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Original Research

Violet Light-Induced Changes in Voice Vitality Indices and Their Associations With Sleep Improvement in Patients With Depression

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Abstract

Background: Violet light (VL, 360–400 nm) has recently emerged as a potential neuromodulatory intervention for depression. Prior randomized controlled trials demonstrated antidepressant and nonspecific sleep-improving effects of VL irradiation. Voice-derived vitality indices, computed from sound pressure change acceleration, have been proposed as non-invasive surrogate markers of depressive symptoms and treatment response. In this study, we examined whether VL irradiation alters voice vitality indices and whether these changes are associated with clinical outcomes, particularly sleep improvement, in patients with depression. **Methods:** This exploratory sub-analysis was derived from a sham-controlled, double-blind, randomized crossover trial (jRCTs032210260) in adults with mild major depressive disorder. Participants received 4 weeks of active or sham VL irradiation. Depressive symptoms, sleep quality, cognition, and voice indices were assessed before and after each intervention period. Two vitality indices were extracted: vitality-all (overall vocal energy) and vitality-depression (segments containing positively valenced words). Statistical analyses were conducted using linear mixed-effects models with subject-specific random intercepts, supplemented by correlation analyses and multiple regression. **Results:** Active VL irradiation significantly improved the depression-specific vitality index (vitality-depression) compared with sham stimulation, as indicated by a significant time-by-intervention interaction, whereas the overall vitality index (vitality-all) did not show a significant interaction. In univariate analyses, higher baseline vitality-all, but not vitality-depression, was significantly correlated with greater sleep quality improvement (i.e., a greater percentage reduction in the Pittsburgh Sleep Quality Index [PSQI] score) under the active VL condition; however, the difference between the active and sham correlations was not statistically significant. When both indices were evaluated simultaneously in a multiple regression model to control for baseline covariates, higher baseline vitality-all emerged as a significant predictor of greater percentage sleep improvement (i.e., a more negative percentage change in PSQI), whereas higher baseline vitality-depression was associated with less sleep improvement or potential worsening of sleep quality (i.e., a more positive percentage change in PSQI). **Conclusions:** VL irradiation was associated with increases in vocal vitality, and these voice changes were further associated with sleep normalization. Voice-derived vitality indices represent promising non-invasive biomarkers; however, their external validation remains limited, and mechanistic interpretations should be considered preliminary. Replication in larger and more diverse samples will be essential to establish their generalizability and clarify their potential clinical utility. **Clinical Trial Registration:** jRCTs032210260. Registered 19 August, 2021, https://jrct.mhlw.go.jp/latest-detail/jRCTs032210260.

Keywords: depressive disorder; photobiomodulation therapy; light; sleep; voice; biomarkers

1. Introduction

Violet light (VL) is a wavelength of natural light that is being lost from modern urban society, especially for people who spend most of their lives indoors. In this context, we have previously reported a systematic review on the importance of exposure to natural light for the mental health of people [1]. We have recently investigated the antidepressant effects of VL in an exploratory sham-controlled crossover randomized controlled trial (RCT) using violet light and reported that VL at 360–400 nm wavelength irradiation significantly improved depressive symptoms assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) in patients with mild depression [2]. Light therapy is known to be effective in reducing depres-

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sive symptoms, and one of the therapeutic mechanisms may be that light stimulation remediates sleep rhythms, which in turn may lead to improvement in depressive symptoms [3]. In our recent intervention study of VL irradiation for mild depression, in addition to specific improvement in depressive symptoms with VL, we also observed non-specific improvement in sleep symptoms as assessed by the Pittsburgh Sleep Quality Index (PSQI) [2].

On the other hand, voice-based assessment has gained attention as a non-invasive and simple method for evaluating depressive symptomatology. Nevertheless, despite growing interest, the external validation of voice-derived biomarkers remains limited, and their generalizability across clinical populations and recording environments has yet to be firmly established. Accordingly, their use in clinical or research settings should be interpreted cautiously until broader validation is achieved.

We recently investigated alterations in voice measures following bilateral transcranial magnetic stimulation (TMS) intervention in patients with treatment-resistant depression and found that changes in voice measures were significantly associated with improvements in depressive symptoms, executive function, and sleep condition following TMS intervention [4].

