task involves

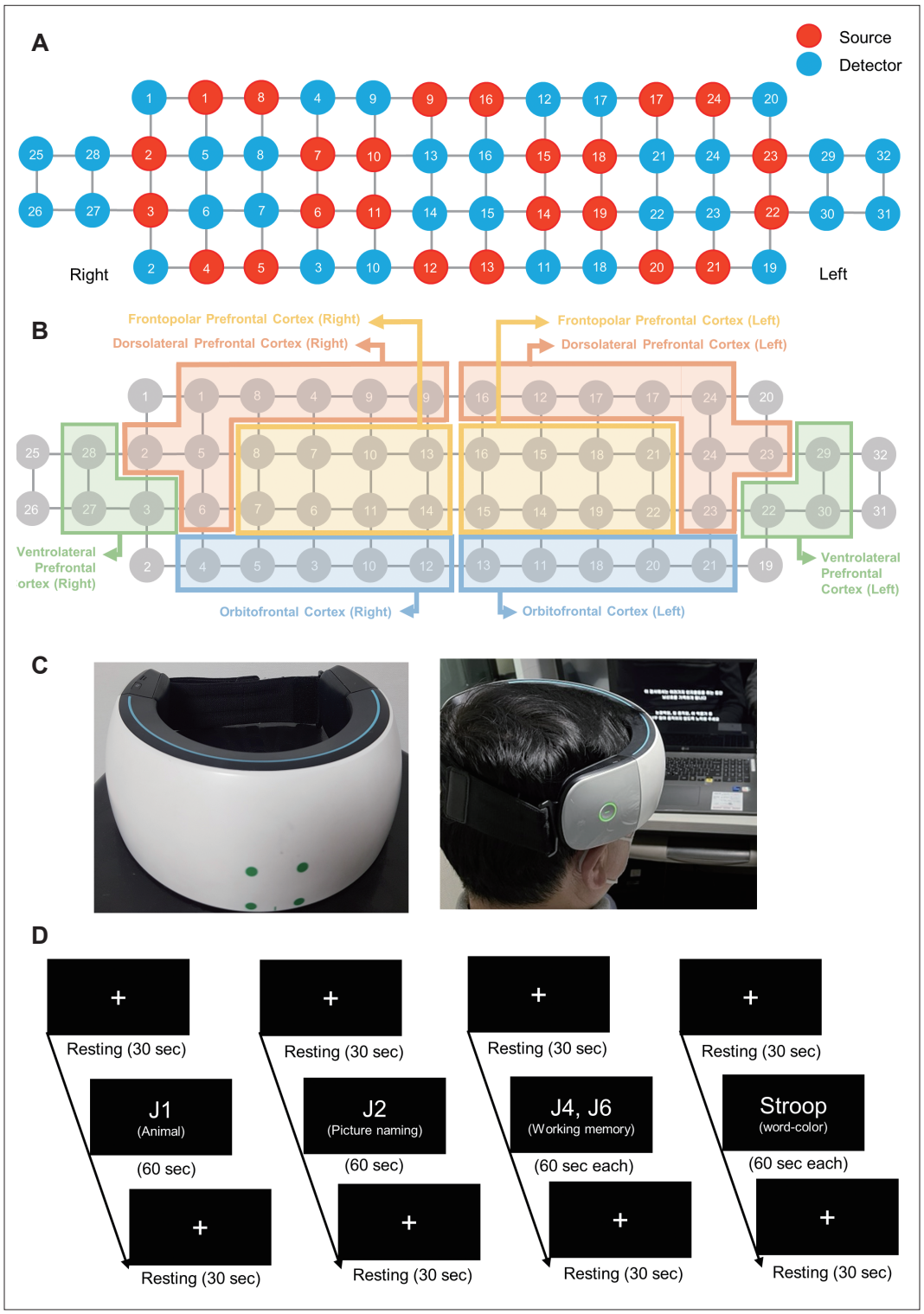

Fig. 1. Basic research methods of the study. The arrangement of fNIRS sources and detectors (A), the locations of the 48 region-of-interest channels (B), an fNIRS device and a photo of performing the fNIRS test (C), and a schematic illustration of the task processes (D). fNIRS, functional near-infrared spectroscopy.

