Early Detection of Mild Cognitive Impairment and Mild Alzheimer's Disease in Elderly using CBF Activation during Verbally-based Cognitive Tests

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Abstract: With the goal of promoting a fruitful and healthy longevity society, this paper presents a verbally-based cognitive task and an early detection method of dementia and mild cognitive impairment for elderly. As designed with conscious of daily conversation, the task is done by verbally responding to questionnaire. An elderly firstly talks about the topics of favorite season, travel, gourmet, and daily life, and then he/she does three cognitive tasks of reminiscence, category recall, and working memory. With the use of the functional near-infrared spectroscopy (fNIRS), which can measure cerebral blood flow activation non-invasively, we had collected 42 CHs fNIRS signals on frontal and right and left temporal areas from 22 elderly participants (7 males and 15 females between ages of 64 to 89) during cognitive tests in a specialized medical institute. All participates are classified into three clinical groups: elderly individuals with cognitively normal controls (CN), patients with mild cognitive impairment (MCI), and mild Alzheimer's disease (AD). In this paper, we report a task effect measurement of the verbally-based cognitive task by the statistical tests of fNIRS signals, and then report the examination of the detection performance by cross-validation using proposed Bayesian classifier, which can discriminate among elderly individuals with three clinical groups: CN, MCI, and AD. Consequently, empirical result indicated that total accuracy rate is more than 95% and the result suggests that proposed approach is adequate practical to screen the elderly with cognitive impairment.

1 INTRODUCTION

It is no secret that dementia is one of the most pressing challenges in developed countries. Current estimates indicate 35.6 million people worldwide are living with dementia but with the world's populations aging, the World Health Organization estimates that number will nearly double every 20 years, to an estimated 65.7 million in 2030, and 115.4 million in 2050. With this serious situation, the first G8 summit on dementia was held in London in December 2013 in order to start global action against dementia, and policy papers of G8 dementia summit agreements (RDD/10495, 2013) were published.

In Japan, the Japanese Ministry of Health, Labour and Welfare (MHLW) has begun projects to improve dementia treatment and quality of life from 2008, and in 2012, MHLW announced five-year measures for dementia care, *Orange Plan*, in which hospitals and geriatric facilities centered dementia care should be shift to home care support and community centered dementia care, for sustaining the elderly's activities of daily life and quality of life. The plan includes provision of various support such as watch over, health care and rehabilitation to community life support service (Nakanishi and Nakashima, 2013).

On the other hand, it is also important to develop a diagnostic tool which can early detect elderly with dementia. To screen for dementia and cognitive impairment, a questionnaire test such as Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Revised Hasegawa's Dementia Scale (HDS-R) (Imai and Hasegawa, 1994), Clinical Dementia Rating (CDR) (Morris, 1993), and Memory Impairment Screen (MIS) (Buschke et al., 1999), is com-

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monly used. These are simple and well-formed tests, but there are several problems in addition to time-consuming consultation with an expert in psychological testing.

- Score may include subjectivity.
- Score may be influenced by education, social class, and gender deference.

MMSE is in widespread use as a practical and clinically useful test for practitioners. However, even if it takes about 10 minutes, patient load goes over the capacity of a general practitioner.

In our previous study, we have studied novel approaches for the early detection of cognitive impairment in the elderly, in which we focused on the prosodic features of speech sound during the subject's answers to the questionnaire; the first was to detect signal and prosodic signs of cognitive impairment (Kato et al., 2011), the second was to take a measurement of cerebral blood flow (CBF) (Kato et al., 2012). We then have developed a prototype of prosody-CBF hybrid screening system and discussed the cost-effectiveness and the discrimination performance (Kato et al., 2013).

In such situation, this paper provides a new discriminative method of MCI and mild AD without score of questionnaire-based test, with the use of just speech voice and fNIRS signals during daily conversation. In Section 3, we firstly propose a block-designed verbally-based cognitive training task for elderly with mild cognitive impairment. As designed with conscious of daily conversation, the task is done by oral answering some questionnaire. An elderly firstly talks about the topics of favorite season, travel, gourmet, and daily life, and then he/she does three cognitive tasks of reminiscence task, category recall, and working memory task. With the use of the functional near-infrared spectroscopy (fNIRS), which can measure cerebral blood flow activation non-invasively, we had collected fNIRS signals on frontal and right and left temporal areas from elderly participants during cognitive tests in a specialized medical institute. In Section 5, we report a task effect measurement by the statistical tests of fNIRS signals. In Section 6, we also report the examination of the detection performance by cross-validation using proposed Bayesian classifier, which can discriminate among elderly individuals with three clinical groups: CN, MCI, and AD.