The objective of this sub-analysis study, derived from the original RCT study, was to investigate the relationship between voice measure indices and clinical measures before and after intervention with active vs. sham VL irradiation. In this study, we hypothesized that (1) VL irradiation of patients with depression may significantly improve voice indices as part of the manifestation of antidepressant effect. Furthermore, we hypothesized that (2) there may be a clinical correlation between the antidepressant effect of VL irradiation and voice indices. We also hypothesized that (3) voice indices may have some relationship with changes in sleep condition and cognitive function, in addition to the antidepressant effect.

2. Materials and Methods

2.1 Study Design and Participants

In this study, voice data collected in a sham-controlled, double-blind, randomized, crossover study of VL irradiation for major depressive disorder (MDD) (jRCTs032210260; https://jrct.mhlw.go.jp/latest-detail/jRCTs032210260; Clinical trial registration date: August 19, 2021) were analyzed in an exploratory manner to evaluate differences in changes in voice indices and their relationship to clinical symptoms after active vs. sham VL irradiation. Recruitment took place at the Shinjuku-Yoyogi Mental Lab Clinic and included Asian Japanese outpatients (ages 20–74) diagnosed with MDD as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. The eligibility criteria for participants included a MADRS score of 15–19 and the ability to use research equipment without ultraviolet-protective or colored lenses for three hours. Exclusion criteria encompassed cerebral organic diseases, seizure history, non-MDD psychiatric diagnoses, recent psychotherapy, mental instability, high suicide risk, severe or unstable physical conditions, significant cataracts, recent ophthalmic surgery, retinal abnormalities, and pregnancy or lactation.

2.2 Outcome Measures

In this subanalysis, the scores in the MADRS [5], the Hamilton Rating Scale for Depression–17-item (HAM-D17) [6], the Japanese version of the Quick Inventory of Depressive Symptomatology (QIDS-J) [7], the Japanese version of the Montreal Cognitive Assessment (MoCA-J) [8], the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) [9], and Beck Scale for Suicide Ideation (BSS) [10] before and after wearing the active and sham VL goggles for 4 weeks were assessed.

2.3 Voice Recording and Vitality Indices

The voice was recorded in a quiet room at the Shinjuku-Yoyogi Mental Lab Clinic before and after the VL intervention. Voice recordings were obtained in a quiet room, with each session lasting approximately 30 seconds, ensuring a controlled acoustic environment suitable for standardized phonetic analysis. They were recorded with a pin microphone (ME52W, Olympus, Tokyo, Japan) attached to the front of the chest, approximately 10 cm below the participant's mouth [11,12], using a portable recorder R-26 (Roland, Shizuoka, Japan) at a sampling rate of 96,000 Hz, 24-bit quantization, and in linear PCM format. Participants were instructed to read a 7-line Japanese phrase at natural speed; 6 lines of the phrase were selected from the 17-line phrase as described in a previous study [12,13,14] and one line of sustained vowel was added. The recorded voice data were converted into the linear PCM format at a sampling rate of 11,025 Hz, 16-bit quantization to comply with the specification of the analyzing application [12,15]. The voice indices were analyzed and extracted from the recorded voice data at the Laboratory for Voice Analysis and Measurement of Pathophysiology, Graduate School of Engineering, The University of Tokyo [16].

In this study, a voice-derived index termed *vitality* was computed for each participant. Two complementary indices were extracted: vitality-all, which quantified vitality across the entire voice-recording segment, and vitality-depression, which specifically evaluated the portion of the voice task involving the reading of positively valenced words. The latter index has been proposed as a more sensitive marker of depressive pathology, as positive-emotion prosody and the ability to produce positively valenced vocal expressions are known to be selectively impaired in depression [16,17,18,19,20,21].

Vitality indices were derived from frame-wise sound pressure change acceleration. For each recording, the amplitude envelope $A(t)$was extracted and smoothed, and vi-

tality was defined as the absolute value of the second-order temporal derivative of the envelope:

$$\text{Vitality}(t) = \left| \frac{d^2 A(t)}{dt^2} \right|.$$

Vitality-all was computed as the mean of Vitality(t) across all frames of the recording:

$$\text{Vitality}_{\text{all}} = \frac{1}{T} \sum_{t=1}^{T} \left| \frac{d^2 A(t)}{dt^2} \right|.$$

Vitality-depression was calculated using the same formulation but restricted to the subset of frames corresponding to positively valenced words:

$$\text{Vitality}_{\text{depression}} = \frac{1}{N} \sum_{t \in \mathcal{P}} \left| \frac{d^2 A(t)}{dt^2} \right|,$$

where $\mathcal{P}$ denotes the set of frames belonging to the positive-valence reading segment. Both indices typically range from 0 to approximately 1.0 in clinical recordings, with higher values indicating greater vocal energy and acceleration. Lower vitality-depression values reflect reduced positive-emotion prosody, whereas higher values indicate more preserved affective vocal expression. These mathematical definitions and interpretive directions are provided to enhance reproducibility and transparency.