simply recording the original word colors. A 30-s rest time was mandatory between each test, and a 3-min intermittent break was allowed given the relatively long period required for completion of all tasks (approximately 15–20 minutes).

fNIRS data analysis

The modified Beer-Lambert law was used to convert the fNIRS time series into oxygenated hemoglobin (HbO_2) concentrations [18]. Artifacts such as ambient noise, motion-related fluctuations, and cardiac pulse-related signals were eliminated via filtering at a signal-to-noise ratio (SNR) <30 dB [19]. Subject raw data were converted to remove unwanted signal components using typical filtering algorithms including principal component analysis, wavelet-based detrending, and bandpass filtering.

Discrete cosine transform

In each 30-s trial, the first and last 5% of all fNIRS data were excluded from the analyses because of possible measurement errors at the beginning and end of each trial. Each baseline was corrected to -5 to 0 seconds and each block to 0 to 30 seconds. Although seldom required, rejected channels were interpolated and replaced with neighboring average signals. The numbers of rejected channels did not differ significantly between the groups. The parameters used for hemodynamic conversions were taken from a previous report [20].

Statistical analysis

All data are presented as mean±standard deviation. Demographic, clinical, and neurophysiological variables were compared between the groups. The clinical results of the cognitive function, anxiety, and depression tests of the normal and MCI groups were compared using the Mann-Whitney U test. As the groups differed in size, the independent t-test was used to evaluate group differences in accumulated HbO_2 levels, with p-value <0.05 considered statistically significant. Pearson correlation coefficients (r values) were calculated for the associations between the CERAD-K scores and the hemodynamic responses during the five tasks for all eight brain areas. All statistical analyses were conducted with SPSS (version 25.0; IBM Corp.) and MATLAB software (R2019b; MathWorks, Inc.). The statistical results were visually displayed using GraphPad Prism software (version 9.0.0; GraphPad Software Inc.). A p-value <0.05 was considered statistically significant.

Results

Demographic information

Of the initial 100 patients, 63 were finally enrolled. Using our MCI definition (CDR score=0.5 and/or GDS score=2 or 3), 49 patients (average age=73.6±7.5 years) were categorized as normal, and the remaining 14 (average age=74.7±6.8 years) were categorized as MCI. Neither the mean pure-tone threshold nor the word recognition score differed significantly between the normal and MCI groups (51.9±12.5 dB and 50.2±8.3 dB for the right side [p=0.879, Mann-Whitney U test]; 54.8±15.1 dB and 57.9±20.2 dB for the left side [p=0.230, Mann-Whitney U test]; 81.0%±14.6% and 75.1%±19.9% for the right side [p=0.230, Mann-Whitney U test]; and 83.9%±10.2% and 78.0%±13.9% for the left side [p=0.078, Mann-Whitney U test], respectively) (Table 1). Most participants, i.e., 37 patients (37/48, 77.1%) in the normal group and 9

Table 1. Clinical outcomes revealed by cognitive function, anxiety, and depression tests of the normal and MCI groups

	Normal group	MCI at risk group	p-value
Number of patients (M:F)	49 (17:32)	14 (10:4)	
Age (yr)	73.6±7.5	74.7±6.8	0.573
PTA (dB)			
Right	51.9±12.5	50.2±8.3	0.879
Left	54.8±15.1	57.9±20.2	0.230
WRS (%)			
Right	81.0±14.6	75.1±19.9	0.230
Left	83.9±10.2	78.0±13.9	0.078
Education level (graduated until)			
College	16	3	
High school	12	5	
Middle school	10	0	
Elementary school	7	4	
No education	4	2	
CDR	0.0±0.0	0.3±0.3	<0.001
GDS	1.8±0.3	3.0±0.3	<0.001
CERAD-K			
J1 (Word fluency)	14.2±4.1	12.0±4.4	0.122
J2 (Boston naming test)	11.1±2.1	10.4±2.9	0.448
J4 (Word list memory)	15.6±3.8	10.4±2.6	<0.001
J6 (Word list recall)	4.6±2.0	2.0±1.6	<0.001
STROOP word-color	36.1±11.2	29.0±9.0	0.019
MOCA-K	22.9±3.9	18.0±5.4	0.001
K-IADL	7.1±1.5	7.6±4.5	0.297
PHQ-9	2.7±2.3	3.3±2.3	0.348

