Evaluation of changes in oxy-Hb during Shiritori task in elderly subjects including those with Alzheimer's disease.

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Abstract

Background: In recent years, as the prevalence of Alzheimer's disease (AD) has increased rapidly, demanded has increased for early detection and treatment. Therefore, discovery

and treatment intervention at the mild cognitive impairment stage are important. Dysfunction of the working memory is known to be conspicuously present in AD patients or mild cognitive impairment subjects from an early stage. Near-infrared spectroscopy (NIRS) is a method to measure haemoglobin concentration changes during an activation task. In the present study, we evaluated the cognitive function of elderly subjects, including those with AD by means of NIRS.

Methods: The subjects were divided into three groups – the AD group, the intermediate group, and the healthy group (HG) – based on assessment of dementia using the Hasegawa's Dementia Scale – Revised , Mini-mental State Examination, and Clinical Dementia Rating . The intermediate group was divided into two groups – the high score group (HSMG) and the low score group(LSMG) – based on Hasegawa's Dementia Scale – Revised and Mini-mental State Examination scores. In this study, during Shiritori tasks using single-event-related NIRS, we analyzed oxyhaemoglobin changes in an area, the peak amplitude, and latency, and compared them among four groups: ADgroups,HSMG,LSMG,and HG.

Result: In the AD group, the area at left Channel (Ch) 9,11, and 19, the area at right Ch22 and the peak amplitude at left Ch11 and 19 and right Ch5, 12, and 22 were significantly

smaller than those in HSMG and HG. Furthermore, the latency of AD group was significantly longer than that of HSMG and HG at all region of interests. However, no significant difference was observed between AD group and LSMG.

Conclusion: These findings suggest that analysis of changes in oxyhaemoglobin during Shiritori tasks may be a useful neuropsychological index for the early diagnosis of AD. Detailed studies will be conducted in LSMG to facilitate the early introduction of NIRS as a screening tool for cognitive impairment.

Key words: Alzeheimer's disease(AD), intermediate group(MG), prefrontal cortex , Shiritori, , , single-event-related near-infrared spectroscopy, working memory.

Introduction

Near-infrared spectroscopy (NIRS) is a method that uses near-infrared light to measure changes in oxy-haemoglobin (oxy-Hb) and deoxyhaemoglobin concentrations while the subject is thinking and acting.[1] Because irradiated near-infrared light is scattered and reflected in the brain, the light path length cannot be accurately measured. Therefore, absolute haemoglobin values cannot be determined. When the brain function in the region of interest (ROI) is evaluated using NIRS, changes in oxy-Hb and deoxyhaemoglobin concentrations during or after a task are compared with their concentrations before the task. In psychiatric diseases, such as schizophrenia, bipolar disorder, depression, and dementia, numerous NIRS studies using verbal fluency tasks have been reported.[1,2,3,4,5,6]

Shiritori is a word production game in which the sound at the end of the previous word is extracted and temporarily retained in the memory; during the retention, a word with this sound at its beginning is thought of, whether the selected word is consistent with the rules of Shiritori is determined, and revision is made. This is a word game that is familiar to Japanese people. As even 3-year-old children are capable of playing Shiritori,[7] it is possible for dementia patients to play it as well. Additionally, similar to games involving word recall and formation played in Western countries, Shiritori involves attention and executive functions, suggesting

that the tasks are associated with the working memory proposed by Baddeley.[8,9,10,11] Subjects may be able to perform Shiritori tasks without difficulty for evaluation of the cognitive function. Inoue et al. performed an functional magnetic resonance imaging (MRI) study while subject completed a Shiritori task, and reported that this task was associated with prefrontal cortex function, mainly involving working memory, particularly attention, executive and language function[12]. Yamamoto et al. performed a magnetoencephalographic study and suggested that Shiritori tasks are suitable for clarification of the brain network associated with language[7]. These reports suggest that Shiritori strongly reflects prefrontal cortex function. However, there have been only a few studies on haemodynamics in the brain and related areas during Shiritori tasks.[13,14] At advanced age , Alzheimer's disease (AD) is known to cause frontal lobe functional decline from an early stage,[15,16] but few studies have been conducted on prefrontal area and working memory functions in early or prodromal AD patients.[5,17]

In addition, besides neuropsycological tests, few screening tools are available for daily medical practice. The applications of functional neuroimaging remain limited, and it cannot be emplyed to screen for the risks of AD progression and mild cognitive impairment(MCI). Therefore, neurologic dysfunction should be examined using NIRS to improve the screening of AD risks and delay AD progression. In the present study, we divided subjects into three groups-the AD group, the intermediate group (MG),and the heaithy group (HG)-and then further divided the intermediate group based on Hasegawa's Dementia Scale-Revised (HDS-R)

and Mini-Mental State Examination (MMSE) scores. MG subjects with HDS-R scores of 25–27 points and MMSE scores of 26–27 points were placed in HSMG, and MG sub- jects with HDS-R scores of 21–24 points and MMSE scores of 24–25 points were placed in LSMG. Using multichannel NIRS, we evaluated changes in oxyHb concentration in the brain during a single-word Shiri- tori task and compared the characteristics of these changes among the groups.