Accordingly, vitality-depression was designated as the primary outcome measure post hoc, with vitality-all treated as a secondary exploratory endpoint in this subanalysis.

2.4 Statistical Analysis

Statistical analyses were performed using Python (version 3.13.5; Python Software Foundation, Wilmington, Delaware, USA) with the statsmodels package (version 0.14.6). In this sub-analysis, the original crossover design was restructured into a repeated-measures framework in which each participant contributed pre- and post-intervention measurements for both active and sham VL irradiation periods. To appropriately account for within-subject dependency, linear mixed-effects models with subject-specific random intercepts were employed.

For each vitality index, the model included time (pre vs. post) as a within-subject factor, intervention (active vs. sham) as a within-subject factor, and their interaction as the primary effect of interest. Sex and age were incorporated as covariates.

Because these evaluations were conducted as a post hoc sub-analysis, to control formultiple testing, exploratory analyses involving multiple voice-derived vitality indices, including correlation analyses and multiple regression models, were adjusted using the Benjamini-Hochberg false discovery rate (FDR) procedure. The primary mixed-effects model evaluating the intervention × time interaction for vitality-depression was not adjusted for multiple comparisons and is reported using unadjusted *p*-values. FDR correction was applied only to families of exploratory secondary analyses. Adjusted *p*-values are reported throughout the Results section, with statistical significance maintained after correction.

Although the parent RCT employed a crossover design, period, sequence, and carryover effects were not modeled in this subanalysis. The original trial intentionally incorporated a one-month washout interval to minimize potential carryover effects, and the parent RCT demonstrated that sequence effects were statistically negligible. Given these design features and the exploratory nature of the present analysis, we adopted a simplified repeated-measures framework without including crossover-specific terms. This approach is now explicitly acknowledged as a methodological limitation.

Baseline measurements shown in Table 1 represent values obtained at the beginning of each crossover period. Because these measurements reflect two distinct period starts, period and order effects could potentially influence paired comparisons between active- and sham-period baselines. This possibility is acknowledged as a methodological limitation of the present subanalysis.

In addition, a multiple regression analysis was conducted to examine associations between vitality indices and sleep improvement. The dependent variable was defined as the percentage change in Pittsburgh Sleep Quality Index (PSQI) score from pre- to post-intervention. The percentage change in PSQI score was calculated as [(Post-intervention PSQI – Pre-intervention PSQI) / Pre-intervention PSQI] × 100, such that negative values indicate improvement in sleep quality and positive values indicate worsening sleep quality. For this exploratory analysis, the dataset was structured at the participant-period level, such that each participant could contribute up to two observations corresponding to the active VL and sham VL intervention periods. Consequently, the regression dataset included repeated observations from the same participants. This regression analysis was performed as an exploratory ordinary least-squares model and did not explicitly incorporate participant-level random effects or clustered variance estimation. Accordingly, the findings should be interpreted as exploratory and hypothesis-generating.

For all models, raw coefficients (β) and standardized coefficients (standardized β) were reported. All estimates are presented with standard errors (SE) and 95% confidence intervals (95% CI). Marginal and conditional R^2 values were used to quantify model fit, and partial eta squared values (ηp^2) were computed using ANOVA decomposition to estimate effect sizes for the interaction term.

Table 1. Baseline demographic and clinical characteristics of the participants.

Characteristics (n = 64)	Values	Min to Max
Age, years (SD)	44.7 (±10.1)	20 to 62
Female (n, [%])	31 [48.4]	
MADRS score	active: 16.5 (±1.5) sham: 16.5 (±1.4) t_{63} = 0.284, p = 0.778	15 to 19 15 to 19
Vitality-all	active: 0.45 (±0.07) sham: 0.45 (±0.09) t_{63} = –0.189, p = 0.851	0.29 to 0.63 0.26 to 0.75
Vitality-depression	active: 0.42 (±0.09) sham: 0.46 (±0.12) t_{63} = 1.887, p = 0.064	0.19 to 0.68 0.20 to 0.79

Footnotes: min, minimum; max, maximum; SD, standard deviation; NA, not applicable; MADRS, Montgomery–Åsberg Depression Rating Scale.