A p-value <0.05 was considered statistically significant. Values are presented as mean±standard deviation unless otherwise indicated. MCI, mild cognitive impairment; M, male; F, female; PTA, pure-tone audiogram; WRS, word recognition score; CDR, Clinical Dementia Rating; GDS, Global Deterioration Scale; CERAD-K, Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Battery; TMT, Trail-Making Test; K-IADL, Korean version of the Instrumental Activities of Daily Living; PHQ-9, Patient Health Questionnaire-9; MOCA-K, Korean version of the Montreal Cognitive Assessment

(9/14, 64.3%) in the MCI group, chose to undergo auditory rehabilitation with hearing aids.

Clinical outcomes cognitive function and anxiety & depression tests

The clinical results of the cognitive function, anxiety, and depression tests for the normal and MCI groups are presented in Table 1. The CERAD-K and MOCA-K scores were both lower in the MCI group (Mann-Whitney U test), reflecting much more severe cognitive decline in that group than in the control group. The scores on the J4 (word list memory), J6 (word list recall), STROOP word-color, and MOCA-K tests were significantly higher in the normal group.

The K-IADL score was higher in the MCI group, indicating that these patients depended much more on others in daily living than did those in the normal group (p=0.297, Mann-Whitney U test), although statistical significance was not attained. The scores on the PHQ-9 test, which explores anxiety and depression symptoms, were higher for the MCI group but did not indicate severe conditions in either group (PHQ-9 scores ≥10 indicate the existence of depressive symptoms).

fNIRS results: hemodynamic response

On most cognitive function tasks, the normal group exhibited significantly higher HbO_2 concentrations; the single exception was the STROOP word-color task (Fig. 2A). The mean accumulated HbO_2 concentration (sum of the values across all areas and cognitive tasks) was significantly higher in the normal group (0.31 μM) than in the MCI group (0.11 μM) (p= 0.035, independent t-test) (Table 2 and Fig. 2B), revealing an overall reduction in frontal lobe cortical activity in the MCI group.

In terms of group differences in the HbO_2 concentrations in the four bilateral frontal regions, the normal group exhib-