METHODS

Subjects

The subjects were 231 elderly people who consulted a memory disorder clinic and underwent a medical examination. The subjects who fulfilled the following criteria were included in an AD group.: (ⅰ) met the National Institute on Aging/Alzeheimer's disease Association Diagnostic Guidelines for AD,[18] met the Diagnostic and Statistical Manual of Mental Disorders 4th edition (text revision), diagnostic criteria for AD[19], (ⅲ) had an HDS-R score ≤ 20[20], (ⅳ) had an MMSE score ≤ 23[21], (Ⅴ) had an Clinical Dementia Rating score ≥ 1[22], and(ⅵ) had no cerebrovascular lesions on head MRI. Subjects were included in the HG group if they had an HDS-R score ≥ 28, an MMSE score ≥ 28, and an Clinical Dementia Rating score of 0. Unhealthy subjects who did not qualify for the AD group were including in the MG and classified as either LSMG(HDS-R score: 21-24; MMSE score: 24-25) or HSMG(HDS-R score: 25-27; MMSE score: 26-27).[23,24] The HG had 91 subjects (14 men,79 women) with a mean age of 72.8±6.0 years . The HSMG had 65 subjects (21 men,44

women) with a mean age of 78.1±6.8 years. The LSMG had 33 subjects (12 men,21 women) with a mean age of 75.8±6.2 years. The AD group had 42 subjects (16 men,26 women) with a mean age of 78.9±5.3 years. There was a significant difference in age between the AD group and both the HSMG and HG. After a screening examination, MRI and voxel-based specyfic regional analysis system for Alzeheimer's disease (VSRAD) advance analysis were perfomed in 55 subjects at Kurume University Hospital (Table1).[25] All subjects were native Japanese speakers and were judged to be right-handed based on the Edinburgh Inventory.[26] Subject had no definite impairment of the verbal, visual, and auditory functions.

Ethical

A written explanation of this study was given to all subjects before it began, informed consent was obtained. This study was performed with the approval of the Ethical Committee of Kurume University.

Mesurement

Cerebral blood flow was measured using a multi – channel NIRS device. (ETG-4000; Hitachi, Tokyo, Japan). OxyHb changes were calculated from the difference in absorbance based on the modified Beer-Lambert law. The middle point of the transmitting-reciving probe pair was defined as a channel (Ch). The NIRS device measured oxyHb concentrations

at points 2-3 cm from the scalp that correspond to the cerebral cortical surface. Per the international 10-20 system,[27] the lowest anterior probes were positioned along Fp1-Fp2 line; left Ch19 and right Ch 22, and oxyHb data were recorded at 22 sites on each of the left side and right side (Fig.1). To avoid movement artifacts, subjects were instructed to minimize their movements, and the jaw was fixed during examination.

The pre-task baseline was decided as the mean 1 s before the word was displayed, whereas the post-task baseline was determined as the mean during 1 second from 11-12 s after the word was displayed. Linear fitting was applied to the data between these two baselines.

For the relationship between each channel and anatomic region, NIRS data were superimposed on a normalized brain image template (3-D composition indication unit; Hitachi). The ROI were: the frontal pole cortex (left Ch19, right Ch22), the dorso lateral prefrontal cortex (DLPFC)(left Ch11, right Ch12), and the parietal association area(left Ch9, right Ch5). It is thought that these regions participate with the working memory mainly (Fig.1).

Task design

Many previous studies using NIRS employed block design.[1,2,3] ; but we thought thatc would be affected by subject's perfomance (e.g. the number of Shiritori words) . Therefore, in the

present study, we referred to event-related brain potential desgin in P300 studies that used a single-word presentation task.[13,1423,24,28] We considered the advantages of a single-word presentation task to be that it has little influence on performance, it is easy to perform artifact removal, and it enables brain activity to be monitored. One session comprised two contrasting conditions (word production tasks, and control conditions), and all subjects alternated between these conditions. Each word was visually displayed on the screen for 0.3 s as an activation task and then a fixed circle was displayed for 12 s. In the activation task, subjects were instructed to say a noun immediately starting with the last kana character of the displayed word. This task was referred to as the Japanese shiritori word game, as well as a word production task. For example, when the noun “I-SU” (chair) was displayed on the screen, the subject said the noun “SU-I-KA” (water melon). Under the control condition, subjects were required to repeatedly say the Japanese syllables “a-i-u-e-o” (Corresponding to the beginning of the English alphabet(a,b,c,and so on)). The word production task was repeated up to 25 times per session. Waveforms of 20 (≥80%) correct responses for each subject were adopted as authorized data, and we excluded waveforms of incorrect responses and responses that occurred more than 1 s after the word was displayed. Averaged waveforms were analyzed using the “integral mode” of the NIRS

device (Fig.2). The integrated waveforms of each group are shown in Figure3. These are referring to Figure3. OxyHb changes between activation and control periods are shown numerically for each 100 ms. Also, NIRS data were calculated from the average wave of oxyHb changes. In this study, the area of the waveform 10 s after the word was displayed was calculated.

Statistical analysis

Changes in oxyHb were examined using the one-way analysis of variance ANOVA(group) for each channel and ROI and then compared among the four groups. The correlations among the oxyHb changes and HDS-R, MMSE and Z-score of VSRAD are expressed as the Pearson's product-moment correlation coefficient (*r*). Furthermore, Bartlett's test was used to evaluate statistical significance, and correlation coefficients were applied as significant at more than 0.4 and less than -0.4. The Bonferroni/Dunn post-hoc test was use to evaluate significant differences among the four groups. A value of $P<0.083$ was adopted as significant. Values are presented as the mean ± standard deviation (SD).