Exploratory correlation analyses underwent FDR correction, and adjusted p-values are reported in the Results section.

Additionally, because the same participants underwent both active and sham VL irradiation, the correlation coefficients obtained for the two conditions represent dependent correlations. To appropriately account for the paired nature of the data, we additionally performed a formal comparison of the two correlations. Fisher's r-to-z transformation was applied to convert the correlation coefficients into z scores, and Steiger's Z test was used to evaluate whether the correlations differed significantly.

2.5 Sample Size Justification

The sample size for the original randomized crossover trial (jRCTs032210260), from which the present subanalysis was derived, was determined a priori based on effect sizes reported in prior light-therapy literature. Randomized trials of bright-light therapy have consistently demonstrated moderate antidepressant effects, with Cohen's d typically ranging from 0.5 to 0.8 [22,23]. These studies provided the initial external benchmark for estimating the expected magnitude of VL-related changes in depressive symptoms.

Based on these historical external data, the initial sample size calculation for the parent RCT was designed to detect a moderate-to-large effect size (Cohen's d ≈ 0.63, reflecting the midpoint of these external benchmarks). Using this estimated effect size, a two-sided α = 0.05, and a statistical power of 0.80, the minimum required sample size for the parent RCT was estimated to be 54 participants. To accommodate an anticipated dropout rate and to ensure sufficient statistical power, the target enrollment for the parent RCT was set at 70 participants, consistent with the trial registration (jRCTs032210260). Seventy participants were enrolled in the parent trial. The present study represents a prespecified secondary analysis of voice recordings obtained during the parent trial and therefore included only participants with usable voice data. Consequently, 64 participants were included in the final voice sub-analysis. The participant selection process is illustrated in **Supplementary Fig. 1**.

Because the present study represents an exploratory secondary analysis of this locked crossover dataset, no additional sample size recalculation was performed for voice-derived vitality indices or sleep-related outcomes. These analyses should therefore be interpreted as strictly hypothesis-generating.

3. Results

The demographic information of the participants included in this sub-analysis study is shown in Table 1.

Vitality-depression was designated as the primary outcome. The linear mixed-effects model revealed a significant intervention × time interaction (β = 0.066, SE = 0.023, 95% CI [0.021, 0.112], p = 0.004), indicating that the pre-to-post increase in depression-related vitality index (vitality-depression) during active VL was substantially greater than that observed during sham VL. Standardized coefficients supported this pattern, demonstrating a medium-to-large interaction effect (standardized β = 0.585, 95% CI [0.192, 0.978], p = 0.004).

A significant main effect of time was also observed (β = –0.050, SE = 0.016, 95% CI [–0.081, –0.019], p = 0.002), reflecting overall improvement across the intervention period. The main effect of intervention did not reach significance (β = –0.027, SE = 0.016, 95% CI [–0.058, 0.005], p = 0.096). Sex was not associated with vitality-depression (β = –0.004, SE = 0.015, 95% CI [–0.034, 0.026], p = 0.783), whereas age showed a significant positive association (β = 0.003, SE = 0.001, 95% CI [0.001, 0.005], p = 0.003), suggesting slightly higher vitality-depression scores among older participants.

Model fit indices indicated that fixed effects explained 20.7% of the variance (marginal $R^2 = 0.207$), while the full model including random intercepts explained 42.6% of the variance (conditional $R^2 = 0.426$). Partial eta squared values demonstrated a small-to-medium interaction effect ($\eta p^2 = 0.0216$).

Overall, these findings indicate a statistically significant but modest improvement in depression-related vitality (vitality-depression) during active VL, consistent with the small-to-medium partial eta squared effect size and the exploratory nature of this subanalysis.

On the other hand, vitality-all was analyzed as an exploratory secondary outcome. The intervention × time interaction was not statistically significant (β = 0.024, SE = 0.017, 95% CI [–0.010, 0.058], $p = 0.161$), indicating that the pre-to-post change during active VL did not differ significantly from that during sham VL. Standardized analyses yielded a similar non-significant pattern (β = 0.266, $p = 0.161$).

A significant main effect of time was observed (β = –0.026, SE = 0.012, 95% CI [–0.049, –0.003], $p = 0.030$), suggesting modest overall improvement across the intervention period. The main effect of intervention was not statistically significant (β = –0.021, SE = 0.012, 95% CI [–0.045, 0.003], $p = 0.073$). Sex and age were significant covariates: vitality-all was modestly lower in males (β = –0.032, SE = 0.016, 95% CI [–0.063, –0.001], $p = 0.044$) and slightly higher with increasing age (β = 0.002, SE = 0.001, 95% CI [0.001, 0.004], $p = 0.009$).