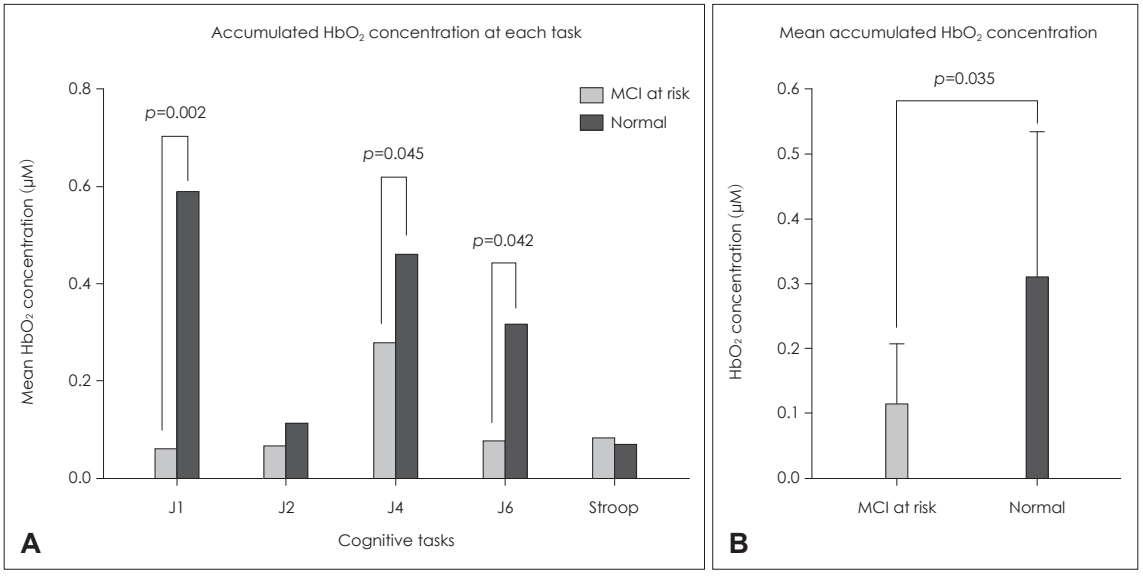

Fig. 2. Comparison of accumulated HbO_2 concentration at each task and mean accumulated HbO_2 concentration between the normal and MCI at risk group. A: The normal group exhibited significantly higher HbO_2 concentrations during the J1, J4, and J6 tasks. B: The mean accumulated HbO_2 concentration (summed across all areas and cognitive tasks) was significantly greater in the normal than the MCI group, revealing an overall reduction in cortical activity in the frontal lobe of patients at risk of MCI. HbO_2, oxygenated hemoglobin; MCI, mild cognitive impairment.

Table 2. Accumulated HbO_2 concentrations (μM) during each task, and the average HbO_2 concentration (μM) derived by summing all area data collected during the cognitive tasks

Cognitive task	HbO_2 concentration (μM)		p-value
	Normal group	MCI at risk group	
J1 (Word fluency)	0.591098181	0.061662951	0.002
J2 (Boston naming test)	0.112639322	0.067816556	0.950
J4 (Word list memory)	0.462381636	0.279503191	0.045
J6 (Word list recall)	0.317429743	0.077695485	0.042
STROOP word-color	0.070642003	0.084063249	0.830
Average	0.310838177	0.114148286	0.035

