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ORIGINAL ARTICLE

Association between loneliness and computation of relationship value appears modulated by autonomic nervous functions

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Abstract

OBJECTIVES: Recently, loneliness and social isolation have become common social problems. Previous research has shown that loneliness affects the brain's structure and function as well as the function of the autonomic nervous system. Our previous study found that loneliness has a negative impact on the computation of relationship value in response to commitment signals from friends. This study investigated whether heart rate variability (HRV), which is thought to reflect autonomic nervous function, is related to loneliness in young Japanese adults and whether experimental improvement of autonomic nervous activities alters the relationship value computation process in response to friends' commitment signals.

DESIGN, MATERIAL AND METHODS: In Experiment 1, Japanese undergraduate students were assessed for loneliness and a resting electrocardiogram to determine HRV. In Experiment 2, other undergraduate students, separated into control and treatment groups, participated in a psychological task assessing responses to commitment signals from friends. The treatment group was subjected to autonomic nervous modulation before and while performing the task.

RESULTS: Experiment 1 (n = 210) indicated that loneliness was negatively correlated with the high-frequency percentage (HF%) and positively correlated with the low-frequency (LF) component/HF ratio. Experiment 2, a pilot intervention study (n = 38), indicated that experimental improvement of HRV improved the subjective rating of the perceived commitment-confirming effect related to loneliness, specifically under high-cost commitment signal conditions.

CONCLUSION: These findings suggest that changes in cognitive functions caused by loneliness may be modifiable; by improving autonomic nervous function, it is possible to improve cognitive functions that have changed due to loneliness.

However, as a pilot intervention study (Experiment 2) with a small sample, these pilot findings require replication in larger, adequately powered trials.

Abbreviations:

HRV	- heart rate variability
HF	- high-frequency
LF	- low-frequency
HPA	- hypothalamic-pituitary-adrenal
MRI	- magnetic resonance imaging
fMRI	- functional magnetic resonance imaging
SAM	- sympathetic nervous-adrenal-medullary
mPFC	- medial prefrontal cortex
OFC	- orbitofrontal cortex
IBI	- interbeat interval
PSD	- power spectrum density
VLF	- very low-frequency
ANOVA	- analysis of variance
SD	- standard deviation
VAS	- visual analog scale
CI	- confidence interval

INTRODUCTION

It has become widely known that the problem of loneliness and social isolation has increased in severity in recent years. In February 2021, an office dedicated to measures against loneliness and social isolation was established in the Cabinet Secretariat in Japan. In a survey of 20,000 men and women aged 16 years and over across Japan, approximately 40% answered that they sometimes felt lonely, especially people in their 20s to 50s, corresponding to prime working years (Cabinet Office, 2024). Loneliness is defined as a perceived or subjective condition wherein an individual is dissatisfied with the quality or quantity of their social relationships or both (Taylor, 2020; Taylor *et al.* 2023). Social isolation is an objective condition characterized by a lack of contact with other people, and disengagement from groups and social activities (Taylor, 2020; Taylor *et al.* 2023). This study focuses on loneliness, a more subjective concept, from an experimental psychological standpoint. Previous research indicates that loneliness is closely related to the state of the brain and body. Inflammation is the body's natural biological response to physical injury (e.g., a cut or bruise) that protects it against infection and aids in healing (Engeland & Gajendrareddy, 2011; Engeland & Marucha, 2009; Van Bogart *et al.* 2021). A recent study found that mental stress such as loneliness, although unaccompanied by direct physical injury, activates the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous-adrenal-medullary (SAM) system, modifying immune function and causing systemic inflammation (Van Bogart *et al.* 2021), which has been linked to several diseases such as cancer (Schetter *et al.* 2010). Additionally, lonelier individuals tend to exhibit greater inflammatory responses to acute psychological stress (Brown *et al.* 2018). Furthermore, voxel-based morphometry using structural magnetic resonance imaging (MRI) has revealed an association between loneliness and structural alterations in the brain (Kong *et al.* 2015; Zheng *et al.* 2023). Previous neuroimaging studies indicate that healthy adults who experience higher loneliness tend to have greater gray matter volume in the dorsolateral prefrontal cortex, which was thought to be associated with emotion regulation deficits and executive dysfunction (Kong *et al.* 2015; Zheng *et al.* 2023). Moreover, functional MRI (fMRI) studies have indicated an association between loneliness and functional alterations in the brain (Courtney & Meyer, 2020; Ohtsubo *et al.* 2020). While the medial prefrontal cortex (mPFC) is activated when we think about ourselves, it is also activated in the same way when we think about close others (Seger *et al.* 2004; Courtney & Meyer, 2020). However, loneliness reportedly attenuates the self-other similarity in the mPFC (Courtney & Meyer, 2020). Our previous fMRI study found that the medial orbitofrontal cortex (OFC), which is known to code the value of various rewards, is involved in the relationship value computation process in response to a friend's commitment signals, and that loneliness is negatively associated with both the OFC activity and subjective rating of the perceived commitment-confirming effect (Ohtsubo *et al.* 2020). It is thought that by receiving a commitment signal that someone values us, we upregulate the relationship value of the signalers (Yamaguchi *et al.* 2015, 2017); however, loneliness is associated with decreased brain activity related to commitment signals and interaction with others.