2 WHY FOCUS ON THE VERBALLY-BASED COGNITIVE ACTIVITIES

The Nun Study is known as a continuing longitudinal study to examine the onset of Alzheimer's Disease focusing on the linguistic ability. Snowdon et al. (Snowdon et al., 1996) found that an essay's lack of linguistic density (e.g., complexity, vivacity, fluency) functioned as a significant predictor of its author's risk for developing Alzheimer's disease in old age. How about the verbal performance?

Relatively infrequent in the literature, but there are several studies that suggest associations with Alzheimer's disease and verbal performance. Taler et al. have reported language performance (Taler and Phillips, 2007), and especially comprehension of grammatical and emotional prosody (Taler et al., 2008) are impaired in elderly patients with Alzheimer's disease (AD). Hoyte et al. (Hoyte et al., 2009) reported that the components of speech prosody are useful for detecting the syntactic structure of speech. Pérez Trullen and Modrego Pardo (Trullen and Pardo, 1996) investigated aprosody in AD and multi-infarct dementia (MID), and reported that aprosody is more frequent and severe in AD. McDowd et al. (McDowd et al., 2011) reported some interesting findings about verbal fluency in healthy aging, Alzheimer's disease, and Parkinson's disease. Carter et al. (Carter et al., 2012) suggested that assessment of patients with mild cognitive impairment (MCI) should include language and semantic memory tests in addition to typical episodic memory tests, as changes within this domain might be a sensitive indication of incipient AD, on the basis of a cross-sectional investigation compared cognitively normal age-matched controls with patients with mild AD and MCI using a detailed neuropsychological assessment. Cognitive models of voice processing by Belin et al. (Belin et al., 2004) propose that there is parallel processing of identity information and emotional content from voices. Hailstone et al. have provided intriguing reports about voice processing (Hailstone et al., 2011) and accent processing (Hailstone et al., 2012) in dementia, on the basis of neuropsychological and neuroanatomical analysis of voice processing.

These reports suggest the possibility of using prosodic feature extracted from elderly speech to screen for dementia. In our previous studies (Kato et al., 2011), (Kato et al., 2012), (Kato et al., 2013), we have focused on the prosodic feature of elderly's speech sounds during orally answering some questionnaire, for early detection of mild cognitive impairment (MCI) and mild Alzheimer's disease (AD) in the

Table 1: A Breakdown List of Participants (N=22).

Age	64-70	71-75	76-80	81-85	86-90	91-93	Total
Male	0(0,0,0)	2(2,0,0)	1(1,0,0)	1(0,0,1)	2(0,2,0)	1(0,1,0)	7(3, 3,1)
Female	4(1,3,0)	2(1,1,0)	4(1,2,1)	3(1,0,2)	2(0,1,1)	0(0,0,0)	15(4, 7,4)
Subtotal	4(1,3,0)	4(3,1,0)	5(2,2,1)	4(1,0,3)	4(0,3,1)	1(0,1,0)	22(7,10,5)

Value in bracket means the number of subjects in CN, MCI, AD clinical groups.

