学位論文（博士）

Effects of Nature-Based Visual Stimuli on Mood and Neurophysiology in Individuals with Depressive and Anxiety Disorders

(自然環境の視覚刺激が抑うつ障害および不安障害の気分と神経生理に及ぼす影響)

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令和６年１２月

学位論文の関連論文の研究背景及び要旨

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〔題名〕
Mood and physiological effects of visual stimulation with images of the natural environment in individuals with depressive and anxiety disorders
（自然環境画像による視覚刺激が抑うつ障害者と不安障害者にもたらす気分向上効果と生理的変化）
Journal of Affective Disorders Vol.356 P.257-266　（令和 6 年 7 月掲載）

〔研究背景〕
抑うつ障害や不安障害の非薬物療法として自然療法が注目されているが、患者を対象として、その効果を明らかにした研究例は少ない。本研究では、我々が健常者で確認した気分向上効果を有する自然環境画像の視覚刺激が、抑うつ障害や不安障害の患者にもたらす効果と生理的変化を明らかにすることを目的とした。

〔要旨〕
【方法】2022 年 5 月から 2023 年 1 月までの間に精神科外来を受診している患者で、精神疾患の診断･統計マニュアル 5 版(DSM-5)で抑うつ障害または不安障害と診断された 20 歳以上 65 歳未満の右利きの者それぞれ 30 名ずつ、計 60 名を対象とした。本研究は、ランダム化クロスオーバーデザインとし、研究対象者を①緑系の自然環境の画像による視覚刺激→対照介入となる人工環境の画像による視覚刺激の介入順序、②対照介入となる人工環境の画像による視覚刺激→緑系の自然環境の画像による視覚刺激の介入順序のいずれかに無作為に割り付け、それぞれの順序に従い介入を行った(**図 1**)。刺激時間は 3 分間で、27 インチの高解像度ディスプレイを用いて、一枚の画像を 15 秒間、それぞれ計 12 枚（合計 3 分間）を提示した。介入中は 2 チャンネル Near-infrared spectroscopy(NIRS)を用いて眼窩前頭皮質をターゲットとして脳活動を反映する酸素化ヘモグロビン濃度を測定し、速度脈波測定システム「アルテット C」を用いて自律神経活動を反映する心拍変動を測定した。介入後の気分評価には、我々が開発した Chen-HAgiwara Mood Test（CHAMT）を用いた。このテストは、感情と覚醒の 2 次元理論に基づくもので、感情価のみを評価する快、感情価と覚醒の組み合わせから生じるリラックス（正の感情価と負の覚醒）および活気（正の感情価と正の覚醒）の 3 項目からなる。複数回答による干渉を避けるため、連続的な 10 cm

視覚アナログスケールを使用し、左端からマークまでの距離（mm）を気分尺度（0～100）として数値化した。2 回目の介入終了後には抑うつ症状を評価する BDI-Ⅱや不安症状を評価する STAI などの心理尺度検査を行った。

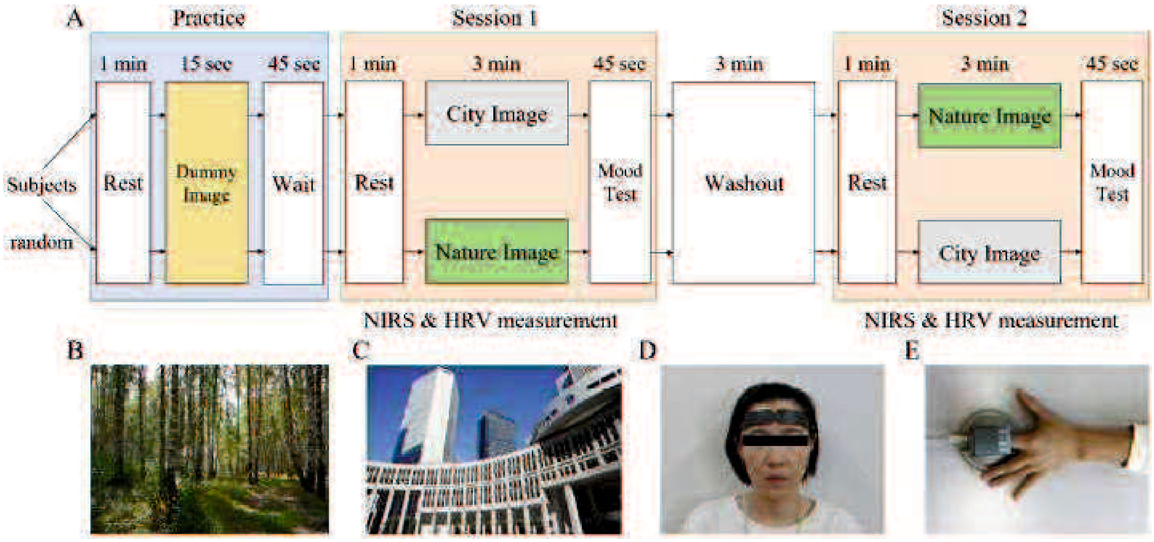

図 1 研究プロトコル、刺激に使用した写真、測定装置の写真。A. 全体のフローチャート。B. 緑豊かな自然のイメージの例。C. 都市画像の例。D. 近赤外分光法（NIRS）プローブ装着のイメージ図。E.心拍変動(HRV)の評価に使用したアルテット C 装着のイメージ図。

【結果】

参加者の特徴：参加者の平均年齢は抑うつ障害で 47.4 歳（標準偏差、SD 9.5）、不安障害で 43.3 歳（SD 11.3）であった。性別では、抑うつ障害群は女性 17 名（56.7 %）、不安障害群は女性 22 名（73.3 %）であった。抑うつ障害群では、24 名（80.0 %）が大うつ病性障害であり、6 名（20.0 %）が持続性うつ病性障害であった。不安障害群では、4 人（13.3 %）が特定恐怖症、14 人（46.7 %）がパニック障害、5 人（16.7 %）が社交不安障害、5 人（16.7 %）が全般性不安障害、2 人（6.7 %）が特定不能の不安障害であった。

気分向上効果：抑うつ障害群と不安障害群ともに快、リラックス、活気のいずれも、対照介入の都市画像と比べて自然画像による視覚刺激後の方が有意に向上した(**図 2**)。

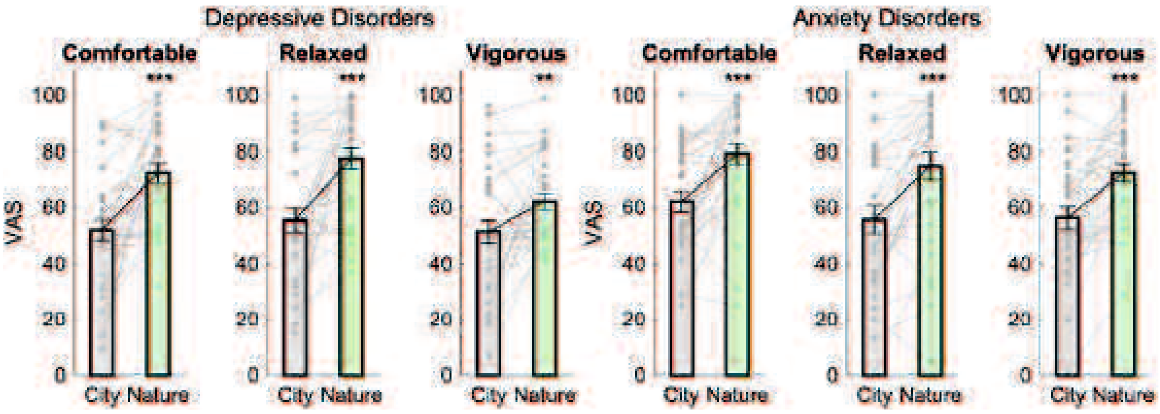

図 2 自然画像による視覚刺激が気分に及ぼす影響。

灰色が都市画像、緑色が自然画像の視覚刺激後の気分値を表す。左が抑うつ障害群の図で右が不安障害群の図。両群とも、自然画像からの視覚刺激ですべての気分項目で有意な気分改善効果が観察された。** $p < 0.01$, *** $p < 0.001$, paired t-test or Wilcoxon rank-sum test. VAS, visual analog scale。

眼窩前頭皮質酸素化ヘモグロビン濃度への影響：自然画像による眼窩前頭皮質酸素化ヘモグロビン濃度変化は、都市画像に比べて、抑うつ障害群では上昇したが、不安障害群では有意な変化はなかった(**図 3**)。

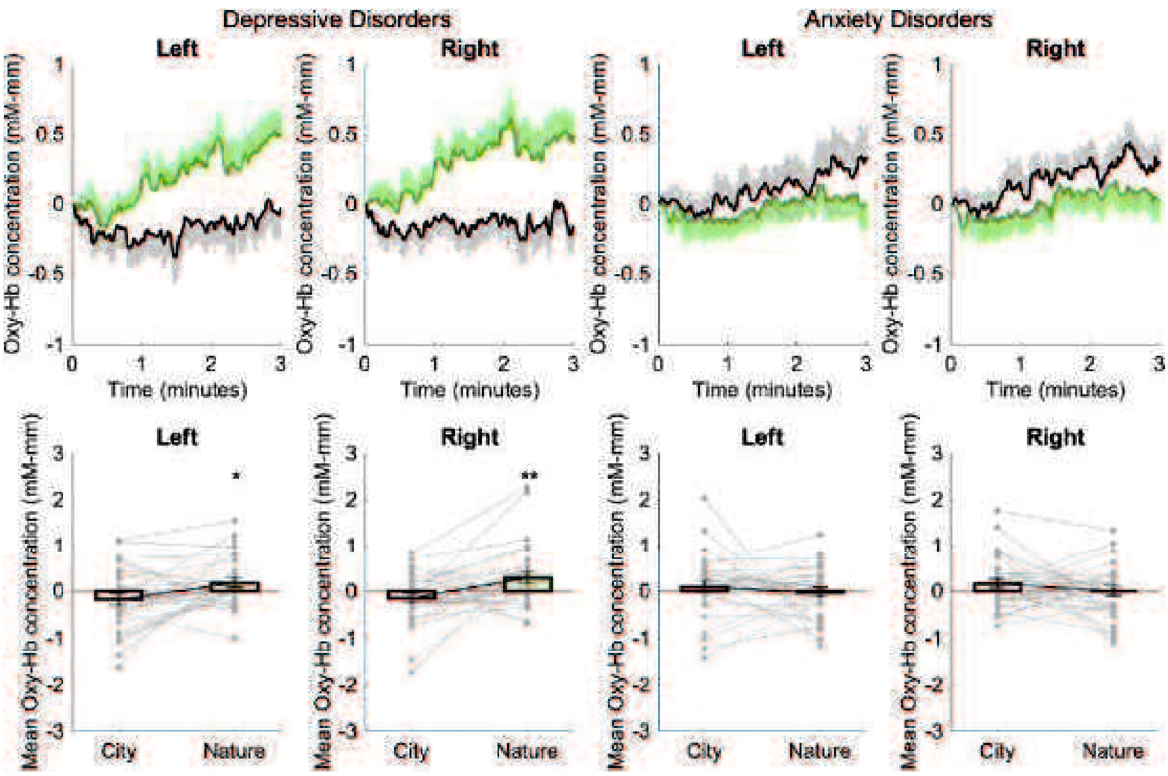

図 3 視覚刺激中の眼窩前頭皮質の酸素化ヘモグロビン濃度。

上図の緑と黒の線は、それぞれ自然（=緑）や都市（=黒）の各参加者の平均酸素 Hb 濃度の経時変化で、緑と黒の影は、標準誤差を表す。下図はそれぞれ 3 分間の平均値で緑が自然、灰色が都市を表す。抑うつ障害群では、自然画像による視覚刺激中に眼窩前頭皮質酸素化ヘモグロビン濃度の有意な上昇がみられた。不安障害群では、有意な変化はみられなかった。* $p < 0.05$、** $p < 0.01$。