HbO_2, oxygenated hemoglobin; MCI, mild cognitive impairment

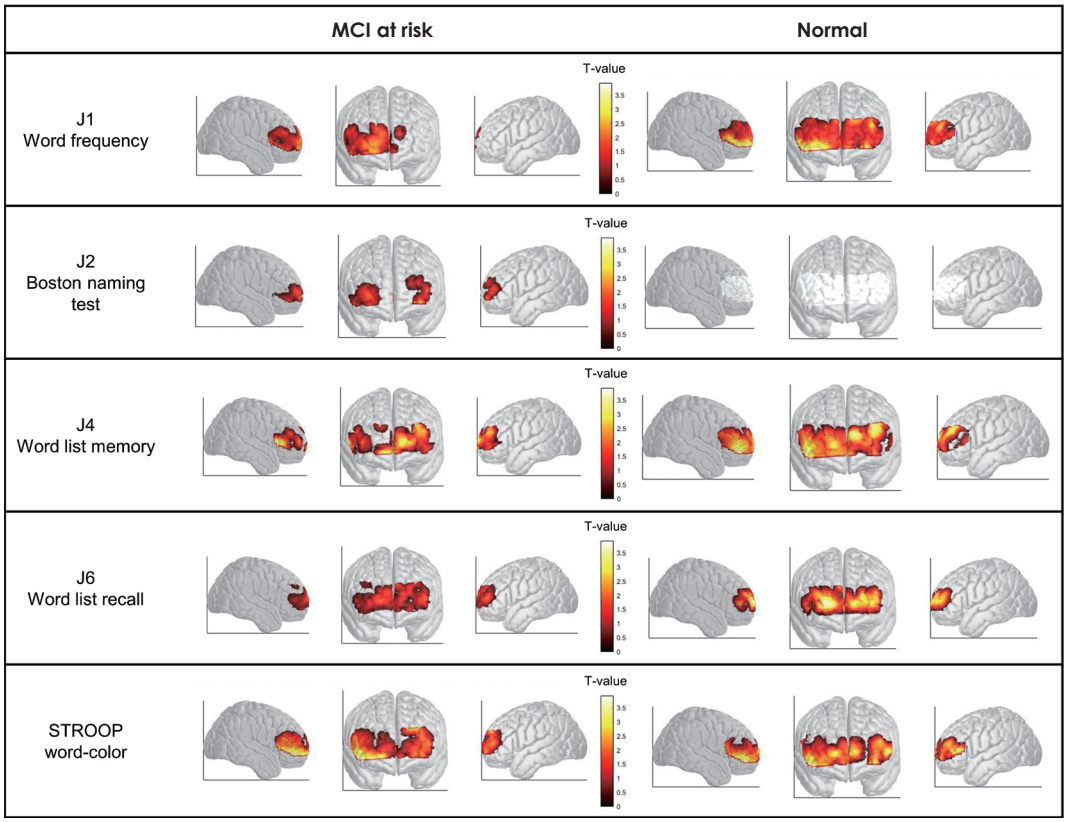

Fig. 3. Summary of general linear model statistical maps derived using the oxygenated hemoblobin (HbO_2) hemodynamic response time series for each of eight Brodmann areas during five different cognitive tasks performed by the two groups. MCI, mild cognitive impairment.

ited an overall higher HbO_2 concentration across the entire frontal lobe, and the MCI group showed asymmetric frontal responses with lower HbO_2 concentrations (independent t-test) (Supplementary Fig. 1 in the online-only Data Supplement). Interestingly, detailed comparisons between the Brodmann areas revealed that the normal group had significantly higher HbO_2 concentrations than the MCI group in the right DLPFC, left DLPFC, VLPFC, frontopolar cortex (FPC), and OFC on the J1 task; in the right VLPFC on the J2 task; and in the right OFC on the J6 task. However, significantly lower HbO_2 concentrations were observed in the normal group for the left DLPFC on the J4 task, the left DLPFC on the J6 task, and the left VLPFC on the STROOP task. General linear model statistical maps based on the HbO_2 hemodynamic response time series in the eight Brodmann areas during the five different cognitive tasks performed by the two groups are shown in Fig. 3.

Discussion

The goal of this study was to evaluate whether fNIRS signals can serve as potential neural biomarkers reflecting hemodynamic changes in elderly patients with hearing loss, and especially whether the signals differed between subjects at risk of MCI and those with normal cognition. In addition, the fNIRS-derived indices, including those for mean HbO_2 in the left and right prefrontal cortex (PFC), were significantly and positively correlated with the clinical scores. Our findings establish a theoretical basis for the use of fNIRS to screen for and diagnose cognitive impairment.

Several hypotheses can be proposed to explain the potential relationship between prolonged auditory deprivation and cognitive impairment: general neurodegeneration caused by aging; cognitive impairment caused directly by auditory deprivation; and the effect of cognitive load on perception (i.e., the impact of depression on cognitive load). An overall decrease in gray matter volume, cortical thinning, and an increased cerebrospinal fluid level are common neurological characteristics of aging [21]. According to the "common cause" hypothesis, hearing loss and cognitive impairment coincide because of the inevitable neurodegenerative course of the aging brain [22]; a shared age-related factor is presumed to trigger degeneration of both cognitive and non-cognitive processes. This is in line with our results, which revealed overall decreases in the cognitive function test scores in both the normal and MCI groups. Nonetheless, it must be noted that

both age-related hearing loss and cognitive impairment are multifactorial and heterogenous, and many factors including microcirculatory insufficiency, general health, genetic components, and/or oxidative stress can also affect both conditions simultaneously [23]. Future studies are needed to distinguish the factors that cause cognitive impairment from those that trigger hearing loss.

Previous studies have performed fNIRS among participants with MCI and healthy controls for the diagnosis of various neurodegenerative disorders as an alternative functional neuroimaging tool. Yeung, et al. [24] revealed that individuals with MCI, unlike healthy controls, did not exhibit significant activation of bilateral frontal areas during high working memory load. Within the verbal fluency task, Katzorke, et al. [7] found that the MCI group showed a decreased activation of bilateral inferior frontotemporal regions compared with the normal group. Our result is in line with these studies, revealing that the hemodynamic activation of frontal lobe, as evidenced by HbO_2 signal patterns, was significantly degraded within the MCI group than that of the normal group when the effect of hearing loss was minimized. This certainly implies that the MCI group might have failed to recruit compensatory frontotemporal resources in response to increased task demands.