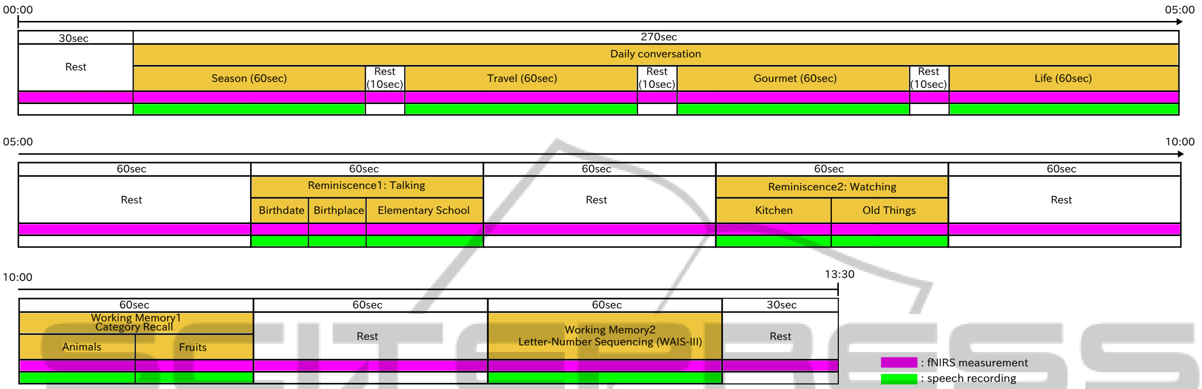

Figure 1: Block Design Task of Cognitive Tests.

elderly.

From the results of the studies, we have designed a verbally-based cognitive training task for elderly with MCI and mild AD. In this paper, we firstly evaluate comparatively the CBF activation during the tasks in cognitively normal controls (CN) and patients with MCI and mild AD. Secondly we propose a Bayesian-based discriminative method of CN, MCI, and AD.

3 VERBALLY-BASED COGNITIVE TASK

3.1 Participants

Twenty two Japanese subjects (7 males and 15 females between the ages of 64 and 93 years) participated in this study. Table 1 shows the breakdown list of participants. In this study, all participants are classified into three clinical groups: elderly individuals with cognitively normal controls (CN), patients with mild cognitive impairment (MCI), and mild Alzheimer's disease (AD). All participants in disease groups are clinically conditioned that the CDR of a participant in MCI group and AD group corresponds to CDR0.5 and CDR1, respectively. The MMSE scores were distributed with 29.30 ± 0.96 (CN), 28.63 ± 1.85 (MCI), and 23.40 ± 2.51 (AD).

3.2 Cognitive Tasks

To measure brain function of an elderly during various cognitive tests including HDS-R, we have made a block designed task shown in Fig. 1, and then conducted simultaneous voice-fNIRS measurement during cognitive tests.

Firstly a participant talks with a clinical psychotherapist (they meet for the first time) about favorite season, travel, gourmet, and daily life. And then, he/she does two reminiscence tasks (1. talking about birthdate and birthplace, 2. watching old-style kitchen and old things), category recall (animals and fruits), and working memory tasks. Under the category recall task, the participant says the name of animals and fruits as many as he/she knows. As the the working memory task, we have adopted letter-number sequencing, a working memory index from Wechsler Adult Intelligence Scale-Third Edition (WAIS-III(Wechsler, 1997)). Under the task, the participant is told three numbers and *hiragana*, a Japanese syllabary, characters and then replies them with sorted in ascending and dictionary order, respectively.

These eight tasks are done for 60 seconds after rest gazing at a single point on the display for 60 seconds interval, and it takes thirteen minutes in the total.

4 fNIRS MEASUREMENT

Functional near-infrared spectroscopy (fNIRS) can measure neural activity of the cerebral cortex using

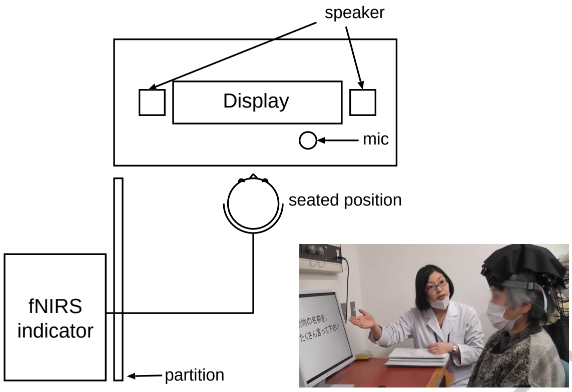

Figure 2: Snapshot of fNIRS measurement of an elderly participant having a cognitive test.