しかし、不安障害群では、都市と比べて自然画像での眼窩前頭皮質酸素化ヘモグロビン濃度が低下するほど、気分向上効果が高まるという相関関係が認められた(**図 4**)。

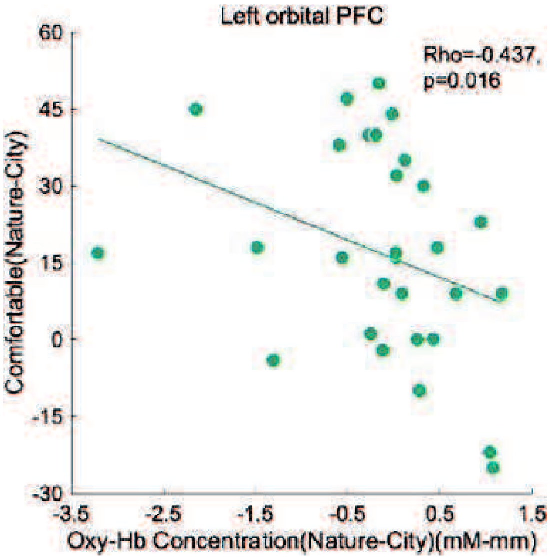

図 4 不安障害群の左眼窩前頭皮質 Oxy-Hb 濃度と気分の相関。
縦軸は自然画像による視覚刺激中の眼窩前頭皮質酸素化ヘモグロビンから対照である都市画像での酸素化ヘモグロビン濃度を引いた値。横軸は快の気分における自然画像による視覚刺激後の値から都市画像の値を引いた値。不安障害では、「自然ー都市」の左眼窩前頭皮質酸素化ヘモグロビン濃度の差と「自然ー都市」の快の気分値の差の間に統計学的に有意な負の相関(Rho=-0.437, p=0.016)が確認された。右では負の相関(Rho=-0.352, p=0.057)があったが統計学的に有意ではなかった。PFC、前頭前皮質。

心拍変動への影響：心拍変動では抑うつ障害群と不安障害群ともに有意な変化はなかった。

介入効果に対する抑うつ症状および不安症状の重症度の影響：抑うつ症状の重症度は介入効果に有意な影響を与えなかった(**図 5**)が、不安症状の亢進はより小さな気分増強効果と関連していた(**図 6**)。

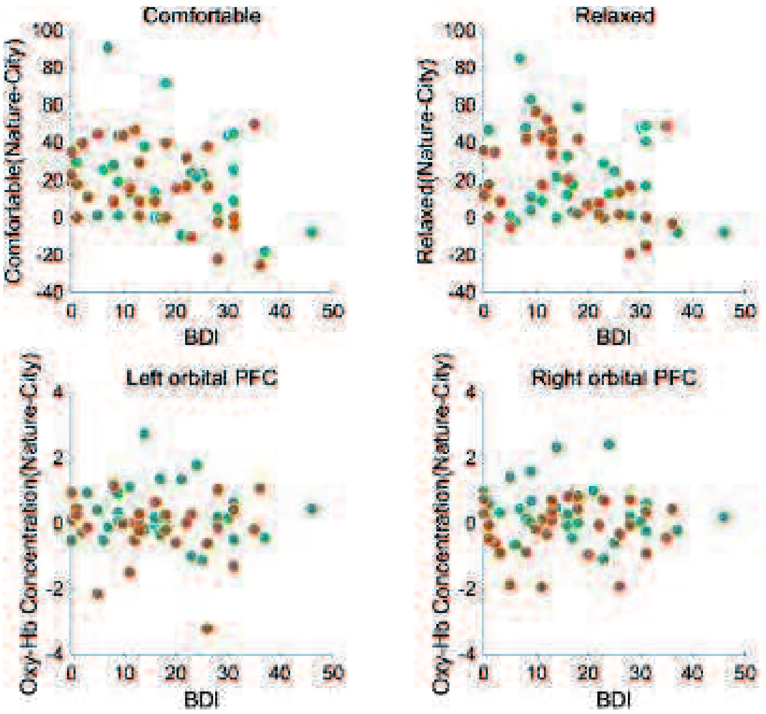

図 5 抑うつ症状（BDI）と気分の変化および自然画像による視覚刺激による眼窩前頭前野酸素化ヘモグロビン濃度の変化との関係。いずれも有意な相関はなかった。PFC、前頭前皮質；BDI、Beck Depression Inventory-II。

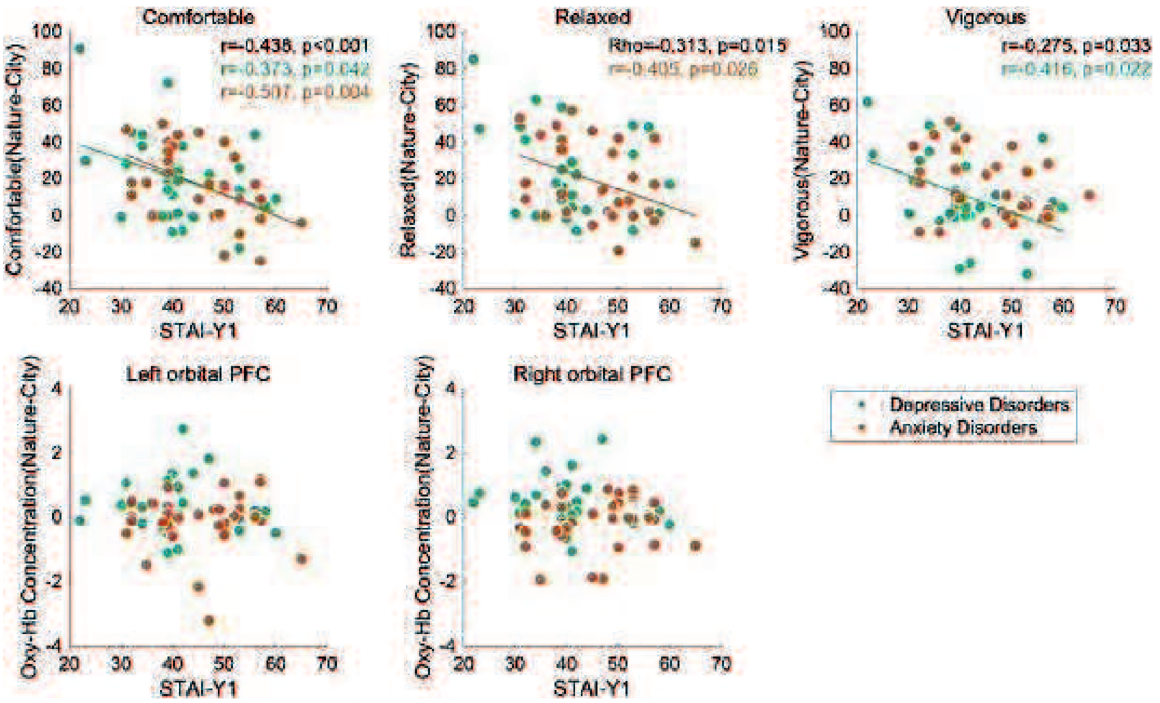

図 6 不安症状（STAI-Y1）と自然画像による視覚刺激による気分変化および眼窩前頭前野

酸素化ヘモグロビン濃度変化との関係。統計的に有意な相関（$p < 0.05$）を示した項目の結果を示す。 黒字は参加者全体、緑は抑うつ障害群、オレンジは不安障害群を表す。回帰直線は、その方向性を明確に視覚化するために、統計的有意に達した相関についてのみ示した。PFC、前頭前皮質；STAI-Y1、State-Trait Anxiety Inventory State Anxiety Subscale。

【考察】本研究において、自然画像の視覚刺激による生理的反応は抑うつ障害と不安障害では異なっていたが、共に健常者を対象とした先行研究と同様に気分向上効果がみられ自然画像による視覚刺激の有用性が確認できた。

我々の知る限り、本研究は自然画像の視覚刺激による抑うつ障害および不安障害の患者に対する気分向上効果と生理的反応を明らかにした初の報告であり、今後の患者の療養環境や自然療法の改良を検討する上で有用な報告と思われる。

Journal of Affective Disorders 356 (2024) 257–266

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Mood and physiological effects of visual stimulation with images of the natural environment in individuals with depressive and anxiety disorders

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ARTICLE INFO

Keywords:
Nature therapy
Mood
Prefrontal cortex
Near-infrared spectroscopy
Heart rate variability

ABSTRACT

Background: Nature therapies are gaining attention as non-pharmacological treatments for depressive and anxiety disorders, but research on their effectiveness in patients is limited. This study investigates the mood-improving effects of visual stimulation with natural environmental images in patients with depressive and anxiety disorders.
Methods: We conducted a randomized crossover comparison trial involving 60 right-handed adult participants with depressive or anxiety disorders and receiving outpatient treatment. Visual stimuli of natural environments consisted of green-themed nature images, while the control stimuli featured urban scenes dominated by buildings. The stimulation lasted for 3 min, during which orbital prefrontal brain activity was measured using a 2-channel Near-infrared Spectroscopy (NIRS) system, and heart rate variability was assessed using fingertip accelerated plethysmography.
Results: Mood enhancement effects were observed in both the depressive and anxiety disorder groups following visual stimulation with nature images. In the depression group, orbital prefrontal oxygenated hemoglobin concentration significantly increased after visual stimulation with nature images, while there were no significant changes in the anxiety group. However, in the anxiety group, a correlation was found between reduced orbital prefrontal oxygenated hemoglobin in response to nature images and increased mood-enhancement. Furthermore, the severity of depressive symptoms did not significantly affect the intervention effects, whereas heightened anxiety symptoms was associated with a smaller mood enhancement effect.
Discussion: Our study demonstrates the benefits of nature image stimulation for patients with depressive and anxiety disorders. Differential orbital prefrontal brain activity impacts notwithstanding, both conditions exhibited mood enhancement, affirming the value of nature image stimulation.

1. Introduction

Depressive and anxiety disorders are pervasive issues worldwide. According to a WHO survey, it is estimated that 4.4 % of the world population suffer from depressive disorders, while 3.6 % suffer from anxiety disorders (WHO, 2017). One of the main reasons for the prevalence of depressive and anxiety disorders is that many patients do not respond to current pharmacological treatments and are prone to relapse even after remission (Kessler and Bromet, 2013). The development of effective non-pharmacological treatments for depressive and anxiety disorders is an urgent issue.