An association has been observed between loneliness and autonomic nervous function, as reflected in heart rate variability (HRV) (Roddick & Chen, 2021). HRV is a physiological index that reflects the modification of heartbeats by autonomic nervous activities, and the high-frequency (HF) components of HRV are thought to reflect parasympathetic nerve function (Shaffer & Ginsberg, 2017). A previous study found that greater chronic loneliness in women predicts lower resting HRV HF components, suggesting lower parasympathetic activity in lonely people (Roddick & Chen, 2021). Peripheral autonomic nerve activity is not only monitored but also controlled by the brain in a top-down manner (Thayer *et al.* 2012). Moreover, emotional and physical reactions are thought to provide important signals in decision-making (the somatic marker hypothesis). The mPFC, including the OFC, may play an important role in this processing (Damasio, 1994). In fact, a previous study reported that increased sympathetic activity and decreased parasympathetic activity seem to be associated with worse performance in cognitive domains (Forte *et al.* 2019). A relationship has been suggested between loneliness, brain functions related to self-other interactions, and autonomic nerve functions, and recent progress in the development of devices that can improve peripheral autonomic nerve functions may also serve in addressing loneliness. For example, previous studies have indicated that non-invasive vagus nerve stimulators (e.g., gammaCore) can reduce the intensity and frequency of cluster headaches (O'Connell *et al.* 2021). Based on these observations, we hypothesized that the relationship value computation process in response to a friend's commitment signals, found to be associated with loneliness in our previous fMRI study, may be altered by experimentally improving autonomic nervous functions. To test this hypothesis, we conducted Experiment 1, which determined whether a similar relationship between loneliness and resting HRV exists among young Japanese adults as found in previous studies, and Experiment 2, an experimental psychological study which examined how friendship value judgments change when peripheral autonomic nervous function is experimentally modulated. This study was attempted as a pilot study to modulate autonomic nerve functions using a non-invasive bioresonance device developed in Japan (Medi-cure II, Aichi Electronics Industry Co., Ltd., Aichi, Japan). As a form of alternative medicine, bioresonance therapy is used effectively by many medical practitioners around the world to treat a variety of ailments, including depression (Muresan *et al.* 2021). While some studies suggest potential benefits of bioresonance therapy, the evidence base remains limited and requires further controlled trials (Marakoğlu *et al.* 2024). Experiment 2 was a pilot study with a small sample size; after confirming the effects of this bioresonance device on autonomic nervous activities, we examined changes in friendship value judgments associated with changes in autonomic nervous system activities.

MATERIAL AND METHODS

Experiment 1

Participants

We utilized data from 210 undergraduate students from Nagoya University, comprising 112 women and 97 men (1 person is unknown as there is no record) aged 18–25 years (mean ± standard deviation [SD] = 19.79 ± 1.61 years). *A priori* power analysis using G*Power version 3.1.9.2 (Faul *et al.* 2007) was used to estimate the necessary sample size for this study as $n = 150$ (correlation; one-tailed t-tests; effect size = 0.2; alpha error = 0.05; 1-beta error = 0.8). This study was approved by the Ethics Committee of Nagoya University (approval number: NUPSY-220402-M-01). All participants provided written informed consent in accordance with the Declaration of Helsinki. Participants were recruited through a psychology subject pool in Nagoya University and received 2,000 yen each (approximately USD 13). The sampling in this study was not completely random, as it targeted students interested in participating in the experiment and who volunteered. Therefore, a certain degree of selection bias was anticipated.

Measurement of Loneliness

The Japanese version of the UCLA Loneliness Scale (Moroi, 1992; Russell *et al.* 1980) comprises 20 items (e.g., "There is no one I can turn to") that are rated on a 4-point scale (1 = "never feel so" to 4 = "frequently feel so"). These 20 items were averaged to obtain a single loneliness score. Recent validation studies have confirmed the reliability of the Japanese UCLA Loneliness Scale in young adults (internal consistency $\alpha = 0.92$) (Arai & Okawa, 2025; Saito *et al.* 2019). Participants who did not respond to all items on the questionnaire were excluded from the analysis. No other exclusions were applied in this experiment.