The oxyHb changes correlate more strongly with blood-oxygen level-dependent signals in functional MRI than do deoxyhaemoglobin changes; therefore, we selected oxyHb changes

in the present study.[28] All analyses were performed using Stat View 5.0(SAS Institute Inc,USA).

RESULTS

The area under waveform and the peak amplitude of waveform were NIRS data of oxyHb changes(Fig.4). In the present study, althogh the time between latency and peak amplitude did not indicate oxyHb changes, we used the latency as refrected values of oxyHb changes, similar to P300.[29]

Area

The area in AD group was significantly smaller than in HSMG and HG at Ch9,11,12,19, and 22 (AD group and HSMG: Ch9=0.0007, Ch11<0.0001, Ch12<0.0022, Ch19<0.0001, Ch22=0.0011; AD group and HG: Ch9=0.0016, Ch11=0.0008, Ch12<0.0001, Ch19<0.0001, Ch22<0.0001). The area in LSMG was significantly smaller than in HSMG and HG at Ch11 and 19 (LSMG and HSMG: Ch11=0.0002, Ch19=0.0018; LSMG and HG: Ch11=0.0005, Ch19=0.0067) (Fig.4).

Peak Amplitude

The peak ampulitude in AD patients was significantly smaller than in HSMG and HG at Ch5,11,12,19, and 22 (AD group and HSMG: Ch5=0.0002, Ch11<0.0001, Ch12=0.0008,

Ch19=0.0002, Ch22<0.0001; AD group and HG: Ch5=0.00015, Ch11<0.0001, Ch12=0.0002, Ch19=0.0006, Ch22;<0.0001).

The peak amplitude in LSMG was significantly smaller than in HSMG and HG at Ch11 and Ch12(LSMG and HSMG: Ch11<0.0001, Ch12=0.0049; LSMG and HG: Ch11=0.0008, Ch12＝0.0002).

Latency

The latency in AD patients was significantly more extended than in HSMG and HG at all channels(AD and HSMG: Ch5<0.0001, Ch9<0.0001, Ch11<0.0001, Ch12<0.0001, Ch19=0.0002, Ch22=0.0009; AD and HG: Ch5<0.0001, Ch9;<0.0001, Ch11<0.0001, Ch12<0.0001, Ch19<0.0001, Ch22=0.0001). The latency in LSMG was significantly more extended than in HSMG and HG at Ch9, 11, and 12 (LSMG and HSMG: Ch9=0.0001, Ch11=0.0002, Ch12=0.0035; LSMG and HG: Ch9=0.0005, Ch11=0.0001, Ch12;=0.0070).

OxyHb change in LSMG and the AD group

No significant difference was observed in the area, peak amplitude, or latency between the AD group and LSMG.

Z score comparison between each group

The Z scores of AD group was significantly larger than that of LSMG($P<0.0001$) , HSMG ($P<0.0001$) and HG ($P<0.0001$). In addition, Z scores of LSMG was significantly larger than that of HSMG ($P<0.0001$) and HG($P<0.0001$). Also, Z scores of HSMG was significantly larger than that of HG ($P<0.0001$).

Correlation of OxyHb changes with HDS-R, MMSE, and Z-score

Change in oxyHb significantly negatively correlated between with HDS-R(Ch11, latency: $r=-0.443$, $p<0.0001$), MMSE(Ch11, latency: $r=-0.430$, $p<0.0001$), and Z-score (Ch11, area $r=-0.408$,$p=0.0137$).

Correlation of age with oxyHb changes, HDS-R, MMSE,and Z-score

No significant correlation was observed between age and oxyHb changes, HDS-R, MMSE, or Z-score.

Sensitivity and specificity in differences among AD,LSMG,HSMG,and HG

From the changes in oxyHb at left Ch11, 87.8% sensitivity(AD group),73.3% sensitivity (LSMG), 77.7% specificity (HSMG), and 78.1% specificity (HG) were obtained.

DISCUSSION

In recent years, it has become widely known that a decrease in the prefrontal cortex function occurs in patients in the early stage of AD.[15] The predictors of AD include impairments of episodic memory and the executive function, which involve prefrontal cor- tex function.[30]

Kugo *et al.* reported impaired execu- tive function based on using the Japanese version of the Frontal Assessment Battery as a frontal lobe function test in patients with early-stage AD.[31] In the present study, Shiritori was employed as a task to activate prefrontal cortext function, mainly working memory, such as directing, executing, or suppressing attention; converting cognitive sets; and recalling languages.[12] Nambu performed elec- tromagnetic recording during a Shiritori task and observed bilateral activation of the lateral part of the frontal lobe, suggesting that verbal tasks such as word retrieval require activation of this region.[32] OxyHb variations due to activation tasks were examined with NIRS, which indicated in the AD group significantly decreased area values and peak amplitudes in the DLPFC and frontal pole cortex regions and significantly prolonged latencies in the AD group as compared with HSMG and HG. As such, because Shiritori activates prefrontal cortex function, our results suggest decreased prefrontal cortex function and working memory in the AD group and LSMG.

