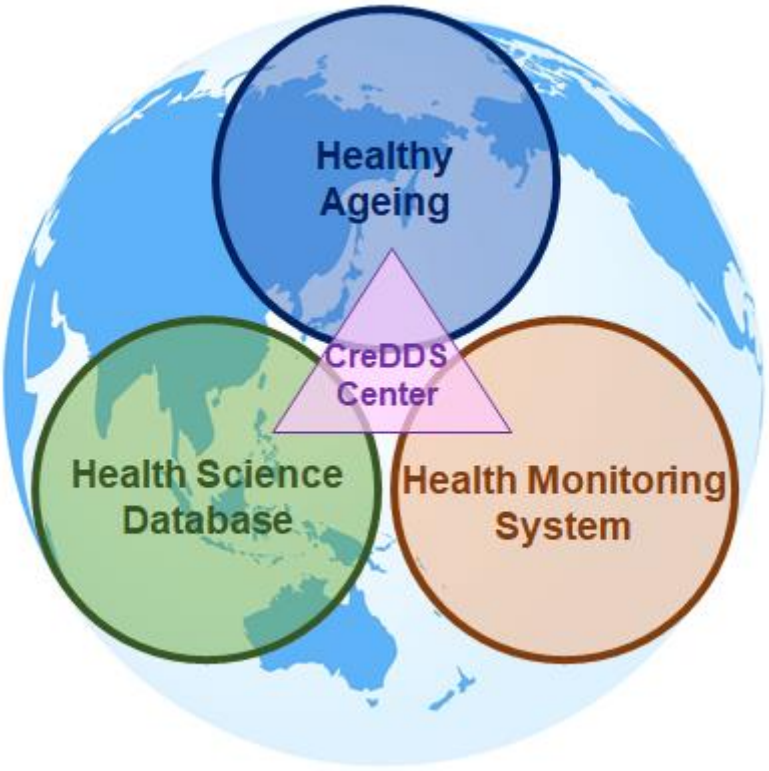
Creative Design and Data Science Center

Annual Report

Achievements in **FY2023**



Akita International University

CreDDS Center - Concept/ Purpose/ Projects

[Denomination] Creative Design and Data Science Center (CreDDS-C)
[Establishment] April 1, 2022

[Concept]

Established as part of AIU's 4th Medium Term Plan (2022~2027), which aims to transform AIU's research, education and public engagement in the context of the pedagogic aspirations of Applied International Liberal Arts (AILA).

Intended to be a central driver of innovative research, education and public engagement under the Institute for Applied International Liberal Arts (AILA Institute, est. March 2022).

Will serve AILA Pedagogy from Levels 100~400 (undergraduate) and beyond (postgraduate).

Will have a synergistic mutually supportive relationship with the Active Learning Center and the Center for Collaborative Research and Outreach with all three centers providing the impetus for the transformations anticipated under AILA.

[Purpose]

Designing and executing projects to nurture inspiring leaders who subscribe to the AILA ideals of integrating profound thought with decisive action in a transnational, transdisciplinary context.

Meeting future needs of society and challenges facing the earth's environment while consolidating on AIU's strengths built up thus far contributing to pedagogic excellence and local-global partnerships.

Integrating transformative technology with the essence of humanity to create caring societies and resilient communities which will contribute to furthering universal values of sustainability and inclusion.

Adding value (environmental, social and economic) through innovative solutions by coupling evidence with insight to achieve the above through the medium of "propulsive projects".

[Projects]

CreDDS Center Projects will integrate evidence with insight through the medium of "propulsive projects", designed to add environmental, social and economic value.

A propulsive project is defined as one which leads to a cluster of affiliated projects whose mutually synergistic relationship with each other could lead to an exponential increase in the above value propositions.

The above projects are to be designed with both a "bird's eye" and a "worm's eye" view, namely, they will seek solutions to global grand challenges which have acute local impacts on communities and the environment.

The project entry point will be challenges faced by local communities but in seeking solutions, the projects will explore collaborative national and transnational partnerships with institutions in AIU's international collaborative ecosystem (ICE).

CreDDS Center Report

Achievements in FY2023

Contents

Current Researchers and Staff Members

Director of Center

Specially Appointed Professor: Dr. Akitoshi SEIYAMA (Doctor of Science)
Research Field: Medical Science, Biomedical Engineering, Data Science

Coordinator of Center

Associate Professor: Dr. Norikazu TAWARA (Ph.D., Economics)
Research Field: Labor and Search Theory, Economic Dynamics
Incentives and Markets

Visiting Researcher

Dr. Nami KONISHI (Doctor of Medical Science)

Dr. Sayaka OKAHASHI (Ph.D.)

Dr. Satoshi SASAYAMA (Doctor of Medical Science)

Dr. Tatsuro MIURA (Doctor of Human Health Sciences)

Research Coordinator

M.A. Travis SENZAKI (Master of Asian Studies)
Area Responsibility: International Collaboration

Dr. Noriko NARISAWA (Doctor of Area Studies)
Research Field: Anthropology, Social Research, African Studies

Staff (Concurrent Office: Office of AILA Advancement)

Yoko ABE (Director)

Yoshinori SAKAMOTO (Head)

Yuka OKURA

Ryuji SHIBUYA

Research Field and Role of Visiting Researcher at CreDDS Center

Dr. Nami KONISHI (Doctor of Medical Science)

Present affiliation and position

Faculty of Nursing
Tachibana University
Lecturer

Research field and importance of collaboration

Dr. Konishi is a nurse involved in teaching and research at the Faculty of Nursing, Kyoto Tachibana University (until March 31, 2024) and Meiji University of Integrative Medicine (from April 1, 2024). Her field of expertise is mental health and psychiatric nursing, which is very important and closely related to one of the aims of our CreDDS center, healthy ageing.

In addition, she is also involved in the development of biosensor systems and the evaluation of volunteers' psychological function using the sensor systems.

This research field, concept and technology are important for the promotion of our CreDDS Center programs, especially in the boundary area between "Health & Human Well-being" and "Lifelines, Transport & Settlement System".

The collaboration with Dr Konishi will be a great asset for the advancement of the CreDDS Center's research projects.

Dr. Sayaka OKAHASHI (Ph. D.)

Present affiliation and position

National Center for Geriatrics and Gerontology
Center for Gerontology and Social Science
Senior research fellow

Research field and importance of collaboration

Dr. Okahashi aims to realize an ideal community-based comprehensive care. To achieve this goal, she conducts observational and interventional studies that contribute toward solving the issues for older adults, such as preventing the adverse prognosis of dementia and improving the quality of life of individuals with dementia, those who need care, and their families.

As practice, through developing Virtual Reality and Augmented Reality technology, Dr. Okahashi is conducting research to observe how physical and mental functions and the level of care needs change in individuals with dementia and their families. Thereby, Dr. Okahashi

is planning to develop care programs for individuals with dementia and their caregivers, verify their effectiveness, and examine measures for social implementation. The above her research field, concept and technology are important for our CreDDS Center programs, especially for “Healthy Ageing” program.

Dr. Satoshi SASAYAMA (Doctor of Medical Science)

Present affiliation and position

Graduate School of Medicine Kyoto University, Human Health Sciences
Advanced Medical Data Intelligence, Laboratory of Information Systems
Associate Professor

Research field and importance of collaboration

Dr. Sasayama aims to build a ubiquitous community home health care and nursing care cooperation system. He is developing a system that realizes smooth sharing of information between healthcare professionals, patients and their families supporting in home medical care. Further, he is creating a bacterial database, an e-Learning system in the field of health science, and interactive teaching materials.

As practice, Dr. Sasayama is engaging in the development of "electronic contact notes for home health care" using tablet terminals that are easy for the elderly to handle. Thereby, he is now practicing providing his technology to make a close relationship between medical staff at core hospitals and patients' families in Kyoto Prefecture. The above her research field, concept and technology are important for our CreDDS Center programs, especially for “Healthy Ageing” program.

Dr. Tatsuro MIURA (Doctor of Human Health Sciences)

Present affiliation and position

National Hospital Organization Kyoto Medical Center
Division of Clinical Laboratory Science
Part-time laboratory scientist

Research field and importance of collaboration

Dr. Miura is working on analyses of various data and construction of sensor systems related to health sciences. At Kyoto Medical Center, he is engaging in measuring physiological function and biochemical tests for patients as a clinical laboratory staff, while at

Kyoto University School of Medicine, he has developed a noninvasive optical monitoring system for blood glucose concentration of diabetic patients. In addition, he has participated in national projects, including with the Ministry of Land, Infrastructure, Transport and Tourism, and the Ministry of Internal Affairs and Communications, and has engaged in developing biosensor systems and evaluating volunteers' physiological function using sensor systems. His research field, concept, and technology are important for the promotion of our CreDDS Center programs, especially for the boundary area between “Health & Human Well-being” and “Lifelines, Transport & Settlement System”.

2023 Research outputs

1. Accepted Publications in International Journals

1) **(Annual Report, p.7)** Taniguchi K, Jinno N, Seiyama A, Shimouchi A. Depression is associated with discoordination between heart rate variability and physical acceleration in older women. ***Health Sci Rep***. 2024;7:e1916. doi:10.1002/hsr2.1916.

2) **(Annual Report, p.15)** Okamoto N, Seiyama A, Hori S, Takahashi S (2024) Role of the left posterior middle temporal gyrus in shape recognition and its reconstruction during drawing: A study combining transcranial magnetic stimulation and functional near infrared spectroscopy. ***PLoS ONE*** 19(5): e0302375. https://doi.org/10.1371/journal.pone.0302375

3) **(Annual Report, p.30)** Otsuka H, Okahashi S, Ishii H, Asaba W, Liu C, Yamamoto G, Seiyama A (2024) Capture of Emotional Responses under a Simulated Earthquake Experience Using Near-Infrared Spectroscopy and Virtual Reality. ***PLoS ONE*** 19(5): e0304107. https:// doi.org/10.1371/journal.pone.0304107

4) **(in press)** Seiyama A, Konishi N, Miura T, Okahashi S, Cassim M. Development of a health- monitoring system for frail people: a preliminary study. ***Adv Exp Med Biol***. 2024.

5) **(in press)** Otsuka H, Okahashi S, Seiyama A. Neural function desynchronization in left and right dorsolateral prefrontal cortices during virtual-reality earthquake video viewing. ***Adv Exp Med Biol***. 2024.

6) **(in press)** Taniguchi K, Seiyama A, Shimouchi A. Relevance between reduction of SpO_2 and parasympathetic nervous activity during sleep.
Adv Exp Med Biol. 2024.

2. Conference Presentations (Presentations by co-authors were excluded.)

1) The 100th Anniversary Annual Meeting of The Physiological Society of Japan
(March 14-16, 2023, Kyoto)
“Studies on early detection of sleep onset signal during driving”

2) The 9th International Conference on Ayurveda, Unani, Siddha and Traditional Medicine
(Sep 8-10, 2023, Colombo University (zoom presentation))
“Near infrared spectroscopy techniques for human Body-Mind-Brain research”

3) The 50th International Society on Oxygen Transport to Tissue (Sep 29–Oct 1, 2023, Tokyo)
“Development of a health-monitoring system for frail people.”

4) The 55th Annual Meeting of The Physiological Society of Tohoku Area.
(Nov 15, 2023, Akita).
“フレイル層の健康管理に向けた遠隔健康管理システムの開発を目指して”

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DOI: 10.1002/hsr2.1916

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Depression is associated with discoordination between heart rate variability and physical acceleration in older women

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Funding information

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Abstract

Background and Aims: It is well known that depression is closely associated with the autonomic nervous system and physical acceleration (PA), which may cause functional time-deviance between these two parameters. Exploring this relationship is important in sustaining the mental and physical health of older adults in daily life. However, few studies have assessed the relationship between depression and the coordination of parasympathetic nervous activity (PSNA) and PA. The present study was designed to investigate whether the coordination between PSNA and PA is associated with the mental state of healthy volunteers in normal daily lives and the underlying mechanism.

Methods: In total, 95 adult women were divided into non-older and older groups comprising 50 (aged 20–59 years) and 45 (aged 60–85 years) women, respectively. PSNA and PA data were simultaneously obtained every minute for 24 h during the free-moving day using the ActiveTracer accelerometer. Lag time was determined as the time difference between PSNA and PA, and it was introduced as a parameter of %lag0, which is the percent ratio of the lag = 0 min between PSNA and PA in 1 h. The General Health Questionnaire 28 (GHQ28) was used to evaluate the effects of psychological distress, including depression.

Results: In the hour before sleep, %lag0 was significantly lower in older women (38.7 ± 6.4) who had higher GHQ28 values (subscale D = 0, $n = 12$) compared with that in older women (19.4 ± 10.5) with lower values (subscale D ≧ 1, $n = 33$) ($p < 0.05$).

Conclusion: Impairments in coordination between PSNA and PA are significantly associated with depression in older women, particularly in the hour before sleep on free-moving days.

KEYWORDS

autonomic nervous system, depression, parasympathetic nervous system, physical activity

1 | INTRODUCTION

Depression is one of the most prevalent mental illnesses globally and is associated with an increased risk of morbidity and suicide.[1] It is associated with physical and cognitive decline, compromised social life, and greater self-neglect, thereby also increasing mortality.[2] According to a survey conducted by the World Health Organization, in 2017, the prevalence of depression was highest in Ukraine (6.3%) followed by the United States, Greece, and Portugal. Moreover, according to the survey, the prevalence of depression is 4.2% in Japan. Moreover, the prevalence of depressive symptoms in patients aged >60 years may reach up to 40%.[3]

Nevertheless, psychological distress is widely used as an indicator of public mental health. Psychological distress implies an undifferentiated combination of symptoms ranging from depression and general anxiety symptoms to personality traits, functional disabilities, and behavioral problems.[3] Reportedly, the incidence of psychological distress in women is approximately twice that in men, although the frequency increases in both men and women with age.[4]

The General Health Questionnaire 28 (GHQ28) has often been utilized for the evaluation of psychological distress from subscales of somatic symptoms, anxiety and insomnia, social impairments, and severe depression.[5,6] Furthermore, the GHQ28 is one of the most widely used and validated questionnaires to screen for emotional distress and depression.[7]

Moreover, physical acceleration (PA) has been utilized to evaluate physical activity in participants with severe mental illnesses[8] and in multiple clinical settings.[9] The health benefits of PA have also been widely studied and were demonstrated as an effective treatment for depression in older patients.[2] Plausible mechanisms to explain the association of PA with depression include PA-induced changes in physiological/neurological and psychological parameters.[10] Overall, PA may prevent depression by increasing the functional activity of monoamines.[11]

Although habitual activity and heart rate variability (HRV) have been reported to differ between men and women,[12,13] during exercise with an increasing PA, an increase in the heart rate and decrease in vagal discharge have been detected.[14] Moreover, heart rate increases immediately after initiating exercise due to a withdrawal of parasympathetic nervous activity (PSNA) and increased sympathetic nervous activity.[15]

HRV is a noninvasive tool for assessing variations in beat-to-beat intervals and autonomic nervous system activity. The HRV spectrum involves the power of high-frequency (HF) and low-frequency (LF) ranges.[16,17] Normalized spectral indices, defined as HFnu = HF/(LF + HF), are regarded as markers of PSNA.[18]

Cross-correlation analysis generates a series of correlation coefficients between two time-series by overlaying and temporally shifting the two series over a range of successive time lags.[19] To investigate the association of HRV with a physiological signal, cross-correlation analysis is widely used.[20] Based on a cross-correlation analysis between the time-series of HRV and PA, we previously reported an increase in lag with age in the daily lives of free-moving adults.[21] Furthermore, we reported that this increase was closely associated with depression, although the sex-specific effect remained unclear owing to the small sample size.[21] Moreover, we recently reported that fatigability in adult women is closely associated with a decline in coordination between PSNA and PA.[22]

Key points

- Impairments in coordination between parasympathetic nervous activity and physical acceleration are associated with depression in older women, particularly in the hour before a night's sleep.
- The lag is determined by the cross-correlation analysis between the time-series of heart rate variability and physical acceleration.
- The coordination between parasympathetic nervous activity and physical acceleration can be performed noninvasively and easily during the free-moving day.

In the present study, we aimed to investigate whether psychological distress is associated with impairments in coordination between PSNA and PA in daily free-moving life in adult women by combining %lag0 and the GHQ28 and the underlying mechanism. To our knowledge, this is the first study to evaluate the relationship between depression and the coordination between PSNA and PA in free-moving adult women.

2 | MATERIALS AND METHODS

2.1 | Participants

A total of 95 healthy women participants aged 22–85 years old were screened from 106 volunteers based on their responses to medical interviews regarding previous and current illnesses, physical findings, blood test results, and electrocardiogram results. Five participants who had consumed alcohol on the day of the experiment, six participants with severe arrhythmias, two participants taking beta-blockers, and three participants with excessive electrical noise in the devices were excluded. These excluded numbers were overlapped. First, the participants were divided into non-older (n = 50) and older age groups (n = 45) based on a cutoff of 22–59 years in the younger group and 60–85 years in the older group (Table 1). Second, participants in each age group were divided into low and high GHQ groups (Table 1 and Figures).

2.2 | Protocols

Participants completed the GHQ28 before or on the day of the assessments before visiting our laboratory at approximately 13:00 and underwent a physical examination and 12-lead electrocardiogram.

TABLE 1 Comparison of the demographic, questionnaire, and extracted parameters between General Health Questionnaire 28 (GHQ28) total scores.

Group	Non-older	Older	*p* Value (*d* value)
Age (years)	<60	≥60	
N	50	45	
Age (years)	42.6 ± 1.7	70.5 ± 0.8*	<0.001 (2.60)
Body mass index	22.0 ± 0.4	22.8 ± 0.55	0.197 (0.27)
Sleeping hours	6.8 ± 0.2	7.5 ± 0.2*	0.038 (0.43)
Frequency of nocturnal awakening	0.48 ± 0.10	1.04 ± 0.13*	0.001 (0.67)
GHQ A: Somatic symptoms	1.9 ± 0.3	2.2 ± 0.3	0.506 (0.14)
GHQ B: Anxiety and insomnia	2.3 ± 0.3	3.0 ± 0.4	0.113 (0.37)
GHQ C: Social impairment	0.7 ± 0.2	1.5 ± 0.3*	0.044 (0.54)
GHQ D: Severe depression	0.5 ± 0.2	1.2 ± 0.3*	0.035 (0.46)
PA (mG)			
Evening	39.0 ± 2.0	40.5 ± 1.9	0.586 (0.11)
Morning	50.2 ± 2.6	51.1 ± 3.2	0.837 (0.05)
HFnu			
Evening	0.24 ± 0.01	0.30 ± 0.02*	0.023 (0.42)
Sleep	0.47 ± 0.02	0.44 ± 0.02	0.403 (0.17)
Morning	0.24 ± 0.01	0.30 ± 0.02*	<0.001 (0.69)

Note: Evening, from the start of the monitoring to sleep at night; Morning, after wake-up to the end of the monitoring; sleep, subjects in bed.
Abbreviations: HFnu, HF/(LF + HF); HF, high-frequency; LF, low-frequency; PA, physical acceleration.
*$p < 0.05$ Non-older versus older.