Measurement of Autonomic Nervous Activities

A resting electrocardiogram was recorded for a short period (1 minute) in the standing position using a simple health management system (SKY10-self, SKY21 Co., Ltd., Okinawa, Japan) with a sampling rate of 1,000 Hz. The interbeat interval (IBI) data were subsequently analyzed to determine HRV, which has been widely used as a quantitative marker of the autonomic nervous system (Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). IBI data were linearly interpolated at 4 Hz, and artifacts were removed using visual inspection and automatic detection algorithms with manual correction when necessary. A power spectrum density (PSD) was obtained using fast Fourier transformation (FFT) with Hanning windowing and 50% overlap, using 256-point FFT. PSD analysis of the frequency domain provides information on how power is distributed (i.e., the variance) as a function of frequency, which allows the autonomic balance to be quantified at any given time. Further, it allows the intensity of the HRV spectral components (i.e., the high-frequency band [HF; 0.15–0.5 Hz], low-frequency band [LF; 0.04–0.15 Hz], and very low-frequency band [VLF; 0.0033–0.04 Hz]) to be determined (Kim *et al.* 2018; Shaffer & Ginsberg, 2017). HF is related to respiratory sinus arrhythmia and is exclusively attributable to parasympathetic influence reflecting vagal activity; LF mirrors the baroreceptor feedback loop that controls blood pressure and appears to reflect both sympathetic and parasympathetic activities. Consequently, the relative power of the HF band (HF% in the total power of VLF, LF, and HF: HF%) and the LF/HF ratio were considered in this study. While current guidelines recommend minimum 5-minute recordings for reliable frequency-domain HRV analysis, our 1-minute duration may have reduced measurement reliability, particularly for frequency-domain metrics (Srirubkhwa *et al.* 2023; Takahashi *et al.* 2017).

Statistical Analyses

Data were analyzed using IBM SPSS Statistics (Version 27.0) predictive analytics software. Pearson's correlation coefficients were computed to determine the association between loneliness and HRV. Furthermore, to remove the influences of several confounding factors, such as age and gender, from the effect of resting autonomic nervous activities on loneliness, we used the following regression model:

$$Y = \beta 0 + \beta 1H + \beta 2S + \beta 3A + \varepsilon$$

In the formula presented above, "H" (HRV) represents a matrix of variables to control for the HRV (HF% or LF/HF). "S" (sex) is a matrix of variables used to control for gender (S = 0 if the participant is female, and S = 1 if the participant is male). "A" (age) represents a matrix of variables used to control for age, whereas "ε" represents the individual-specific error.

<u>*Experiment 2*</u>

Participants

We utilized data from 38 undergraduate students from Aichi Medical University, which included 28 women and 10 men aged 19–29 years (mean ± standard deviation [SD] = 20.9 ± 1.89 years). *A priori* power analysis using G*Power version 3.1.9.2 (Faul *et al.* 2007) was used to estimate the necessary sample size for this study as $n = 38$ (Means: Difference between two dependent means (matched pairs); one-tailed *t*-tests; effect size = 0.6; alpha error = 0.05; 1-beta error = 0.8). This study was approved by the Ethics Committee of Aichi Medical University (approval number: 2022-M006). All participants provided written informed consent, in accordance with the Declaration of Helsinki. The participants were recruited through a school-wide e-mail disseminated at Aichi Medical University and received 8,000 yen each (approximately USD 53). The sampling in this study was not completely random, as it targeted students who were interested and volunteered to participate in the experiment. Therefore, a certain degree of selection bias is anticipated.

Psychological Task Procedure

The task was adapted from the fMRI study by Ohtsubo *et al.* (2020), which was conducted while sitting on a chair. A personal computer with a 21-inch display was placed on the desk, and participants used a mouse to follow the instructions on the screen to complete their evaluations. Participants were exposed to 30 commitment-signal-related scenarios and asked to imagine that the events described in each scenario had occurred with a real friend. Each scenario comprised a situation and a commitment signal section. There were 10 situations (e.g., you passed a test for an important qualification), each accompanied by three commitment signal conditions: the high-cost (e.g., your friend treated you to dinner to celebrate your achievement), low-cost (e.g., your friend sent you a short message of congratulations), and signal failure (e.g., your friend did not notice your achievement), resulting in 30 scenarios (i.e., 10 situations × 3 signal conditions). The full list of these 30 scenarios was presented in the previous study (Ohtsubo *et al.* 2020). In brief, before the experiment, participants were asked to think of one particular friend throughout the experiment. Although participants were asked to assume that the real-life friend was the protagonist in every scenario, they were also asked to treat each scenario as an independent event by ignoring the previous scenarios when reading a new one. In each trial of the study, participants were first presented with a situation scenario for 10 seconds (situation phase), followed by a friend's behavior scenario for 10 seconds (signal phase). Participants then rated the extent to which each event would improve or deteriorate their bond with their friend within five seconds using a visual analog scale (VAS) slider (rating phase). The two poles of the slider were labeled "deteriorate it greatly" (converted to 0) and "improve it greatly" (converted to 100). The VAS score was considered a subjective rating of the upregulation of the friend's relationship value. The next trial was initiated after 10 seconds (resting phase). Participants underwent three training trials before the experiment to familiarize themselves with the procedure. Before the noninvasive pulse heat treatment, 15 scenarios (5 situations × 3 conditions) were presented. After the treatment, participants were presented with the remaining 15 vignettes. The 10 × 3 conditions were presented pseudo-randomly through the whole experiment. The order of the three conditions was counterbalanced across participants.