Miyakawa *et al.* performed a NIRS study similar to ours using a verbal fluency task in which changes in oxyHb waveforms were quantitatively calculated in elderly patients with AD and healthy subjects and reported a significant decrease in the frontal lobe in elderly patients with AD relative to the healthy sub- jects.[33] Similar to previous reports, our findings showed a significant decrease in oxyHb changes in the DLPFC and frontal pole cortex.[33] In addition, the parietal association cortex, involved in the working memory of spatial vision and the processing of spa- tial information, showed significantly decreased area values, peak amplitude, and extended latency in the AD group. These results may reflect reduced spatial cognitive function, a characteristic symptom of AD.[34,35] Arai *et al.* reported that the oxyHb changes in the frontal lobe and bilateral parietal lobe in the AD group significantly decreased compared to healthy controls in a study using NIRS.[5] This is similar to our result. In the present study, LSMG showed the same tendency for all ROI as the AD group. Subjects were placed in MG based on their HDS-R and MMSE scores, and we found similar changes in oxyHb between the AD group and LSMG and between HG and HSMG.

Recent findings have indicated that the prefrontal cortex is critical for maintaining memory function. Based on this, Uemura *et al.* used NIRS to determine oxyHb change in the prefrontal cortex during word recall.[36] As a result, reduction in oxyHb change (i.e.

decreased activity) in the bilateral DLPFC during word recall may indicate impaired memory functions, providing a marker for amnestic MCI. In addition, Uemura *et al.* suggested that whether the reduction in oxyHb in the area serves as a predictor of AD should be examined. Using Shiritori as the language recall task, we found a reduction in oxyHb in the bilateral DLPFC in LSMG, which indicates potential MCI, and a more significant reduction in the AD group. This suggests that the decreased activity in the bilateral DLPFC during Shiritori could serve as a predictor of AD, including for LSMG subjects who convert to AD or amnestic MCI.

HDS-R and MMSE are widely used as neuropsy- chological screening tools for AD in daily clinical practice because of their simplicity.[21,22] In our find- ings, there was a significant negative correlation between latency of the left Ch11 (approximately left DLPFC) and HDS-R and MMSE scores. Therefore, HDS-R and MMSE scores may be useful as dementia screening markers for the latency of left Ch11. How- ever, few end-points of prefrontal cortex functions can be determined based on HDS-R or MMSE, and these tests may be insufficiencient for detecting pre- frontal functional decline in early-stage dementia. Forstein,[37] a developer of the MMSE, recognized the need to use other cognitive function tests to better detect prefrontal area functional disorder. Because evaluations using HDS-R and MMSE scores tend to be emphasized in general clinic or hospital medical care, decreased prefrontal cortex functions may be overlooked. NIRS tests are convenient because of their reduced invasiveness and high portability, which enables them to be employed in small clinics and hospitals and during health examinations and home visit care.

VSRAD advance (Eisai Co., LTD., Tokyo, Japan) is image processing and statistical analysis software that assesses the atrophic level of the parahippo- campal gyrus in early-stage AD, including the prodro- mal period, based on an MRI.[25] A previous study found that the correct diagnosis rate in early-stage AD patients and healthy elderly individuals was 91.6%.[25] Z-scores >2 suggest the possibility of AD with statistically significant differences. This is con- sistent with our result (Z-score in the AD group: 2.6±0.7). In addition, the LSMG's Z-score of 1.8±0.7 may indicate possible convsion to AD. Nagata *et al.* demonstrated a significant correla- tion between parahippocampal atrophy and execu- tive dysfunction; in amnestic MCI and early-stage AD patients, the go/no-go score of the Frontal Assess- ment Battery significantly

decreased as the parahip- pocampal atrophy became more severe based on VSRAD Z-scores.[38] The go/no-go test, which is associated with suppression and conversion of cog- nitive set, is similar to Shiritori. In the present study, our results demonstrated that the Z-score signifi- cantly increased in across the groups, from HG to the AD group, which supports the idea that parahip- pocampal atrophy is significantly correlated with executive dysfunction. Takahashi *et al.* reported that, based on a positron emission tomography study, the neural networks between hippocampus and prefron- tal cortex areas influenced executive function, includ- ing working memory.[39] Also, in our study, the Z-scores were significantly negatively correlated with the area of left Ch11 corresponding to the left DLPFC region. Thus, the area of left Ch11 may serve as a marker of hippocampal atrophy. These results sug- gest that NIRS tests using Shiritori in non-demented groups, which are likely to be followed up in clinical settings, may provide psychophysiological markers to facilitate the implementation of head MRI and more detailed neuropsychological tests.

In recent years, as the population of dementia patients has grown, much work has been done on early detection and early treatment. However, more accurate screening tests are still required. In particu- lar, measurements to reflect the functions of the pre- frontal cortex region, in which dysfunction is noted in initial dementia and its previous stages, are needed, as these are strongly associated with diagnostic accuracy.