Thereafter, participants wore a portable monitor (Active Tracer AC301; GMS Inc.) to record their PA and R–R intervals for 24 h. The sampling frequency of the AC301 was 1 kHz. During monitoring, participants were instructed to continue with their usual lives but to avoid bathing. After the 24-h monitoring period, participants returned to the laboratory. The experimental protocols have been described in detail in our previous studies.[21–23]

2.3 | Questionnaires

We used the Japanese version of the GHQ28 to evaluate psychological distress (Nihon Bunka Kagakusya Co., Ltd.).[24] The GHQ28 is a self-report instrument frequently used to indicate psychological well-being and the psychological dimensions of quality of life.[5] It has four subscales: (A) somatic symptoms, (B) anxiety and insomnia, (C) social impairment, and (D) severe depression.[5] Each of these subscales includes seven items, scored using 2-point scores of 0-0-1-1. The sum of scores indicated the severity of mental or psychological distress.[5] The GHQ scores were defined as low (total < 8, A and B < 2, C and D = 0) and high (total ≥ 8, A and B ≥ 2, C and D ≥ 1).[24]

2.4 | PA

To measure PA, an ActiveTracer equipped with a triaxial accelerometer (72 g) was used.[25] The body of the accelerometer was positioned on the frontal midline of the waist above the navel to avoid disturbing sleep or free movement. The resolution of acceleration was 2 mG, and the sensitivity ranged between 0 and 4.0 G. The absolute values of the resultant vectors, calculated from the signals of triaxial acceleration, were averaged for every minute. The times at which participants fell asleep and woke up were estimated based on records they maintained and changes in body positions were evaluated from the acceleration vectors. We defined three periods: evening, from the start of the monitoring to sleep at night; sleep, time on the bed; and morning, from wake-up to the end of the monitoring.

2.5 | HRV analysis

The HRV was analyzed at 1-min intervals using the MEMCalc System software (Suwa Trust Co., Ltd.). One-min HRV analysis was performed in mobile settings described in a previous study.[26] The method was based on a maximal entropy combined with the least square method and was useful for frequency analyses using small sample size data.[27] LF (0.04–0.15 Hz) and HF power (0.15–0.40 Hz) were analyzed as HRV parameters.[16] In this study, PSNA was defined as HFnu = HF/(LF + HF).[16]

2.6 | Definition of %lag

The definition of %lag is shown in previous literature.[21,22] In brief, we determined lag time by the maximum correlation coefficient obtained from the cross-correlation analysis between PSNA and PA. Each cross-correlation coefficient was calculated over 10-min time-windows during 60-min consecutive periods. Our preliminary cross-correlation analysis confirmed that similar results were obtained regardless of whether the implemented time window was 10 or 20 min for evaluating the lag between PSNA and PA (data not shown). When the correlation coefficient of HFnu and PA showed maximum correlation at lag = 0 min, the HFnu and PA were synchronized. If this synchronization continued for 1 h, then the %lag0 = 100%. Thus, low levels of %lag0 indicated an impairment in the coordination between PSNA and PA.

2.7 | Statistical analyses

Data are expressed as mean ± standard error of the mean. Statistical analysis was performed using the Student's *t*-test, Mann–Whitney *U*-test, and Bonferroni procedure for multiple comparison correction using Excel and SPSS 21.0, as appropriate. The significance of the cross-correlation coefficient at match position was evaluated based on Pearson correlation coefficients. For significant differences, we calculated Cohen's *d* effect size. $p < 0.05$ was considered statistically significant.

3 | RESULTS

As shown in Table 1, older participants had longer sleep duration and experienced more nocturnal awakenings than younger participants. There were no significant differences between groups in the subscale scores of GHQ28 A: somatic symptoms and B: anxiety and insomnia; however, the older group had significantly higher scores in the GHQ28 subscale C: social impairment and D: depression. The older group had significantly higher HFnu in the evening and morning than the non-older group but not during sleep.

To understand %lag0 better, an example is shown in Figure 1. Figure 1 illustrates a participant's HFnu and PA in 1 h. The top panel shows lag = 0 min, and the next panel shows 5 min PA precedence (lag = 5). The bottom panel shows that the correlation coefficient was calculated every minute from HFnu precedence 10 min to PA precedence 10 min. This case indicated that the time-series between them were synchronized because their correlation coefficient indicated maximal correlation at lag = 0 min. If this synchronization continues for 1 h, the %lag0 = 100%, as defined in Section 2.

Figure 2 illustrates the %lag0 between PSNA and PA 1 h before sleep. At 1 h before sleep, the older group with higher total GHQ and GHQ A–D scores had significantly lower %lag0 than the non-older group (#, $p < 0.05$). Remarkably, the older group with high GHQ D scores (lowest Figure 2) showed significantly lower %lag0 between the time-series of PA and HFnu than the older group with low GHQ D scores 1 h before sleep (*, $p < 0.05$, Cohen's $d = 0.55$). Nonetheless, in the non-older group, no significant differences were found in the % lag0 between those with low and high GHQ total and A–D scores.

Figure 3 illustrates the %lag0 between PSNA and PA 1 h after sleep. At 1 h after wake-up, the older group with high GHQ A–D scores had significantly lower %lag0 than the non-older group (#, $p < 0.05$), except in %lag0 of PA and HFnu in GHQ B ($p > 0.05$, Cohen's $d = 0.41$) and C ($p > 0.05$, Cohen's $d = 0.43$), although they indicated the same tendency. However, no significant difference was observed between the older group with high GHQ D scores and the older group with low GHQ D scores.

4 | DISCUSSION

In our previous report, we demonstrated that %lag0 after wake-up is significantly reduced with aging even in healthy adult women.[21] In this study, older women with depression (high GHQ D > 1) had

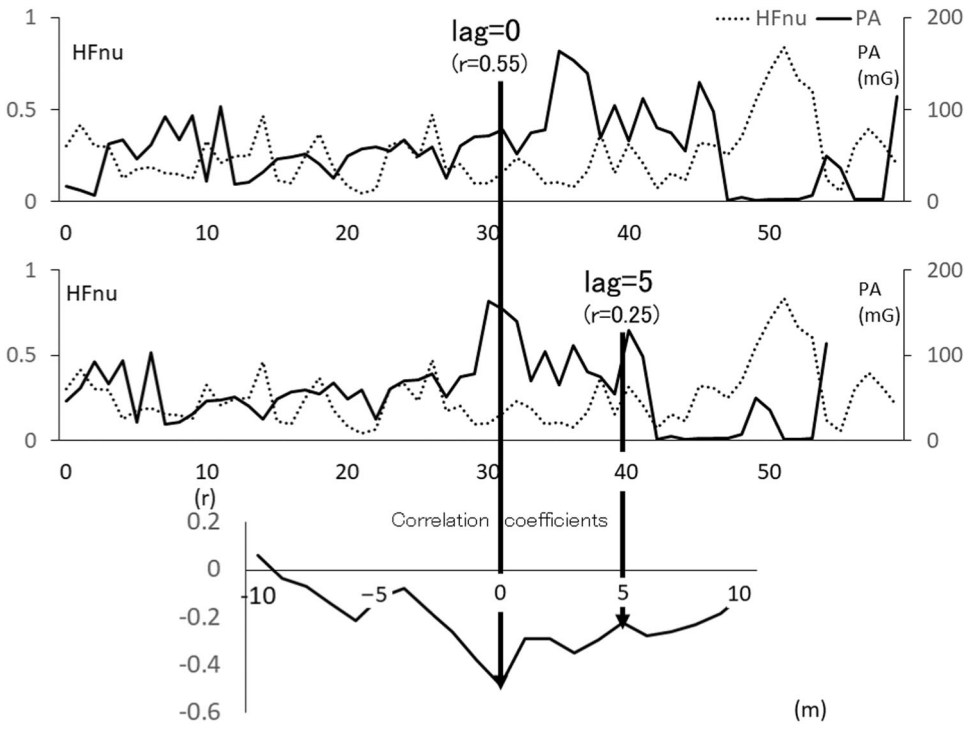

FIGURE 1 An example of the lag calculation. Top figure: correlation between HFnu and PA gives a negative maximum correlation ($r = -0.55$, see bottom figure) without shift of PA signal, which means inverse relation of the two signal shapes at lag time (lag) = 0 min with $r = 0.55$. Middle figure: the two signals gave a negative correlation ($r = -0.25$) after +5 min-shift of the PA signal (lag = 5). HFnu, HF/(LF + HF); HF, high-frequency; LF, low-frequency; PA, physical acceleration.

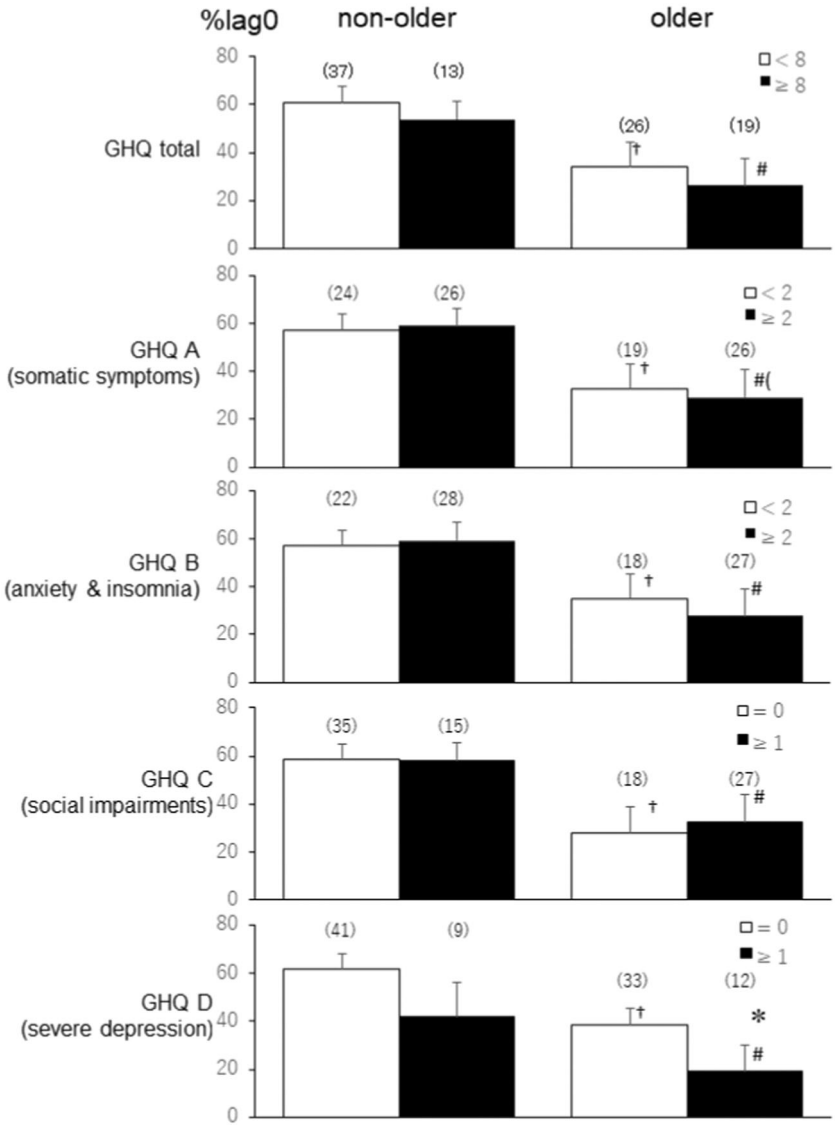

FIGURE 2 Relationships between %lag0 and GHQ scores in the non-older and older groups 1 h before sleep. Values above the error bars show the number of participants. †$p < 0.05$ non-older versus older participants with low GHQ scores (GHQ total: $p = 0.013$, $d = 0.72$, GHQ A: $p = 0.045$, $d = 0.52$, GHQ B: $p = 0.033$, $d = 0.59$, GHQ C: $p = 0.008$, $d = 0.82$, GHQ D: $p = 0.033$, $d = 0.61$); $^{\#}p < 0.05$ non-older versus older participants with high GHQ scores (GHQ total: $p = 0.031$, $d = 0.68$, GHQ A: $p = 0.001$, $d = 0.95$, GHQ B: $p = 0.028$, $d = 0.70$, GHQ C: $p = 0.009$, $d = 0.86$, GHQ D: $p = 0.032$, $d = 0.63$); $^{*}p < 0.05$, older participants with low GHQ D (depression) score versus older participants with high GHQ D scores ($p = 0.034$, $d = 0.55$). Error bars represent standard error. The vertical axis shows each %lag0 value. Open bar: low GHQ scores (total < 8, A and B < 2, C and D = 0). Closed bar: high GHQ scores (total ≥ 8, A and B ≥ 2, C and D ≥ 1). GHQ, General Health Questionnaire; HFnu, HF/(LF + HF); HF, high-frequency; LF, low-frequency.

significantly lower %lag0 1 h before sleep. These results indicate that depression is closely associated with impairments in the coordination between PSNA and PA before sleep in older women.

In this study, we divided the participants into non-older and older age groups based on a cutoff of 22–59 years in the younger group and 60–85 years in the older group. In our previous study, participants were divided into three groups, young (20–39 years), middle-aged (40–59 years), and older (≥60 years).[21] Significant differences were observed in the %lag0 between the middle and older groups in 1 h before sleep; however, o significant differences were observed between the young and middle-aged groups. Therefore, we divided the participants into non-older (20–59 years) and older (≥60 years) in this study.

We defined lag = 0 as the time difference within −30 to 30 s indicated by the minimum *p*-value obtained from an analysis of the cross-correlation between the HFnu and PA. Active and passive changes in fundamentally different cardiovascular effects for approximately 20 s (within 30 s) involve the central command, muscle receptors, and high- and low-pressure receptors.[28] Therefore, the definition of lag was based on the hypothesis that PA causes an immediate PSNA response under healthy conditions. We determined lag = 0 (−30 to 30 s) as an indicator of the coordination between PSNA and PA.

In this study, no significant differences in %lag0 were detected between participants with irregular sleep cycles or without incidents of nocturnal awakening on the experimental day, based on the questionnaires (data for reviewers). Patients with depression have also been reported to have sleep disorders and low sleep efficiency,[29,30] and participants with sleep difficulties are threefold to fourfold more likely to be depressed. PA and PSNA discoordination before sleep, especially 1 h before sleep, may be associated with reduced sleep efficiency and quality.

The total GHQ28 reflects the level of psychological stress[31]; this is demonstrated in our results showing depressive tendencies in older and non-older individuals based on their GHQ28 D subscale scores and lower %lag0 between HRV and PA. However, the decrease in %

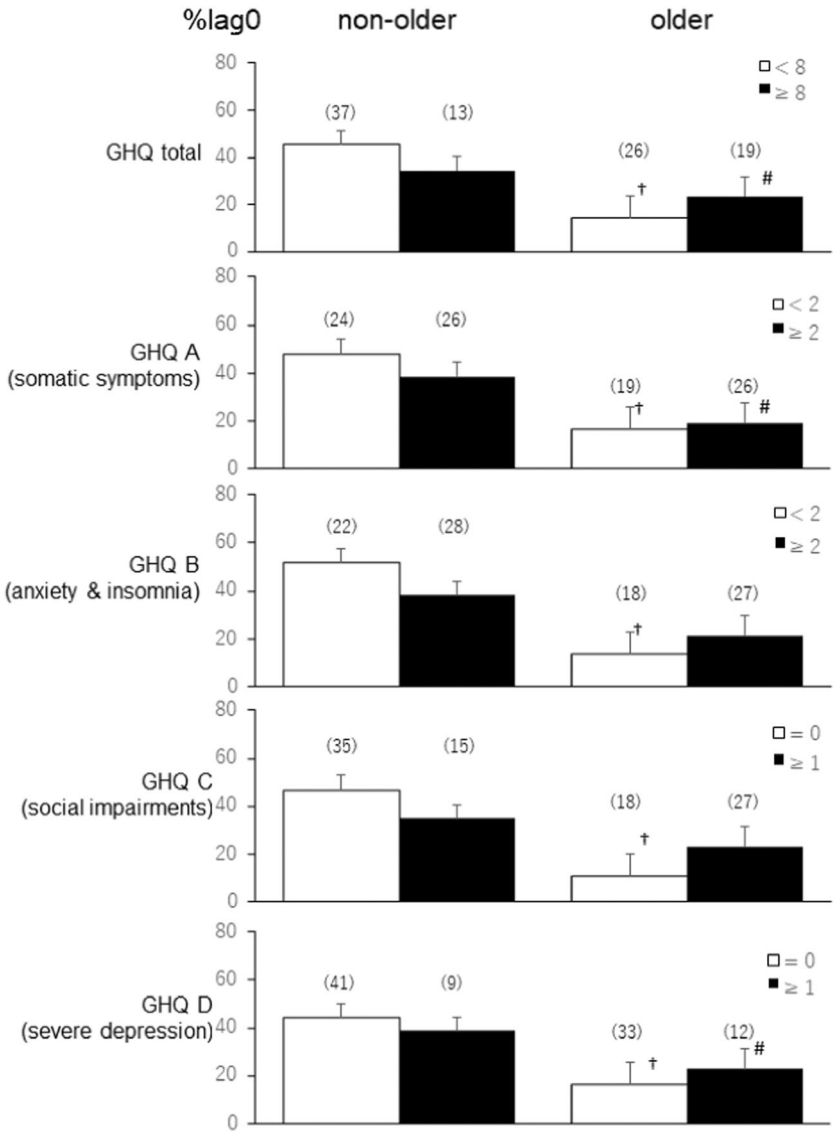

FIGURE 3 Relationships between %lag0 and GHQ scores in the non-older and older groups 1 h after sleep. Values above the error bars show the number of participants. †$p < 0.05$ non-older versus older participants with low GHQ scores (GHQ total: $p < 0.001$, $d = 1.03$, GHQ A: $p < 0.001$, $d = 1.13$, GHQ B: $p < 0.001$, $d = 1.46$, GHQ C: $p < 0.001$, $d = 1.19$, GHQ D: $p = 0.004$, $d = 0.91$); $^{\#}p < 0.05$ non-older versus older participants with high GHQ scores (GHQ total: $p = 0.048$, $d = 0.42$, GHQ A: $p = 0.046$, $d = 0.52$, GHQ D: $p = 0.044$, $d = 0.50$); Error bars represent standard error. The vertical axis shows each %lag0 value. Open bar: low GHQ scores (total < 8, A and B < 2, C and D = 0). Closed bar: high GHQ scores (total ≥ 8, A and B ≥ 2, C and D ≥ 1). GHQ, General Health Questionnaire; HFnu, HF/(LF + HF); HF, high-frequency; LF, low-frequency.

lag0 was not significant in non-older individuals. These results indicate that depression is only significantly associated with the discoordination between HRV and PA in older women, particularly 1 h before sleep.