Non-Invasive Autonomic Nervous Modulation

In this study, a non-invasive bioresonance device developed in Japan (Medi-cure II, Aichi Electronics Industry Co., Ltd., Aichi, Japan) was used. This device requires probes to be attached to the palms, abdomen, and soles of the feet, and the device delivers thermal, far infrared, and acoustic stimulation through probes attached to specific body locations (pulse heat treatment device). Participants were asked to engage in the experiment in same-sex pairs; one person was randomly assigned to the control group and the other to the treatment group using block randomization. Randomization sequence was generated using a computer-based random number generator by an independent researcher not involved in data collection. Allocation was concealed using sequentially numbered, opaque, sealed envelopes opened only after baseline measurements were completed. There were no significant differences in loneliness, age, or sex between the randomly assigned control and treatment groups. Both participants started the experiment simultaneously, and after completing 15 scenarios (two runs), were fitted with therapeutic probes while sitting on a chair. In addition, both participants were fitted with electrodes to record their electrocardiograms. After the probe and electrodes were attached, participants were asked to rest for 5 minutes without doing anything (baseline). After the baseline mood evaluation, the machine was started only for the treatment group, who received a 10-minute treatment while remaining in the resting state (under treatment). After the 10-minute treatment, the device was stopped and their mood status was evaluated. Subsequently, the device was again started only for the treatment group, and these participants performed the second psychological task while undergoing treatment. In the control group, participants completed the psychological tasks without the device being started. After completing the psychological task, a final mood state evaluation was performed.

Measurement of Mood States

To evaluate the mood states of the participants, they were asked to subjectively evaluate their present emotions by rating each of the following nine questions on a scale ranging from 1 (not at all) to 7 (yes, extremely): "Do you feel peaceful at present?" (pleasantness); "Do you feel uneasy at present?" (anxiety); "Do you feel tired at present?" (fatigue); "Do you feel highly energetic at present?" (vigor); "Are you well at present?" (pleasantness); "Are you relaxed at present?" (relaxation): "Do you feel refreshed at present?" (vigor): "Are you irritated at present?" (irritation); and "Do you feel happy at present?" (happiness). Mood state scores were calculated for each criterion (pleasantness, vigor, anxiety, fatigue, relaxation, irritation, and happiness), and the mood state before and after treatment, and after the second psychological task were assessed as previously described (Matsunaga *et al.* 2009). Questionnaire order was fixed.

Measurement of Autonomic Nervous Activities

Electrocardiograms were continuously recorded during the experiment using the Biopac system (BIOPAC Systems, Inc., Goleta, CA, USA) with a sampling rate of 1,000 Hz. The IBI data were subsequently analyzed to yield HRV, similar to the process in Experiment 1. HF% and the LF/HF ratio were calculated using a 5-minute baseline recording before treatment and a 10-minute recording during treatment. Participants whose HRV could not be properly analyzed because of excessive noise were excluded from the analysis.

Statistical Analyses

Psychological data were analyzed using IBM SPSS Statistics (Version 27.0) predictive analytics software. The rating for each mood state in the questionnaire was compared using a two-factor (group [control or treatment] and period [baseline, after treatment, or after the second task]) analysis of variance (ANOVA) followed by Bonferroni's multiple comparisons test. HF% and LF/HF were also compared using a two-factor (group [control or treatment] and period [baseline or under treatment]) ANOVA followed by Bonferroni's multiple comparisons test. The rating score of the relationship value of the friend was compared using a two-factor (group [control or treatment] and period [before or after treatment]) ANOVA followed by Bonferroni's multiple comparison test. We calculated the effect size of the multivariate test (takes a value between 0 and 1; the closer it is to 0, the less error this analysis of variance will have) and the observed power (takes a value between 0 and 1; the closer to 1, the more sufficient data has been analyzed for this analysis of variance), were presented as "η^2p" and "power", respectively.