Taken together, vitality-all showed a trend toward improvement, but the magnitude of the active VL effect was small-to-moderate and did not reach statistical significance. Given the exploratory nature of this outcome and the application of FDR correction, these findings should be interpreted with particular caution.

Correlation analyses for the primary outcome, vitality-depression, revealed no significant associations with clinical symptom measures, including MADRS, HAM-D17, QIDS-J, or MoCA-J scores, in either the active or sham VL periods. Likewise, changes in sleep symptoms assessed by the PSQI were not significantly correlated with vitality-depression in either condition.

To further examine the combined baseline predictors of sleep improvement, a multiple regression analysis was conducted with the percentage change in the PSQI score as the dependent variable. After adjusting for demographic covariates (age and sex), baseline sleep severity (baseline PSQI), and the intervention condition, the multivariate model demonstrated a significant overall fit, explaining 13.7% of the total variance (Model $R^2 = 0.137$, adjusted $R^2 = 0.094$, $F(6, 121) = 3.199$, $p = 0.00597$).

Crucially, Cwithin this simultaneous framework, baseline vitality-all emerged as a significant negative predictor of the percentage change in PSQI score (β = –105.9521, SE = 36.688, 95% CI [–178.586, –33.319], raw $p = 0.005$, FDR-adjusted $p < 0.05$), indicating that higher baseline vitality-all was associated with greater percentage sleep improvement. Conversely, baseline vitality-depression was identified as a significant positive predictor of the percentage change in (β = 91.6568, SE = 27.314, 95% CI [36.581, 145.732], raw $p = 0.001$, FDR-adjusted $p < 0.01$), indicating that higher baseline vitality-depression was associated with less sleep improvement or potential worsening of sleep quality.

Among the covariates, sex demonstrated a nominal association with the outcome based on its uncorrected p-value (β = –9.9171, SE = 4.779, 95% CI [–19.378, –0.457], raw $p = 0.040$), but it did not survive strict FDR multiple comparison correction (FDR-adjusted $p > 0.05$). None of the other variables reached statistical significance, including baseline PSQI score (β = –1.2046, SE = 0.651, raw $p = 0.067$), the intervention condition (β = –1.7721, SE = 4.524, raw $p = 0.696$), and age (β = –0.2878, SE = 0.240, raw $p = 0.232$).

Moreover, in the subanalyses, the percent change in sleep symptoms (PSQI) showed a significant negative correlation with baseline vitality-all in the active VL condition (FDR-adjusted $p = 0.043$, r = –0.254, n = 64). This analysis used baseline vitality-all as the predictor and the percentage change in PSQI as the outcome variable in the statistical model, indicating that a higher baseline vitality-all score was statistically related to a greater percentage reduction in PSQI scores (i.e., greater improvement in sleep quality) following active VL irradiation. No such relationship was observed in the sham condition (FDR-adjusted $p = 0.757$, r = 0.040, n = 64) (Fig. 1). Importantly, a formal paired comparison of these two dependent correlations using Fisher's r-to-z transformation and Steiger's Z test indicated that the difference between the active and sham correlations did not reach statistical significance (Z = –1.65, $p = 0.098$), suggesting only a marginal trend toward a condition-specific difference.

Vitality-depression was designated as the primary outcome measure for the present voice-analysis study because of its conceptual relevance to depressive symptomatology. Consistent with the Statistical Analysis section, the primary intervention × time interaction analysis for vitality-depression was reported using unadjusted p-values, whereas exploratory secondary analyses involving multiple voice-derived vitality measures were subjected to Benjamini-Hochberg FDR correction.