On the other hand, there have been discrepancies over the changes and outcomes of hemodynamic responses in MCI participants. Kim, et al. [25] found a higher hemodynamic activation within the PFC in individuals with MCI during a verbal fluency task, suggesting that MCI patients required more hemodynamic resources than the healthy control group to compensate for functional loss during the same task. Similarly, Yoon, et al. [17] found a hyperactivation of the right PFC in patients with non-amnestic MCI and hypoactivation in those with amnestic MCI during the STROOP test. In this context, the authors assumed that the PFC of individuals with MCI would rather actively engage in neural compensatory efforts to overcome functional decline of brain due to MCI.

Our fNIRS data revealed lower hemodynamic concentrations in the MCI group compared to the control group during the word fluency (J1), working memory (J4), and memory retrieval (J6) tasks in terms of average HbO_2 concentrations (Table 2). The sensory deprivation hypothesis [26] postulates that prolonged peripheral auditory deprivation affects the brain structure, triggering compensatory cortical reorganization and neural alterations and thus disrupting the normal cognitive and emotional processes [23], as evidenced by reduced grey matter volumes in the auditory cortices [27]. Several human studies supported the association between age-related hearing loss and a smaller brain volume, concluding that hearing impairment accelerated the progression of brain atrophy [28,29]. The fMRI study of Peelle, et al. [30] revealed such an association; moderate peripheral auditory deprivation triggered downregulation of neural activities in specific cortical areas (i.e., the bilateral superior temporal gyri, thalamus, and brainstem) during speech processing and may also have contributed to gray matter volume losses in the primary auditory cortex and/or frontal cortex [30,31]. Specifically, we found that the MCI group exhibited significant HbO_2 reductions in the prefrontal regions compared to the normal group. Given that the gray matter declines in the PFC reduced the HbO_2 level in the MCI group, especially during working memory tasks, our results shed light on the strong link between cognitive decline and hemodynamic inactivation within PFC.

The PFC is commonly known to be the cognitive cortex and responsible for higher-level neural information processing functions. Specifically, within the PFC, the DLPFC generally occupies the key position in working memory, attention, and executive functions, which is closely related to dual-tasking ability [32]. Zhang, et al. [32] showed that the mean HbO_2 concentration of patients at three different stages of AD (subjective cognitive decline, MCI, and AD) during resting state decreased sequentially in the Lt. DLPFC, indicating that the impairment of Lt. DLPFC may be the crucial cause for the aggravation of AD. Similar with our study protocol, Uemura, et al. [33] revealed a reduced activation in the MCI group at bilateral DLPFC during the memory retrieval task of ten target words. Our results are in accordance with these results, demonstrating a significantly lower HbO_2 concentration for the MCI group at bilateral DLPFC during J1 task. However, it was also noted that Lt. DLPFC during J4 and J6 tasks conversely showed a significantly reduced HbO_2 concentration within the normal group. These paradoxical hemodynamic responses may be due to the involvement of default mode network (DMN), which is primarily associated with the medial frontoparietal network, particularly the dorsomedial PFC, and activated while an individual is at rest or during mind wandering. That is, the DMN is deactivated to minimize distractions from the surroundings when an individual is focused on performing a specific task and the attention is required [34]. Thus, it can be hypothesized that the function of the DMN may have been deteriorated in patients with MCI, resulting in the abnormal activation during cognitive tasks and increase of HbO_2 concentration. A recent fMRI study by Høgestøl, et al. [35] supports this theory, showing higher DMN activity in fatigued subjects with multiple sclerosis than those with depression. To overcome these converse results, future researches with functional connectivity are guaranteed to clearly investigate hemodynamic differences and functional

relationships between groups within each cortical area.