In recent years, nature therapies, including forest therapy and horticultural therapy, have gained attention as non-pharmacological treatments. Nature therapy, involving activities like walking in the woods, observing natural landscapes, and interacting with plants (trees, flowers, etc.) through the senses, offers therapeutic healing effects (Chen, 2018; Chen and Nakagawa, 2018, 2019; Miyazaki, 2018; Song et al., 2016). Many studies report that nature therapy alleviates stress, improves mood, reduces depressive and anxious symptoms, and enhances cognitive function in healthy individuals (Song et al., 2016;

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https://doi.org/10.1016/j.jad.2024.04.025
Received 7 December 2023; Received in revised form 2 April 2024; Accepted 5 April 2024
Available online 7 April 2024

Hansen et al., 2017; Ross and Mason, 2017; Rosa et al., 2021). Interactions with nature have been shown to reduce activity in the prefrontal cortex (PFC, Bratman et al., 2015; Song et al., 2020) and the amygdala (Sudimac et al., 2022), and stimulate the parasympathetic nervous system (Jo et al., 2019a). There are also reports of reduced concentrations of stress hormones like cortisol and adrenaline (Li et al., 2008; Park et al., 2007; Sung et al., 2012). The prefrontal cortex and the amygdala are areas reported to have abnormal activity in depressive and anxiety disorders (Ho et al., 2020; McTeague et al., 2020; Mizzi et al., 2022). In studies involving clinical patients, improvements in mood have been reported in cases of depressive disorders by walking in a wooded park for 50 min (Berman et al., 2012) and experiencing a one-hour nature walk in urban parks (Watkins-Martin et al., 2022). For anxiety disorders, cross-sectional studies have reported a lower prevalence in areas abundant with plants (Maas et al., 2009; Hystad et al., 2019).

Recent studies have focused on understanding which features of natural stimuli bring about such healing effects and the physiological changes that occur in response. Studies have reported mood-improving effects from visual stimuli like images of forests, autumn leaves, and waterfalls (Song et al., 2018a; Jo et al., 2022a; Jo et al., 2022b), auditory stimuli such as the sound of forest streams or ambient sounds of a riverside in autumn (Jo et al., 2019a; Ochiai et al., 2023), and olfactory stimuli from dried cypress chips, essential oils extracted from cypress leaves, and the primary scent component of forests, α-pinene (Ikei et al., 2015a; Ikei et al., 2015b; Ikei et al., 2016). In our preliminary research on healthy individuals, we found that a 3-min visual stimulus of green natural environments improved feelings of pleasure and relaxation and observed a decrease in activation of the right orbital PFC (Yamashita et al., 2021).

Whether such visual contact with nature can bring therapeutic effects to patients with depressive or anxiety disorders remains unknown. If it does have mood-improving effects, it could lead to improvements in patient care environments and further development of nature therapy. This research aims to elucidate the effects and physiological changes of visual stimuli from natural environments, which we confirmed to have mood-improving effects in healthy individuals, on patients with depressive and anxiety disorders.

2. Methods

2.1. Participants

From May 2022 to January 2023, we enrolled 60 patients, 30 each with depressive disorder and anxiety disorder, who were visiting an outpatient psychiatric clinic. The distribution of depression severity among these participants, as assessed by BDI (Beck et al., 1996) was: 27 participants (45 %) exhibited minimal depression, 10 participants (16.7 %) had mild depression, 13 participants (21.7 %) showed moderate depression, and 10 participants (16.7 %) had severe depression. Regarding anxiety levels, evaluated using the STAI State Anxiety Subscale (Himeno et al., 2005), the severity distribution was: 4 participants (6.7 %) experienced minimal anxiety, 28 participants (46.7 %) mild anxiety, 13 participants (21.7 %) moderate anxiety, and 15 participants (25 %) severe anxiety. This sample size was deemed appropriate since a minimum of 27 subjects were required to detect an effect size of $d = 0.57$ using paired-test, as reported in our previous study conducted in healthy subjects (Yamashita et al., 2021), ensuring a power of 0.8 and an alpha of 0.05, two-sided.

Individuals who were currently attending a psychiatric clinic and met the specified inclusion criteria, while not fulfilling the exclusion criteria, were selected to participate in the study. The inclusion criteria were as follows: having been diagnosed with "Depressive Disorders" or "Anxiety Disorders" according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), aged between 20 and 64 years at the time of consent, no self-reported color vision impairment, visual acuity (including corrected vision) of 0.6 or higher or no hindrance in daily life (colored glasses not permitted), right-handed, and those who have received a thorough explanation, fully understood the study, and provided written consent based on their free will. The exclusion criteria were strong suicidal ideation, or anyone deemed inappropriate for the study.

This study was approved by the Institutional Review Board of Yamaguchi University Hospital and was registered in advance on University hospital Medical Information Network (UMIN) for clinical trials. The implementation adhered to the latest version of the Helsinki Declaration.

2.2. Procedures

Participants in this study were informed in advance to adhere to three conditions: (1) get adequate sleep the night before, (2) refrain from vigorous exercise and smoking for at least 2 h prior to the experiment, and (3) avoid the consumption of coffee and energy drinks. If participants felt unwell, the experimental date was rescheduled. On the day of the experiment, participants first completed a questionnaire on age, sex, smoking and drinking habits, educational background, etc. and confirmed compliance with the above instructions.

This study employed a randomized crossover design (as shown in Fig. 1A) and assigned participants either to: ① visual stimulation using images of natural environments (Fig. 1B) followed by visual stimulation using images of man-made environments (Fig. 1C), or ② the reverse order. Interventions were carried out accordingly.

After fitting participants with the PocketNIRS DUO (2ch) probe (Figs. 1D), which measures the concentration of oxygenated hemoglobin (Oxy-Hb) reflecting orbital PFC activation, and the fingertip accelerated plethysmography (Fig. 1E), which assesses heart rate variability (HRV) indicative of autonomic nervous activity, an initial practice session was conducted. This session aimed to allow participants to familiarize themselves with the actual intervention process and to alleviate any initial nervousness, a common occurrence in many participants that can lead to exaggerated increases in brain activity (Song et al., 2018a). For this practice session, participants were exposed to an image of a brick (a single image for 15 s) after a 1-min rest. This was followed by a 45-s wait.

Following the practice session, participants underwent visual stimulation sessions in the order assigned. Each session consisted of rest, visual stimulation with images, and mood assessment. To eliminate carryover effects, a 3-min rest period, also referredto as a washout period, was placed between the first and second interventions. After the second intervention, assessments including the Beck Depression Inventory-II (BDI) to evaluate depressive symptoms and the State-Trait Anxiety Inventory (STAI) for state anxiety symptoms were conducted.

2.3. Visual stimuli

The visual stimuli were administered in the same manner as our previous study (Yamashita et al., 2021). Specifically, for the visual stimuli of a natural environment, we displayed photos of green natural settings (Fig. 1B), and for the control intervention of man-made environments, we displayed city photos with buildings as the central focus (Fig. 1C) on a 27-in. high-resolution display. Each image was presented for 15 s, with a total of 12 images shown (totaling 3 min).

2.4. Mood assessment

The mood assessment used the Chen-HAgiwara Mood Test (CHAMT) that we developed (Aga et al., 2021; Chen et al., 2024; Watarai et al., 2023; Yamashita et al., 2021). This test, based on the valence-arousal two-dimensional theory of emotion (Russell, 2003), comprises three items: Comfort (or Pleasure), which assesses only the emotional valence, and Relaxation (positive emotional valence and negative arousal) and

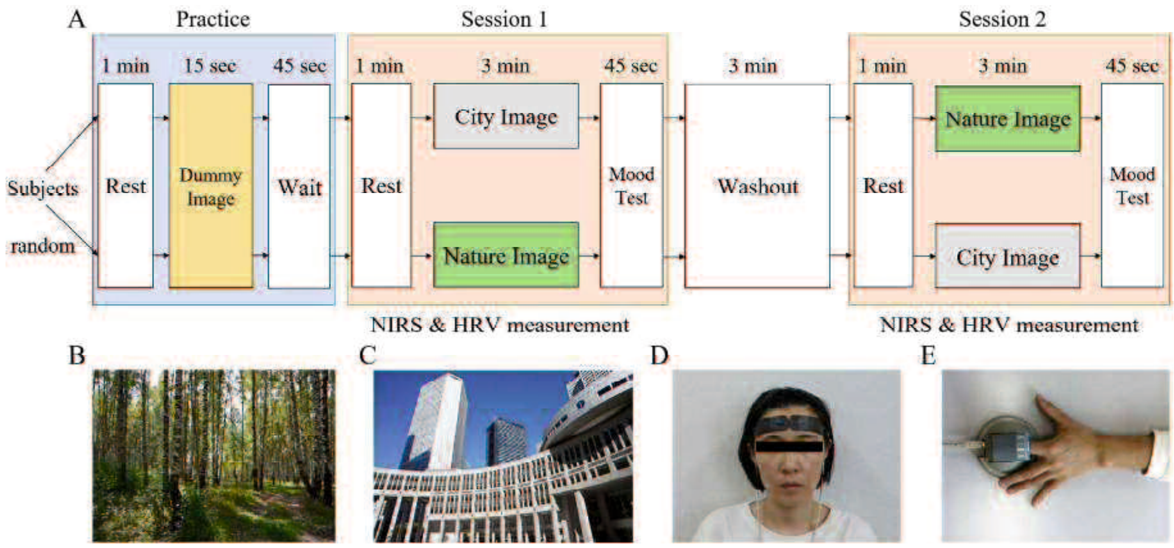

Fig. 1. Study protocol, photographs used for stimuli, and photographs illustrating the measuring equipment. A. Overall flowchart. B. Example of a green nature image. C. Example of a city image. D. Illustration of the near-infrared spectroscopy (NIRS) probe placement. E. Illustration of the fingertip accelerated plethysmography (ARTETT), used for evaluation of heart rate variability (HRV). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Vigor (positive emotional valence and positive arousal), which emerge from the combination of emotional valence and arousal. Compared to traditional assessments that evaluate emotional valence and arousal separately, this can evaluate mood enhancement more precisely. To avoid interference from multiple responses, we used a continuous 10 cm visual analog scale and assessed the aforementioned three items by asking, "How do you feel right now?" The left end of each scale read "Very Uncomfortable," "Very Tense," and "Very Mentally Exhausted," while the right end read "Very Pleasant," "Very Relaxed," and "Very Energetic." Participants were instructed to mark the spot they identified with using an "×", and the distance (in mm) from the left end to the mark was quantified as a mood scale (0−100).