The menopausal years in Japanese women reportedly begin at approximately 52 years of age.[32] We divided participants into non-older (≤59 years) and older (≥60 years) groups. Therefore, the older group might have comprised postmenopausal women alone. Conversely, some participants in the non-older group might also have been postmenopausal, as they were in their late 40s and early 50s. Estrogen reportedly reduces cardiomyocyte contractile function and sympathovagal nervous activity, whereas androgen enhances them.[32] Estrogen acts on the central nervous system to reduce sympathovagal activity.[33] In postmenopausal women, sympathovagal nervous activity is elevated due to changes in the hormonal balance.[34] Further, menopause or the menstruation cycle can also affect depression.[35] In the present study, we could not establish whether menopause affected the %lag0 in non-older and older women. Therefore, further studies are needed to investigate the effects of the menstruation cycle on the coordination of HRV and PA.

This study has some limitations. First, the analytical method used to evaluate the coordination between the PSNA and PA has limitations. The reason for the significant reduction of %lag0 in older people with depression remains unclear. Second, we could not explain why menopause affected the %lag0 in non-older and older women. Third, this study did not control for the comorbidity score or physical condition of participants. All participants had no or mild diseases. Fourth, in this study, we defined the times at which the participants fell asleep and woke up based on the records of changes in body position evaluated from the acceleration vectors. Although the times obtained by this method may differ from the actual time, they did not significantly affect the %lag0, even when the exact time of falling asleep was off by approximately 10 min. Fifth, menopause may be an important factor that could have affected our results. However, as described above, our previous experiments showed no significant difference between the 20–39 years and 40–59 years

groups, whereas a significant difference was observed between the 40–59 years and ≥60 years groups. Lastly, as the number of participants was limited, the effects of diseases on %lag0 remained unclear. Taking the above limitations into consideration, further controlled studies are required in the future.

5 | CONCLUSIONS

Using the "%lag0" index, determined by using the time-series correlation analysis between PSNA and PA, this study suggests that impairments in the coordination between PSNA and PA are closely associated with depression in older women, particularly 1 h before sleep on free-moving days. Although further studies are required in the future, this parameter may be useful as a noninvasive index to detect depression in older women in clinical or even home settings.

AUTHOR CONTRIBUTIONS

Kentaro Taniguchi: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; resources; software; validation; visualization; writing—original draft. **Naoya Jinno**: Data curation; investigation; methodology; visualization; writing—review & editing. **Akitoshi Seiyama**: Conceptualization; methodology; project administration; supervision; writing—review & editing. **Akito Shimouchi**: Conceptualization; data curation; funding acquisition; investigation; methodology; project administration; supervision; validation; visualization; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Ethics Committee at the National Cerebral and Cardiovascular Research Center (M18-19-2, M26-158), Chubu University (280031), and Nagahama Institute of Bio-Science and Technology (006). All participants provided written informed consent before participation in this study.

TRANSPARENCY STATEMENT

The lead author Kentaro Taniguchi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. Figueiredo B, Pinto TM, Pacheco A, Field T. Fetal heart rate variability mediates prenatal depression effects on neonatal neurobehavioral maturity. *Biol Psychol*. 2017;123:294-301. doi:10.1016/j.biopsycho.2016.10.013
2. Schuch FB, Vancampfort D, Rosenbaum S, et al. Exercise for depression in older adults: a meta-analysis of randomized controlled trials adjusting for publication bias. *Rev Bras Psiquiatr*. 2016;38(3):247-254. doi:10.1590/1516-4446-2016-1915
3. Jacomo RH, Alves AT, Garcia PA, et al. Risk factors for mild depression in older women with overactive bladder syndrome—a cross sectional study. *PLoS One*. 2020;15(1):e0227415. doi:10.1371/journal.pone.0227415
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Vol 14, 5th ed. American Psychiatric Association; 2014.
5. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. *Psychol Med*. 1979;9(1):139-145. doi:10.1017/S0033291700021644
6. Iwata N, Saito K. The factor structure of the 28-item General Health Questionnaire when used in Japanese early adolescents and adult employees: age- and cross-cultural comparisons. *Eur Arch Psychiatry Clin Neurosci*. 1992;242(2-3):172-178. doi:10.1007/BF02191565
7. Sterling M. General Health Questionnaire-28 (GHQ-28). *J Physiother*. 2011;57(4):259.
8. Dubbert PM, White JD, Grothe KB, O'Jile J, Kirchner KA. Physical activity in patients who are severely mentally ill: feasibility of assessment for clinical and research applications. *Arch Psychiatr Nurs*. 2006;20(5):205-209. doi:10.1016/j.apnu.2006.04.002
9. Bauman A, Merom D, Bull FC, Buchner DM, Fiatarone Singh MA. Updating the evidence for physical activity: summative reviews of the epidemiological evidence, prevalence, and interventions to promote "active aging". *Gerontologist*. 2016;56(suppl 2):S268-S280. doi:10.1093/geront/gnw031
10. Loprinzi PD, Herod SM, Cardinal BJ, Noakes TD. Physical activity and the brain: a review of this dynamic, bi-directional relationship. *Brain Res*. 2013;1539:95-104. doi:10.1016/j.brainres.2013.10.004
11. Craft LL, Perna FM. The benefits of exercise for the clinically depressed. *Prim Care Companion J Clin Psychiatry*. 2004;6(3):104-111. doi:10.4088/pcc.v06n0301
12. Aoyagi Y, Shephard RJ. Sex differences in relationships between habitual physical activity and health in the elderly: practical implications for epidemiologists based on pedometer/accelerometer

data from the Nakanojo Study. *Arch Gerontol Geriat*. 2013;56(2): 327-338. doi:10.1016/j.archger.2012.11.006
13. Koenig J, Thayer JF. Sex differences in healthy human heart rate variability: a meta-analysis. *Neurosci Biobehav Rev*. 2016;64: 288-310. doi:10.1016/j.neubiorev.2016.03.007
14. Proper KI, Staal BJ, Hildebrandt VH, van der Beek AJ, van Mechelen W. Effectiveness of physical activity programs at worksites with respect to work-related outcomes. *Scand J Work Environ Health*. 2002;28(2):75-84.
15. Rowell LB, O'Leary DS. Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *J Appl Physiol*. 1990;69(2):407-418. doi:10.1152/jappl.1990.69.2.407
16. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation*. 1996;93(5):1043-1065. doi:10.1161/01.CIR.93.5.1043
17. Kleiger RE, Bigger JT, Bosner MS, et al. Stability over time of variables measuring heart rate variability in normal subjects. *Am J Cardiol*. 1991;68(6):626-630. doi:10.1016/0002-9149(91)90355-O
18. Stein C, Dal Lago P, Ferreira JB, Casali KR, Plentz RDM. Transcutaneous electrical nerve stimulation at different frequencies on heart rate variability in healthy subjects. *Auton Neurosci*. 2011;165(2):205-208. doi:10.1016/j.autneu.2011.07.003
19. Chatfield C. Theory and practice. The analysis of time series. In: Bar MS, ed. *Monographs on Statistics and Applied Probability*. Springer; 1975: 33-59.
20. Abdullah H, Maddage NC, Cosic I, Cvetkovic D. Cross-correlation of EEG frequency bands and heart rate variability for sleep apnoea classification. *Med Biol Eng Comput*. 2010;48(12):1261-1269. doi:10.1007/s11517-010-0696-9
21. Taniguchi K, Shimouchi A, Seki J, Jinno N, Shirai M, Seiyama A. Factors affecting coordination between heart rate variability and physical acceleration in daily lives of free-moving adults. *Adv Biomed Eng*. 2015;4:35-41. doi:10.14326/abe.4.35
22. Taniguchi K, Shimouchi A, Jinno N, Seiyama A. Coordination between heart rate variability and physical activity may be diminished by fatigability in non-older women in the hour before sleep. *Physiol Rep*. 2021;9(22):e15126. doi:10.14814/phy2.15126
23. Taniguchi K, Shimouchi A, Jinno N, Okumura N, Seiyama A. Parasympathetic nervous activity associated with discoordination between physical acceleration and heart rate variability in patients with sleep apnea. *Adv Exp Med Biol*. 2021;1269:229-234. doi:10.1007/978-3-030-48238-1_36
24. Nakagawa Y, Daibo I. *Seishin kenkou cyousahyou tebiki [Guide to the General Health Questionnaire – Japanese Version of the GHQ]*. Nihon Bunka Kagakusha; 1985. (in Japanese)
25. Iwashita S, Takeno Y, Okazaki K, et al. Triaxial accelerometry to evaluate walking efficiency in older subjects. *Med Sci Sports Exerc*. 2003;35(10):1766-1772. doi:10.1249/01.mss.0000089350.54959.cb
26. Salahuddin L, Cho J, Jeong MG, Kim D. Ultra short term analysis of heart rate variability for monitoring mental stress in mobile settings. *Annu Int Conf IEEE Eng Med Biol Soc*. 2007;2007:4656-4659.
27. Sawada Y, Ohtomo N, Tanaka Y, et al. New technique for time series analysis combining the maximum entropy method and non-linear least squares method: its value in heart rate variability analysis. *Med Biol Eng Comput*. 1997;35(4):318-322. doi:10.1007/BF02534083
28. Borst C, Wieling W, Van Brederode JF, Hond A, De Rijk LG, Dunning AJ. Mechanisms of initial heart rate response to postural change. *Am J Physiol*. 1982;243(5):H676-H681. doi:10.1152/ajpheart.1982.243.5.H676
29. Franzen PL, Buysse DJ. Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. *Dialogues Clin Neurosci*. 2008;10:473-481. doi:10.31887/DCNS.2008.10.4/plfranzen
30. Almeida OP, Pfaff JJ. Sleep complaints among older general practice patients: association with depression. *Br J Gen Pract*. 2005;55: 864-866.
31. Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and heart rate variability: a meta-analysis and review of the literature. *Psychiatry Investig*. 2018;15(3):235-245. doi:10.30773/pi.2017.08.17
32. Gold EB. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *Am J Epidemiol*. 2001;153(9): 865-874. doi:10.1093/aje/153.9.865
33. Joyner MJ, Barnes JN, Hart EC, Wallin BG, Charkoudian N. Neural control of the circulation: how sex and age differences interact in humans. *Compr Physiol*. 2015;5(1):193-215. doi:10.1002/cphy.c140005
34. Magri F, Gabellieri E, Busconi L, et al. Cardiovascular, anthropometric and neurocognitive features of healthy postmenopausal women: effects of hormone replacement therapy. *Life Sci*. 2006;78(22): 2625-2632. doi:10.1016/j.lfs.2005.10.036
35. Payne JL, Roy PS, Murphy-Eberenz K, et al. Reproductive cycle-associated mood symptoms in women with major depression and bipolar disorder. *J Affect Disord*. 2007;99(1-3):221-229. doi:10.1016/j.jad.2006.08.013

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PLOS ONE

RESEARCH ARTICLE

Role of the left posterior middle temporal gyrus in shape recognition and its reconstruction during drawing: A study combining transcranial magnetic stimulation and functional near infrared spectroscopy

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Abstract

There are numerous reports of enhanced or emerged visual arts abilities in patients with semantic impairment. These reports led to the theory that a loss of function on the language side of the brain can result in changes of ability to draw and/or to paint. Further, the left posterior middle temporal gyrus (l-pMTG) has been revealed to contribute to the higher control semantic mechanisms with objects recognition and integration of visual information, within a widely distributed network of the left hemisphere. Nevertheless, the theory has not been fully studied in neural bases. The aim of this study is to examine role of the l-pMTG on shape recognition and its reconstruction within drawing behavior, by using a combining method of the repetitive transcranial magnetic stimulation (rTMS) and functional near-infrared spectroscopy (fNIRS). Eighteen healthy participants received a low frequency inhibitory rTMS to their l-pMTG during the drawing task of the Benton Visual Retention Test (BVRT). There was a significant decrease of the mean accuracy of reproductions in the Complex designs of the BVRT, compared to the Simple and Medium designs. The fNIRS data showed strong negative correlations with the results of the BVRT. Though our hypothesis had a contradiction that rTMS would have inhibited the brain activity in the stimulated site, the results suggest that shape recognition and its reconstruction such as the BVRT require neural activations of the l-TL as well as that of the l-pMTG.

Introduction

There are a number of reports of newly developed or enhanced artistic creativity in patients with brain dysfunction (s). In particular, patients suffering from neurological and structural

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diseases, such as frontotemporal dementia [1], semantic dementia, primary progressive aphasia [2] and Alzheimer's disease [3], have shown signs of visual arts abilities throughout the progression of their cognitive deterioration. Such cases led to the theory [4, 5] that a loss of function on the language side of the brain results in an enhancement of visual art processing, even though artistic abilities has been suggested to be right hemispheric dominant. However, the theory has not been fully studied in neural bases because of its multifunctional and multiregional processes of drawing.

It has been suggested that the drawing process encompasses visuospatial skills, attention mechanisms, mental representations of space, conceptual knowledge and semantic cognition, and motion planning and control mechanisms [6, 7]. A number of functional neuroimaging studies about drawing behavior have revealed an implication of semantic and phonological networks while drawing, showing a strong bi-hemispheric activation of a widely distributed network of the frontal, parietal, and temporal lobes [8, 9]. A study about drawing by using mental imagery, drawing familiar objects compared to drawing unfamiliar objects (non-objects), showed greater activation in the left inferior temporal cortex, suggesting its involvement in the selection of specific semantic features of the object as well as retrieval of information regarding the perceptual aspects of the object [10]. A clinical report in associative agnosia, the patients showed an inability to copy a very simple figure, even though they were able to retrieve the meaning of the figure [11].There have been other ways of deficits, despite the inability to recognize an object, the patients were able to copy figures accurately, which was usually associated with the brain dysfunction of the left frontotemporal lobe. These reports suggest that, drawing processes involve different neuronal circuits, that processing verbally associable figures and/or non-verbally associable figures. We suppose that, though the language area has not been suggested as the critical region for visual art activities in general, it seems that semantic representations are involved in the processes of drawing, especially in shape recognition and its reconstruction of the verbally associable images (complex figures).

Studies in semantic recognition by using TMS explored an important role of the widely connected network of the left inferior frontal gyrus and the l-pMTG [12]. It has been suggested that there are two distinctive neural structures of semantic processes, for processing weak associations (complex figures) with executive control semantic activation in the l-pMTG, and for processing strong associations (simple figures) with automatic spreading activation in the left angular gyrus [13, 14]. Furthermore, the l-pMTG has been revealed to contribute to higher control semantic mechanisms with manipulation of conceptual knowledge retrieval and the selection of semantic knowledge [15]. Based on these studies, the l-pMTG is possibly involved in shape recognition and its reconstruction during drawing.

The Benton Visual Retention Test (BVRT) has been a reliable tool for both clinical and experimental research, and has been used for many forms of brain impairments and diseases such as Alzheimer's disease, dementia, aphasia, geriatrics, schizophrenia and children with learning disabilities [16, 17]. The test assesses visual perception, short-term visual memory, and visuo-constructional ability. However, a number of studies that used the BVRT suggested that a verbal mediation component is thought to be associated, due to the use of verbally associable geometric figures ranging from strongly associable images (simple designs. e.g., a pentagon) to weakly associable images (complex designs. e.g., a mixture of geometric figures) [18, 19]. Clinical studies have often reported hearing patients repeat the names of the shapes aloud to themselves as they view the figures before they attempt to produce them, and as they draw them [18]. We adopted this verbal mediation of the BVRT into our experiment, to test shape recognition and its reconstruction during drawing the complex designs of the BVRT.

The aim of this study is to investigate the relationship between the neural activities of specific regions of the l-pMTG and behavioral effects on the shape recognition and its

reconstruction during drawing. We employed a combining method of the repetitive transcranial magnetic stimulation (rTMS) and functional near-infrared spectroscopy (fNIRS) [20–22], with the drawing task of the Benton Visual Retention Test (BVRT). rTMS is a noninvasive technique whereby magnetic pulses transiently disrupt neural processing causing behavioral changes [23–25]. By using rTMS, temporally impaired neural situations that supposed to be like patients are created in healthy participants. fNIRS is an optical and wearable neuroimaging techniques that has great advantages of higher time resolutions and make no interference against metallic materials and devices generating electricity or magnetism, which is unlikely to PET and fMRI, and is an ideal candidate for integrated use with TMS, in normal seated positions. We employed rTMS and fNIRS measurements during the drawing test of the BVRT to examine the relationship between neural functions and the behavior.

The aim of the study is to test our hypothesis that inhibitory rTMS to the l-pMTG suppresses the BVRT reproducibility. Furthermore, we discussed the role of the l-pMTG for the shape recognition and its reconstruction during drawing the Complex designs of the BVRT.

Materials and methods

Participants

Eighteen healthy volunteers (7 male and 11 female, mean age 27.2 years; range 21–41 years, SD = 5.67, right-handed). Using G*Power 3.1.9.2, pre-analysis for the required minimum sample size resulted in 15 persons, assuming effect size = 0.80, α error probability = 0.05, and power (1-β error) = 0.80. Participants were recruited from undergraduates, graduate students, and people with normal learning ability. All participants were confirmed to have no history of epilepsy, intracranial lesions, medications or alcohol dependence, and no neurological or psychiatric disorders and/or learning disabilities. The recruitment period for the participants in this experiment was from March 1, 2014 to May 31, 2014. Prior to the experiment, all participants provided both written and verbal informed consent. The methods were carried out in accordance with the relevant guidelines and regulations. All experimental protocols were approved by the Kyoto University Graduate School and the faculty of the medical ethics committee (The approval number: Reception No. E1269) and adhered to the tenets of the Declaration of Helsinki.