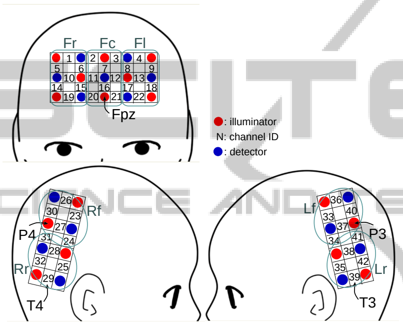

Figure 3: Channel arrangement of fNIRS measurement.

infrared rays that are safe to living organisms (Villringer and Chance, 1997). fNIRS monitors regional relative changes of oxy/deoxygenated hemoglobin concentration to measure cortical activation utilizing the tight coupling between neural activity and regional cerebral blood flow (Villringer and Firnafl, 1995). This measurement method requires only compact experimental systems and can eliminate physical restraint from a subject by non-invasive procedures. Fig. 2 shows a snapshot of fNIRS measurement of an elderly participant having a cognitive test. As the figure, an elderly participant, with 32 fNIRS probes mounted on his/her head, seats in front of the LCD display and microphone. While measurement, he/she does casual talks and cognitive tasks as mentioned above.

We used the fNIRS topography system FOIRE-3000 Near-Infrared Brain Function Imaging System (Shimadzu, Kyoto, Japan), which uses near-infrared light with wavelengths of 780, 805, and 830 nm. We set 16 illuminators and 15 detectors in lattice pattern to form 42 channels (CHs) (22 CHs on frontal lobe, 10 CHs on right parietal and temporal lobe, 10 CHs on left parietal and temporal lobe) shown in Fig. 3.

5 TASK EFFECT ASSESSMENT

Toward personalized cognitive training, we assess a task effect. We have conduct statistical tests of between-group significant differences using fNIRS signals of oxy-Hb during cognitive task of

- Daily Conversation: talking about favorite season, travel, gourmet, and daily life;
- Reminiscence Task 1: talking about birthdate;
- Reminiscence Task 2: watching old things;
- Category Recall: answering the name of fruits as many as he/she knows;
- working memory tasks.

We used Welch's t-test with significance level of ($P < 0.001$) after applying Bonferroni's adjustment (1/42). Fig. 4 and 5 show the results of t-test for significant differences in channel-wise fNIRS signals between any single pair from CN, MCI, and AD groups. The CHs that exhibited significant oxy-Hb increase are colored according to the t-values, as shown in the color bar, while those below the threshold are indicated in gray. The higher absolute value of a t-value indicates the larger difference between two groups. In Fig. 4 D-(a), for example, red colored mapping on frontal lobe indicates that the brain function in frontal lobe of elderlies with cognitively normal is significantly more active than that of elderly patients with MCI. In Fig. 4 D-(c), for example, blue colored mapping on left temporal lobe indicates that the brain function in left temporal lobe of elderly patients with MCI is significantly more calm than that of elderly patients with mild AD.

5.1 Results

5.1.1 Daily Conversation

Fig. 4 indicates the significant difference of fNIRS signals between normal group and disease groups for all topics of the conversation. Speech contains non-verbal elements known as paralanguage, including voice quality, rate, pitch, volume, and speaking style, as well as prosodic features such as rhythm, intonation, and stress. Conversation, even if it is just a casual conversation about daily living, requires lot of interpersonal communication skills of not only linguistic competence but also some nonverbal competencies so as to recognize partner's paralanguage and to control self paralanguage appropriately. For this reason, the results indicate that elderly people with cognitively normal use their brain function more actively than those who are with MCI and AD group.