The present study had some limitations. Firstly, the effects of cerebral cortex atrophy cannot be exluded. The measurement sensitivity of NIRS decreases in the cerebrospinal fluid layer when it is more severely atro- phied than the cerebral cortex.[40] Further investigation is needed to clarify the relationship between atrophy of each area of Brodmann and changes in oxyHb. Secondly, we could not sufficiently classify each group according to frontal lobe function. A clearer classification using a test battery such as the Frontal Assessment Battery or Trail making test will be neces- sary in the future. Thirdly, we did not match sex, aca- demic background, and age in this study. In the future, it will be necessary to investigate matched groups. Similarly, future investigations should follow up on the association between MG and MCI.[41]

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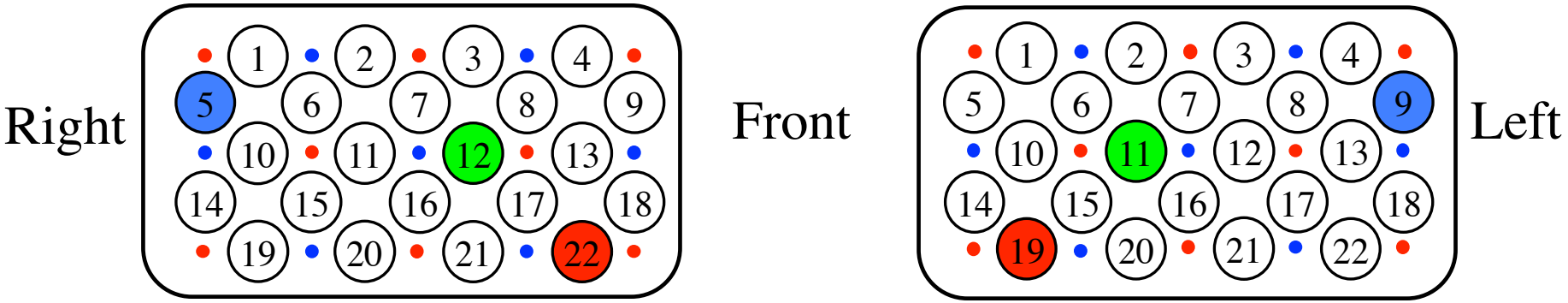
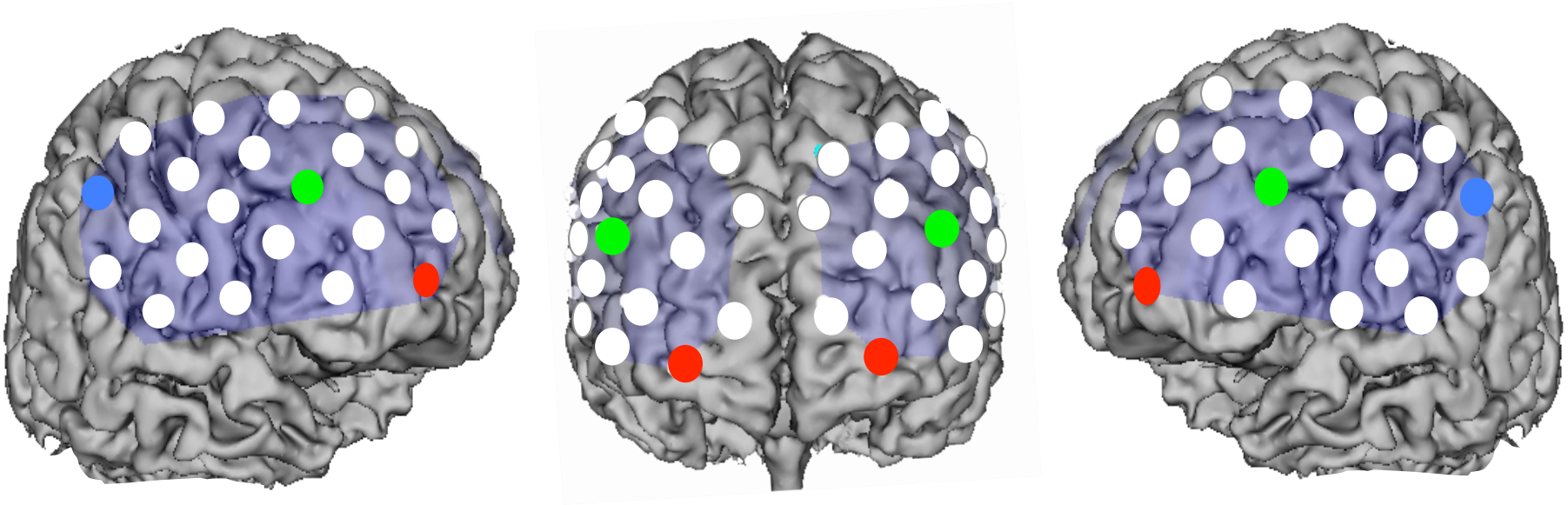
Profile