4. Discussion

This study was conducted as a subanalysis based on the crossover RCT of VL interventions for patients with depression. The results showed that the change in the voice "vitality" index measured before and after the VL intervention was significantly different between the active and sham conditions, and that the active VL condition showed a significant improvement in the voice vitality index of patients with depression compared to the sham VL condition. These

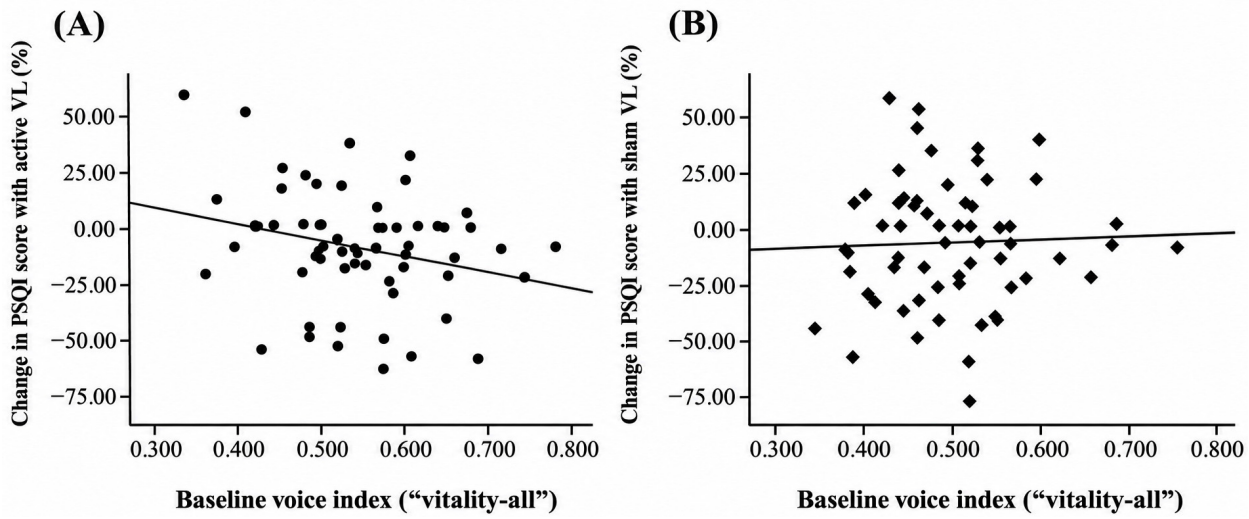


Fig. 1. Association between baseline vitality-all and percentage change in PSQI. Legend: Scatter plots depict the relationship between baseline vitality-all (predictor) and the percentage change in Pittsburgh Sleep Quality Index (PSQI) (outcome) following 4 weeks of active (left) and sham (right) VL stimulation. Percentage change in PSQI was calculated as ((Post-intervention PSQI – Pre-intervention PSQI) / Pre-intervention PSQI) × 100. Negative values indicate reduced PSQI scores and therefore improved sleep quality, whereas positive values indicate increased PSQI scores and therefore worsened sleep quality. A significant negative correlation was observed in the active condition (FDR-adjusted $p = 0.043$, r = –0.254, n = 64), indicating that higher pre-intervention overall vocal energy was associated with a greater subsequent percentage reduction in PSQI score (i.e., greater improvement in sleep quality). No significant association was detected in the sham condition (FDR-adjusted $p = 0.757$, r = 0.040, n = 64). The paired correlation comparison using Fisher's r-to-z transformation and Steiger's Z test indicated that the difference between the two correlations was not statistically significant (Z = –1.65, $p = 0.098$).

findings suggest potential clinical relevance, although the novelty of the vitality indices warrants cautious interpretation. Given the exploratory nature of these indices, their clinical interpretability requires further validation.

Importantly, vitality-all and vitality-depression exhibited opposite directions in their associations with the percentage change in PSQI score in the multivariate model, despite the lack of a significant univariate correlation for vitality-depression. This divergence suggests that the indices may be associated with different aspects of vocal expression; furthermore, the emergence of vitality-depression as a significant positive predictor of PSQI percentage change only in the regression model may indicate a statistical suppressor effect, where controlling for global vocal energy (vitality-all) and baseline sleep severity unmasks a distinct association in which higher baseline positive-emotion prosody (vitality-depression) is linked to less sleep improvement (or a relative worsening of PSQI score), whereas higher global vocal energy (vitality-all) is associated with greater sleep improvement. However, the underlying mechanisms cannot be inferred from the present correlational data. Vitality-all may correlate with global arousal or psychomotor activation, whereas vitality-depression may be associated with positively valenced prosody, but these interpretations should be viewed cautiously. These interpretations remain preliminary and require replication in independent cohorts.