RESULTS

Association between Resting Autonomic Nervous Activities and Loneliness

Figure 1 illustrates the association between loneliness and HRV in Experiment 1. Correlation analyses indicated that loneliness was positively correlated with LF/HF ($r[209] = 0.199$, $p = 0.004$; Figure 1A) and negatively correlated with HF% ($r[209] = -0.159$, $p = 0.022$; Figure 1B). Tables 1 and 2 show the results of the multiple regression analysis, which tested the hypothesis that

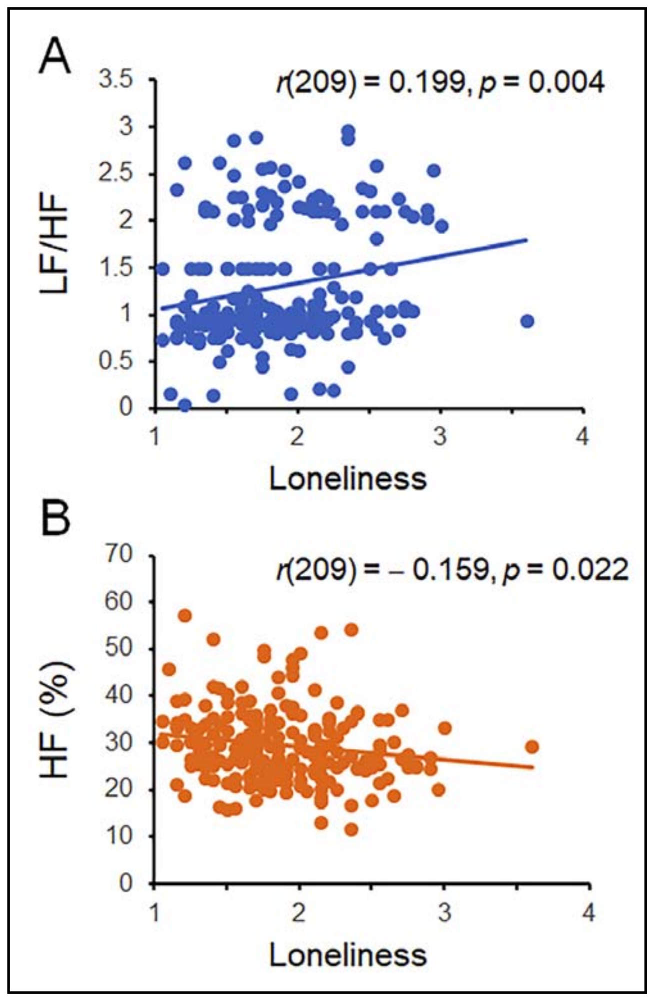

Fig. 1. Associations between loneliness and resting HRV. (A) The scatterplot demonstrates the positive correlation between loneliness and the LF/HF ratio (n = 209). (B) The scatterplot demonstrates the negative correlation between loneliness and high-frequency percentage (HF%) (n = 209). HRV, heart rate variability; LF, low frequency; HF, high frequency

Tab. 1. Results from the regression analysis examining the association between loneliness and HRV LF/HF.

Predictor variables	*β*	t	*p*	95% CI
LF/HF	**0.195**	**2.813**	**0.005**	**0.041-0.235**
Sex	0.106	1.557	0.121	-0.026-0.218
Age	0.006	0.089	0.929	-0.036-0.040
N	207			
Adjusted R^2	0.054			

All predictor variables were included in the regression analysis. Boldface indicates statistically significant variables. *β*: Standardized beta coefficient. HRV, heart rate variability; LF, low frequency; HF, high frequency; CI, Confidence interval.

Tab. 2. Results from the regression analysis examining the association between loneliness and HRV HF.

Predictor variables	*β*	t	*p*	95% CI
HF%	**-0.145**	**-2.095**	**0.037**	**-0.016-0.000**
Sex	0.112	1.632	0.104	-0.021-0.224
Age	0.027	0.396	0.693	-0.030-0.046
N	207			
Adjusted R^2	0.038			

All predictor variables were included in the regression analysis. Boldface indicates statistically significant variables. β: Standardized beta coefficient. HRV, heart rate variability; HF, high frequency; CI, Confidence interval.

Tab. 3. Effect of non-invasive treatment on mood states.