BVRT procedure

The tests were conducted individually for each participant in the laboratory. Before the real tests, all participants were exposed to the sample designs in order to understand the procedure. To avoid practice effects, participants were asked to perform two different sets of equivalent forms, which were designated as control and rTMS respectively. The form consisting of ten designs was shown one by one to the participants (Fig 1A). Each design was made up of one or three-figures, consisting of two large central geometric forms and one small peripheral figure, printed on a card (8.5 × 5.5 in.). We employed the method type of Administration A, that is, the participants were exposed to each design for ten seconds and were then asked to reproduce them on a sheet of plain paper immediately after the original design was removed, within twenty seconds in this experiment. Additionally, after the test, participants were interviewed by the examiner about how they remembered the design.

The BVRT scores were assessed by the mean correct scores and the total number error scores with six categories, in accordance with the test manual [26]. The number correct scores are calculated based on an all-or-nothing approach; points are awarded if the reproduction of the design matches the original. The error scores were calculated with six types of major categories such as omissions, distortions, perseverations, rotations, misplacements, and size errors.

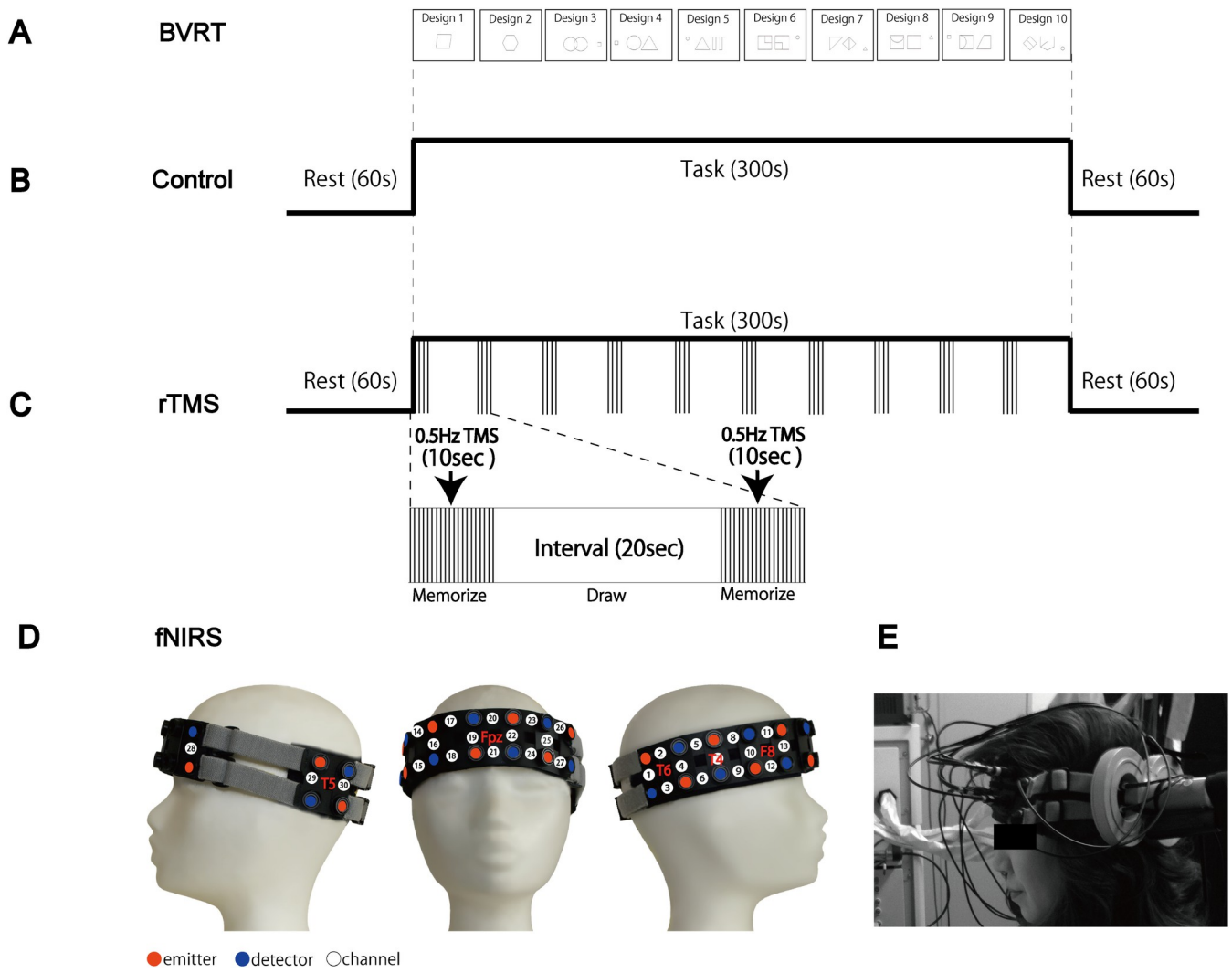

Fig 1. Experimental procedure. (A) Ten designs used in the BVRT (One of the two forms). The form consists of ten various designs, starts from simple to complex. The participants were exposed to the design for ten seconds and were then asked to draw them on a sheet of plain paper immediately after the original design was removed. **(B)** Protocol of the control with 0% stimulus output. **(C)** rTMS protocol with a frequency of 0.5 Hz (150 pulses) and a stimulus intensity with 100% of RMT. **(D)** Twelve pairs of emitting and detecting optical fibers were placed based of the International 10–20 system, creating thirty measuring points (channels). **(E)** An 8-figure coil was applied to the l-pMTG, corresponding to the brain area T5 (International 10–20 system).

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An analysis on the degree of complexity of the designs was assessed by making a comparison among the Simple designs (the design 1–3), the Medium designs (the design 4–7) and the Complex designs (the design 8–10).

rTMS protocol

We used a magnetic stimulator (SMN-1200, Nihon Koden, Japan) with an 8-figure coil (YM-131B, Nihon Koden, Japan). A low frequency stimulation of 0.5 Hz rTMS (150 pulses) was applied to the l-pMTG, corresponding to the brain area T5 (International 10–20 system) (Fig 1E). Although many studies have used 1 Hz stimulations as a low frequency rTMS, in this study, we rather employed 0.5 Hz to 1 Hz in order to reduce side effects, such as loud clicking noises from the device. However, 0.5 Hz stimulations has also been found to be effective to inhibit neural activities [27, 28]. Additionally, in control, participants underwent a task with

hearing the recorded clicking sound of the rTMS, to reduce the environmental difference of sound affects between control and rTMS.

Prior to the experiment, the stimulus intensity for each participant was determined individually with the minimum intensity of 50 μV with 20% probability in a fully relaxed muscle (resting motor threshold: RMT). We monitored the motor-evoked potential (MEP) of the left first dorsal interosseous muscle by placing the coil over the right primary motor area of the participants. In addition, five of the eighteen participants received the stimulus intensity of 65% of the stimulator output, due to uncomfortable feelings caused by rTMS. Two conditions, control (0% of stimulator output) and rTMS (100% of RMT), were performed on one day with thirty-minute interval. Each task lasted for a total of seven minutes with rest (60 seconds), BVRT (300 seconds), rest (60 seconds) (Fig 1B and 1C).

fNIRS data acquisition

Brain activity was observed by functional near infrared spectroscopy (fNIRS) (FOIRE-3000, Shimazu Corp, Japan). fNIRS is a non-invasive optical imaging method used to measure changes in the concentration of oxygenated hemoglobin (oxy-Hb) at a depth of 20–30 mm under the scalp [20, 21]. Twelve pairs of emitting and detecting optical fibers were placed on the participant's head, creating thirty measuring points (channels). The distance between each fiber was 30 mm. The locations of the fNIRS measurement points were determined based on the international 10–20 system for the electrode placements and adjusted with elastic bands to fit each participant's head (Fig 1D).

A number of base measuring points were set according to the international 10–20 system for each ROIs: the center of the Ch1-Ch4 corresponding to the T6 was set on the right temporal lobe (r-TL), the centered point between the Ch20 and the Ch21 corresponding to the Fpz was set to determine the right and left prefrontal cortex (r-PFC; Ch16—Ch19 and l-PFC; Ch22-Ch25), the center of the Ch10-Ch13 corresponding to the F8 was set on the right frontotemporal lobe (r-FTL) and the centered point between Ch29 and Ch30 corresponding to the T5 was set on the left temporal lobe (l-TL) [29]. In addition, we observed brain activity on the l-pMTG, where the magnetic coil of the TMS was applied, by passing the fibers through the hole of the coil (Fig 1E).

The total fNIRS measurement time was set at 420 seconds (rest 60—task 300—rest 60) for control and rTMS. The fNIRS data analysis was performed for the 300 seconds (from 0.91 seconds to 299.15 seconds), omitting 60 seconds of the rest before and after the task. The fNIRS data that were outside the software's acceptable range were automatically deleted. After performing a low-pass filter of 0.01Hz, data were analyzed by using Modified Beer-Lambert Law (S1 Data Raw data of NIRS). In each channel averaged data were obtained without standardized individual data. We calculated an integral value of changes in oxy-Hb for each channel.

The autonomic nervous system analysis

We assessed the participants' physical stress by the autonomic nervous system analysis. The autonomic nervous system function was determined by the spectral analysis of heart rate variability, which was measured by pulse oximetry (OLV-3100, Nihon Koden, Japan). All participants were wearing the fiber plug of the pulse oximetry on their left middle finger during the entire experiment. We used the principle of maximum entropy method (MEM) with the program (Map1060, Bio Field, Japan). The heart rate variability's power spectra were divided into a very low-frequency (VLF) of 0.003–0.040 Hz, a low-frequency (LF) of 0.04–0.15 Hz, and a high frequency (HF) of 0.15–0.40 Hz. In general, HF fluctuations are mediated by both the sympathetic and parasympathetic nervous systems, and LF fluctuations are mediated by the

parasympathetic nervous system. The ratio of LF/HF was estimated as the levels of the sympathetic nervous activity representing the participants' stress conditions. And the ratio of HF/Total (defined as VLF+LF+HF) was estimated as parasympathetic nervous system representing the participants' relaxed conditions.

Statistical analysis

Statistical analysis for the BVRT data, a paired t-test was used on the number correct scores and the number error of the BVRT and on the autonomic nervous system function.

For the NIRS data, after confirming normal distribution and homoscedasticity by using the Shapiro-Wilk test and the Kolmogorov-Smirnov test, we conducted a nonparametric analysis of the Mann-Whitney U-Test with the Bonferroni corrections. Data were expressed as mean ±SE. Values of $p < 0.05$ and $p < 0.01$ were considered statistically significant. The effect size (Cohen's d) was calculated.

Results

BVRT scores

The BVRT scores were assessed by the mean correct scores and the total number error scores with six categories, in accordance with the test manual [26]. The number correct scores were calculated if the participants accurately drew the designs matched to the original. The error scores were calculated with six types of major categories such as omissions, distortions, perseverations, rotations, misplacements, and size errors. We compared the mean accuracy of the drawings calculated with the correct scores and the total number error scores with six categories of all the participants (n = 16/18; two participants were excluded due to an imperfection in the process), between under control and rTMS.

In the correct scores, there was a significant decrease in the Design 8 under rTMS (t (30) = 2.63, p = 0.01, d = 0.96) (Fig 2A, S1 Table for BVRT Correct). In the error scores, there was a significant increase of the total error scores in the design 8 under rTMS (t (30) = -2.60, p = 0.01, d = -0.95) (Fig 2B and S2 Table for BVRT Error). Furthermore, there was a significant increase in the "distortions" error scores in the design 8 under rTMS, which often appears in the patients with dementia [30] (t (30) = -2.27, p = 0.031, d = -0.83).

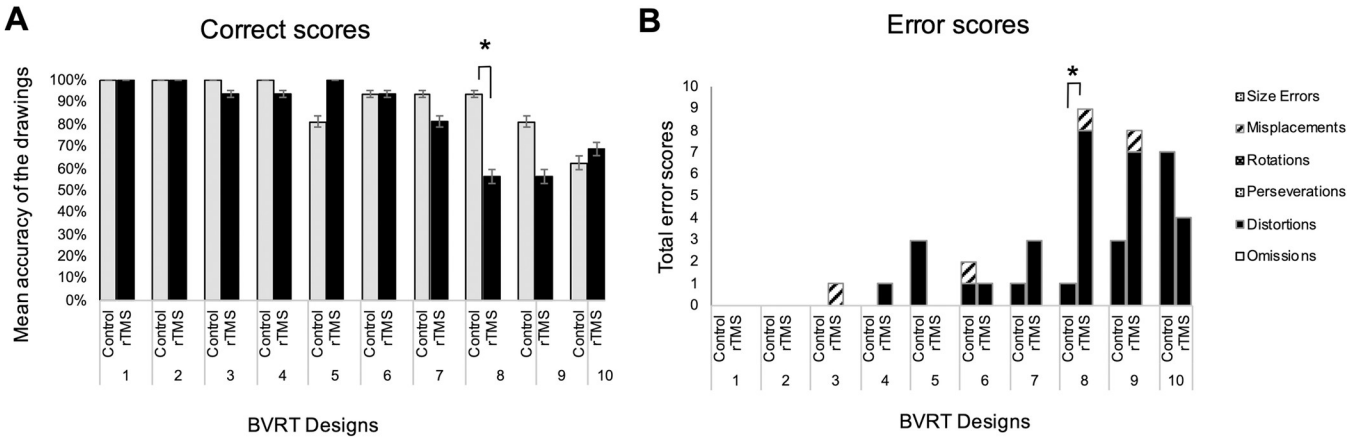

Fig 2. The correct scores and the error scores of the BVRT for control and rTMS. (A)The graph indicates the mean accuracy of the BVRT of all participants under control (gray) and rTMS (black), displayed with percentages. Data are shown as mean +/- SE (n = 16). *: $P < 0.05$, (d = 0.96). (B)The graph indicates the total error scores of all participants for control and rTMS. Each bar consists of six types of categories such as omissions (white), distortions (black), perseverations (spots), rotations (gray), misplacements (slash) and size errors (check). Data are shown as mean +/- SE (n = 16). *: $P < 0.05$, (d = -0.95).

https://doi.org/10.1371/journal.pone.0302375.g002

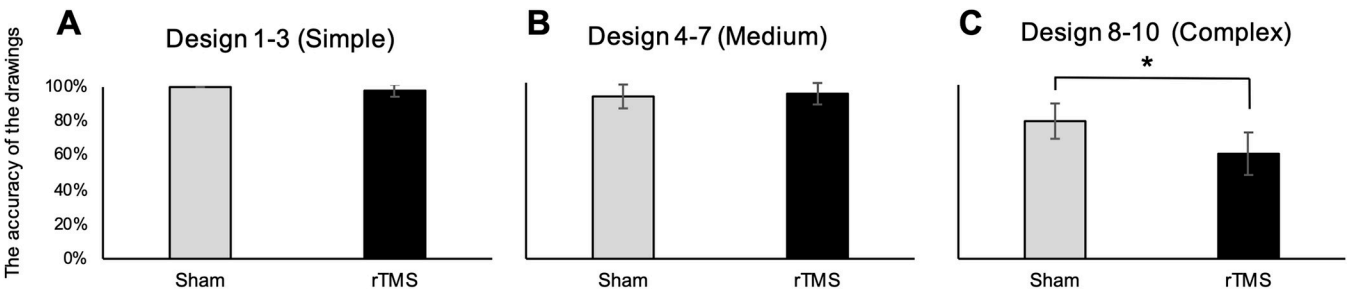

Fig 3. The mean accuracy of the BVRT between under control (gray) and rTMS (black), for the design 1–3 (Simple), the designs 4–7 (Medium) and the designs 8–10 (Complex). Ten designs were divided into three groups, from the design 1 to the design 3 as the Simple designs (A), from the design 4 to the design 7 as the Medium designs (B) and from the design 8 to the design 10 as the Complex designs (C). The graphs indicate the ratio of the mean accuracy of the BVRT of all participants under control (gray) and rTMS (black) displayed with percentages. Data are shown as mean +/- SE ($n = 16$). *: $P < 0.05$, ($d = 0.42$).

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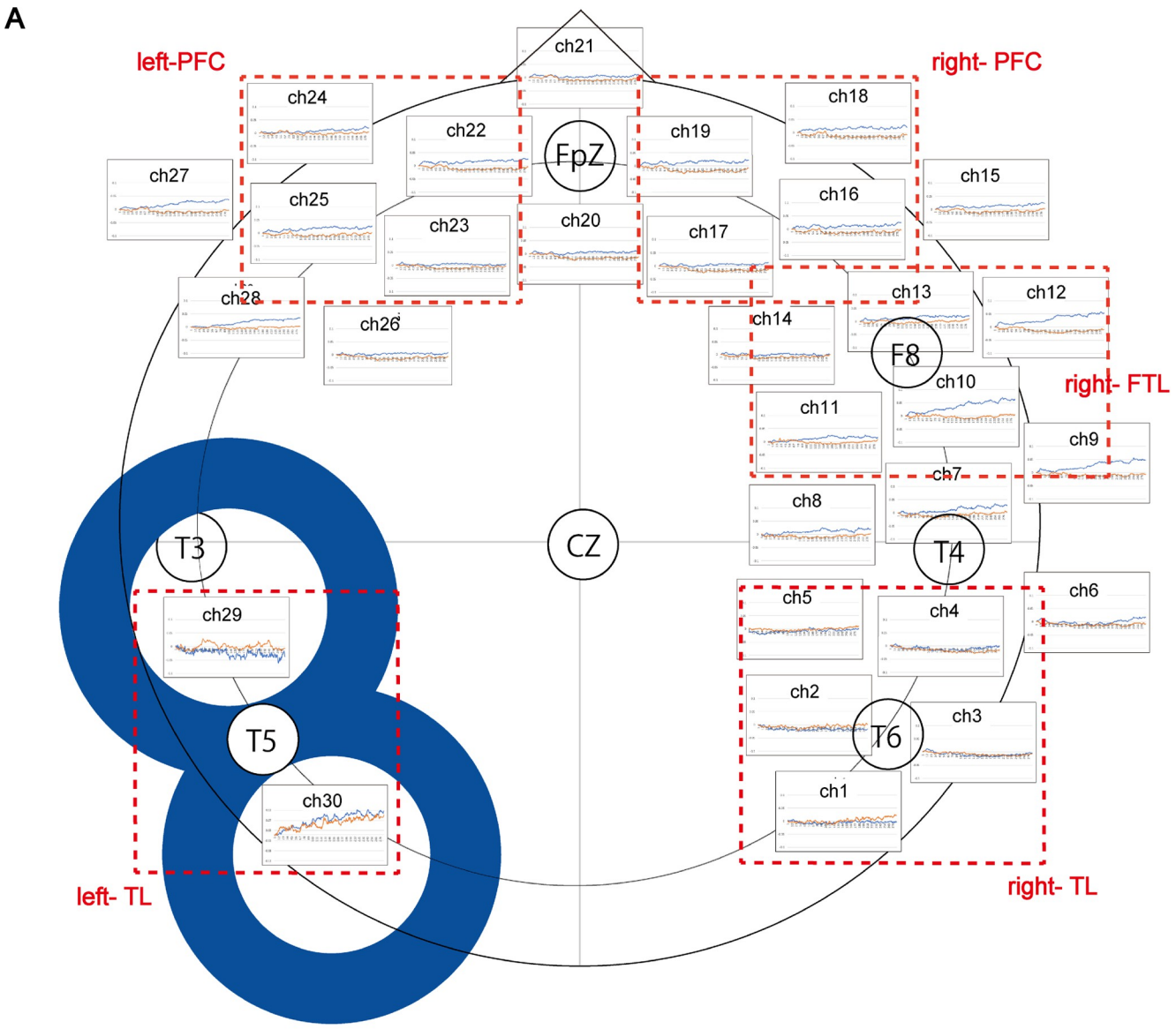
Furthermore, we examined the impact of degree of complexity of the designs of the BVRT on participants' performances of drawings. The BVRT suggested that a verbal mediation component is thought to be associated, due to the use of verbally associable geometric figures ranging from strongly associable images (simple designs) to weakly associable images (complex designs). We compared the mean accuracy of the BVRT drawings of all participants between under control and rTMS, dividing all designs into three groups, the designs 1–3 (Simple), the designs 4–7 (Medium) and the designs 8–10 (Complex). There was a significant decrease in the mean accuracy of the BVRT in the Complex designs under rTMS (t (92) = 1.85, $p = 0.04$, $d = 0.42$, Fig 3C), while there were no significant differences in the Simple (Fig 3A) and the Medium designs (Fig 3B).