2.5. Measurement of Oxy-Hb in the orbital PFC

In this study, we used the PocketNIRS DUO (2ch) from Dynasense, a subsidiary of Hamamatsu Photonics K.K. (Ochiai et al., 2017; Song et al., 2018b). Near-infrared spectroscopy (NIRS) is a method that uses near-infrared light to measure Oxy-Hb, with measurements being taken by attaching a probe to the head. The probe emits near-infrared light, which is then absorbed by another probe, measuring the difference in light quantity. Since near-infrared light is specifically absorbed by Oxy-Hb, a larger difference indicates a higher amount of Oxy-Hb. A higher amount of Oxy-Hb suggests an increase in the volume of blood carrying it (Obrig and Villringer, 2003). Generally, a positive correlation between brain activation and blood flow is believed to exist, so NIRS results are also used for observing brain activation (Ferrari and Quaresima, 2012). In this study, we attached the probes of the 2ch NIRS targeting the orbital PFC, referring to the international 10–20 system for EEG and our 52-channel NIRS attachment method (Yamashita et al., 2021).

2.6. HRV

Using the fingertip accelerated plethysmography ARTETT-C (U-Medica Inc., Osaka, Japan), we analyzed HRV for the periods between consecutive R-waves (RR intervals) in the electrocardiogram (Song et al., 2018b; Jo et al., 2022a). The power levels of the high-frequency component (HF; 0.15–0.40 Hz) and the low-frequency component (LF; 0.04–0.15 Hz) of HRV were calculated using the maximum entropy method (Takada et al., 2008; Takada et al., 2010). HF is considered an index of parasympathetic nervous activity, while LF/HF is considered an index of sympathetic nervous activity (Camm et al., 1996; Kanaya et al., 2003).

2.7. Blinding and debriefing

To exclude the effect of expectations regarding the mood-improving effects of the natural environment, we employed blinding (Yamashita et al., 2021). When explaining the study to participants, the purpose of the research was presented as "the impact of daily activities on brain function," and participants were told they were assigned to the "image viewing" group. The reason given for the second intervention was "to verify experimental results under different conditions." To ensure that the participants did not recognize the true objective of the study, we omitted any mention of relevant activities like the "mood survey" during the study explanation and consent process. The true objective of the study was explained to the participants after its completion. After the experiment concluded and the true objective was explained, a survey was conducted to assess the participants' understanding of the original intent during the experiment. This procedure was approved by our Institutional Review Board.

From the experimenter's side, both the staff providing the explanation and obtaining consent, and the staff conducting the experiment, were kept unaware of the order of the images until just before the intervention. Also, during initial data analysis, the order was represented as 1 and 2 to ensure the analyst could not discern the specific sequence of interventions.

2.8. Statistical analysis

For the analysis of this study, Matlab R2018b and IBM SPSS Statistics 28.0 were used. Normality was tested using the Shapiro-Wilk test. For comparison of within-subject repeated measurements, paired *t*-tests or Wilcoxon rank-sum tests were used depending on the normality of the data. For correlation analysis, Pearson's or Spearman's correlation was employed depending on the normality of the data. In analyses that used participants' recognition of the study's true objective (whether they noticed it during the experiment) as a covariate, repeated measures analysis of variance (ANOVA) or linear regression analysis was employed. The threshold for statistical significance was set at $p < 0.05$, two-sided.

3. Results

3.1. Participants' characteristics

The demographic and clinical characteristics of the participants are shown in Table 1. The average age was 47.4 (standard deviation or SD 9.5) years for those with depressive disorders and 43.3 (SD 11.3) years for those with anxiety disorders. In terms of sex, 17 females (56.7 %) were in the depressive disorder group and 22 females (73.3 %) were in the anxiety disorder group. Among the depressive disorder group, 24 individuals (80.0 %) had major depressive disorder, while 6 individuals (20.0 %) had persistent depressive disorder. In the anxiety disorder group, 4 individuals (13.3 %) had specific phobias, 14 (46.7 %) had panic disorder, 5 (16.7 %) had social anxiety disorder, 5 (16.7 %) had generalized anxiety disorder, and 2 (6.7 %) had unspecified anxiety disorder.

3.2. Mood effects

In the depressive disorder group, scores for "Comfortable" ($t = 4.659$, $p < 0.001$, $d = 0.851$), "Relaxed" ($U = 20.000$, $z = -4.272$, $p < 0.001$, $d = 0.929$), and "Vigorous" ($U = 82.000$, $z = -2.757$, $p = 0.006$, $d = 0.478$) all significantly improved with visual stimulation from nature images compared to city images (see Fig. 2, left).

In the anxiety disorder group ($n = 30$) as well, scores for "Comfortable" ($U = 44.000$, $z = -3.485$, $p < 0.001$, $d = 0.825$), "Relaxed" ($U = 35.000$, $z = -3.701$, $p < 0.001$, $d = 0.885$), and "Vigorous" ($t = 5.047$, $p < 0.001$, $d = 0.921$) all significantly improved with visual stimulation from nature images compared to city images (see Fig. 2, right).

Table 1
Demographic and clinical characteristics of participants.

Demographic & clinical characteristics Mean ± SD / n (%)	Depressive disorders (*n* = 30)	Anxiety disorders (n = 30)
Age, years	47.4 ± 9.5	43.3 ± 11.3
Sex		
Female	17(56.7 %)	22(73.3 %)
Male	13(43.3 %)	8(26.7 %)
Education levels		
≦High school	10(33.3 %)	15(50.0 %)
Vocational school/ Junior college	7(23.3 %)	9(30.0 %)
≧University	13(43.3 %)	6(20.0 %)
Diagnosis	Major depressive disorder 24(80.0 %, of which 18 or 60 % were recurrent) Persistent depressive disorder 6(20.0 %)	Specific phobia 4(13.3 %) Panic disorder 14(46.7 %) Social anxiety disorder 5(16.7 %) Generalized anxiety disorder 5(16.7 %) Unspecified anxiety disorder 2(6.7 %)
Comorbid conditions	Anxiety disorders 4(13.3 %) Eating disorders 1(3.3 %)	Depressive disorders 6 (20.0 %) Bipolar disorders 1(3.3 %)
Smoking		
Yes	5(16.7 %)	4(13.3 %)
No	25(83.3 %)	26(86.7 %)
Alcohol		
Yes	12(40 %)	9(30 %)
No	18(60 %)	21(70 %)
Drug		
Antidepressant	27(90.0 %)	27(90.0 %)
Antianxiety	8(26.7 %)	19(63.3 %)
Antipsychotics	11(36.7 %)	5(16.7 %)
Mood stabilizer	1(3.3 %)	2(6.7 %)
Depressive symptoms (BDI)	16.9 ± 11.5	16.1 ± 10.8
State anxiety(STAI-Y1)	40.9 ± 9.1	45.2 ± 8.9
Trait anxiety(STAI-Y2)	50.6 ± 13.2	51.2 ± 10.2

SD, standard deviation; BDI, Beck Depression Inventory-II; STAI, State-Trait Anxiety Inventory.

3.3. Effects on Oxy-Hb in the orbital PFC

In the depression group, both the left orbital PFC ($t = 2.355$, $p = 0.025$, $d = 0.430$) and the right orbital PFC ($U = 98.000$, $z = -2.766$, $p = 0.006$, $d = 0.545$) showed a statistically significant increase in the concentration of Oxy-Hb when visually stimulated by nature images compared to city images (Fig. 3, left).

On the other hand, in the anxiety disorder group, both the left orbital PFC ($t = -0.722$, $p = 0.476$, $d = -0.132$) and the right orbital PFC ($U = 269.000$, $z = -0.751$, $p = 0.453$, $d = -0.204$) showed a trend of decreased Oxy-Hb concentration when visually stimulated by nature images compared to city images. However, there was no statistically significant change (Fig. 3, right).

Yet, when investigating the relationship between the change in orbital prefrontal Oxy-Hb concentration due to visual stimulation with nature images and mood changes in the anxiety disorder group, a significant negative correlation (Rho = −0.437, $p = 0.016$) was confirmed between the change in left orbital prefrontal Oxy-Hb concentration and the change in the "Comfortable" mood (Fig. 4). This indicates that the greater the reduction in orbital prefrontal Oxy-Hb concentration when visually stimulated by nature images compared to city images, the greater the mood-improving effect in the "Comfortable" category. On the other hand, for "Relaxed", there was no significant correlation in either the left orbital PFC (Rho = −0.126, $p = 0.508$) or the right orbital PFC (Rho = −0.138, $p = 0.468$). Similarly, for "Vigorous", there was no significant correlation in either the left orbital PFC (Rho = −0.155, $p = 0.412$) or the right orbital PFC (Rho = −0.116, $p = 0.541$).

3.4. HRV effects

In the depression group, neither HF ($t = -0.808$, $p = 0.426$, $d = -0.150$) nor LF/HF ($t = 1.266$, $p = 0.216$, $d = 0.235$) showed statistically significant changes when comparing visual stimuli from city and nature images (Fig. S1, left).

Similarly, in the anxiety disorder group, neither HF ($U = 228.000$, $z = 0.227$, $p = 0.820$, $d = 0.171$) nor LF/HF ($U = -299.000$, $z = 1.762$, $p = 0.078$, $d = 0.337$) exhibited statistically significant changes (Fig. S1, right). Subsequent analysis investigating the association between changes in HRV and mood changes revealed no significant correlations in either the depressive or anxiety disorder groups (Table S1).

3.5. Intervention effects of visual stimuli from nature images reflecting the impact of study objective recognition

To exclude the impact of expectations on the mood-improving effects of natural environments, this study was conducted in a blinded manner. After the experiment, recognition of the study's objective (whether participants noticed it during the experiment) was utilized as a covariate to investigate the effects of visual stimuli from nature images on mood, Oxy-Hb concentration in the orbital PFC, and HRV using a repeated measures ANOVA. The results are presented in Table S2.

For the depression group, significant mood improvement effects due to visual stimuli from nature images were observed for "Comfortable" and "Relaxed" moods, consistent with the previously mentioned results. However, no significant effect was found for "Vigorous." In the anxiety disorder group, significant mood-improving effects were observed for all mood items, consistent with previous results.