Criteria	Group	Period		
		Baseline	Post 10 min treatment	Post second task
Pleasantness	Control	10.368 (0.478)	10.474 (0.457)	10.211 (0.527)
	Treatment	10.684 (0.478)	11.368 (0.457)*	12.158 (0.527)**,†,‡
Vigor	Control	8.632 (0.450)	8.263 (0.472)	8.105 (0.528)
	Treatment	8.316 (0.450)	9.579 (0.472)**	10.053 (0.528)**,‡
Anxiety	Control	2.684 (0.311)	2.105 (0.254)	2.211 (0.216)
	Treatment	2.000 (0.311)	1.632 (0.254)	1.421 (0.216)‡
Fatigue	Control	3.053 (0.359)	3.526 (0.336)	3.316 (0.301)
	Treatment	3.789 (0.359)	2.579 (0.336)**	2.105 (0.301)**, ‡‡
Relaxation	Control	5.474 (0.294)	5.263 (0.240)	5.053 (0.248)
	Treatment	5.368 (0.294)	5.895 (0.240)	6.211 (0.248)*, ‡‡
Irritation	Control	1.421 (0.184)	1.421 (0.184)	1.684 (0.176)
	Treatment	1.579 (0.184)	1.421 (0.184)	1.211 (0.176)
Happiness	Control	4.158 (0.317)	4.053 (0.280)	4.158 (0.293)
	Treatment	4.368 (0.317)	4.842 (0.280)	5.000 (0.293)*, ‡

The results are expressed as means (standard error of the mean). The variables were compared using repeated-measures analysis of variance followed by Bonferroni-corrected multiple comparisons. *$p < 0.05$ vs. baseline in each criteria; **$p < 0.01$ vs. baseline in each criteria; †$p < 0.05$ vs. post 10 min treatment in each criteria; ‡$p < 0.05$ vs. control in each period; ‡‡$p < 0.01$ vs. control in each period.

either LF/HF or HF% predicts loneliness, even after controlling for the potentially confounding variables of age and sex. The regression model using LF/HF was statistically significant ($F[3, 204] = 3.846$, $p = 0.010$), supporting our hypothesis ($\beta = 0.195$ (95% Confidence interval (CI): 0.041-0.235), t = 2.813, $p = 0.005$). In addition, the regression model using the HF% showed that it predicts loneliness ($\beta = -0.145$ (95% CI: -0.016-0.000), t = -2.095, $p = 0.037$; Table 2), and had a significant trend ($F[3, 204] = 2.651$, $p = 0.050$].

Intervention Findings

We conducted an intervention experiment by randomly assigning 19 participants each to a control group and an experimental group. First, we verified the effectiveness of our treatment. Regarding mood states, two-factor

Tab. 4. Effect of non-invasive treatment on HRV.

Component	Group	Baseline	Under treatment
HF%	Control	26.994 (4.245)	21.103 (3.905)
	Treatment	19.974 (4.245)	28.868 (3.905)*
LF/HF	Control	1.479 (0.661)	2.151 (0.520)
	Treatment	3.289 (0.661)	1.654 (0.520)*

The results are expressed as means (standard error of the mean). The variables were compared using repeated-measures analysis of variance followed by Bonferroni-corrected multiple comparisons. HRV, heart rate variability; LF, low frequency; HF, high frequency. *$p < 0.05$ vs. baseline in each component.

Tab. 5. Effect of non-invasive treatment on computation of relationship value.

Condition	Group	Before	After
High-cost signal	Control	76.000 (2.331)	76.632 (2.713)
	Treatment	74.667 (2.331)	78.618 (2.713)*
Low-cost signal	Control	69.586 (2.559)	68.070 (2.610)
	Treatment	70.737 (2.559)	68.982 (2.610)
Signal failure	Control	39.818 (2.000)	39.453 (1.748)
	Treatment	38.660 (2.000)	38.877 (1.748)

The results are expressed as means (standard error of the mean). The variables were compared using repeated-measures analysis of variance followed by Bonferroni-corrected multiple comparisons. *$p < 0.05$ vs. before treatment in each condition.

repeated measures ANOVA showed a significant interaction between group (control or treatment) and period (before treatment (baseline), after treatment (post 10 min treatment), and after second task (post second task)) in the rating of pleasantness ($F[2, 35] = 4.227$, $p = 0.023$, $\eta^2p = 0.195$, power = 0.703), vigor ($F[2, 35] = 6.068$, $p = 0.005$, $\eta^2p = 0.257$, power = 0.857), fatigue ($F(2, 35) = 7.342$, $p = 0.002$, $\eta^2p = 0.296$, power = 0.918), and relaxation ($F[2, 35] = 5.119$, $p = 0.011$, $\eta^2p = 0.226$, power = 0.789; Table 3). Bonferroni's multiple comparisons test indicated that pleasantness after the second task was significantly increased compared to before ($p = 0.003$) and after treatment ($p = 0.016$). Vigor after the second task ($p = 0.002$) and after treatment ($p = 0.003$) significantly increased from before treatment. Fatigue after the second task ($p = 0.001$) and after treatment ($p = 0.001$) was significantly lower than before treatment. Relaxation after the second task ($p = 0.014$) was significantly higher than before treatment. Furthermore, two-factor repeated measures ANOVA showed a significant interaction between group (control vs. treatment) and period (baseline vs. under treatment) for HF% ($F[1, 26] = 6.895$, $p = 0.014$, $\eta^2p = 0.210$, power = 0.715; Table 4) and LF/HF ($F[1, 26] = 7.485$, $p = 0.011$, $\eta^2p = 0.224$, power = 0.750; Table 4). Bonferroni's multiple comparisons test indicated that the HF% during treatment was significantly increased ($p = 0.034$) and LF/HF was significantly decreased ($p = 0.011$) in the treatment group compared to baseline, whereas no significant change was observed in the control group.