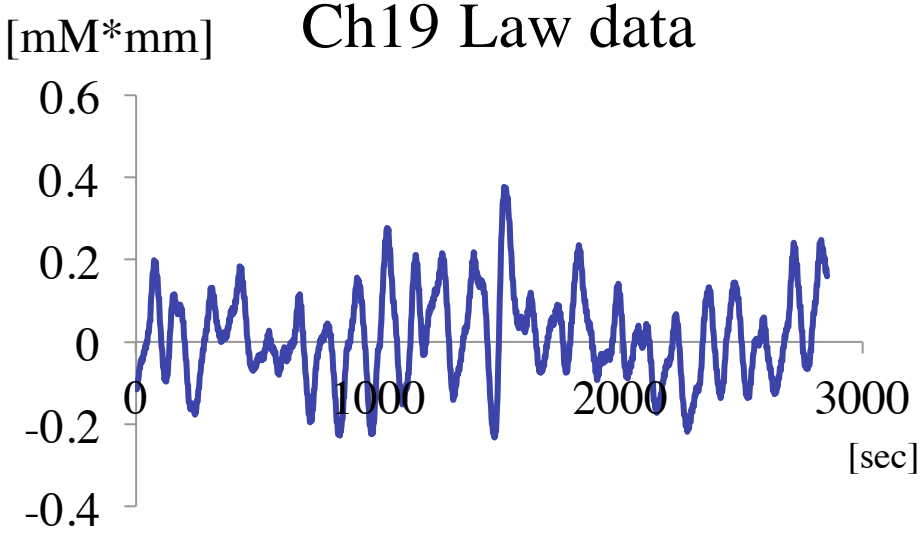
	HC	LRMG	HRMG	AD	Post hoc comparisons		
	(n=91)	(n=65)	(n=33)	(n=42)	Bonferroni/Dunn (p value < 0.0083)		
					HC vs AD	***LRMG vs AD***	***HRMG vs AD***
Male/Female	14/79	21/44	12/21	16/26			
Age (years)	72.8 ±6.0	75.8 ±6.2	78.1 ±6.8	78.9 ±5.3	p < 0.0001	p = 0.0068	p = 0.6960
HDS-R score	29.2 ±0.8	26.4 ±1.5	23.5 ±1.8	17.9 ±4.1	p < 0.0001	p < 0.0001	p < 0.0001
MMSE score	29.2 ±0.8	27.1 ±1.3	25.4 ±1.3	20.4 ±3.0	p < 0.0001	p < 0.0001	p < 0.0001
CDR score	0.07 ±0.1	0.3 ±0.2	0.5 ±0.2	1.2 ±0.4	p < 0.0001	p < 0.0001	p < 0.0001
VSRAD Z-score	0.8 ±0.3	1.1 ±0.5	1.8 ±0.7	2.6 ±0.7	p < 0.0001	p < 0.0001	p < 0.0001

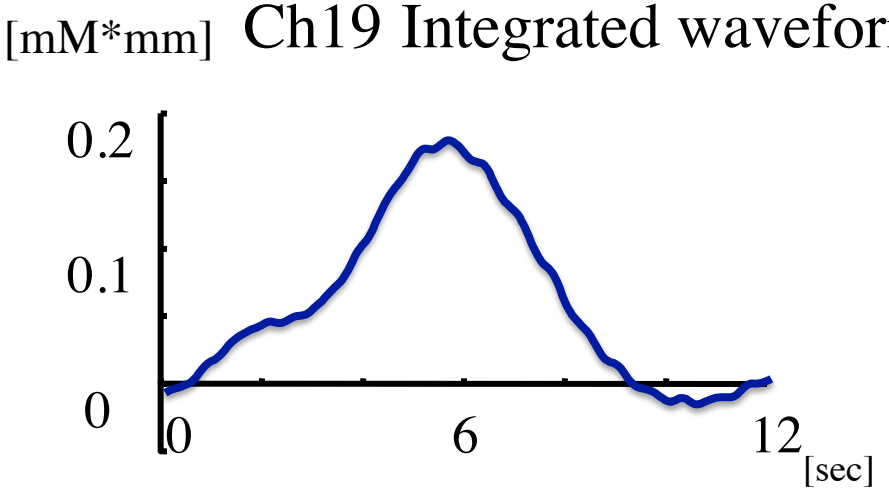
Values are presented the mean + standard deviation.



* Transmitting probe (●) , Receiving probe (●).