Regarding Oxy-Hb concentration in the orbital PFC, there was a

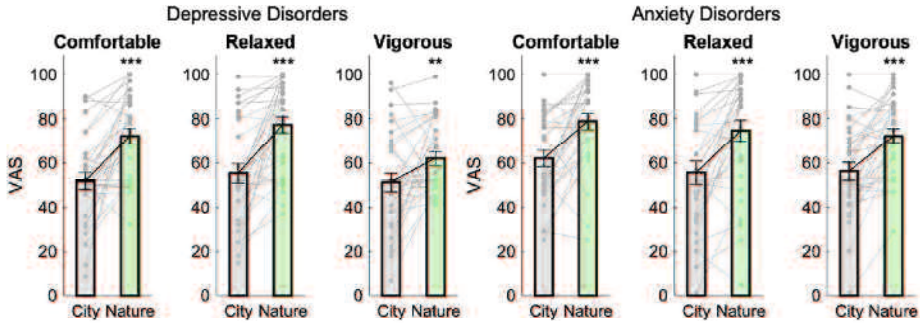

Fig. 2. The effect of visual stimulation by nature images on mood. Bars colored in gray represent mood scores after viewing city images, while those in green indicate mood scores after viewing nature images. The left graph is for the depressive disorder group, and the right graph is for the anxiety disorder group. In both groups, significant mood improvement effects were observed in all mood items with visual stimulation from nature images. ** $p < 0.01$, *** $p < 0.001$, paired *t*-test or Wilcoxon rank-sum test. VAS, visual analog scale. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

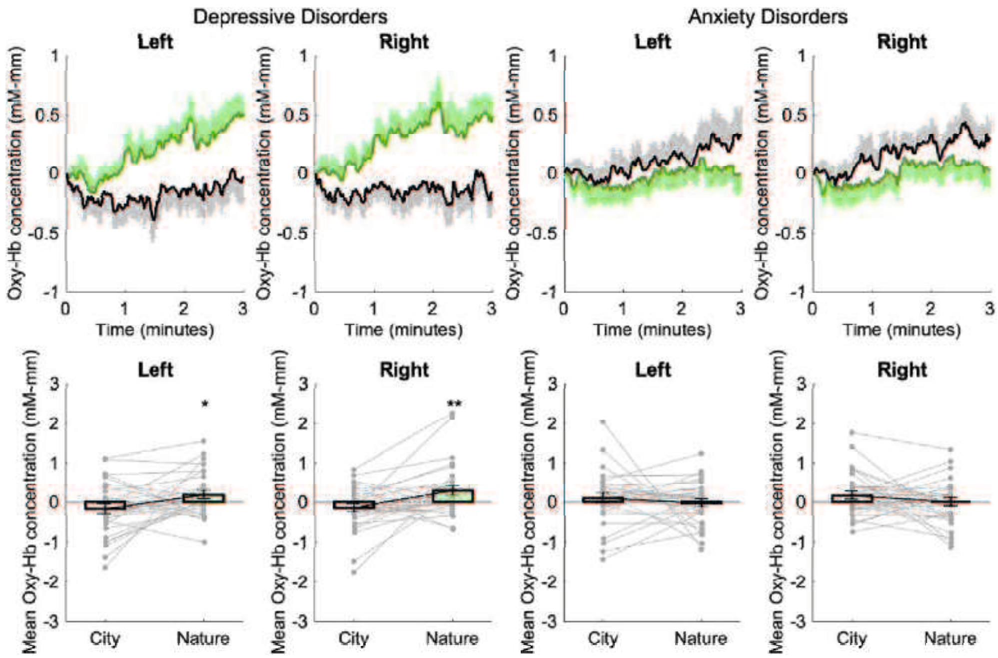

Fig. 3. The impact of visual stimulation by nature images on the concentration of oxygenated hemoglobin (Oxy-Hb) in the orbital PFC. The green and black lines in the top graph represent the temporal changes in the Oxy-Hb average concentration during the intervention in the nature (=green) and city (=black) conditions, respectively. The shaded areas in green and black represent the standard error. The bottom graph depicts the average values during the intervention, with green representing nature and gray representing city. In the depression group, a significant increase in the concentration of Oxy-Hb in the orbital PFC was observed due to visual stimulation by nature images. No significant changes were observed in the anxiety disorder group. * $p < 0.05$, ** $p < 0.01$, paired *t*-test or Wilcoxon rank-sum test. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

significant increase in the depression group during visual stimuli from nature images compared to city ones, while no significant change was observed in the anxiety disorder group. For HRV, no significant changes were observed in either group, consistent with previous results.

To investigate the impact of study objective recognition on the relationship between changes in Oxy-Hb concentration in the orbital PFC and mood changes due to visual stimuli from nature images in the anxiety disorder group, a regression analysis was conducted. Changes in Oxy-Hb concentration in the orbital PFC, recognition of the study's objectives, and their interaction were used as independent variables, with mood changes as the dependent variable. Consistent with previous results, a significant relationship between changes in the left orbital prefrontal Oxy-Hb concentration and "Comfortable" mood changes was observed ($B = -23.963$, $p = 0.013$) (Table S3). Additionally, a regression analysis was conducted to examine the relationship between HRV changes and mood changes due to visual stimuli from nature images, and no significant relationships were observed (Table S3).

3.6. *Intervention effects in the pure depression group, pure anxiety disorder group, and comorbidity group*

Participants without comorbid anxiety disorders in the depression group were classified as the pure depression group ($n = 26$). Participants without comorbid depression in the anxiety disorder group were classified as the pure anxiety disorder group ($n = 24$). Participants with both depressive and anxiety disorders were classified as the comorbidity group ($n = 10$). For each group, the intervention effects of visual stimuli from nature images on mood, Oxy-Hb concentration in the orbital PFC,

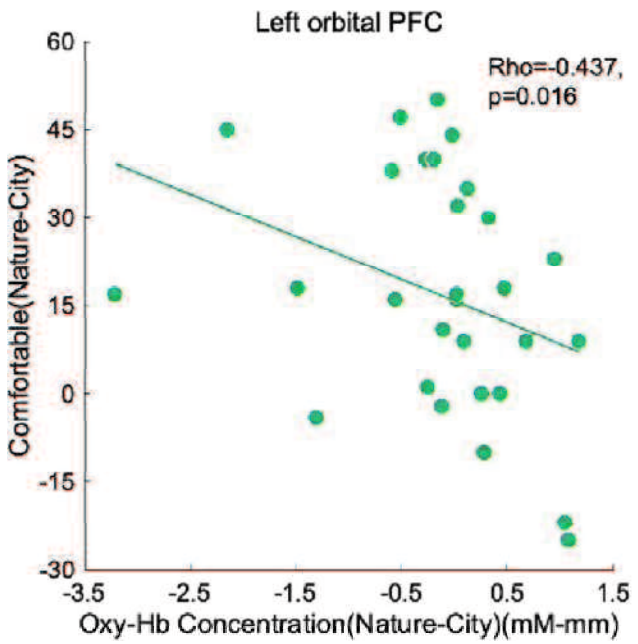

Fig. 4. Association between changes in the concentration of oxygenated hemoglobin (Oxy-Hb) in the orbital PFC and mood changes due to visual stimulation by nature images in the anxiety disorder group. The horizontal axis indicates the change in concentration of Oxy-Hb in the orbital PFC due to visual stimulation by nature images compared to the control, which is the city image; it represents the result of subtracting the value for city images from the value for nature images. The vertical axis indicates the mood change in "Comfortable" due to visual stimulation by nature images compared to city images; it represents the result of subtracting the value for city images from the value for nature images. In the anxiety disorder group, a statistically significant negative correlation was observed between the change in the concentration of Oxy-Hb in the left orbital PFC and the change in "Comfortable" (Rho $= -0.437$, $p =$ 0.016). A regression line is plotted to visually represent this association. PFC, prefrontal cortex.

and HRV were analyzed.

In the pure depression group, repeated measures ANOVA was conducted using recognition of the study's objectives as a covariate to investigate the intervention effects of visual stimuli from nature images on mood, Oxy-Hb concentration in the orbital PFC, and HRV. For mood, as with the results in the depression group ($n = 30$) reported earlier, significant mood-improving effects were observed in "Comfortable" and "Relaxed" from visual stimuli of nature images. Furthermore, "Vigorous," which was not significant in the depression group, also showed a significant improvement here (Fig. S2). The Oxy-Hb concentration in the orbital PFC significantly increased for both the left and right sides due to the visual stimuli from nature images, similar to the results in the depression group (Fig. S3). For HRV, there were no significant changes, similar to the depression group (Fig. S5).

Similarly, in the pure anxiety disorder group, a repeated measures ANOVA was conducted. For mood, significant mood-improving effects were observed in "Relaxed" and "Vigorous," similar to the results in the anxiety disorder group (n = 30) reported earlier, but no significant mood-improving effects were observed for "Comfortable" (Fig. S2). There were no significant changes in the Oxy-Hb concentration in the orbital PFC, consistent with the results in the anxiety disorder group (Fig. S3). A regression analysis was conducted to investigate the relationship between changes in the Oxy-Hb concentration in the left orbital prefrontal cortex and mood changes due to the visual stimuli from nature images. A significant relationship was observed between changes in the left orbital PFC Oxy-Hb concentration and "Comfortable" mood changes (B = -24.141, $p = 0.015$) (Table S4, Fig. S4), consistent with the results in the anxiety disorder group. There were no other significant relationships. For HRV, there were no significant changes, consistent with the results in the anxiety disorder group (Fig. S5). A regression analysis was conducted to examine the relationship between HRV changes and mood changes due to visual stimuli from nature images, but no significant changes were observed (Table S4).

In the comorbidity group, a repeated measures ANOVA was similarly conducted. For mood, a significant mood-improving effect was observed for "Relaxed," but there were no significant changes for "Comfortable" and "Vigorous" (Fig. S2). There were no significant changes in the Oxy-Hb concentration in the orbital PFC (Fig. S3). A regression analysis was conducted to investigate the relationship between changes in the Oxy-Hb concentration in the orbital prefrontal cortex and mood changes due to visual stimuli from nature images, but no significant relationship was found. For HRV, there were no significant changes as determined by the repeated measures ANOVA (Fig. S5). Furthermore, regression analyses were conducted to examine the relationships between changes in Oxy-Hb concentration or HRV and mood changes due to visual stimuli from nature images, but no significant changes were found in either case (Table S4).

3.7. The relationship between the severity of depressive symptoms and anxiety symptoms, and the intervention effects

To investigate the impact of the severity of depressive and anxiety symptoms on the intervention effects, we conducted correlation analyses between BDI/STAI-Y1, and the changes in mood, changes in orbital prefrontal Oxy-Hb concentration, and HRV changes in the entire group of participants ($n = 60$) as well as in the depressive disorder group ($n =$ 30) and the anxiety disorder group (n = 30).

As a result, in all groups (entire participants, depressive disorder group, and anxiety disorder group), there were no significant correlations between BDI and mood changes, changes in orbital prefrontal Oxy-Hb concentration (Fig. 5), or HRV changes (Fig. S6). This means that the severity of depressive symptoms did not influence the intervention effects.

On the other hand, in the entire group of participants, there was a significant negative correlation between STAI-Y1 and the changes in all mood items (Fig. 6). The results indicated that the greater the severity of anxiety symptoms, the smaller the mood-improving effects of visual stimulation by nature images. However, even in cases of high severity, mood-improving effects were observed in most subjects. Regarding results by disease group, in the depressive disorder group, there was a significant negative correlation between STAI-Y1 and the changes in "Comfortable" and "Vigorous", while in the anxiety disorder group, there was a significant negative correlation between STAI-Y1 and the changes in "Comfortable" and "Relaxed" (Fig. 6). There were no significant correlations between STAI-Y1 and changes in orbital prefrontal Oxy-Hb concentration (Fig. 6) or HRV changes (Fig. S7).

4. Discussion

Both the depressive disorder group and the anxiety disorder group showed mood-improving effects from visual stimulation by nature images, consistent with previous reports in healthy subjects (Song et al., 2018a; Yamashita et al., 2021). While the benefits of exposing the five senses to natural stimuli for depressive and anxiety disorders have been suggested (Berman et al., 2012; Watkins-Martin et al., 2022; Maas et al., 2009; Hystad et al., 2019), this study confirmed that visual stimuli from nature alone can produce mood-improving effects in both depressive and anxiety disorders. Furthermore, this mood-improving effect was observed regardless of whether the participants were aware of the research's objectives.