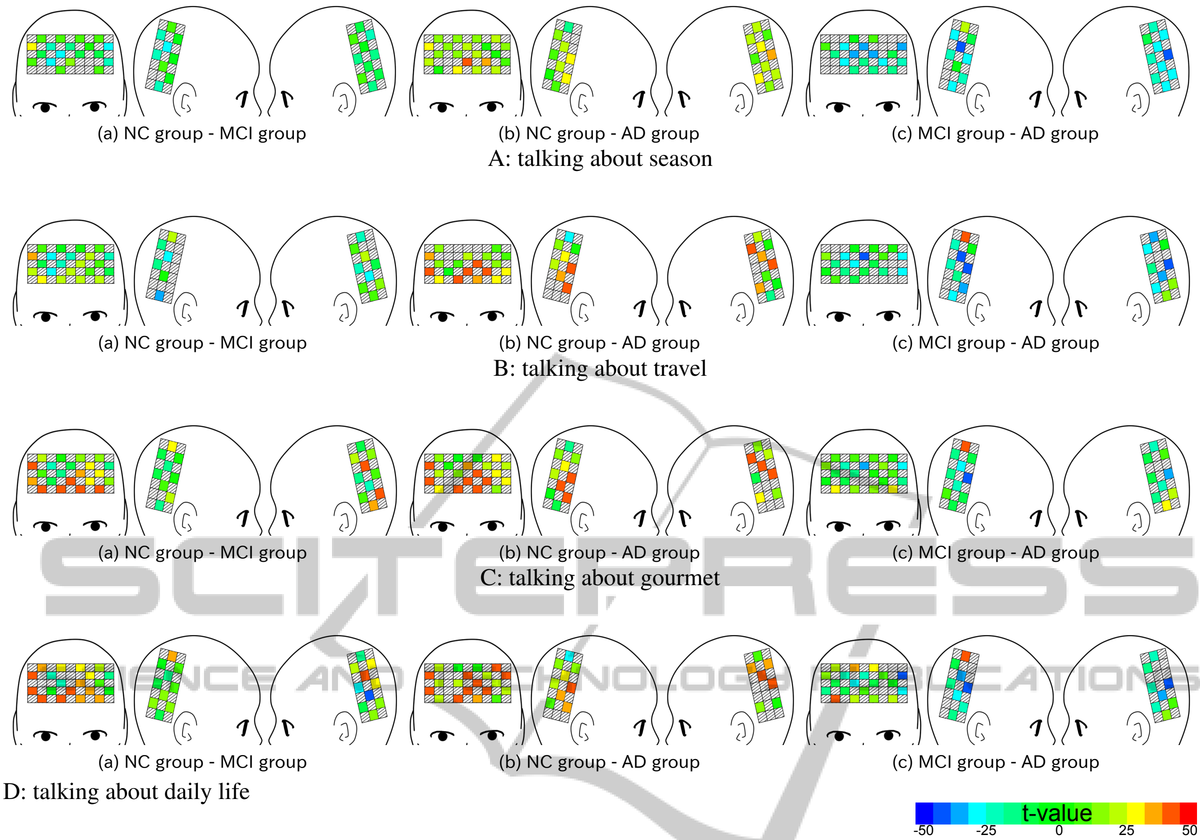

Figure 4: Results of t-test for significant differences in channel-wise fNIRS signals between any single pair from CN, MCI, and AD groups (daily conversation).

Maybe it is because some participants talked heated gradually, the difference becomes larger as a conversation progresses.

5.1.2 Reminiscence Talk, Category Recall, and Working Memory

Fig. 5 indicates the significant but slight difference of fNIRS signals between normal group and disease groups for the later three tasks. With respect to the reminiscence task 1, for this particular participants, regardless of whether they have cognitive impairment or not, answering his/her birthdate is very easy; it is no need to use their brain function actively. With respect to the category recall and working memory tasks, for an elderly participant, it is a little too hard to say the name of fruits as many as he/she knows for long time (30 seconds), and is also a little too difficult to listen numbers and *hiragana* characters and sort them in ascending and dictionary order, at once. With respect to the reminiscence task 2, we failed to collect fNIRS signals for adequate analysis because the visual stimulation was not enough to prompt a verbal response from participants.

6 CLASSIFICATION OF CN, MCI, AD GROUPS USING fNIRS SIGNALS

The section describes a Bayesian classifier using fNIRS signals of elderlies during cognitive tests, which can discriminate among elderly individuals with three clinical groups: cognitively normal controls (CN), patients with mild cognitive impairment (MCI), and Alzheimer's disease (AD). To design an algorithm for computer-aided diagnosis of cognitive impairment in the elderly, we consider the screening process by a specialist in geriatrics. We thus propose a two-phase Bayesian classifier shown in Fig. 6 on the assumption of screening process, that firstly checks the suspicion of the cognitive impairment (CI) or not (CN) from given fNIRS signals; if any, and then secondly judges the degree of the impairment: MCI or AD.