Brain activity

Brain activity was measured by fNIRS, whereby to assess activations with changes in the concentration of oxygenated hemoglobin (oxy-Hb). Fig 4A shows the mean changes in oxy-Hb for 30 channels. Five regions of interest (ROIs) were defined, the right temporal lobe (r-TL; Ch1- Ch4), the right frontotemporal lobe (r-FTL; Ch10- Ch13), the right prefrontal cortex (r-PFC; Ch16—Ch19), the left prefrontal cortex (l-PFC; Ch23- Ch25) and the left temporal lobe (l-TL; Ch29 and Ch30). We performed a statistical analysis for each channel between under control and rTMS. The results showed a significant decrease in the Ch 2–13 and the Ch15-28 under rTMS. Furthermore, only the Ch29 where was adjacent to the stimulated site, showed a significant increase under rTMS (Fig 4B).

Fig 5A shows the mean oxy-Hb under control and rTMS for five ROIs. In the l-TL, the mean oxy-Hb showed a higher percentage than other regions over the time course of 300 sec, both under control and under rTMS (the left graph in Fig 5A). In addition, the mean oxy-Hb was higher in r-FTL under control than in other regions. (the second graph from the right in Fig 5A).

Fig 5B shows correlation between the two variables of the mean oxy-Hb (n = 18) and the mean accuracy of the BVRT (n = 16) under control and rTMS were examined in five ROIs. There were strong negative correlations between two values in the r-TL under rTMS ($r = -0.81$, $p < 0.01$), the r-FTL under rTMS ($r = -0.73$, $p < 0.05$), the l-PFC under rTMS ($r = -0.72$, $p < 0.05$) and the l-TL for both under control ($r = -0.74$, $p < 0.05$) and rTMS ($r = -0.80$, $p < 0.01$). Furthermore, there were negative correlation between the two variables in the r-FTL under control ($r = -0.50$, $p < 0.05$), r-PFC for both under control ($r = -0.50$, $p < 0.05$) and rTMS ($r = -0.60$, N/S) and the l-PFC under control ($r = -0.64$, $p < 0.05$). In addition,



B

ch1	ch2	ch3	ch4	ch5	ch6	ch7	ch8	ch9	ch10	ch11	ch12	ch13	ch14	ch15	ch16	ch17	ch18	ch19	ch20	ch21	ch22	ch23	ch24	ch25	ch26	ch27	ch28	ch29	ch30
–	**	**	**	**	**	**	**	**	**	**	**	**	–	**	**	**	**	**	**	**	**	**	**	**	**	**	**	**	–

Fig 4. Brain activities under control and rTMS. (A) The mean brain activities of the participants for thirty channels between under control (blue) and rTMS (orange). Five regions of interest (ROIs) were selected from the 30 channels, the right temporal lobe (r-TL; Ch1- Ch4), the right frontotemporal lobe (r-FTL; Ch10- Ch13), the right prefrontal cortex (r-PFC; Ch16—Ch19), the left prefrontal cortex (l-PFC; Ch23- Ch25) and the left temporal lobe (l-TL; Ch29 and Ch30). Each region is surrounded by red dotted line. **(B)** Statistical analysis was performed on each channel between control and rTMS. Data are shown as mean (n = 18). *: $P < 0.05$, **: $P < 0.01$ and the "–" denotes no significant.

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there was no correlation between the two variables in the r-TL under control (Fig 5B and S3 Table for correlation).

Furthermore, we examined an impact by complexity of the BVRT designs on ROI. The mean oxy-Hb over a time course of 300 seconds for10 designs was divided into three groups: the Simple (0–90 sec.), the Medium (91–219 sec.) and the Complex (210–300 sec.), and compared between under control and rTMS. As a result, in the right and left PFC and the r-FTL,

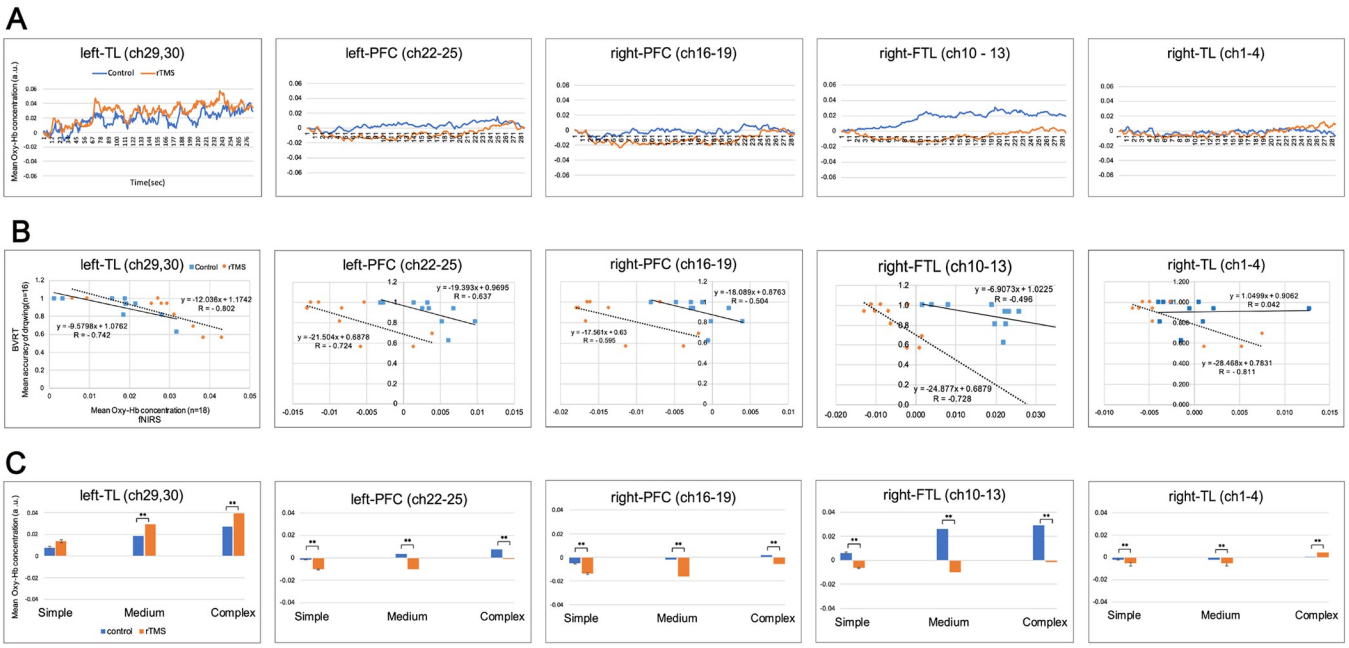

Fig 5. Relationship between BVRT and fNIRS in regions of interest (ROIs). (A) Changes of the mean oxy-HB for five ROIs, the right temporal lobe (r-TL; Ch1- Ch4), the right frontotemporal lobe (r-FTL; Ch10- Ch13), the right prefrontal cortex (r-PFC; Ch16—Ch19), the left prefrontal cortex (l-PFC; Ch23-Ch25) and the left temporal lobe (l-TL; Ch29 and Ch30). **(B)** Correlation between two variables of the mean oxy-Hb (n = 18) and their performances of the BVRT (n = 16) for five ROIs. Mean oxy-Hb over a time course of 300 seconds was divided into 10 parts and corresponded to 10 BVRT drawings, and examined the correlation between those two values under control and rTMS. **(C)** An impact by complexity of the BVRT designs on ROIs. The mean oxy-Hb (n = 18) over a time course of 300 seconds during drawings 10 designs was divided into 10 sequences. Data are shown as mean +/- SE (n = 18). **: $p < 0.01$.

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there were significant decreases of the mean oxy-Hb in all the three groups under rTMS. In the r-TL, there were significant decreases of the mean oxy-Hb in the Simple and the Medium designs, and a significant increase in the Complex designs under rTMS. On the other hand, in the l-TL, there were significant increases of the mean oxy-Hb in the Medium and the Complex designs under rTMS (Fig 5C).

The autonomic nervous system analysis

From the interviews about the participants' stress levels from the devices, ten of the eighteen participants stated that they felt certain levels of stress due to restriction by the headsets, and twelve participants reported that they were irritated by the clicking sounds and the flicking feeling of the rTMS. We examined the participants' stress levels by using the autonomic nervous system analysis. There were no significant differences in the ratio of LF/HF between control and rTMS. Furthermore, there were also no significant differences in the HF/Total between control and rTMS.

Discussion

The aim of this study was to investigate the implication of the semantic processing of the l-pMTG in drawing behavior, with combining rTMS and fNIRS.

In the result of the BVRT, the total number correct scores of the BVRT showed a significant decrease of the Design 8 under rTMS (Fig 2A), and the total number error scores of the BVRT showed a significant increase of the Design 8 under rTMS (Fig 2B). These results suggest that the rTMS to the l-pMTG have an impact on drawing the Design 8 of the BVRT. The Design 8

is composed of three figures, it is not possible to name them at first glance. We suggest that more linguistic and semantic activities were necessary to recognize and reconstruct the figures. In addition, since the Design 8 was the first design to enter the phase of the Complex designs toward the Design 10, it could have had the greatest impact on participants' performance.

To examine the relationship between complexities of the BVRT and effects of rTMS, the BVRT results of the 10 designs were analyzed by dividing into three groups, the Simple, the Medium and the Complex design, between under control and rTMS (Fig 3). There was a significant decrease in the mean accuracy of the BVRT in the Complex designs under rTMS (Fig 3C), while there were no significant differences in the Simple (Fig 3A) and the Medium designs (Fig 3B). This suggests that magnetic stimulations to the l-pMTG had an impact on drawing the Complex designs of the BVRT.

The BVRT was developed to assess visual perception, visual short-term memory, and visuoconstructive abilities [26], however, a verbal mediation component is thought to be associated, due to the use of verbally associable geometric figures [18, 19]. In fact, in the present study, seventeen of the eighteen participants reported that they memorized the designs by naming the figures, and they recited those names silently in their mind as they drew them on a sheet of paper. Four participants reported that they remembered the designs as they looked when those designs were very simple, but when the designs became complex, they used verbal association such as "it is a triangle in the square like a face" or "9:00 and 6:45". In addition, two participants used unique strategies by associating the designs with real life objects, or even creating a short sentence. For example, "A hexagon nut for a bolt" or "The moon is shining on the top-left side of the house". Furthermore, two participants reported that they felt it more difficult to memorize the Complex designs which included the figures unable to be named. These testimonies of the participants match to the reports of the verbal mediation component of the BVRT.

Furthermore, from the result of specific types of error scores of the BVRT, there was a significant increase in the category of one of the six types of error "distortion" in the Design 8 (the Complex designs), under rTMS (Fig 2B). The reports of patients using the BVRT in Alzheimer's disease demonstrated the correlation between the severity of impairment and the increase of the number error scores in the types of "omissions" and "distortions", suggesting impairments of visuospatial cognition function [30, 31]. It is reported that the dementia patients produced disordered composition, less active brush strokes, more facial distortion, and the use of fewer and unnatural colors in their drawings, compared to healthy participants [32]. Another study reported that the drawings made by dementia patients seemed more realistic and precise, or in turn, less realistic and abstract with an exaggeration of particular parts [1]. These reports suggest that semantic representations are involved in the processes of drawing, and impairing these functions might change or enhance visual art activities. We assume that the significant increase of the error type "distortions" under rTMS in this study, could possibly has connections with suppression of semantic processes by rTMS.

In the result of fNIRS, a statistical analysis showed significant differences between control and rTMS at 28 locations. Only the Ch29, which was adjacent to the stimulation site, showed a significant increase under rTMS (Fig 4B). The results contradicted our hypothesis that the 0.5Hz of low frequency rTMS was expected to decrease the oxy-Hb in the stimulated site. These results are not consistent with general efficiency of a low frequency rTMS [33]. Studies combining TMS and NIRS have shown that the oxy-Hb significantly reduced following the low frequency of the 1Hz rTMS, compared to the increases observed in both high frequency of the 2Hz and 5Hz rTMS [34–36]. The possibility of the increased activity of the stimulated site could be related to the cerebral blood flow (CBF). It has been suggested that rTMS affects not only neurons but also the vascular system [20, 37]. We assumed that the BVRT-induced increases of cerebral blood flow (CBF) might have surpassed the rTMS-induced decreases of

CBF, which were caused by the effects of hard task conditions and unusual environmental situations. However, the mechanism of rTMS on neurons is still unclear and is expected to be elucidated in the future.

We considered the brain activities between control and rTMS in five ROIs; r-TL, r-FTL, r-PFC, l-PFC and l-TL (Fig 5A). In under control, the mean oxy-Hb showed higher percentage at r-FTL, than at other regions (Fig 5A). It might be possible that performing the BVRT was basically related to the function of the r-FTL, In addition, the mean oxy-Hb in the r-FTL significantly reduced under rTMS. It is curious that rTMS to l-pMTG could have affected the contralateral brain. The r-FTL is located at F8 (10–20 method) and adjacent to the amygdala, which is known for controlling stress and anxiety and/or mood and emotion [38]. In this study, we examined the participants' stress levels by using the autonomic nervous system analysis. There were no significant differences in the ratio of LF/HF between control a rTMS, suggesting no side effect of stress from rTMS devises.

Furthermore, we tested correlations between the two values of the mean accuracy of the BVRT and the mean oxy-Hb under control and rTMS, for five ROIs (Fig 5B and S3 Table). There was a strong significant negative correlation between those two values in r-TL, r-FTL, l-PFC and the l-TL under rTMS. There were significant negative correlations between the two values in the r-FTL, r-PFC, l-PFC and l-TL under control. The only region did not show the correlation was the r-TL under control. Although the results showed the opposite effects of the rTMS on the stimulated site, the rTMS had stronger impacts on the brain activities and on recognition and its reconstruction of the BVRT. It was suggested that the rTMS to l-pMTG affected not only the stimulated side but also other regions including the contralateral side, resulting in reduced BVRT performance. The broad effects of rTMS in this study might be related to the widely distributed neural network of semantic control functions. Studies about semantic processes suggested that there are two distinctive neural structures for processing weak associations with executive control semantic activation in the l-pMTG, and for processing strong associations with automatic spreading activation in the left angular gyrus [14, 39, 40].

Furthermore, we considered relationship between the mean oxy-Hb and the complexities of the BVRT (the Simple, Medium, and Complex designs), in ROIs. Fig 5C shows that there were significant decreases of the mean oxy-Hb in the three groups under rTMS, in the r-TL, the right and left PFC and the r-FTL, except in the r-TL in the Complex designs under rTMS. In contrast, there were significant increases of the mean oxy-Hb in the Medium and the Complex designs under rTMS, in the l-TL. Furthermore, in l-TL, the accuracy of BVRT decreased as the design became more complex, and the mean oxy-Hb also decreased. These results suggest that there was a connection between the decreases of reproduction and reconstruction of the Complex designs and the rTMS to the l-pMTG. However, it is difficult to explain the direct causal relationship between functions of the l-pMTG and BVRT, because the semantic processing network is assumed to be a broad function that includes not only l-TL but also other areas.

The present study has several limitations. Firstly, the effects of vascular system were not separated from the fNIRS signals. Therefore, it was not entirely clear whether the activation of oxy-Hb under rTMS was due to neural activity or CBF, and further data analysis will be needed. Secondly, there were no other stimulated brain areas that could be compared to the l-pMTG. To clarify the role of l-pMTG in shape recognition and its reconstruction, it would have been better if there were at least two stimulation sites, such as the left angular gyrus. Thirdly, there were no other tasks to assess semantic cognitive functions, such as nonverbal-verbal tasks, naming tasks or word-picture matching tasks. Finally, although this experiment was conducted with an appropriate sample size through power analysis, however, further experiments with larger sample sizes are needed and would be more beneficial to include patients.

Although further investigations are required, the techniques used in this study that combining rTMS and fNIRS with reliable drawing tests are useful to investigate mechanisms of shape and figure recognition during drawing. We believe that this study will lead to clinical research and treatments for patients such as semantic dementia and left temporal lobe dysfunctions. Furthermore, we hope that it will lead to interdisciplinary research in the fields of neurocognitive science, anthropology, and arts.

Conclusion

We conclude that the inhibitory rTMS to the l-pMTG suppressed the reproducibility of the BVRT, especially the Complex designs.