Regarding the concentration of orbital prefrontal Oxy-Hb, different trends were observed between the depressive disorder group and the anxiety disorder group. In the depressive disorder group, the

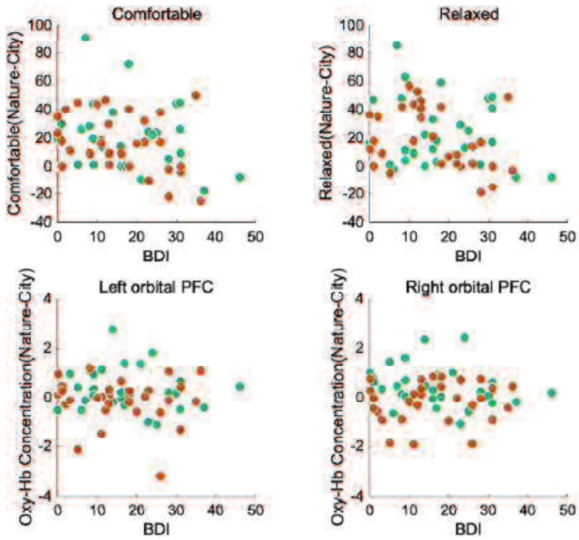

Fig. 5. The relationship between depressive symptoms (BDI) and the mood changes and changes in orbital prefrontal oxygenated hemoglobin concentration due to visual stimulation by nature images. No significant correlations were found in either case. BDI, Beck Depression Inventory-II; PFC, prefrontal cortex.

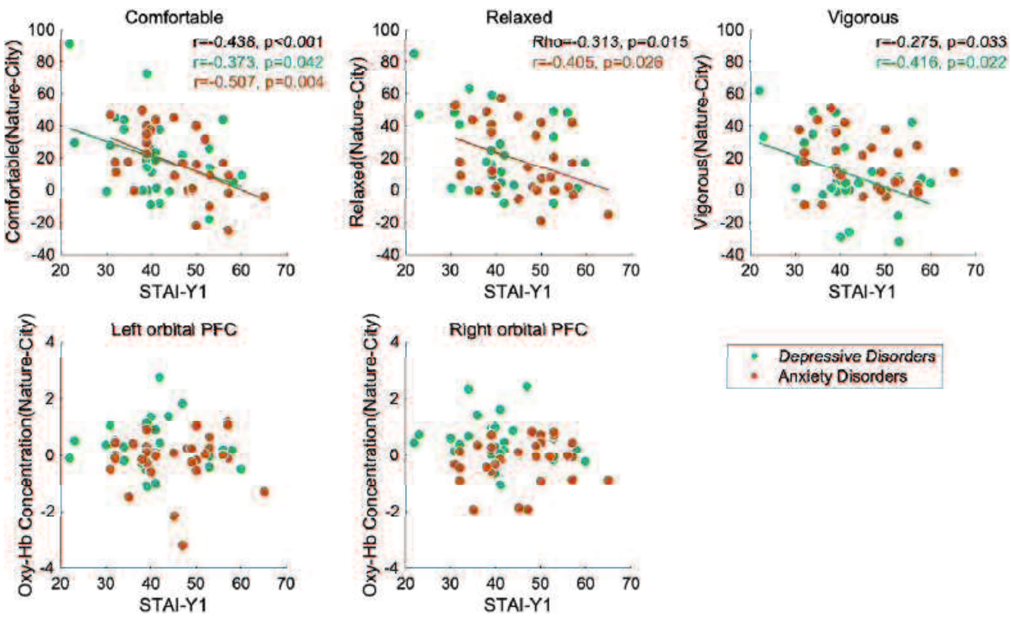

Fig. 6. The relationship between anxiety symptoms (STAI-Y1) and the mood changes and changes in orbital prefrontal oxygenated hemoglobin concentration due to visual stimulation by nature images. The results for items with statistically significant correlations ($p < 0.05$) are indicated. Black text represents the entire group of participants, green represents the depressive disorder group, and orange represents the anxiety disorder group. Regression lines are presented exclusively for correlations that reached statistical significance to offer a clear visualization of their directionality. PFC, prefrontal cortex; STAI-Y1, State-Trait Anxiety Inventory State Anxiety Subscale. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

concentration of orbital prefrontal Oxy-Hb increased with visual stimulation from nature images. In contrast, in the anxiety disorder group, although no significant change was observed, there was a negative correlation between the change in the concentration of orbital prefrontal Oxy-Hb and the mood-improving effect of "Comfortable".

In previous reports on healthy subjects, visual stimulation from nature resulted in a decrease in the concentration of prefrontal Oxy-Hb and an increase in parasympathetic nervous system activity, which was interpreted as the brain relaxing (Jo et al., 2019b; Chen and Nakagawa, 2019). Consistent with the reports on healthy individuals, in the present study, the greater the decrease in the concentration of orbital prefrontal Oxy-Hb in the anxiety disorder group, the greater the improvement in "Comfortable". Given that hyperactivity in the prefrontal region is characteristic of anxiety disorders (Aupperle and Paulus, 2010; Bruehl et al., 2014; Mizzi et al., 2022) and that a reduction in prefrontal Oxy-Hb concentration during anxiety improvement in exposure therapy has been reported (Rosenbaum et al., 2020), it is believed that visual stimuli from nature images relaxed the orbital prefrontal area of patients with anxiety disorders, leading to the mood-improving effect of "Comfortable". On the other hand, no significant changes in orbital prefrontal Oxy-Hb were observed for "Relaxed" and "Vigorous". In healthy individuals, walking in a natural environment can lead to a decrease in amygdala activity (Sudimac et al., 2022) and a decrease in anterior cingulate cortex activity (Bratman et al., 2015). The mood-improving effects of "Relaxed" and "Vigorous" from visual stimuli of nature images might be due to effects on deeper brain areas, such as the amygdala and anterior cingulate cortex, which cannot be observed by NIRS (Chen and Nakagawa, 2019).

For the depressive disorder group, an increase in orbital prefrontal Oxy-Hb concentration was observed, resulting in findings opposite to those in healthy individuals. It has been pointed out that patients with depressive disorder exhibit decreased cerebral blood flow in the prefrontal region and hypoactivation (Hosokawa et al., 2009; Nixon et al., 2013; Rive et al., 2013; Korgaonkar et al., 2013; Arias et al., 2020; Ho et al., 2020). Moreover, there is a report that neurofeedback training that activates the left orbitofrontal cortex in patients with depression led to alleviation of depressive symptoms (Takamura et al., 2020). Thus, it is believed that the visual stimulation from nature images activated the orbital prefrontal area of patients with depressive disorders, resulting in mood-improving effects.

In this study, the physiological changes due to nature image stimulation differed between depressive disorders and anxiety disorders, but both showed a mood-improving effect. The benefits of nature stimulation have been reported for various conditions, such as depression (Berman et al., 2012), alcohol dependency (Shin et al., 2012), gambling addiction (Ochiai et al., 2023), and depression and anxiety in chronic stroke patients (Chun et al., 2017). Based on the results of this study and previous research, the mood-improving effects of nature stimulation may not arise from a uniform physiological change but are possibly induced by individual physiological changes specific to each condition. Recent studies have reported that with visual stimulation of roses, if initial sympathetic activity was high, it decreased, and if initial activity was low, it increased (Ikei et al., 2023), suggesting that nature stimulation might influence the body's homeostasis.

In this study, no changes in HRV were observed in both the depressive disorder and anxiety disorder groups. A possible reason for this could be that both depressive and anxiety disorders are reported to have decreased HRV compared to healthy individuals (Kemp et al., 2010; Chalmers et al., 2014; Wang et al., 2023). The response of HRV to visual stimulation from nature images might differ in these patients compared to healthy individuals. It is possible that a more potent stimulus is required to induce changes in HRV in patients with depressive or anxiety disorders.

Regarding the association between the severity of depressive and anxiety symptoms and the intervention effect, the severity of depressive symptoms did not affect the intervention effect. This means that regardless of the severity of depressive symptoms, we can expect intervention effects from visual stimulation by nature images. For the severity of anxiety symptoms, there was no effect on the intervention outcomes of orbital prefrontal Oxy-Hb concentration or HRV. However, as the severity of anxiety symptoms increased, the mood-improving effect diminished. Nevertheless, for most participants, even with high severity of anxiety symptoms, a mood-improving effect was observed. In other words, patients with strong anxiety can expect a mood-improving effect from nature visual stimuli, albeit modest. For these patients, it may be necessary to consider additional interventions beyond nature stimuli.

For the comorbidity group, the mood-improving effect of visual stimulation by nature images was only observed in "Relaxed", and there were no significant changes in orbital prefrontal Oxy-Hb concentration or HRV. It has been reported that the comorbidity of depressive and anxiety disorders tends to be resistant to treatment (Chen, 2022), suggesting that interventions using visual stimulation from nature images may also be less effective.

This study has several limitations. First, this study did not evaluate whether each patient was in an acute or remission phase, and there is a need to investigate the effect according to the condition of the illness. Secondly, while we observed that the concentration of orbital prefrontal Oxy-Hb increased in cases of depression and decreased in anxiety, additional research is necessary to confirm if these changes are specific to depression and anxiety by comparing them with healthy control subjects. Thirdly, we only examined the effects of brief visual stimulation by nature images, and the effects of repeated and prolonged stimulation remain unknown. It is necessary to verify the enduring effects and elucidate clinical significance, such as in preventing onset or recurrence. Fourthly, the NIRS measurement method used in this study can only examine relative values. There is a method for measuring absolute values in NIRS called time-resolved spectroscopy (TRS). Using such methods to measure absolute values in the future may contribute to understanding the neural foundation of mood enhancement by nature, and elucidating the pathology of depressive and anxiety disorders.

5. Conclusion

In this study, while the orbital prefrontal Oxy-Hb responses differed between depressive and anxiety disorders, both showed mood-improving effects, confirming the utility of visual stimulation by nature images. To the best of our knowledge, this study is the first report elucidating the mood-improving effects and physiological responses to visual stimulation by nature images in patients with depressive and anxiety disorders. It may contribute insights for refining therapeutic environments and enhancing the development of nature-based therapies in the future.

Funding

This research was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant Number JP 22K15764) to CC.

CRediT authorship contribution statement

Tomohiro Mizumoto: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis. **Harumi Ikei:** Writing – review & editing, Resources, Methodology. **Kosuke Hagiwara:** Writing – review & editing, Resources, Investigation. **Toshio Matsubara:** Writing – review & editing, Resources. **Fumihiro Higuchi:** Writing – review & editing, Resources. **Masaaki Kobayashi:** Writing – review & editing, Resources. **Takahiro Yamashina:** Writing – review & editing, Software. **Jun Sasaki:** Writing – review & editing, Resources. **Norihiro Yamada:** Writing – review & editing, Resources. **Naoko Higuchi:** Writing – review & editing, Resources. **Kenichi Haraga:** Writing – review & editing, Resources. **Fumiaki Kirihara:** Writing – review & editing, Resources. **Emi Okabe:** Writing – review & editing, Methodology, Investigation. **Kumi Asai:** Writing – review & editing, Methodology, Investigation. **Masako Hirotsu:** Writing – review & editing, Methodology, Investigation. **Chong Chen:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization. **Yoshifumi Miyazaki:** Writing – review & editing, Resources, Methodology. **Shin Nakagawa:** Writing – review & editing, Resources.