Exploratory analyses examining relationships between vitality indices and clinical outcomes revealed that baseline vitality-all, not vitality-depression, was associated with the percentage change in sleep symptoms (PSQI) during active VL irradiation. Although no such significant association was observed in the sham condition, the statistical difference between the two correlation coefficients was not significant, indicating that a definitive condition-specific association cannot be established. Thus, vitality-all may serve as a statistical indicator associated with sleep-related changes. Furthermore, in the multiple regression analysis, baseline vitality-all and vitality-depression demonstrated significant negative and positive associations with the percentage change in PSQI score, respectively—indicating that higher baseline vitality-all was associated with greater sleep improvement, whereas higher baseline vitality-depression was associated with less sleep improvement or potential worsening of sleep quality. While counterintuitive given the univariate correlations, this divergence statistically points to a suppressor effect. Controlling for global psychomotor/vocal energy (vitality-all) appears to unmask an inverse relationship between depression-related vocal features (vitality-depression) and sleep improvement. Nevertheless, because these relationships are derived from an exploratory regression model, they do not imply causality and require validation in independent cohorts.

Our recent VL intervention trial demonstrated significant improvement in MADRS scores with active VL stimulation, indicating that VL may have antidepressant effects [2]. In this subanalysis, voice data were collected before and after VL intervention, and vitality indices were extracted. Prior studies have suggested that voice-derived measures may reflect depressive symptoms and may be associated with treatment-related changes in mood, sleep, and cognition [4,13,14,16,17,24]. Thus, the present findings may link VL-related antidepressant effects with voice-based markers of mood and sleep.

Specifically, active VL irradiation was associated with increases in voice vitality indices, while in the simultaneous multivariate regression model, higher baseline vitality-all scores were associated with greater percentage sleep improvement, whereas higher baseline vitality-depression scores were associated with less sleep improvement. These findings represent associations rather than causal effects. Nevertheless, these indices remain exploratory, and broader validation across diverse populations and recording environments is required.

From a mechanistic perspective, vitality-depression may reflect VL-associated changes in affective prosody; however, this interpretation is correlational, and any involvement of neuropsin (OPN5)-related or circadian–limbic pathways remains hypothetical. These mechanistic explanations are speculative and should be interpreted cautiously. The current study was not designed to directly test mechanistic pathways, and therefore such interpretations should be considered preliminary. In contrast, vitality-all may reflect broader psychomotor or autonomic activation, although this interpretation is tentative and requires further empirical validation. Overall, mechanistic interpretations remain hypothetical because the present study did not directly evaluate biological pathways.

Hence, VL irradiation was associated with increases in voice-derived vitality indices, and baseline vitality-all was associated with sleep improvement. These associations do not establish causal pathways, and should be interpreted as correlational rather than causal.

Regarding the underlying biology, light therapy is known to alleviate depressive and sleep symptoms potentially by normalizing circadian rhythms and modulating neural circuits involved in emotional regulation. Prior literature suggests that light stimulation may influence biological pathways related to OPN5 signaling, circadian pacemaking via the suprachiasmatic nucleus, and emotional processing via the lateral habenula [25,26,27,28,29,30]. However, because the present study did not directly evaluate molecular, neurophysiological, or imaging pathways, these specific circadian–limbic mechanisms remain strictly tentative. Future research using biological or imaging modalities is required to determine whether VL irradiation directly engages these systems.

Greater emphasis is placed on the validity, reproducibility, and clinical interpretability of the voice-derived vitality indices. Their reproducibility has been demonstrated only in limited settings, and broader evaluation, including test–retest reliability and robustness across environments, is required.

Clinically, vitality-depression and vitality-all may capture distinct aspects of vocal expression, but their interpretability requires further investigation, particularly regarding their relationship to established markers of depressive severity, psychomotor change, or sleep physiology. Thus, while promising, these indices should currently be regarded as preliminary biomarkers requiring extensive validation.

To our knowledge, this is the first study to investigate the relationship between changes in sleep-related measures and voice features before and after the VL intervention in individuals with mild depressive symptoms, thereby providing preliminary evidence of an association between sleep improvement and voice-based biomarkers in this population.

Limitations

This study has several limitations. First, this investigation represents a secondary analysis of a previously conducted RCT, and the analytic framework, sample characteristics, and intervention parameters were determined by the original study design rather than optimized specifically for validating voice-derived vitality indices. In addition, the vitality indices themselves remain exploratory biomarkers, and their external validity has not yet been firmly established. Therefore, the present findings should be interpreted with caution.

Although the parent study employed a crossover design, the present subanalysis did not model period, sequence, or carryover effects. The original RCT incorporated a one-month washout period to minimize potential carryover influences, and sequence effects were statistically negligible. Based on these considerations, we adopted a simplified repeated-measures analytic framework. We acknowledge this as a methodological limitation of the current subanalysis.