Supporting information

S1 Table for BVRT correct. The number correct scores are calculated based on an all-or-nothing approach; points are awarded if the reproduction of the design matches the original.
(TIF)

S2 Table for BVRT error. The error scores were calculated with six types of major categories such as omissions, distortions, perseverations, rotations, misplacements, and size errors. Integral averaging points.
(TIF)

S3 Table for correlation between fNIRS and the BVRT. The table shows the result of correlation between two variables of the mean oxy-Hb (n = 18) and their performances of the BVRT (n-16) under control and rTMS, for five regions of interest (ROIs), the right temporal lobe (r-TL; Ch1- Ch4), the right frontotemporal lobe (r-FTL; Ch10- Ch13), the right prefrontal cortex (r-PFC; Ch16—Ch19), the left prefrontal cortex (l-PFC; Ch23- Ch25) and the left temporal lobe (l-TL; Ch29 and Ch30).
(TIF)

S1 Data. S4 NIRS data for control and S4 NIRS data for rTMS. The total fNIRS measurement time was set at 420 seconds (rest 60—task 300—rest 60) for control and rTMS. Smoothing Pinto is 15 points. The fNIRS data that were outside the software's acceptable range were automatically deleted. After performing a low-pass filter of 0.01Hz, data were analyzed by using Modified Beer-Lambert Law.
(ZIP)

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Investigation: Nakako Okamoto.

Methodology: Nakako Okamoto.

Supervision: Akitoshi Seiyama.

Visualization: Nakako Okamoto.

Writing – original draft: Nakako Okamoto.

Writing – review & editing: Akitoshi Seiyama, Satoru Takahashi.

References

1. Miller BL, Cummings J, Mishkin F, Boone K, Prince F, Ponton M, et al. Emergence of artistic talent in frontotemporal dementia. Neurology. 1998; 51: 978 LP– 982. Available: http://www.neurology.org/content/51/4/978.abstract, https://doi.org/10.1212/wnl.51.4.978 PMID: 9781516
2. Seeley WW, Matthews BR, Crawford RK, Gorno-Tempini ML, Foti D, Mackenzie IR, et al. Unravelling Boléro: Progressive aphasia, transmodal creativity and the right posterior neocortex. Brain. 2008; 131: 39–49. https://doi.org/10.1093/brain/awm270 PMID: 18057074
3. van Buren B, Bromberger B, Potts D, Miller B, Chatterjee A. Changes in painting styles of two artists with Alzheimer's disease. Psychol Aesthet Creat Arts. 2013; 7: 89–94. https://doi.org/10.1037/a0029332
4. Miller BL, Hou CE. Portraits of Artists Emergence of Visual Creativity in Dementia STUDIES. 2015; 72. https://doi.org/10.1001/jamaneurol.2014.4477 PMID: 25822631
5. Snyder A. Explaining and inducing savant skills: privileged access to lower level, less-processed information. Philos Trans R Soc Lond B Biol Sci. 2009; 364: 1399–405. https://doi.org/10.1098/rstb.2008.0290 PMID: 19528023
6. Trojano L, Grossi D, Flash T. Cognitive neuroscience of drawing: Contributions of neuropsychological, experimental and neurofunctional studies. Cortex. 2009; 45: 269–277. https://doi.org/10.1016/j.cortex.2008.11.015 PMID: 19131051
7. McCrea S M. Free-Drawing from Memory in Constructional Apraxia: A Case Series. American Journal of Psychiatry and Neuroscience. 2015. https://doi.org/10.11648/j.ajpn.20150306.15
8. Farias D, Davis C, Harrington G. Drawing: Its contribution to naming in aphasia. Brain Lang. 2006; 97: 53–63. https://doi.org/10.1016/j.bandl.2005.07.074 PMID: 16129481
9. Makuuchi M, Kaminaga T, Sugishita M. Both parietal lobes are involved in drawing: a functional MRI study and implications for constructional apraxia. Cognitive brain research. 2003; 16: 338–347. https://doi.org/10.1016/s0926-6410(02)00302-6 PMID: 12706214
10. Harrington GS, Farias D, Davis CH. The neural basis for simulated drawing and the semantic implications. Cortex. 2009; 45: 386–393. https://doi.org/10.1016/j.cortex.2007.10.015 PMID: 19111291
11. Mendez MF. Dementia as a window to the neurology of art. 2004; 1–7. https://doi.org/10.1016/j.mehy.2004.03.002 PMID: 15193339
12. Jefferies E. The neural basis of semantic cognition: Converging evidence from neuropsychology, neuroimaging and TMS. Cortex. 2013; 49: 611–625. https://doi.org/10.1016/j.cortex.2012.10.008 PMID: 23260615
13. Whitney C, Kirk M, O'Sullivan J, Lambon Ralph, Matthew A.Jefferies E. The neural organization of semantic control: TMS evidence for a distributed network in left inferior frontal and posterior middle temporal gyrus. Cerebral Cortex. 2011; 21: 1066–1075. https://doi.org/10.1093/cercor/bhq180 PMID: 20851853
14. Davey J, Cornelissen PL, Thompson HE, Sonkusare S, Hallam G, Smallwood J, et al. Automatic and Controlled Semantic Retrieval: TMS Reveals Distinct Contributions of Posterior Middle Temporal Gyrus and Angular Gyrus. Journal of Neuroscience. 2015; 35: 15230–15239. https://doi.org/10.1523/JNEUROSCI.4705-14.2015 PMID: 26586812
15. Whitney Carin, Kirk Marie, Jamie O'Sullivan, Matthew A. Lambon Ralph EJ. Executive Semantic Processing Is Underpinned by a Large-scale Neural Network: Revealing the Contribution of Left Prefrontal, Posterior Temporal, and Parietal Cortex to Controlled Retrieval and Selection Using TMS. J Cogn Neurosci. 2012; 24: 133–147. https://doi.org/10.1162/jocn_a_00123 PMID: 21861680
16. Kawas CH, Corrada MM, Brookmeyer R, Morrison A, Resnick SM, Zonderman AB, et al. Visual memory predicts Alzheimer's disease more than a decade before diagnosis. Neurology. 2003; 60: 1089 LP–1093. Available: http://n.neurology.org/content/60/7/1089.abstract https://doi.org/10.1212/01.wnl.0000055813.36504.bf PMID: 12682311
17. Snow JH. Clinical use of the Benton Visual Retention Test for children and adolescents with learning disabilities. Arch Clin Neuropsychol. 1998; 13: 629–36. https://doi.org/10.1016/S0887-6177(97)00098-X PMID: 14590624
18. Moses JA. Factor structure of Benton's tests of visual retention, visual construction, and visual form discrimination. Archives of Clinical Neuropsychology. 1986; 1: 147–156. https://doi.org/10.1016/0887-6177(86)90014-4 PMID: 14589648

19. Takiura T. Standardization of the Benton Visual Retention Test in Japan: A review of the literature. Department of Humanities Hiroshima Shudo University. 2007.

20. Seiyama A, Seki J, Tanabe HC, Sase I, Takatsuki A, Miyauchi S, et al. Circulatory basis of fMRI signals: relationship between changes in the hemodynamic parameters and BOLD signal intensity. Neuroimage. 2004; 21: 1204–1214. https://doi.org/10.1016/j.neuroimage.2003.12.002 PMID: 15050548

21. Seiyama A. Dissociation of stimulus-induced responses in regional cerebral blood flow and blood volume in the visual cortex of humans. Health Science. 2007; 7–18.

22. Hori S, Mori K, Mashimo T, Seiyama A. Effects of Light and Sound on the Prefrontal Cortex Activation and Emotional Function: A Functional Near-Infrared Spectroscopy Study. Front Neurosci. 2017; 11: 321. https://doi.org/10.3389/fnins.2017.00321 PMID: 28649190

23. Pascual-Leone A, Walsh V, Rothwell J. Transcranial magnetic stimulation in cognitive neuroscience—virtual lesion, chronometry, and functional connectivity. Curr Opin Neurobiol. 2000; 10: 232–237. https://doi.org/10.1016/s0959-4388(00)00081-7 PMID: 10753803

24. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Avanzini G, Bestmann S, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical Neurophysiology. 2009; 120: 2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016 PMID: 19833552

25. Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clinical neurophysiology. 2006; 117: 2584–2596. https://doi.org/10.1016/j.clinph.2006.06.712 PMID: 16890483

26. Benton A.L., translated by Takahashi T. The revised visual retention test:A test manual for the Benton Visual Retention Test (Japanese version). Sankyobo; 1996.

27. Sato A, Torii T, Nakahara Y, Iwahashi M, Ito Y, Iramina K. Effects of stimulation points and stimulus frequency to event-related potentials by repetitive transcranial magnetic stimulation. IEEJ Transactions on Fundamentals and Materials. 2013;133. https://doi.org/10.1541/ieejfms.133.445

28. Wang C, Zeng Q, Yuan Z, Wang W, Shen M. Effects of Low-Frequency (0.5 Hz) and High-Frequency (10 Hz) Repetitive Transcranial Magnetic Stimulation on Neurological Function, Motor Function, and Excitability of Cortex in Ischemic Stroke Patients. Neurologist. 2023; 28: 11–18. https://doi.org/10.1097/NRL.0000000000000435 PMID: 35452441

29. Zama T, Shimada S. Simultaneous measurement of electroencephalography and near-infrared spectroscopy during voluntary motor preparation. Sci Rep. 2015. https://doi.org/10.1038/srep16438 PMID: 26574186

30. Toshihiko H. Sevierity of Alzheimer's disease and the significance of a dementia test battery. Tokyo Jikeikai Medical Journal. 2004; 119: 41–50.

31. Massaldjieva RI. Differentiating Normal Cognitive Aging from Cognitive Impairment No Dementia: A Focus on Constructive and Visuospatial Abilities. Gerontology. InTech; 2018. https://doi.org/10.5772/intechopen.73385

32. Rankin KP, Ph D, Liu AA, Howard S, Slama H, Hou CE. A Case-Controlled Study of Altered Visual Art Production in Alzheimer ' s and FTLD. 2009; 20: 48–61. https://doi.org/10.1097/WNN.0b013e31803141dd PMID: 17356345

33. Furubayashi T, Mochizuki H, Terao Y, Arai N, Hanajima R, Hamada M, et al. Cortical hemoglobin concentration changes underneath the coil after single-pulse transcranial magnetic stimulation: A near-infrared spectroscopy study. J Neurophysiol. 2013; 109: 1626–1637. https://doi.org/10.1152/jn.00980.2011 PMID: 23274310

34. Curtin A, Tong S, Sun J, Wang J, Onaral B, Ayaz H. A systematic review of integrated functional near-infrared spectroscopy (fNIRS) and transcranial magnetic stimulation (TMS) studies. Front Neurosci. 2019; 13. https://doi.org/10.3389/fnins.2019.00084 PMID: 30872985

35. Parks NA. Concurrent application of TMS and near-infrared optical imaging: Methodological considerations and potential artifacts. Frontiers in Human Neuroscience. Frontiers Media S. A.; 2013. https://doi.org/10.3389/fnhum.2013.00592 PMID: 24065911

36. Li R, Potter T, Wang J, Shi Z, Wang C, Yang L, et al. Cortical hemodynamic response and connectivity modulated by sub-threshold high-frequency repetitive transcranial magnetic stimulation. Front Hum Neurosci. 2019; 13. https://doi.org/10.3389/fnhum.2019.00090 PMID: 30941025

37. Näsi T, Mäki H, Kotilahti K, Nissilä I, Haapalahti P, Ilmoniemi RJ. Magnetic-stimulation-related physiological artifacts in hemodynamic near-infrared spectroscopy signals. PLoS One. 2011;6. https://doi.org/10.1371/journal.pone.0024002 PMID: 21887362

38. Foster Paul S., Harrison David W. The relationship between magnitude of cerebral activation and intensity of emotional arousal. International Journal of Neuroscience. 2009;Volume 112, 2002: 1463–1477.

39. Zhang Y, Wu W, Mirman D, Hoffman P. Representation of event and object concepts in ventral anterior temporal lobe and angular gyrus. Cerebral Cortex. 2024;34. https://doi.org/10.1093/cercor/bhad519 PMID: 38185997

40. Ralph MAL, Jefferies E, Patterson K, Rogers TT, Ralph AL. The neural and computational bases of semantic cognition. 2017 Jan.

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RESEARCH ARTICLE

Capture of emotional responses under a simulated earthquake experience using near-infrared spectroscopy and virtual reality

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Abstract

Aim

In a previous study, we reported that watching two-dimensional videos of earthquakes significantly reduced sympathetic nerve activity in healthy young adults. In the present study, we aimed to investigate the emotional responses to earthquakes using immersive virtual reality (VR), which can provide a more realistic experience.

Methods

In total, 24 healthy young adults (12 males, 21.4 ± 0.2 years old) participated. Participants were required to watch earthquake and neutral videos while wearing a head-mounted display and near-infrared spectroscopy (NIRS), during which physiological signals, including pulse rate and cerebral blood flow (CBF) in the dorsolateral prefrontal cortex, were measured. We also analyzed changes in sympathetic and parasympathetic indices and obtained seven emotion ratings: valence, arousal, dominance, fear, astonishment, anxiety, and panic.

Results

The VR earthquake videos evoked negative subjective emotions, and the pulse rate significantly decreased. Sympathetic nerve activity tended to decrease, whereas CBF in the left prefrontal cortex showed a slight increase, although this was not significant.

Conclusions

This study showed that measurements combined with NIRS and immersive VR have the potential to capture emotional responses to different stimuli.

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Introduction

When natural disasters such as earthquakes and floods occur, people must evacuate calmly, even though they may be emotionally distressed. Negative emotions (e.g., fear, astonishment, and anxiety) are often elicited in such situations [1]. The degree of fear when encountering an earthquake is related to personal factors, such as gender, age, and the scale of perceived damage [2]. Strong emotional arousal can cognitively disturb thinking calmly and cognitive decision-making [3]. However, the relationship between emotional responses and brain activity during natural disasters remains unclear. Thus, it is important to clarify subjective/objective emotional reactions when encountering disasters, which could be a milestone in designing individualized efficient support in this era of increasing global natural disasters.

Previously, we studied emotional reactions in healthy young adults using earthquake-related videos and recorded physiological indices (e.g., prefrontal cortex blood flow changes) using near-infrared spectroscopy (NIRS) [4]. We found that the sympathetic index significantly decreased under the earthquake video-watching condition, which evoked negative emotions, compared with the neutral video-watching condition. Emotional responses to different stimuli (i.e., earthquake vs. neutral moving images) were also obtained. However, there were some limitations in the experimental setting, in that the two-dimensional (2D) images on the screen might not be realistic enough visually and auditorily. Therefore, we plan to provide a more realistic disaster experience and sufficient emotional arousal using immersive virtual reality (VR).

It is reported that the prefrontal cortex blood flow increased under the immersive nature of images and presentation of various audiovisual stimuli in a virtual space with a greater sense of reality [5]. Related studies have reported multiple NIRS measurements in immersive VR experiences focusing on cognitive functions [6, 7]. However, there are no reports on the emotional/physiological responses to disaster experiences using VR.

In this study, we investigated the human emotional reactions to earthquakes using immersive VR. Specifically, we focused on the changes in cerebral blood flow (CBF) and pulse rate, compared the indexes between the earthquake and neutral videos, and then discussed the differences from the results of our previous study using 2D videos [4]. We hypothesized that the VR earthquake experience will evoke more negative emotions, lower pulse rate, and sympathetic activity and increase CBF in the right prefrontal cortex compared with screen-based video viewing. By clarifying the changes in physiological indices during the simulation of a specific scene, such as an earthquake, this study contributes to the understanding of emotional reactions when encountering an actual earthquake.

Materials and methods

Participants

In total, 24 healthy young adults (12 males and 12 females, aged 21.4 ± 0.2 years) participated in the study. Using G*Power 3.1.9.2, pre-analysis for the required minimum sample size resulted in 15 persons, assuming effect size = 0.80, α error probability = 0.05, and power (1-β error) = 0.80. The eligibility criteria were as follows: no history of visual, hearing, verbal comprehension, or mental disorders that might interfere with the performance of the tasks in this study and had never experienced VR sickness prior to this experiment. In addition, the Impact of Event Scale-Revised (IES-R: Japanese version of the revised Impact of Event Scale) was conducted to confirm the absence of prior trauma to earthquake, and individuals with a cutoff value of 24 points or less were included.

This study was approved by the Kyoto University Medical Ethics Committee (R2855). All participants were fully informed before the beginning of the experiment, and informed consent was obtained through both oral and written consent.

Visual stimulation

Two types of videos were used, earthquake and neutral, described as follows. They were presented via an Oculus Rift head-mounted display (HMD).

Earthquake video. An environment for experiencing an earthquake in an immersive VR space was constructed based on a three-dimensional (3D) reconstruction system [8, 9] that captures an indoor environment with an RGB-D camera and reconstructs a 3D environment from the acquired point clouds. In this study, three common environments for the participants: a living room (Fig 1(A)), conference room (Fig 1(B)), and laboratory office (Fig 1(C)), were selected for the content of earthquake videos.

The VR earthquake videos were displayed for 100 s to evoke emotional changes in the event of an earthquake that was closer to reality. They were constructed for experimental use by intervening with visual elements, such as the resolution and behavior of objects and scenes, and auditory elements, such as the rumbling and collision sounds of objects [8, 9].

Fig 1. Sample images of the VR earthquake videos. (a) Living room, (b) conference room, and (c) laboratory videos were created using a three-dimensional reconstruction system [8, 9].

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Neutral video. As a control condition for earthquake images, two 100-s neutral video clips were created by adding pink noise to images of natural scenery [10]. The environments included rivers and grasslands in the neutral image; each neutral image is a moving image containing a waterfall flowing grass and trees rustling in the wind. Pink noise, characterized by a soft and pleasant sound whose energy is inversely proportional to its frequency, with strong lows and weak highs, was used to control the auditory stimulus conditions in the seismic video.

Procedure

First, the participants provided their personal information and completed anxiety and personality trait rating scales. Next, the participants watched videos wearing NIRS and HMD and responded to a subjective evaluation of each video. As shown in Fig 2, a block design comprising earthquake and neutral video viewing conditions for each 100 s duration was used. The Self Assessment Manikin (SAM), a non-verbal picture-based questionnaire, was used to evaluate the participant's feelings and emotions [11]. The subjective evaluation was conducted on a 9-point Likert scale ranging from 1 to 9 for valence, arousal, and dominance of the SAM and 7-point Likert scale ranging from 1 to 7 for fear, astonishment, anxiety, and panic.