Declaration of competing interest

C.C. is the author of CleverLand: The Psychology of How Nature Nurtures. The other authors declare no conflict of interest.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.04.025.

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Mood and physiological effects of visual stimulation with images of the natural environment in individuals with depressive and anxiety disorders

Supplementary material

Table S1. Relationship between HRV changes and mood changes due to visual stimulation by nature images. We conducted Pearson or Spearman correlation analyses, and statistically significant results (p<0.05) are highlighted in bold.

	Depressive Disorders		Anxiety Disorders	
	Ln(HF)	Ln(LF/HF)	Ln(HF)	Ln(LF/HF)
Comfortable	Rho=-0.217 p=0.259	r=0.302 p=0.111	Rho=-0.179 p=0.352	r=0.138 p=0.475
Relaxed	Rho=-0.129 p=0.506	Rho=0.086 p=0.658	Rho=-0.316 p=0.095	r=0.171 p=0.375
Vigorous	Rho=-0.254 p=0.184	r=0.185 p=0.336	Rho=-0.366 p=0.051	r=0.302 p=0.111

Table S2. Intervention effects of visual stimulation by nature images reflecting the influence of research objective recognition. We conducted a repeated measures ANOVA with the recognition of the study's objective as a covariate. Statistically significant results (p<0.05) are highlighted in bold.

		Mood			NIRS (Oxy-Hb Concentration)		HRV	
		Comfortable	Relaxed	Vigorous	Left orbital PFC	Right orbital PFC	Ln(HF)	Ln(LF/HF)
Depressive Disorders	Intervention	**F＝11.702** **p=0.002**	**F=12.649** **p=0.001**	F=2.295 p=0.141	**F=8.473** **p=0.007**	**F=9.716** **p=0.004**	F=0.001 p=0.971	F=0.259 p=0.615
	Interaction	F=0.147 p=0.704	F=0.586 p=0.450	F=0.870 p=0.359	F=2.641 p=0.115	F=1.427 p=0.242	F=1.204 p=0.282	F=0.611 p=0.441
	Knowledge of true objective	**F=5.410** **p=0.027**	**F=4.290** **p=0.048**	**F=6.558** **p=0.016**	F=0.501 p=0.485	F=2.572 p=0.120	F=0.015 p=0.904	F=3.367 p=0.078
Anxiety Disorders	Intervention	**F=5.025** **p=0.033**	**F=11.474** **p=0.002**	**F=9.021** **p=0.006**	F=2.071 p=0.161	F=1.489 p=0.233	F=2.743 p=0.109	F=0.629 p=0.435
	Interaction	F=4.149 p=0.051	F=0.097 p=0.758	F=1.612 p=0.215	**F=9.792** **p=0.004**	**F=11.120** **p=0.002**	F=2.120 p=0.157	F=0.843 p=0.367
	Knowledge of true objective	F=2.244 p=0.145	F=0.633 p=0.433	F=0.384 p=0.541	F=0.073 p=0.790	F=1.503 p=0.230	F=0.464 p=0.502	F=0.046 p=0.832

Table S3. Analysis of the relationship between changes in orbital prefrontal oxyhemoglobin concentration/HRV and mood changes due to visual stimulation by nature images reflecting the influence of research objective recognition. We conducted a regression analysis with the changes in the orbital prefrontal oxygenated hemoglobin concentration/HRV, the recognition of the study's objective, and their interaction as independent variables, and mood changes as the dependent variable. Statistically significant results ($p<0.05$) are highlighted in bold.

			Depressive Disorders			Anxiety Disorders		
			Comfortable	Relaxed	Vigorous	Comfortable	Relaxed	Vigorous
NIRS (Oxy-Hb Concentration)	Left orbital PFC	Left orbital PFC	B=-2.870 p=0.663	B=-3.065 p=0.632	B=-6.661 p=0.279	**B=-23.963 p=0.013**	B=-9.111 p=0.423	B=-3.411 p=0.711
		Knowledge of true objective	B=1.539 p=0.879	B=4.730 p=0.632	B=4.212 p=0.653	B=8.013 p=0.303	B=2.353 p=0.806	B=8.000 p=0.311
		Interaction	B=12.858 p=0.370	B=14.535 p=0.300	B=10.734 p=0.418	**B=24.570 p=0.022**	B=12.867 p=0.316	B=4.705 p=0.649
	Right orbital PFC	Right orbital PFC	B=1.657 p=0.817	B=-3.794 p=0.589	B=5.522 p=0.405	B=-11.360 p=0.289	B=-7.777 p=0.522	B=-4.654 p=0.633
		Knowledge of true objective	B=3.882 p=0.716	B=4.946 p=0.635	B=12.217 p=0.218	B=11.224 p=0.199	B=1.475 p=0.881	B=7.938 p=0.319
		Interaction	B=1.041 p=0.938	B=2.770 p=0.834	B=-11.045 p=0.377	B=9.962 p=0.421	B=8.680 p=0.538	B=5.846 p=0.605
HRV	Ln(HF)	Ln(HF)	B=-0.810 p=0.948	B=-1.208 p=0.926	B=-7.239 p=0.556	B=4.129 p=0.453	B=1.091 p=0.842	B=2.236 p=0.593
		Knowledge of true objective	B=-0.693 p=0.948	B=6.411 p=0.552	B=4.809 p=0.634	B=14.284 p=0.076	B=-1.877 p=0.810	B=3.671 p=0.539
		Interaction	B=-17.686 p=0.560	B=-1.013 p=0.973	B=-9.003 p=0.751	B=-23.053 p=0.178	**B=-49.290 p=0.007**	**B=-44.727 p=0.002**
	Ln(LF/HF)	Ln(LF/HF)	B=8.007 p=0.419	B=-2.252 p=0.819	B=2.335 p=0.809	B=-2.417 p=0.728	B=-0.618 p=0.936	B=4.113 p=0.503
		Knowledge of true objective	B=-4.520 p=0.649	B=-1.035 p=0.917	B=2.440 p=0.802	B=10.700 p=0.206	B=-2.984 p=0.747	B=3.487 p=0.636
		Interaction	B=26.039 p=0.218	B=37.250 p=0.082	B=21.812 p=0.292	B=13.405 p=0.256	B=16.632 p=0.209	B=8.503 p=0.414

Table S4. Analysis of the relationship between changes in orbital prefrontal oxyhemoglobin concentration/HRV and mood changes due to visual stimulation by nature images in pure depression group, anxiety disorder group, and comorbidity group. We conducted a regression analysis using changes in orbital prefrontal oxygenated hemoglobin concentration/HRV, recognition of the study's objective, and their interactions as independent variables, and mood changes as the dependent variable. Statistically significant results (p<0.05) are presented in bold.

			Only Depressive Disorders			Only Anxiety Disorders			Comorbid Disorders		
			Comfortable	Relaxed	Vigorous	Comfortable	Relaxed	Vigorous	Comfortable	Relaxed	Vigorous
NIRS (Oxy-Hb Concentration)	Left orbital PFC	Left orbital PFC	B=-4.621 p=0.510	B=-3.742 p=0.568	B=-7.736 p=0.187	**B=-24.141 p=0.015**	B=-9.315 p=0.421	B=-3.409 p=0.694	B=18.620 p=0.444	B=15.614 p=0.598	B=-31.895 p=0.266
		Knowledge of true objective	B=-0.652 p=0.953	B=7.163 p=0.496	B=0.433 p=0.963	B=12.890 p=0.178	B=12.510 p=0.294	B=13.470 p=0.139	B=19.953 p=0.147	B=-9.554 p=0.541	B=3.760 p=0.793
		Interaction	B=18.624 p=0.262	B=23.467 p=0.135	B=18.128 p=0.188	**B=30.259 p=0.011**	B=15.864 p=0.255	B=3.288 p=0.751	B=-26.438 p=0.306	B=-10.349 p=0.734	B=38.996 p=0.199
	Ricgt orbital PFC	Right orbital PFC	B=-1.102 p=0.889	B=-5.409 p=0.472	B=4.017 p=0.548	B=-13.716 p=0.270	B=-10.665 p=0.439	B=-4.163 p=0.677	B=15.318 p=0.395	B=14.288 p=0.493	B=1.940 p=0.928
		Knowledge of true objective	B=0.266 p=0.982	B=4.514 p=0.687	B=7.171 p=0.475	B=14.652 p=0.180	B=8.645 p=0.471	B=10.544 p=0.233	B=20.531 p=0.146	B=-8.662 p=0.569	B=13.221 p=0.418
		Interaction	B=7.992 p=0.656	B=12.317 p=0.470	B=-4.906 p=0.746	B=16.140 p=0.284	B=10.979 p=0.510	B=-0.686 p=0.955	B=-20.221 p=0.300	B=-10.210 p=0.642	B=4.007 p=0.862
HRV	Ln(HF)	Ln(HF)	B=0.259 p=0.985	B=-2.183 p=0.870	B=-2.122 p=0.855	B=2.523 p=0.671	B=-0.879 p=0.877	B=2.239 p=0.581	B=33.583 p=0.123	B=35.515 p=0.155	B=18.373 p=0.501
		Knowledge of true objective	B=-1.844 p=0.875	B=8.398 p=0.461	B=1.960 p=0.844	B=11.120 p=0.275	B=0.541 p=0.955	B=6.808 p=0.326	B=25.949 p=0.092	B=-1.324 p=0.931	B=21.336 p=0.275
		Interaction	B=-18.550 p=0.558	B=1.587 p=0.958	B=-12.554 p=0.639	B=-31.814 p=0.163	**B=-57.557 p=0.013**	**B=-47.889 p=0.005**	B=-33.139 p=0.304	B=-46.704 p=0.226	B=-36.148 p=0.412
	Ln(LF/HF)	Ln(LF/HF)	B=7.807 p=0.447	B=-1.786 p=0.856	B=0.599 p=0.947	B=-2.711 p=0.717	B=0.047 p=0.996	B=3.962 p=0.533	B=-12.357 p=0.767	B=-14.357 p=0.761	B=-73.624 p=0.068
		Knowledge of true objective	B=-6.811 p=0.537	B=-0.167 p=0.987	B=-0.999 p=0.918	B=2.601 p=0.817	B=2.111 p=0.870	B=9.760 p=0.312	B=17.450 p=0.380	B=-10.778 p=0.621	B=36.021 p=0.056
		Interaction	B=27.641 p=0.217	B=35.785 p=0.104	B=21.736 p=0.271	B=29.119 p=0.083	B=19.670 p=0.294	B=8.040 p=0.558	B=10.653 p=0.808	B=18.735 p=0.707	B=79.779 p=0.063