Subsequently, we analyzed subjective ratings of the commitment-confirming effect of the friend's behavior in each experimental condition of the psychological task. Two-factor repeated measures ANOVA showed a significant main effect of period (before vs. after) on subjective rating score in the high-cost signal condition ($F[1, 36] = 4.230$, $p = 0.047$, $\eta^2p = 0.105$, power = 0.517; Table 5), whereas no significant main effect of period was observed in the low-cost signal ($F[1, 36] = 2.476$, $p = 0.124$) and signal failure conditions ($F[1, 36] = 0.004$, $p = 0.948$). Bonferroni's multiple comparisons test indicated that the subjective rating score in the high-cost signal condition in the treatment group increased significantly after treatment ($p = 0.017$), whereas no significant change was observed in the control group ($p = 0.691$).

DISCUSSION

A relationship between loneliness, brain functions related to self-other interactions, and autonomic nerve functions has been previously indicated. The present study hypothesized that the relationship value computation process in response to a friend's commitment signals associated with loneliness might be altered by experimentally improving autonomic nervous function. In this study, we first determined whether there was a relationship between resting HRV (recording 1-min standing) and feelings of loneliness in young Japanese adults, as seen in previous studies. As expected, in Experiment 1, we found that loneliness was positively correlated with LF/HF ratio and negatively correlated with HF% (Figure 1). As we were able to confirm the relationship between loneliness and HRV among the target sample (young Japanese adults), we subsequently conducted an intervention experiment (Experiment 2). First, we verified whether it was possible to change peripheral autonomic nerve function experimentally by operating a device. Comparing HRV at baseline (5-min recording) and during treatment (10-min recording), we observed that HF% significantly increased and LF/HF significantly decreased (Table 4). In addition, alongside changes in autonomic nerve activity, mood status also improved, with positive mood factors increasing (pleasantness, vigor, and relaxation) and negative factors decreasing (fatigue; Table 3). Since the order of questionnaire items was fixed, there is a possibility of potential order effects; however, having confirmed that the experimental manipulation was appropriate, we verified whether the calculation of relationship value was altered, which was the main focus of this study. Previous research has shown that the more costly commitment signals a friend provides, the better the relationship will be evaluated (Ohtsubo *et al.* 2020). Therefore, in the psychological task, we set conditions wherein the degree of commitment signals from friends varied (high-cost, low-cost, and signal failure) and examined the effects of modulating autonomic nerve activity on relationship value calculation. As presented in Table 5, the subjective rating of the perceived commitment-confirming effect was altered by autonomic nervous modulation, and in the high-cost condition, participants evaluated the value of the relationship better than before the treatment when they received a costly commitment signal from their friend.

When the brain senses stress, the HPA axis and SAM system are activated, and various stress responses occur, including the activation of the sympathetic nervous system and the secretion of cortisol (James *et al.* 2023). Acute stress responses are important processes for adaptation, such as producing energy to induce fight-or-flight behavior or preparing for wound healing; however, chronic stress negatively affects the body. People experiencing chronic stress are at increased risk of digestive and gastrointestinal problems, depression, and anxiety disorders (James *et al.* 2023). Based on evidence from animal studies, chronic stress has been found to alter the structure and function of the prefrontal cortex (Goldwater *et al.* 2009; McEwen *et al.* 2016). Previous human studies have also shown a relationship between brain structure and function, and feelings of loneliness (Courtney & Meyer, 2020; Kong *et al.* 2015; Ohtsubo *et al.* 2020; Zheng *et al.* 2023). However, this study suggests that the changes in brain structure and function caused by stress may be modifiable. In addition, previous studies have reported changes in cortical volume as a result of interventions to improve HRV using biofeedback training (Yoo *et al.* 2022). This may be the first step in treating loneliness, which is currently a global problem.