Finally, the participants answered a questionnaire on their previous earthquake experiences that asked about the maximum earthquake intensity according to the definition of the Japan Meteorological Agency (JMA) seismic scale [12], location, emotion, and behavior. Personal information included age, sex, educational and occupational history, dominant hand, intelligence quotient (IQ) assessed using the Japanese Adult Reading Test (JART), visual acuity, and sleeping time at night. The Japanese version of the State-Trait Anxiety Inventory (STAI-JYZ: new version STAI) was used as the anxiety scale, which is a self-report questionnaire that measures two aspects: anxiety responses to anxiety-provoking events in a person's temporary state (state anxiety) and the tendency toward anxiety in a steady state (trait anxiety). The Maudsley Personality Inventory (MPI) was used to measure personality and two basic personality characteristics: neuroticism (N scale) and extraversion-introversion (E scale) [13]. Each experiment took approximately 90 min and included an explanation.

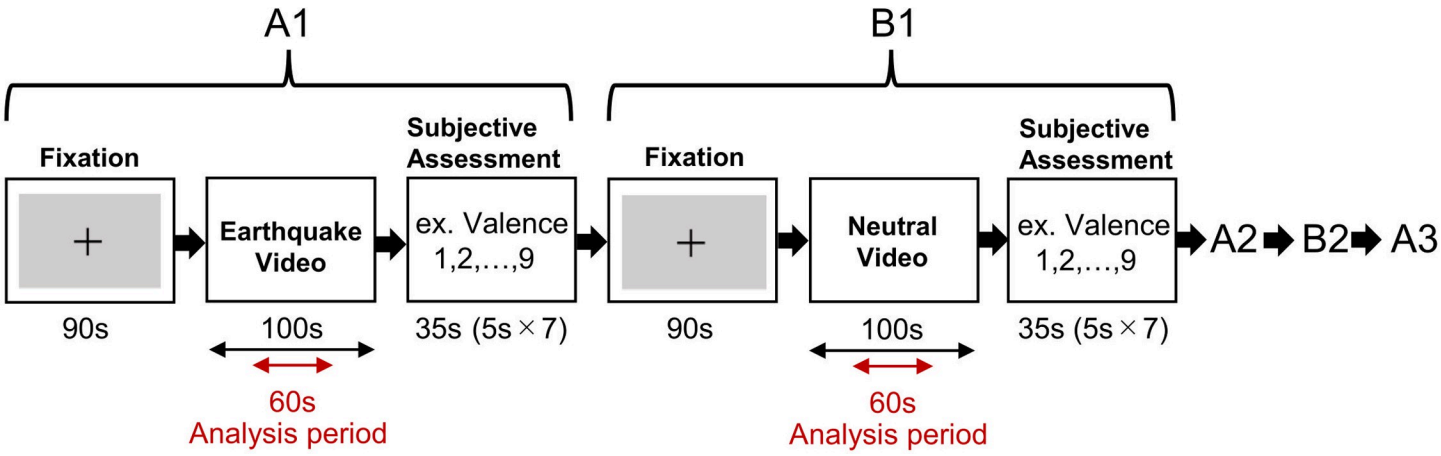

Fig 2. Experimental procedure of watching VR videos. Three earthquake videos and two neutral videos were shown alternately. Subjective assessments were conducted after each video presentation. The subjective assessment included seven items (valence, arousal, dominance, fear, astonishment, anxiety, and panic).

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NIRS data acquisition

NIRS device (portable brain activity measurement device HOT-2000-VR, NeU, Japan) with two channels was used to measure CBF. The sampling rate of this device was 100 ms, consisting of a light-emitting diode (LED) with a wavelength of 810 nm, one on each side of the headset, and two sensor units (approximately 1 cm and 3 cm from the LED). The two NIRS channels were located in the bilateral dorsolateral prefrontal cortex (DLPFC, left Fp1-F7 and right Fp2-F8 using the international 10–20 method), and the top of the face cushion of the HMD and the NIRS probe were superimposed approximately 3 cm above the nasion. This device calculates the changes in total hemoglobin (delta-totalHb) in the right and left hemispheres (cerebral cortex) using a method called real-time scalp signal separation [14]. Previous studies have shown that wavelength at 810 nm is near or just an isosbestic point of oxy-Hb and deoxy-Hb *in vivo*, and thus, delta-totalHb reflects delta-oxyHb [15, 16]. Hence, in this study, the total-Hb was used as an index to reflect CBF changes. Additionally, the pulse rate (beats/min) estimated from the sensor readings was recorded.

Data analysis

NIRS signal processing was conducted as previously described [4]. The specific methods used are described below.

Autonomic nervous system indices. We first performed a derivative and normalization of the signal reflecting the scalp blood flow recorded by a sensor unit positioned 1 cm away from the LED, emitting near-infrared light in the right channel of the NIRS. Next, the pulse wave peak was estimated based on the preprocessed scalp blood flow signal, and the peak-to-peak interval time was calculated. Autonomic indices, such as cardiac sympathetic index (CSI) and cardiac vagal index (CVI), were calculated using the Lorenz plot method proposed by Toichi et al. [17].

Cerebral blood flow change and lateral index. First, a moving average every 3 s (30 points) was applied to the total-Hb [measured values] acquired using NIRS every 0.1 s to remove high-frequency noise. Next, the trends and periodic fluctuations were removed, and the data were processed using a moving median filter as follows: Trend variations were noise due to continuous changes, such as sweating or increased temperature at the point of measurement, and periodic variations were noise due to heartbeat or respiration variations. The residual y(n) at a given time n, obtained using Eq (1), is a pure signal of the brain activity. V_{trend} (n) is a third-order polynomial approximated by minimizing the residual y(n), that is, the trend variation. V_{period} (n) means the periodic variation, which shows a sinusoidal periodic variation of delta-Hb_{total} (n) - V_{trend} (n). The period of periodic variation was 1/2 of all measurement times to minimize the standard deviation of the residual y(n), which was the residual obtained by dividing the trend variation by the periodic variation.

$$y(n) = \text{delta} - Hb_{total}(n) - \left\{V_{trend}(n) + V_{period}(n)\right\} \quad (1)$$

A moving median filter of 200 points was used to reduce the noise. The moving average t (n) represents the true change in total hemoglobin, and the left and right t(n) are named delta-totalHb(L) and delta-totalHb(R). The units for delta-totalHb(L) and delta-totalHb(R) are expressed in arbitrary units (a.u.) in this study because the values are the product of the unit of total hemoglobin concentration (millimol/L: mM) and the unit of optical path length (cm) of the reflected light received by the light-receiving probe. The lateral index (LI) was determined as an index of CBF asymmetry in the left and right dorsolateral prefrontal cortices based on a previous study by Ishikawa et al. [18].

Statistical analysis

All results are presented as the mean ± standard error. First, the mean values of CSI, CVI, CVI/CSI, pulse rate, delta-totalHb(L), delta-totalHb(R), LI, and subjective evaluations (valence, arousal, dominance, fear, astonishment, anxiety, and panic) were obtained for three earthquake videos and two neutral videos. Autonomic indices, pulse rate, and change in CBF were calculated for the data during the 60 s from 20 s to 80 s after starting the 100 s video.

After confirming the normality of data using the Shapiro-Wilk test, a Wilcoxon signed-rank test with Bonferroni correction was performed to examine the differences between the seismic and neutral videos for each index. Furthermore, among the subjective ratings, emotional valence, arousal, and dominance of the SAM were tested using the Mann-Whitney U-test with Bonferroni correction with independent samples between the VR video in this study and screen images from our previous study [4]. The IBM SPSS Statistics Version 27 and College Analysis Ver. 8.4 [19] was used for analysis, and the significance level of 5 percent was Bonferroni-corrected for each subjective evaluation, physiological index, and comparison of the subjective evaluation of VR video and screen images. We used the effect size (r) of the Wilcoxon signed-rank test (paired) and the Mann-Whitney U-test (unpaired), r = 0.1 (small effect size), r = 0.3 (medium effect size), and r = 0.5 (large effect size) [20].

Results

The following are the results of the participants' character, a comparison of subjective evaluations, and physiological indicators between the two conditions.

Participant characteristics

In this study, data from 21 participants (10 males and 11 females, aged 21.4 ± 0.2 years) were analyzed, with 3 of the 24 participants excluded because they had temporarily interrupted the measurement owing to physical conditions or were unable to view the video owing to strong drowsiness. Heart rate data were used for 19 participants, excluding 2 more participants owing to measurement errors. The 21 participants had an educational history of 14.8 ± 0.2 years, slept 6.5 ± 0.2 h the previous day, were right-handed, had an IQ of 108.7 ± 1.1 on the JART, and had visual acuity >0.7 in both eyes. The IES-R was 1.4 ± 0.8 points, and none of the participants were excluded owing to earthquake trauma. For the STAI scores, the scores for state anxiety and trait anxiety were 33.2 ± 1.5 and 39.0 ± 1.8, respectively; for the MPI scores, the N scale was 17.1 ± 2.5, and the E scale was 31.8 ± 2.2. When asked about the earthquakes they had actually experienced, three (14.3%) had experienced six earthquakes referring to the JMA scale, five (23.8%) had experienced a maximum intensity of 5+, and all had experienced a maximum intensity of 3 or higher, except for one respondent who was unsure. The locations where they had experienced earthquakes included bedrooms (n = 7), living rooms (n = 4), and outdoors (n = 2). In terms of feelings during the earthquake, some were astonished (n = 15), upset and confused (n = 15), fearful (n = 11), fearful (n = 10), worried (n = 6), and impatient (n = 6). In terms of behavior, some participants said that they moved away from where objects might fall (n = 6), cowered under a sturdy desk or table (n = 6), or were too frustrated or afraid to move (n = 4).

Subjective evaluation

Individual changes in the subjective ratings (filled black circles) and means (unfilled black circles) are shown in Fig 3, and the raw scores are shown in S1 Table (columns B to AJ). Comparisons between the conditions showed that valence, arousal, dominance, fear, astonishment,

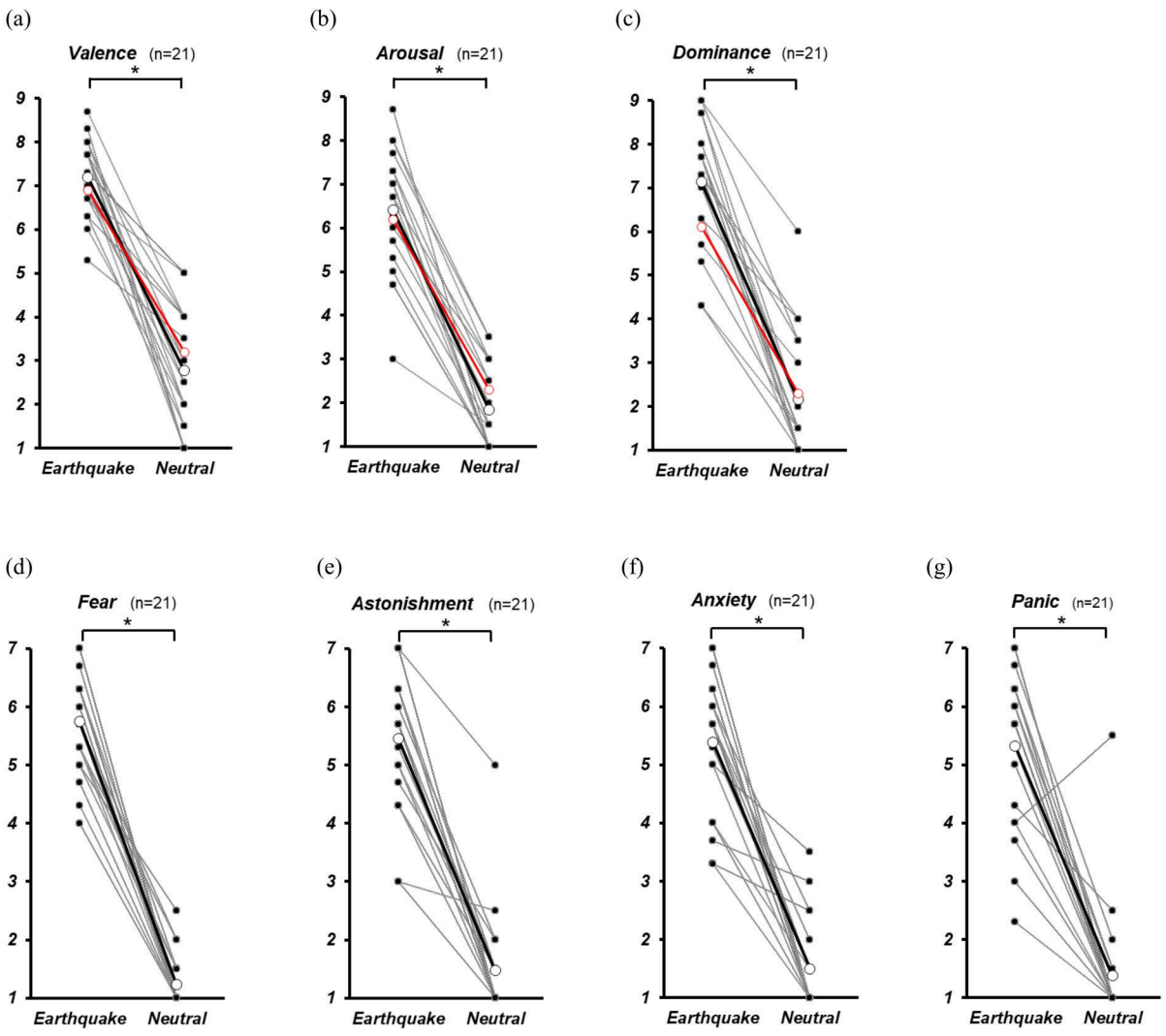

Fig 3. Comparison of subjective evaluation between earthquake and neutral conditions. The mean rate values of the three earthquakes or two neutral images for individual participants (filled black circles) and all participants (unfilled black circles) in the current VR condition are shown. The averages of all the participants (unfilled red circles) in the previous study [4] are also shown for (a) valence, (b) arousal, and (c) dominance. Statistical analyses were performed using Wilcoxon signed-rank tests with Bonferroni correction. *: $p < 0.0071$.

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anxiety, and panic were significantly higher in the earthquake condition than in the neutral condition ($p < 0.001$). For valence, arousal, and dominance, we compared these results with those of our previous study (unfilled red circles in Fig 3), which used a 2D video. Although no significant differences were observed, a moderate effect was observed for the dominance of earthquakes, which was higher in the VR condition than in the 2D video condition. (7.1 ± 0.3 (VR) vs. 6.1 ± 0.4 (2D video), $p = 0.03$, $r = -0.37$) (see S2 Table).

Autonomic indices, pulse rate and cerebral blood flow changes

The results for each physiological index are shown in Fig 4. In each figure, the means of viewing the three seismic and two neutral videos for each participant are plotted in black, with the open circles indicating the means for all participants. The values of each physiological indicator are shown in S1 Table (columns AK to BS).

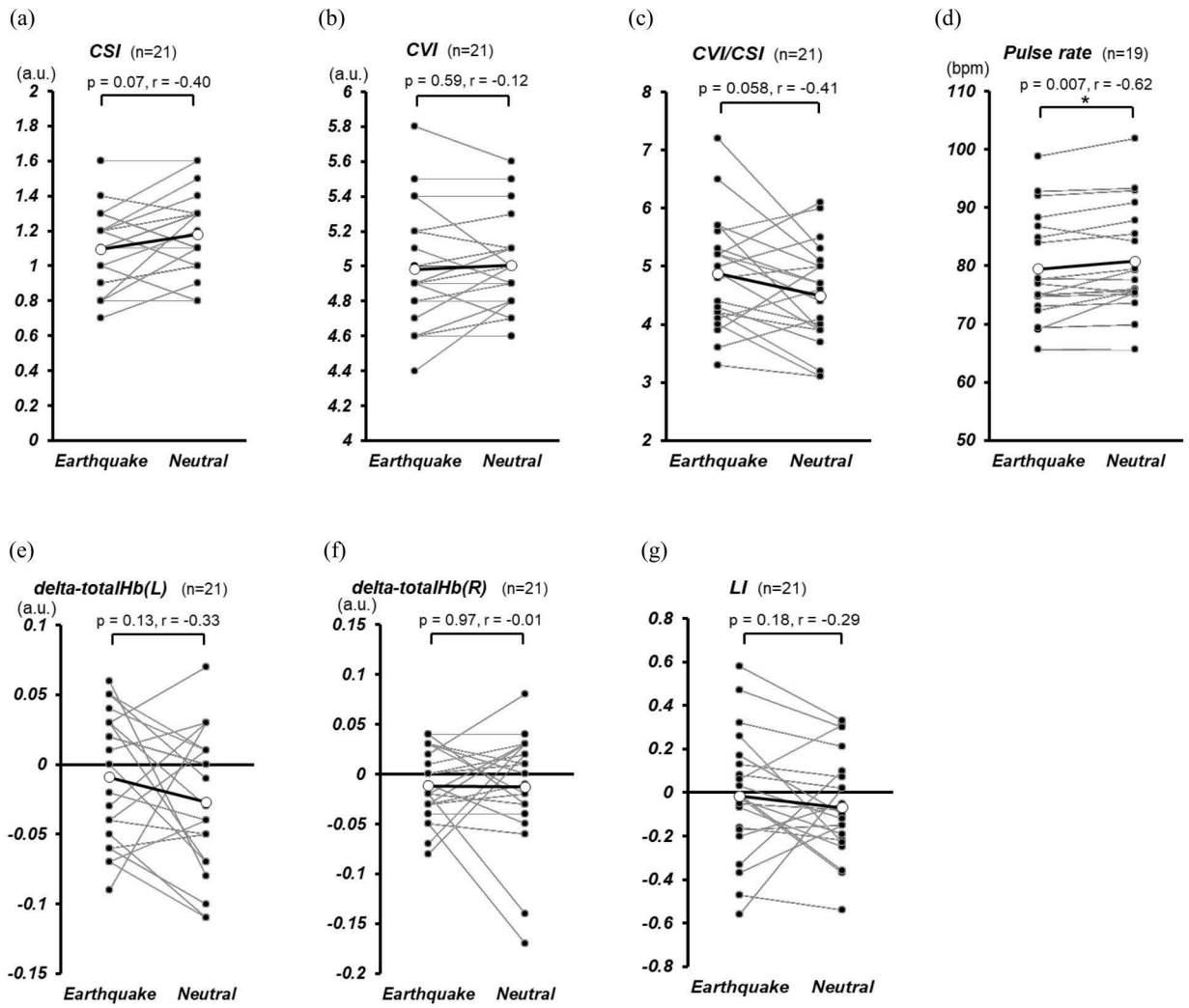

Fig 4. Comparison of physiological indices between earthquake and neutral conditions. The mean rate values of the three earthquakes or two neutral images for individual participants (filled circles) and all participants (unfilled circles) are shown. Statistical analyses were performed using Wilcoxon signed-rank tests with Bonferroni correction. *: $p < 0.0071$. CSI: cardiac sympathetic index, CVI: cardiac vagal index, delta-totalHb: the change in total hemoglobin, LI: lateral index.