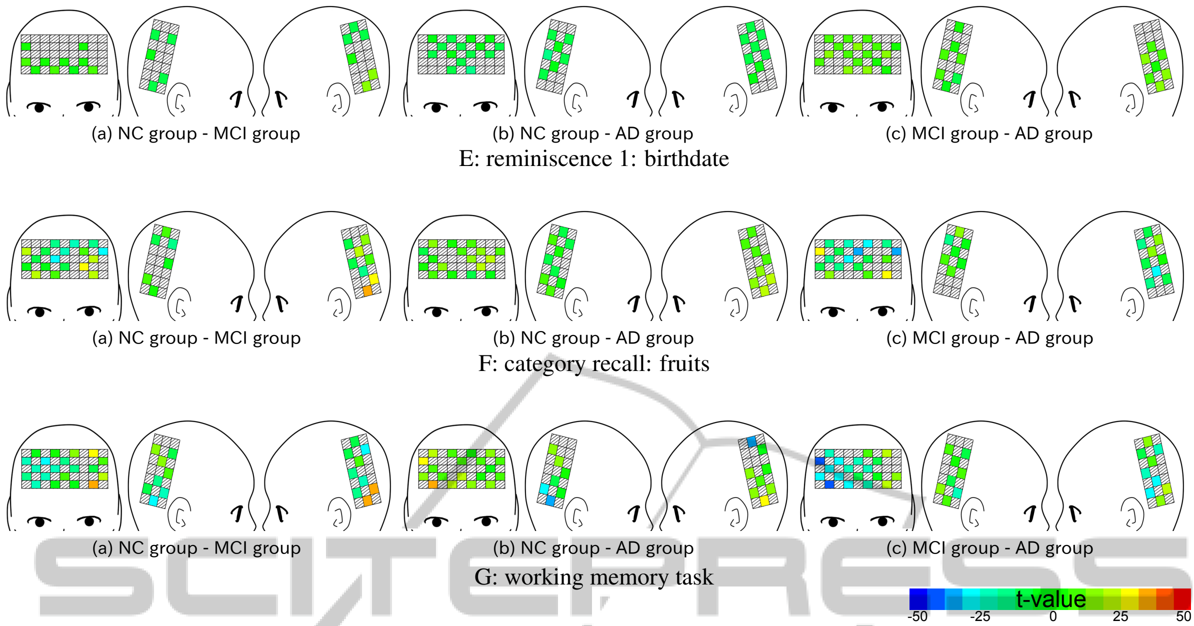

Figure 5: Results of t-test for significant differences in channel-wise fNIRS signals between any single pair from CN, MCI, and AD groups (later three tasks).

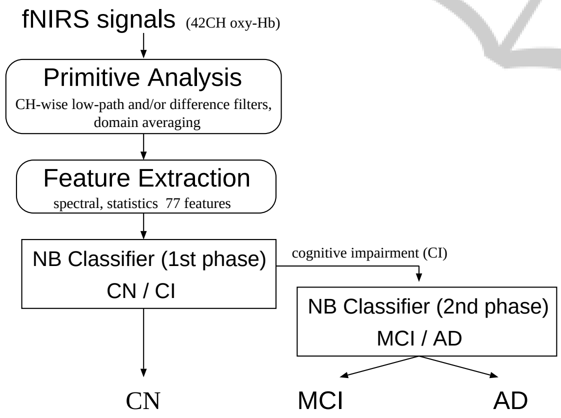

Figure 6: Classification of CN/MCI/AD by two-phase Bayesian Classifier.

6.1 Primitive Analysis of fNIRS Signals

In advance of Bayesian classification, we make a primitive signal processing fNIRS signals. Firstly, we make five fNIRS signals every channels such that noise is reduced by channel-wise smoothing through three low-pass filters (F1: 1.92 [Hz], F2: 0.96 [Hz], F3: 0.48 [Hz]) and difference filters (F1-3 and F2-3). Secondly, we segregate 42 CHs into the seven brain areas (see Fr, Fc, Fl, Rf, Rr, Lf, and Lr in Fig. 3) and then make signal averaging that integrates fNIRS signals within each of the areas.