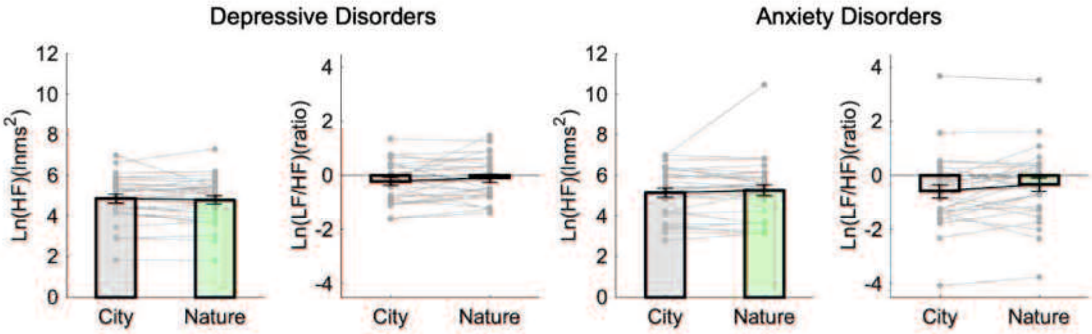

Figure S1. The effect of visual stimulation by nature images on HRV. Ln(HF) is the natural logarithm of the average value of HF over 3 minutes. Ln(LF/HF) is the natural logarithm of the 3-minute average value of the LF to HF ratio. Considering the significant variability present in HRV data, it is common practice to apply a natural logarithm transformation during the analysis phase to stabilize variance (Song et al., 2018b). A higher Ln(HF) reflects an increase in parasympathetic nervous activity. A higher Ln(LF/HF) indicates increased sympathetic nervous activity. The results on the left pertain to the depression group, while the results on the right are for the anxiety group. No significant changes were observed in either group using paired t-tests or the Wilcoxon rank-sum test. Due to missing data, one case from each of the depression and anxiety groups was excluded, resulting in a sample size of n=29 for both groups.

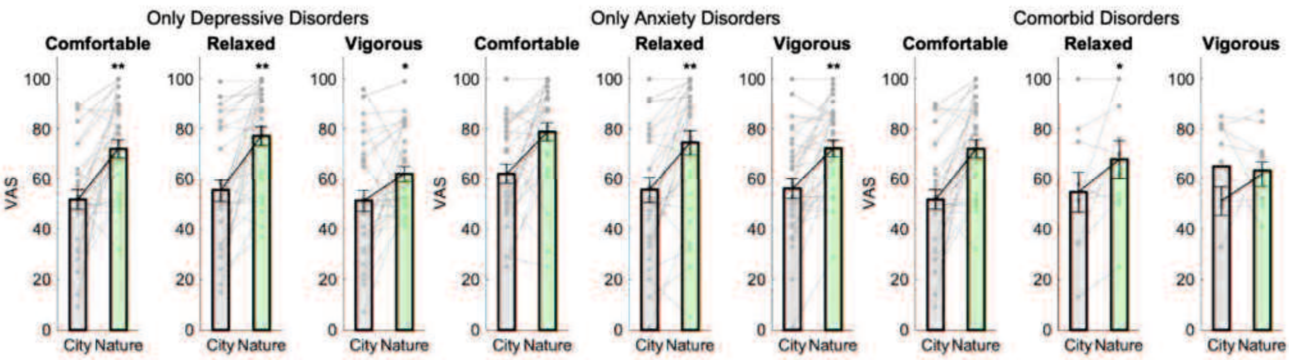

Figure S2. The effect of visual stimulation by nature images on mood in pure depression group, anxiety disorder group, and comorbidity group. Gray represents mood values after viewing city images, while green indicates mood values after viewing nature images. The left diagram represents the pure depression group, the center diagram represents the pure anxiety group, and the right diagram represents the comorbidity group. In the pure depression group, there was a significant improvement in all mood items. In the anxiety group, significant improvements were observed in the "Relaxed" and "Vigorous" categories. In the comorbidity group, a significant improvement was seen only in the "Relaxed" category. * $p < 0.05$, ** $p < 0.01$, repeated measures ANOVA with the study's purpose recognition as a covariate.

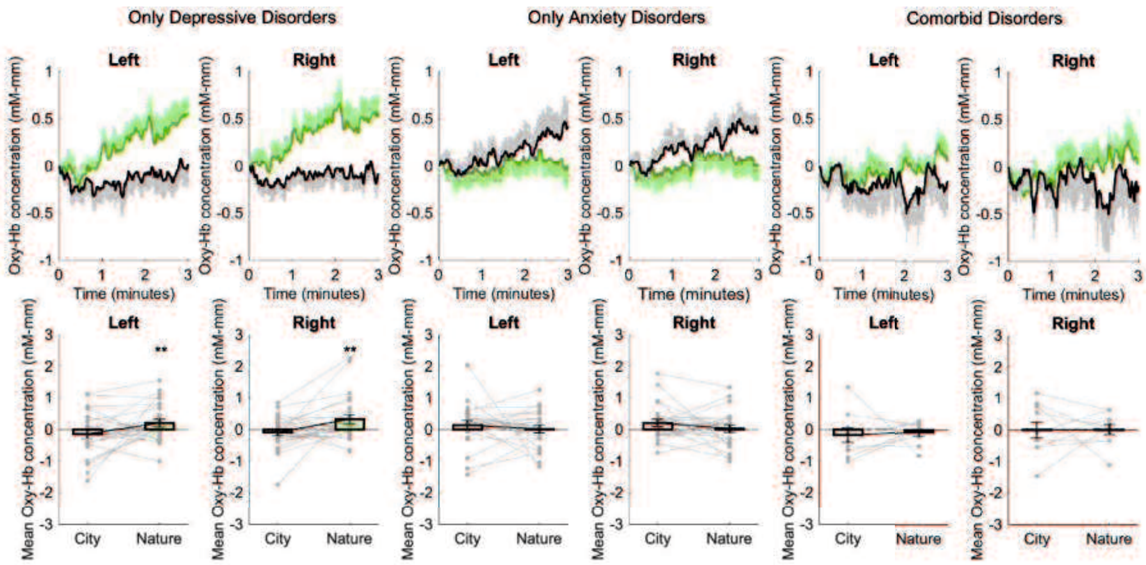

Figure S3. The effect of visual stimulation by nature images on orbital prefrontal oxyhemoglobin concentration in pure depression group, anxiety disorder group, and comorbidity group. In the upper panels, the green and black lines represent the temporal changes in the average oxygenated Hb concentration during the intervention for nature (= green) and city (= black) images, respectively. The green and black shadows indicate the standard error. The lower panels show the average values during the intervention, with green representing nature and gray representing city. In the pure depression group, a significant increase in the orbital prefrontal oxygenated hemoglobin concentration was observed after visual stimulation by nature images. No significant changes were observed in the anxiety group or the comorbidity group. ** $p < 0.01$, repeated measures ANOVA with the study's objective recognition as a covariate.

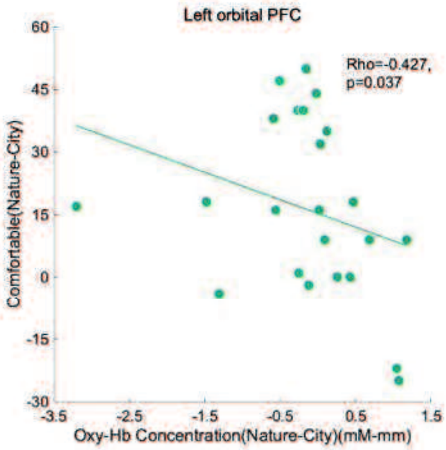

Figure S4. Relationship between changes in orbital prefrontal oxyhemoglobin concentration and mood changes due to visual stimulation by nature images in the pure anxiety disorder group. The horizontal axis represents the change in the concentration of orbital prefrontal oxygenated hemoglobin due to the visual stimulation of nature images compared to the control, which is city images. This result is derived by subtracting the values from the city images from those of the nature images. The vertical axis represents the mood change in "Comfortable" due to visual stimulation of nature images compared to urban ones, and again, the result is obtained by subtracting the values from the city images from those of the nature images. In the pure anxiety disorder group, a statistically significant negative correlation was observed between the change in left orbital prefrontal oxygenated hemoglobin concentration due to the visual stimulation of nature images and the change in "Comfortable" (Rho=-0.427, p=0.037). A regression line is plotted to visually represent this association. PFC, prefrontal cortex.

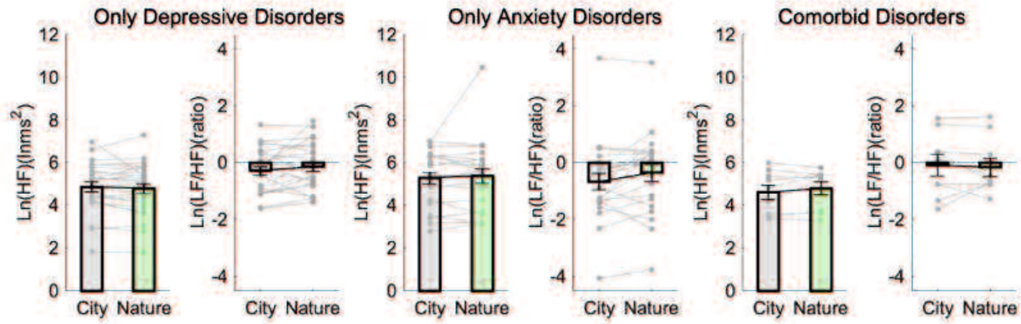

Figure S5. The effect of visual stimulation by nature images on HRV in pure depression group, anxiety disorder group, and comorbidity group. Ln(HF) is the natural logarithm of the average value of HF during the intervention. Ln(LF/HF) is the natural logarithm of the average value of the LF to HF ratio during the intervention. A higher Ln(HF) reflects increased parasympathetic nervous activity. A higher Ln(LF/HF) indicates increased sympathetic nervous activity. The left results are from the pure depression disorder group, the center results are from the pure anxiety disorder group, and the right results are from the comorbidity group. In the repeated measures ANOVA with the study's objective recognition as a covariate, no significant changes were observed in any groups. Due to missing data, one case each was excluded from the pure anxiety disorder group and the comorbidity group, resulting in n=23 for the pure anxiety disorder group and n=9 for the comorbidity group.

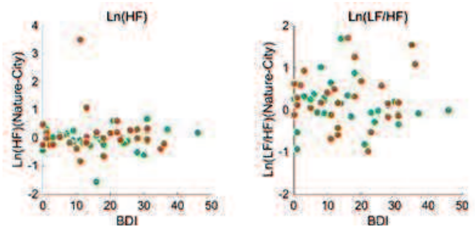

Figure S6. Relationship between depressive symptoms and HRV changes due to visual stimulation by nature images. No significant correlations were found.

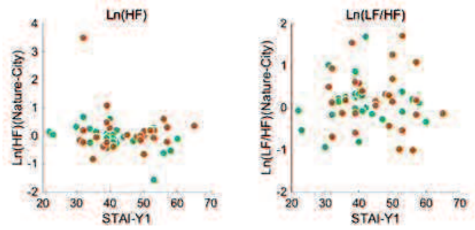

Figure S7. Relationship between anxiety symptoms and HRV changes due to visual stimulation by nature images. No significant correlations were found.