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Comparison by video condition showed that the pulse rate was significantly lower in the seismic condition than in the neutral condition (p = 0.007, r = -0.62, Fig 4(D)); the other indices had no significant differences. However, there was a tendency for CSI to decrease, CVI/CSI to increase, and delta-totalHb(L) to increase slightly under seismic conditions, and the effect sizes were moderate for CSI (p = 0.07, r = -0.40, Fig 4(A)) and CVI/CSI (p = 0.058, r = -0.41, Fig 4(C)) and delta-totalHb(L) (p = 0.13, r = -0.33, Fig 4(E)).

Discussion

This study aims to investigate the capture of emotional responses during disaster experiences in an immersive and realistic VR environment. We compared physiological indices such as CBF, pulse rate, and autonomic nervous system activity while viewing earthquake and neutral videos using a NIRS system that can be worn simultaneously with an HMD.

Subjective evaluation of earthquake vs. neutral

First, in the subjective evaluation of the earthquake and neutral videos, the earthquake videos scored significantly higher than the neutral videos in terms of emotional valence, arousal, dominance, fear, astonishment, anxiety, and panic (Fig 3). In other words, it was confirmed that the earthquake video induced more negative emotions than the neutral one.

Physiological indices of earthquake vs. neutral

Second, in the physiological indices, the pulse rate was significantly lower when the earthquake video was viewed compared to the neutral video (Fig 4(D)). In addition, although there was no significant difference in the autonomic index, there was a trend toward a decrease in the CSI, which indicates sympathetic activity, and an increase in the CVI/CSI, which indicates parasympathetic dominance, under earthquake conditions (Fig 4(A) and 4(C)). These results support our hypothesis that pulse rate and sympathetic activity are decreased by the VR earthquake experience.

Previous studies have reported that heart rate decreases more for unpleasant auditory and visual stimuli than for pleasant stimuli [21, 22], as well as for fear of imminent threats, disgust associated with physical mutilation, and sudden sadness [23]. The finding that the VR earthquake videos evoked significantly more negative emotions than the neutral film in the present subjective rating suggests that the negative emotions evoked in the present study reduced sympathetic nerve activity and pulse rate.

Conversely, we discuss the fact that the parasympathetic index (CVI) showed little difference between the seismic and neutral conditions (Fig 4(B)). Berntson et al. reported that sympathetic and parasympathetic activities may be non-interactive and independent [24], and Kreibig reported that disgust associated with body mutilation stated that the associated decrease in pulse rate may be caused by sympathetic withdrawal rather than parasympathetic influence [23]. Therefore, we assume that the results of this study were caused by an independent decrease in the sympathetic nervous system activity due to negative emotional arousal.

In addition, the comparison between the earthquake and neutral conditions in the indices of CBF change (delta-totalHb(L), delta-totalHb(R), and LI) showed no significant differences (Fig 4(E)–4(G)), which did not support our hypothesis that CBF changes in the prefrontal cortex increase during the viewing of earthquake images. The results also did not support Marumo et al.'s report [25] that oxy-Hb in the right lateral ventral prefrontal cortex and supplementary motor cortex increased when fearful facial expressions were presented or Hoshi et al.'s report [26] that oxy-Hb in the bilateral lateral ventral prefrontal cortex increased when unpleasant pictures were presented. However, there was a slight tendency for delta-totalHb(L) to increase more in the earthquake condition than in the neutral condition (Fig 4 (E)) since the right amygdala is associated with the rapid processing of emotional stimuli, while the left is associated with maintaining impulsive stimuli [27]; the present results may reflect emotional responses to sustained stimuli.

Impact of VR videos on emotional change

Third, we compared the results of our previous report [4], in which 2D video clips were projected onto a common projection screen.

As shown in Fig 3 and S2 Table, regarding the subjective evaluation of the earthquake video, the dominance of SAM showed higher trends in the VR video than in the 2D video presentation in the previous report [4], and the mean values of emotional valence and arousal were higher than the previous time, although not significant. This suggests that the VR images in the present study were more realistic earthquake experiences than the screen images and

nearly supports the hypothesis of the present study that earthquake experiences in VR space increased negative emotions more than 2D images.

We observed the same trend as in our previous study [4] for pulse rate and autonomic activity. Referring to the p-values and effect sizes, sympathetic activity and pulse rate tended to decrease more in the earthquake condition than in the neutral condition, and there was little difference in the parasympathetic response between the earthquake and neutral conditions, similar to the findings of a previous study.

Although there was no significant difference in CBF change between the seismic and neutral conditions in both the present and the previous study, the mean value of delta-totalHb(L) was higher in the seismic condition than in the neutral condition. There was almost no difference in delta-totalHb(R) between the seismic and neutral conditions, which was a common point. For delta-totalHb(L), the effect size was larger this time than in the previous study, with $p = 0.13$ and $r = -0.33$.

These results suggest that viewing earthquake videos decreases sympathetic activity and pulse rate and that immersive VR video viewing may induce greater emotional changes and increase brain activity in the left DLPFC than 2D video on screen display.

Novelty of simultaneous measurement using NIRS and VR

Finally, we discuss the novelty of our experimental technique for NIRS measurement and immersive VR experience. There have already been several reports of NIRS measurements during VR experiences. A previous study measured brain activity using NIRS while firefighters performed a fire task in a VR environment [6], and another report measured brain activity while firefighters performed a line division bisection task using a VR helmet modified with multichannel NIRS and an HMD [7]. The present study is novel because it used NIRS to capture emotional responses during a VR disaster experience where no cognitive task was imposed. This is the first research finding obtained using NIRS and VR.

Moreover, in the questionnaire regarding individual experiences of earthquakes, some were able to take protective actions after an earthquake of intensity JMA scale 3 or higher, while others were unable to act because of surprise or fear, suggesting that there were individual differences between those who were able to take appropriate actions and those who were not. It has been reported that heart rate variability during arousal and changes in CBF in the left and right DLPFC differ depending on the degree of emotional trauma, even in disaster victims [28].

As a limitation, since this study was an exploratory investigation with a small number of participants in a specific group (healthy young adults), further validation with a larger variety of participants is needed to consider individual differences in disaster experiences and psychological trauma caused by disasters. Furthermore, the number of CBF measurements in this study was limited to two areas, at the left- and right-DLPFC, because the NIRS model that allows simultaneous attachment with a head-mounted VR system was used. The DLPFC, as well as the overall PFC area, reflects the emotional change as described by Bendall et al. [29]; however, the responses are very complex. Therefore, more studies targeting the entire brain using a multichannel-NIRS will be required to fully understand the VR-induced emotional change in humans.

Conclusions

In this study, we investigated the capture of emotional responses in an immersive VR environment using NIRS that can be simultaneously worn with an HMD. The presentation of earthquake videos using VR evoked negative emotions subjectively and possibly enabled a more realistic earthquake experience than a 2D video using a screen. Under this VR earthquake

experience, the pulse rate significantly decreased, and sympathetic nerve indices showed a decreasing trend. Furthermore, while CBF in the DLPFC did not significantly differ between the seismic and neutral conditions, there was a trend toward increased activity in the left frontal lobe in the VR environment compared to the screen-based 2D video presentation. While further investigations with a larger variety of participants are required, and modalities utilizing VR and NIRS measurements would be useful in capturing emotional responses to emotionally arousing experiences such as fear and anxiety.

Supporting information

S1 Table. Individual subjective evaluation scores and physiological index values.
(XLSX)

S2 Table. Comparison of subjective evaluation between VR video and 2D video conditions. Values are presented as means ± standard error. Statistical analyses were performed using the Mann-Whitney U-test with Bonferroni correction ($p < 0.008$). n = 21 for VR videos in the present study and n = 12 for 2D videos in the previous study [4].
(PDF)

S1 Appendix. English translation of the analysis method section of Ref. 4.
(PDF)

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Funding acquisition: Akitoshi Seiyama.

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Supervision: Akitoshi Seiyama.

Writing – original draft: Hikari Otsuka.

Writing – review & editing: Sayaka Okahashi, Hirotake Ishii, Wataru Asaba, Chang Liu, Goshiro Yamamoto, Akitoshi Seiyama.

References

1. Nakamura M. Emotional experiences in large-scale disasters: A questionnaire study on the emotional experience of 3.11 Disasters in Japan (1), Journal of the Faculty of International Studies, Utsunomiya University. 2013; 36: 125–136. (in Japanese).
2. Prati G, Saccinto E, Pietrantoni L, Pérez-Testor C. The 2012 Northern Italy Earthquakes: modelling human behaviour. Nat Hazards. 2013; 69: 99–113. https://doi.org/10.1007/s11069-013-0688-9

3. Kitamura H. Mood states and information processing strategies (1)—On the Arguments of the Mood-and-General-Knowledge Assumption—, Bulletin of the Faculty of Sociology. Toyo University. 2003; 40: 61–74. (in Japanese).
4. Otsuka H, Okahashi S, Seiyama A. Evaluation of emotional changes during earthquake video watching: A Wearable NIRS Study, Hum Interface. 2022; 24: 239–248. https://doi.org/10.11184/his.24.4_239 (in Japanese).
5. Okada T, Hitomi T, Itasaka N. VR and brain activity measurement, J Imaging Society Jpn. 2019; 58: 324–331. doi: 10.11370/isj.58.324. (in Japanese).
6. Tyagi O, Hopko S, Kang J, Shi Y, Du J, Mehta RK. Modeling brain dynamics during virtual reality-based emergency response learning under stress. Hum Factors. 2021: 187208211054894. https://doi.org/10.1177/00187208211054894 PMID: 34865562
7. Seraglia B, Gamberini L, Priftis K, Scatturin P, Martinelli M, Cutini S. An exploratory fNIRS study with immersive virtual reality: a new method for technical implementation. Front Hum Neurosci. 2011; 5: 176. https://doi.org/10.3389/fnhum.2011.00176 PMID: 22207843
8. Asaba W, Harazono Y, Ishii H, Shimoda H. Development of a VR disaster experience environment construction system with automatic object material recognition. International Symposium on Socially and Technically Symbiotic Systems (STSS), Okayama, November 15– 17, 2021.
9. Asaba W, Ueda K, Ishii H, Shimoda H. Evaluation of the effect of VR disaster experience in familiar environment. In: Ahram T, Karwowski W, Bucchianico PD, LucaCasarotto RT, Costa P, editors. Intelligent human systems integration (IHSI 2023): integrating people and intelligent systems. AHFE 2023 International Conference. AHFE Open Access, vol 69. https://doi.org/10.54941/ahfe1002889
10. Unity asset store, mountain environment–dynamic. Nature. [Cited 9 July 2023]. Available from: https://assetstore.unity.com/packages/3d/vegetation/mountain-environment-dynamic-nature-191851.
11. Bradley MM, Lang PJ. Measuring emotion: the self-assessment manikin and the semantic differential. J Behav Ther Exp Psychiatry. 1994; 25: 49–59. https://doi.org/10.1016/0005-7916(94)90063-9 PMID: 7962581
12. Japan Meteorological Agency. Earthquake information, Explanation of the seismic intensity. [Cited 9 July 2023]. Available from: https://www.data.jma.go.jp/multi/quake/quake_advisory.html?lang=en.
13. Eysenck HJ. London: Maudsley Personality Inventory, University of London Press Ltd.; 1959.
14. Kiguchi M, Funane T. Algorithm for removing scalp signals from functional near-infrared spectroscopy signals in real time using multidistance optodes. J Biomed Opt. 2014; 19: 110505. https://doi.org/10.1117/1.JBO.19.11.110505 PMID: 25437633
15. Seiyama A, Hazeki O, Tamura M. Noninvasive quantitative analysis of blood oxygenation in rat skeletal muscle. J Biochem. 1988; 103: 419–424. https://doi.org/10.1093/oxfordjournals.jbchem.a122285 PMID: 3391996
16. Nozawa T, Sakaki K, Ikeda S, Jeong H, Yamazaki S, Kawata KHDS, et al. Prior physical synchrony enhances rapport and inter-brain synchronization during subsequent educational communication. Sci Rep. 2019; 9: 12747. https://doi.org/10.1038/s41598-019-49257-z PMID: 31484977
17. Toichi M, Sugiura T, Murai T, Sengoku A. A new method of assessing cardiac autonomic function and its comparison with spectral analysis and coefficient of variation of R-R interval. J Auton Nerv Syst. 1997; 62: 79–84. https://doi.org/10.1016/s0165-1838(96)00112-9 PMID: 9021653
18. Ishikawa W, Sato M, Fukuda Y, Matsumoto T, Takemura N, Sakatani K. Correlation between asymmetry of spontaneous oscillation of hemodynamic changes in the prefrontal cortex and anxiety levels: a near-infrared spectroscopy study. J Biomed Opt. 2014; 19: 027005. https://doi.org/10.1117/1.JBO.19.2.027005 PMID: 24549440
19. Fukui M. "Ideal for Graduation Thesis," College. Analysis Ver: 8.4, a free software for statistical and social system analysis. [Cited 9 July 2023]. Available from: https://www.heisei-u.ac.jp/ba/fukui/analysis.html. (in Japanese).
20. Mizumoto A, Takeuchi O. Basics and considerations for reporting effect sizes in research papers. Studies in English Language Teaching. 2008; 31: 57–66. (in Japanese).
21. Bradley MM, Lang PJ. Affective reactions to acoustic stimuli. Psychophysiology. 2000; 37: 204–215. https://doi.org/10.1111/1469-8986.3720204 PMID: 10731770
22. Palomba D, Sarlo M, Angrilli A, Mini A, Stegagno L. Cardiac responses associated with affective processing of unpleasant film stimuli. Int J Psychophysiol. 2000; 36: 45–57. https://doi.org/10.1016/s0167-8760(99)00099-9 PMID: 10700622
23. Kreibig SD. Autonomic nervous system activity in emotion: a review. Biol Psychol. 2010; 84: 394–421. https://doi.org/10.1016/j.biopsycho.2010.03.010 PMID: 20371374

24. Berntson GG, Cacioppo JT, Quigley KS, Fabro VT. Autonomic space and psychophysiological response. Psychophysiology. 1994; 31: 44–61. https://doi.org/10.1111/j.1469-8986.1994.tb01024.x PMID: 8146254

25. Marumo K, Takizawa R, Kawakubo Y, Onitsuka T, Kasai K. Gender difference in right lateral prefrontal hemodynamic response while viewing fearful faces: a multi-channel near-infrared spectroscopy study. Neurosci Res. 2009; 63: 89–94. https://doi.org/10.1016/j.neures.2008.10.012 PMID: 19056435

26. Hoshi Y, Huang J, Kohri S, Iguchi Y, Naya M, Okamoto T, et al. Recognition of human emotions from cerebral blood flow changes in the frontal region: a study with event-related near-infrared spectroscopy. J Neuroimaging. 2011; 21: e94–e101. https://doi.org/10.1111/j.1552-6569.2009.00454.x PMID: 20002968

27. Kohno S, Noriuchi M, Iguchi Y, Kikuchi Y, Hoshi Y. Emotional discrimination during viewing unpleasant pictures: timing in human anterior ventrolateral prefrontal cortex and amygdala. Front Hum Neurosci. 2015; 9: 51. https://doi.org/10.3389/fnhum.2015.00051 PMID: 25713527

28. Wei C, Han J, Zhang Y, Hannak W, Dai Y, Liu Z. Affective emotion increases heart rate variability and activates left dorsolateral prefrontal cortex in post-traumatic growth. Sci Rep. 2017; 7: 16667. https://doi.org/10.1038/s41598-017-16890-5 PMID: 29192184

29. Bendall RC, Eachus P, Thompson C. A brief review of research using near-infrared spectroscopy to measure activation of the prefrontal cortex during emotional processing: the importance of experimental design. Front Hum Neurosci. 2016; 10: 529. https://doi.org/10.3389/fnhum.2016.00529 PMID: 27812329

External Research Funds in 2023-2024

<Grants-in-Aid for Scientific Research (KAKENHI)>

Title: Development of shortwave infrared fluorescence molecular imaging for optical diagnostics of human breast cancer
Project/Area Number: 22H03930
Research Category: Grant-in-Aid for Scientific Research (B)
Section: General
Review Section Basic Section: 90110: Biomedical engineering-related
Research Institution: Institute of Physical and Chemical Research
Principal Investigator: Takashi Jin (RIKEN)
Co-Investigator (Kenkyū-buntansha): Akitoshi Seiyama (AIU)
Project Period (FY): 2022-04-01 – 2025-03-31

Title: Creation of "Virtual Art" through the practical fusion experiments of "neuroscience and arts"
Project/Area Number: 21K00229
Research Category: Grant-in-Aid for Scientific Research (C)
Section: General
Review Section Basic Section: 01070: Theory of art practice-related
Research Institution: AIU
Principal Investigator: Akitoshi Seiyama
Co-Investigator (Kenkyū-buntansha): Sayaka Okahashi (NIGG)
Project Period (FY): 2021-04-01 – 2024-03-31

<Industry-academia Collaborative Research Funding>

Title: Measurement of biological information and system development
Collaboration with Sony Semiconductor Solutions Co.
1st: FY2023/12 - FY2024/3:
2nd: FY2024/4 - FY2025/3:

Editor’s Postscript

The Creative Design and Data Science Center (CreDDS Center) at AIU was established on April 1, 2022. as the newest of three centers of Akita International University (AIU). This center represents a new endeavor for AIU, which is famous as a liberal arts university and for education in foreign language since its establishment in 2004.

Through scientific research, the CreDDS Center has a synergistic and mutually supportive relationship with the other two centers, the Active Learning Center (ALC) and the Center for Collaborative Research and Outreach (CCRO).

Within this relationship, the CreDDS Center provides the impetus for the transformations anticipated under Institute of Applied International Liberal Arts (AILA) for contribution to Akita Prefecture and world-wide through industry-government-academia collaboration.

June 30, 2024

Akitoshi SEIYAMA
Director
CreDDS Center

The FY2023 CreDDS Center logo shown on the cover *represents the research themes established during the first two years (FY2022 and 2023) of the CreDDS Center, because the research papers published in 2023 were mainly related to health and the environment. The main theme, “Healthy ageing”, is no longer just an issue of individual health but is also linked to socio-economic and environmental issues. Therefore, it is also a global issue that should be addressed through collaboration between industry, government and academia. The Editor hopes that human wisdom in creating new science and technology will become a savior in the face of our accelerating super-ageing society and environmental problems.*

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