With respect to the cognitive performance results, this study demonstrated significant differences in J4, J6, and STROOP word-color test results between the normal and MCI groups (i.e., left DLPFC on the J4 and J6 task, and left VLPFC on the STROOP task), but not in J1 and J2. These results suggest that impairments in the MCI group are more pronounced in cognitive domains associated with working memory, episodic memory retrieval, and cognitive control. These tasks are closely related to the function of the DLPFC, medial temporal lobe, hippocampus, and anterior cingulate cortex, indicating potential dysfunction in these regions [32,36,37]. In contrast, J1 and J2, which are primarily related to language processing and semantic memory, did not show any significant differences, suggesting that these cognitive domains might be less affected in the early stages of cognitive impairment observed in MCI. Additionally, detailed comparisons between the Brodmann areas (Fig. 3) indicated that during the J4, J6, and Stroop test tasks, the left DLPFC and VLPFC show increased HbO_2 concentrations in the MCI group. This increase is likely a compensation hypothesis, reflecting the brain's effort to recruit additional neural resources to maintain cognitive performance and compensate for various neural or behavioral deficits [38].

Although hearing loss has been primarily correlated with depressive symptoms, increased levels of depression can also exert a significant negative impact on cognitive decline independent of hearing loss. This negative effect may be explained by the hypothesis that depression increases the cognitive load; this is the "cognitive load on perception" hypothesis. Moreover, isolation caused by anxiety and/or depression may also exacerbate cognitive decline; this is the "information degradation" hypothesis [39]. Our results are consistent with the latter association; the PHQ test scores were higher in the MCI group, although statistical significance was not attained. Despite these possible explanations, discrepancies are still apparent regarding the significance of the relationship between depression and cognition. Indeed, our study does not clearly show a causal relationship; depression may independently induce cognitive decline or hearing loss may exert an additional negative influence on the progression of cognitive loss. Further longitudinal studies on changes in cognitive function after treatment of depression and/or auditory rehabilitation are needed to corroborate the relationships among hearing loss, depression, and cognitive decline.

Given that all participants showed at least moderate sensorineural hearing loss, auditory rehabilitation (hearing aids or cochlear implants) can increase hearing ability and may even suppress cognitive decline. In other words, sensory stimulation may prevent a decrease in gray matter volume. A future longitudinal study should use fNIRS both pre- and post-treatment (i.e., auditory rehabilitation with hearing aids or cochlear implants) to analyze the impact of auditory rehabilitation to changes in cognitive function, giving an insight to a possible association between hearing loss and cognitive function decline. Also, other neuro-radiological imaging methods including fMRI could help identify all cerebral hemodynamic responses of the brain.

This study has several limitations, in terms of its design and methodology, which may affect the interpretation of the results. First, the number of patients, especially in the MCI group, was relatively small, reducing the statistical power. Second, fNIRS mainly targeted the bifrontal cortex; we lacked neuro-radiological data on other cortical areas. Third, we did not consider whether participants were right- or left-handed. Thus, any laterality of neural activation was not explored when interpreting the fNIRS data. Fourth, we did not measure the levels of serum biomarkers, which are known markers of cognitive decline. For example, amyloid-beta (Aβ), tau, α-synuclein, and TAR DNA-binding protein 43 (TDP-43) are known serum biomarkers of proteinopathies in individuals with neurodegenerative diseases. Especially, deposition of Aβ is a distinct neuropathological feature of AD [40] and may thus afford a more accurate diagnosis of MCI. Despite these limitations, future work will focus on the possible preventative role played by auditory rehabilitation in cognitive function decline.

In conclusion, measurements of fNIRS signals from the frontal lobes after minimizing the effect of hearing loss revealed that the HbO_2 signal patterns differed between the normal group and the group at risk of MCI. Our findings establish a theoretical basis for the utility of fNIRS in terms of screening for and diagnosing cognitive impairment. Future studies should explore the causal link between hearing loss and cognitive impairment by seeking improvements in cognitive function after hearing rehabilitation.

Supplementary Materials

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Conflicts of Interest

The authors have no financial conflicts of interest.

Author Contributions

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