Table 2: fNIRS Feature Candidates.

fNIRS filtered	Feature / Statistics
Filter 1 (F1)	Mean value (mean)
	Fundamental Frequency (f0)
	Centroidal Frequency (fc)
Filter 3 (F3)	Maximum value (max)
	Minimum value (min)
	Variance (var)
	Mean value (mean)
	Fundamental Frequency (f0)
	Gradient of the linear regression line (gr)
Filter1-3 (F1-3)	Variance (var)
Filter2-3 (F2-3)	Variance (var)

6.2 Extraction of fNIRS Features

We enumerate features that represent fluctuations of regional cerebral blood flow if it is the slightest effective in detection of cognitive impairment, and extract 11 features shown in Table 2 from fNIRS signals in each of the seven brain areas.

6.3 Bayesian Classifier

In this paper, we adopted naive Bayes classifier (NB), (Langley et al., 1992) which is a simple Bayesian classifier with strong independence assumption of attributes. We construct two classifiers: $NB_{CN/CI}$, which checks the suspicion of the cognitive impair-

Table 3: Selected fNIRS Features.

Classifier	Selected Features
$NB_{CN/CI}$	Lr_F3_gr, Rf_F1_mean, Rf_F3_mean, Fl_F3_f0
$NB_{MCI/AD}$	Rr_F3_min, Fr_F3_f0, Rr_F1-3_var, Lf_F3_gr, Fc_F3_gr

Table 4: Classification Results.

detection / clinical	CN	MCI	AD	accuracy
CN	7	0	0	100%
MCI	1	9	0	90%
AD	0	0	5	100%
predictive value	87.5%	100%	100%	95.5%

ment (CI) or not (CN) at the first phase, if any suspicion, and $NB_{MCI/AD}$, which judges the degree of the impairment (MCI or AD) at the second phase.

6.4 Classification Assessment

We have examined discrimination performance by modeling two-phase Bayesian classifiers for discriminating among elderly individuals with NL, MCI, and AD, by using fNIRS signals of oxy-Hb during daily conversation (travel) (see Fig. 1) collected from 22 participants (see Table 1). Table 3 shows the selected fNIRS features by each of NB classifiers. To evaluate detection performance, we adopted leave-one-out cross-validation.

Table 4 shows the confusion matrices and the statistics of classification results using two-phase classifiers consist of $NB_{CN/CI}$ and $NB_{MCI/AD}$. The results indicate that total accuracy rate is 95.5% and the accuracy rate of AD and the predictive value of CN are both 100%. Table 4 shows that only one subject in MCI groups are misclassified into CN group and other all subjects are classified correctly. This suggests that proposed approach is sufficient practical to screen the elderly with cognitive impairment.

7 CONCLUSIONS

With the goal of promoting a fruitful and healthy longevity society, this paper presented a verbally-based cognitive task and an early detection method of dementia and mild cognitive impairment for elderly.

With conscious of daily conversation, we firstly designed eight cognitive tasks, under which an elderly individual talks about some topics and orally answering some questionnaire. With the use of the functional near-infrared spectroscopy (fNIRS), we evaluated comparatively the cerebral blood flow (CBF) activation during the tasks in cognitively normal controls (CN) and patients with mild cognitive impairment (MCI), and mild Alzheimer's disease (AD), by the statistical tests of fNIRS signals between any single pair from CN, MCI, and AD. Then we confirmed the significant difference of CBF activation between normal group and disease groups for casual conversation. Consequently, the results suggested that proposed cognitive tasks, especially casual conversation, are adequate practical to training of brain function activation for elderly people.

We secondly proposed a two-phase Bayesian classifier using fNIRS signals, which can discriminate among elderly individuals with three clinical groups: CN, MCI, and AD. Then we examined the detection performance with total accuracy rate of 95.5% was reported by cross-validation. Consequently, the empirical results suggested that proposed approach is sufficient practical to screen the elderly with cognitive impairment. However, the results are limited in the small number of participants. Cognitive functioning are continuous within each category, there is a range of severity and functional ability. In future work, we will dedicate to much more clinical trials to validate the practicality of proposed method. We will also dedicate to division of MCI group with clinical subtypes of amnestic MCI and non-amnestic MCI.

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