Methodology

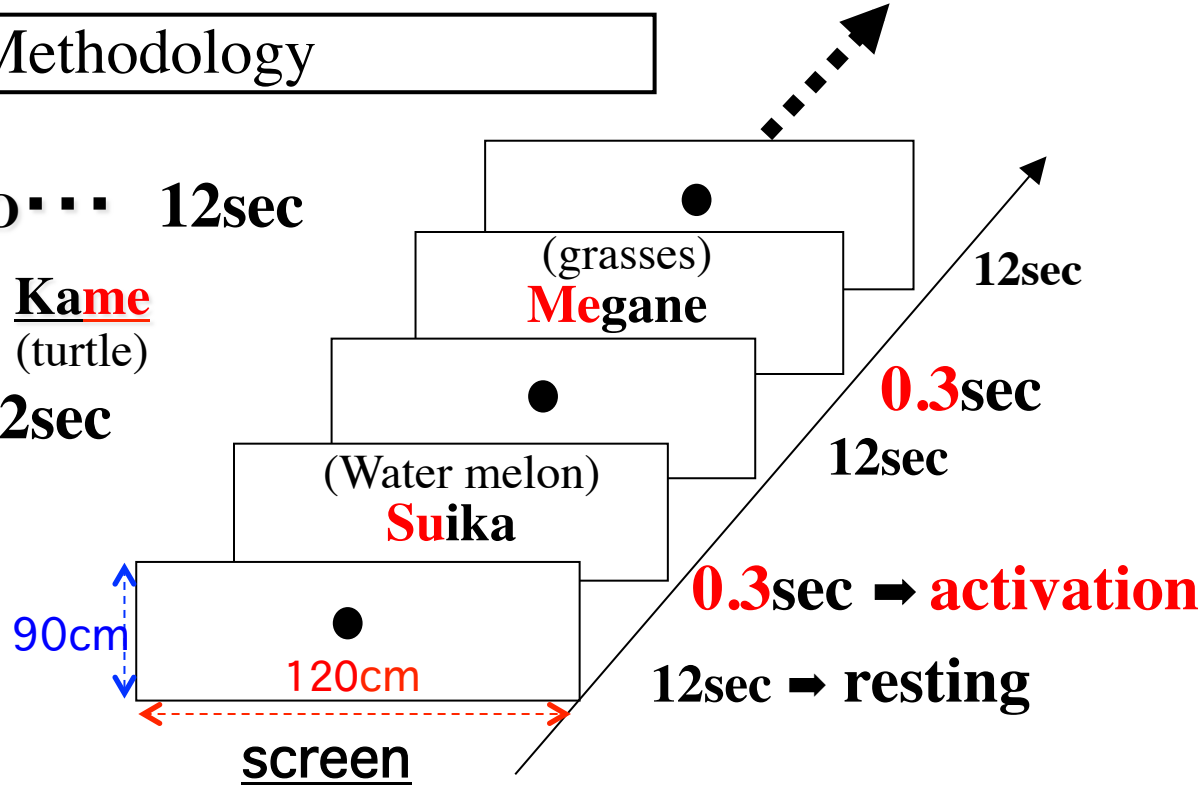
A~I~U~E~O・・・ 12sec

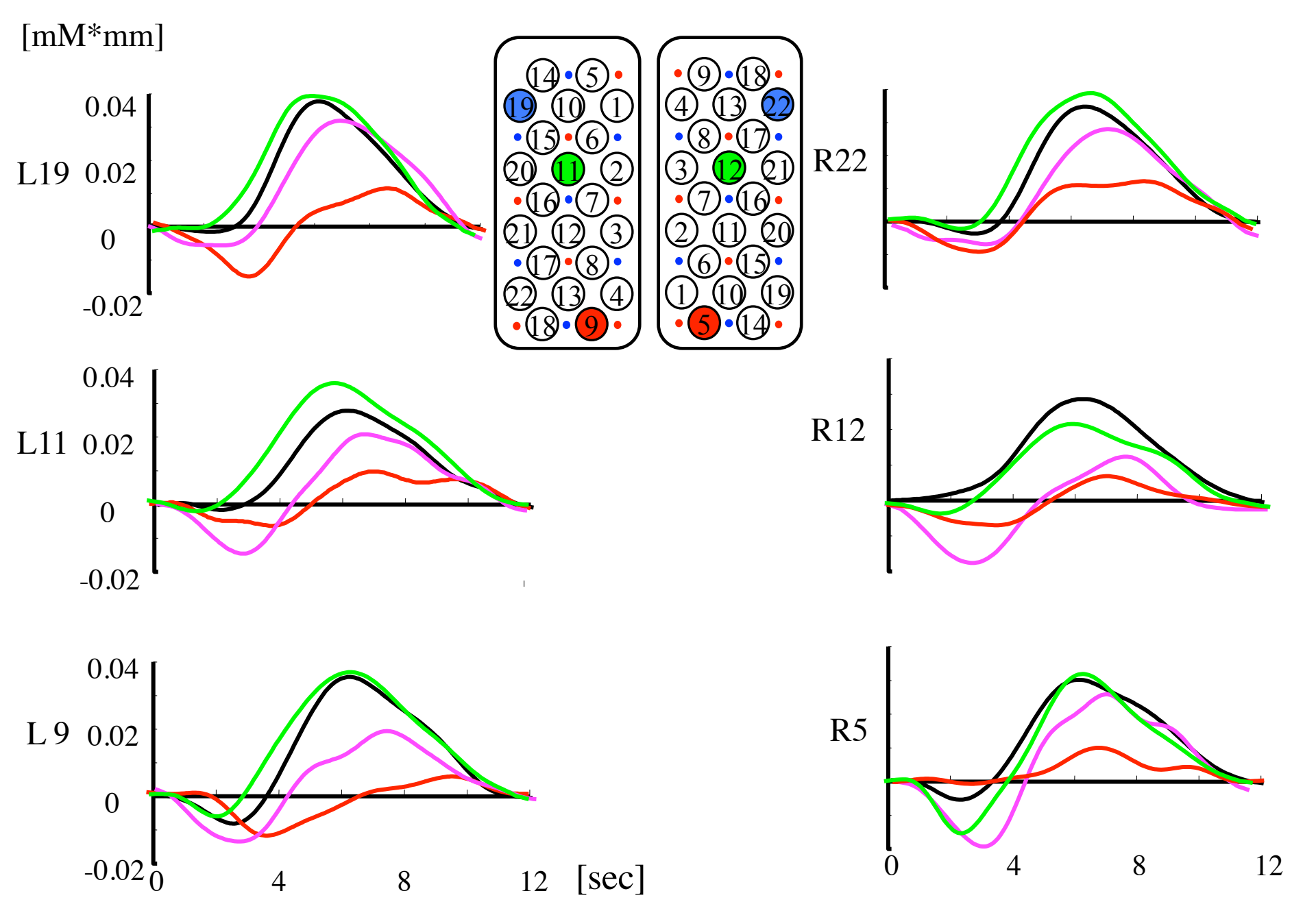
Kame
(turtle)