On the other hand, susceptibility to loneliness has been reported as being genetically determined (Lucht *et al.* 2009; Meng *et al.* 2017). A prior study indicated an association between loneliness and single nucleotide polymorphisms (SNPs) in the oxytocin receptor gene (Lucht *et al.* 2009). The oxytocin system is well-known for its putative association with social dysfunction (Alvares *et al.* 2017). Another study reported that the association between loneliness and brain microstructure differs depending on gene polymorphism of brain-derived neurotrophic factor (BDNF), a protein of the neurotrophin family that is important for the survival, development, differentiation, morphology, and function of neurons (Meng *et al.* 2017). Additionally, environmental factors such as family dynamics during childhood greatly influence feelings of loneliness (Kamiya *et al.* 2014). In the future, it will be necessary to investigate how the relationships between such innate backgrounds and feelings of loneliness affect intervention studies.

Limitations and Future Directions

Our study had several limitations. First, the HF model showed an unfortunately significant trend in Experiment 1 (Table 2). The HF regression model achieved borderline statistical significance ($p = 0.050$), requiring cautious interpretation of this finding. HRV reportedly changes depending on the measurement posture, suggesting that the HF% may be smaller when measured in the standing position than the supine (Ravé & Fortrat, 2016). Furthermore, there may be differences in resting HRV between men and women (Kwon *et al.* 2022). Moreover, the number of cases may have been too few. Such effects may have prevented the HF% model from becoming significant, and additional studies are required in the future. Second, although our previous study indicated an association between loneliness and the commitment-confirming effect under the low-cost commitment signal condition in an fMRI-assessed task (Ohtsubo *et al.* 2020), in the present study, the effect of modulating autonomic nerve activity was found only under the high-cost condition. Thus, Experiment 2 findings are pilot, condition-specific (high-cost only), and require replication. The moderate observed power (0.517) suggests the study may have been underpowered to detect smaller effects. Regarding why results were only achieved under high-cost conditions, our previous parametric modulation analysis indicated a positive correlation between the OFC activity and the upregulation of perceived commitment in response to the three types of signals (signal failure, low-cost commitment, and high-cost commitment), suggesting that the OFC is more active under high-cost conditions. It is conceivable that the effect of modulating autonomic nervous function becomes more pronounced when the OFC is highly active. On the other hand, it is also possible that the adjustment of autonomic nervous function in this study did not directly affect OFC but instead affected value judgments through the activity of other brain regions. For example, the insular cortex is also thought to monitor the state of the body and influence decision-making (Loued-Khenissi *et al.* 2020; Matusik *et al.* 2023). Further neuroimaging studies are required to address this issue. Third, our non-invasive pulsed heat treatment was able to experimentally alter autonomic nervous activity, in addition to positively altering mood states. This led to ambiguity regarding whether the results of this study were due to an improvement in autonomic nerve activity or a mood congruence effect (Mohammed & Lyusin, 2022). The concurrent improvement in both mood states and HRV parameters makes it difficult to isolate the specific contribution of autonomic modulation versus mood enhancement effects on relationship value computations. In many cases, changes in autonomic nerve activity and mood state occur simultaneously; therefore, it is extremely difficult to conduct experiments wherein they are separated. However, if possible, we would like to conduct a follow-up of this study using non-invasive vagus nerve stimulators. Fourth, in this experiment, participants who did not complete the questionnaire and participants whose HRV could not be measured properly were excluded from the analysis, although no other exclusion criteria (cardiovascular disease, arrhythmias, beta-blockers, psychotropics, caffeine/nicotine before ECG, recent exercise, fever, etc.) were applied. Therefore, how the results change when these factors are controlled will need to be examined.

CONCLUSION

In this study, we first demonstrated that HRV is associated with loneliness in young Japanese adults, and then showed that experimental improvement of HRV using a non-invasive method could improve subjective rating of the perceived commitment-confirming effect related to loneliness. These results provide important insights not only in the field of experimental psychology but also in various fields such as social science, hygiene, and mental health. However, Experiment 2 was a pilot with only 38 participants, yielding just 0.517 power and limiting the robustness of its findings. Thus, the present study requires replication in larger, adequately powered trials.

DECLARATIONS

The authors report there are no competing interests to declare.

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COMPETING INTERESTS

The authors have no competing interests to declare.

CODE AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author, Masahiro Matsunaga. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

AUTHORS' CONTRIBUTION

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Masahiro Matsunaga and Keiko Ishii. The first draft of the manuscript was written by Masahiro Matsunaga and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

INFORMED CONSENT

This study was approved by the Ethics Committees of Nagoya University (approval number: NUPSY-220402-M-01) and Aichi Medical University (approval number: 2022-M006). All participants provided written informed consent, in accordance with the Declaration of Helsinki.

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