To strengthen future research, prospective studies specifically designed to evaluate and validate vitality indices, including larger validation cohorts, repeated longitudinal measurements, standardized recording protocols, objective sleep assessments, and comparisons with established voice biomarkers, will be essential to substantiate and extend the current exploratory observations. Moreover, although the sham condition involved only one-tenth of the VL intensity used in the active intervention, minimal VL exposure was still present, raising the theoretical possibility of residual biological effects. This represents an additional limitation, and future wavelength- and dose-controlled studies will be necessary to fully disentangle VL-specific effects from general light stimulation.

Second, since the RCT with the VL intervention included only patients with mild depression, the pathophysiology of patients with more severe depression may not be reflected in the results of the study. Therefore, future clinical trials should incorporate patients with more severe depression.

Third, because the previous RCT study of VL was an exploratory phase of interventional study, the intensity of the VL intervention may have been relatively weak to produce robust antidepressant and sleep improvement effects. Furthermore, the exploratory regression analysis examining predictors of sleep improvement was performed using participant-period observations derived from the crossover design. Although this approach increased the number of available observations, repeated observations originating from the same participant were not explicitly modeled within the regression framework. Therefore, the independence assumption may not have been fully satisfied. Future studies should consider mixed-effects regression models, generalized estimating equations, or participant-clustered standard errors to more rigorously account for within-subject dependency. In the future, it may be necessary to extend the daily wearing time of the VL irradiation goggles and the duration of the intervention with a larger sample size.

5. Conclusions

This study demonstrated that violet light irradiation significantly improves the depression-specific voice vitality index (vitality-depression) in patients with depression, whereas no significant interaction effect was observed for the overall vitality index (vitality-all). Notably, higher baseline vitality-all was statistically associated with greater percentage improvement in sleep symptoms (i.e., a greater percentage reduction in PSQI score) in univariate analysis under the active condition, though this correlation did not differ significantly from that of the sham condition, and multivariate regression further revealed divergent associations between the two vitality indices and sleep outcomes. These findings suggest that specific vocal features may be statistically associated with changes in sleep quality and highlight the potential utility of the depression-specific voice index as a non-invasive, scalable biomarker for monitoring treatment response in light-based neuromodulation.

Abbreviations

BSS, Beck Scale for Suicide Ideation; HAM-D17, Hamilton Rating Scale for Depression–17-item; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MoCA-J, Montreal Cognitive Assessment–Japanese; OPN5, neuropsin; PSQI, Pittsburgh Sleep Quality Index; QIDS-J, Quick Inventory of Depressive Symptomatology–a 16-item self-report, Japanese version; RCT, randomized controlled trial; SD, standard deviation; TMS, transcranial magnetic stimulation; VL, violet light.

Availability of Data and Materials

Data supporting the findings of this study are available from the corresponding author upon reasonable request. The specific data and associated documents shared depend on the individual request's nature and will be documented in a formal data-sharing agreement.

Author Contributions

Conceptualization: KT; SM; and YN. Data curation: MN. Formal analysis: MN. Funding acquisition: KT. Investigation: YN, RK and KT. Methodology: KT; SM; and ST. Study design: MH. Project administration: YN and MH. Resources: KT and RK. Supervision: YN, KT and MM. Validation: YN. Visualization: YN. Interpretation of the findings: MH, RK and MM. Writing – original draft: YN. Writing – review & editing: MN; MH; RK; SM; ST; MM; and KT. KT's contributions reflect his role as an individual investigator and co-author and were performed independently of any corporate role at Tsubota Laboratory, Inc. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The protocol received approval from the Certified Review Board of the Hattori Clinic (CRB3180027) and was registered in the Japan Registry of Clinical Trials (jRCTs032210260). The study adhered to ethical guidelines including the Clinical Trials Act in Japan and complied with the Declaration of Helsinki. All participants provided written informed consent.

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Conflicts of Interest

Given his role as the Editorial Board member and the Guest Editor, Yoshihiro Noda had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the edito-

rial process for this article was delegated to Bettina Platt. Kazuo Tsubota is the founder, Chief Executive Officer, and a shareholder of Tsubota Laboratory, Inc. However, Tsubota Laboratory, Inc. had no role in the study design, data collection, data analysis, data interpretation, manuscript preparation, or the decision to submit the manuscript for publication. KT contributed to this study in his capacity as an academic investigator and co-author. The remaining authors declare no competing interests.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/JIN55734.

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