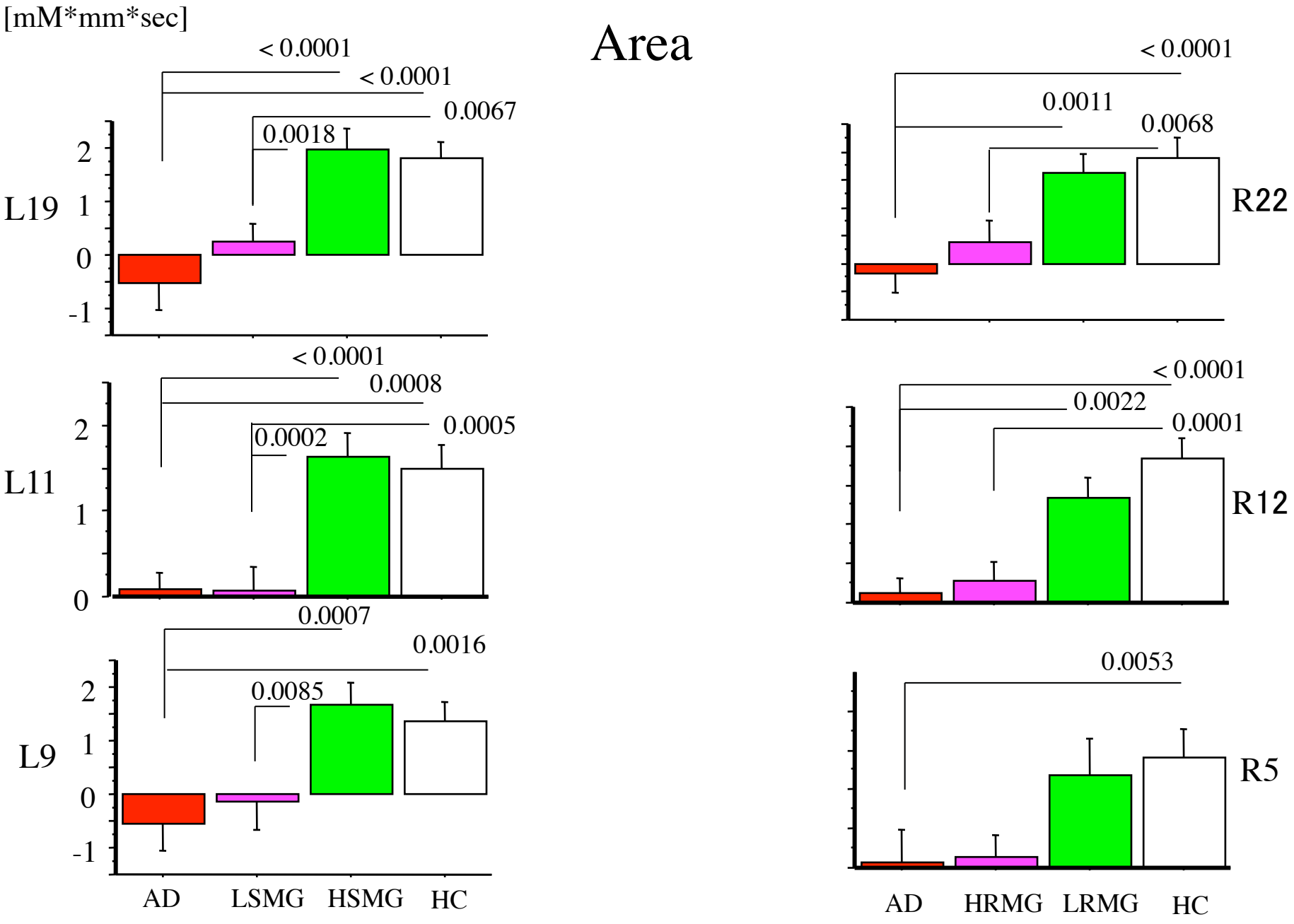
A~I~U~E~O・・・ 12sec

Isu
(Chair)

A~I~U~E~O・・・ 12sec




[mM*mm]
L19
L11
L 9
R22
R12
R5
0.04
0.02
0
-0.02
0
4
8
12
[sec]
14 5
19 10 1
15 6
20 11 2
16 7
21 12 3
17 8
22 13 4
18 9
9 18
4 13 22
8 17
3 12 21
7 16
2 11 20
6 15
1 10 19
5 14


[mM*mm*sec]
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< 0.0001
0.0067
0.0018
L19
2
1
0
-1
< 0.0001
0.0008
0.0005
0.0002
L11
2
1
0
0.0007
0.0016
0.0085
L9
2
1
0
-1
AD
LSMG
HSMG
HC
< 0.0001
0.0011
0.0068
R22
< 0.0001
0.0022
0.0001
R12
0.0053
R5
AD
HRMG
LRMG
HC