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Horticultural activity in soil inoculated with *Streptomyces rimosus* improved depressive mood with altered electroencephalogram and serum metabolism in adults

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This study investigated the psychophysiological and metabolomic changes during horticultural activities involving the inhalation of volatile organic compounds (VOCs) in individuals experiencing depressive mood based on the presence or absence of the soil microbe *Streptomyces rimosus*, which emits VOCs. Thirty participants met the specific depression and anxiety criteria and engaged in horticultural activities using soil inoculated with *S. rimosus* (experimental group) or medium (control group). Electroencephalogram (EEG) was used to analyze the resulting psychophysiological response, and blood samples were collected after each activity. Significant increases were observed in the FZ channel of the central frontal lobe for relative theta, relative alpha, relative slow alpha, ratio of sensorimotor rhythm mid beta to theta, and ratio of alpha to high beta, whereas significant decreases were noted for relative beta, relative high beta, and relative gamma and spectral edge frequency 50% and 90%. GC-TOF-MS analysis identified 44 altered serum metabolites, showing an increasing trend in succinate, glycolate, glycerate, acetate, palmitate, myristate, laurate, caprynate, and octanoate, which are related to the citrate cycle, glyoxylate and dicarboxylate metabolism, and fatty acid biosynthesis. In conclusion, this study suggests that inhalation of VOCs during horticultural activities can help alleviate depression and depressive moods.

Keywords Depressive mood, Soil microorganism, Volatile organic compounds, Electroencephalogram, Serum metabolomics, Horticultural therapy

The importance of mental health has grown with the advancement of society. In South Korea, which has the highest suicide mortality rate among OECD countries, "several days of continuous depressive mood" and "several days of continuous anxiety" are the second and fourth most experienced mental health issues at 40.2% and 34.1% of the total population, respectively[1,2]. However, only 27.7% individuals have sought professional help to resolve these issues[1]. The most prominent reason that Korean citizens are reluctant to seek medical help is their negative view of seeking treatment for mental health problems. Not thinking of it as a big issue, worry about potential downfalls due to medical reports, and the belief that mental health problems should be handled alone are some other reasons[1]. Therefore, alternative methods for alleviating and preventing mental health issues must be explored.

Plant-mediated therapy (PMT) can be described as an alternative treatment that is provided by a trained professional and involves horticultural activities with a therapeutic goal and objective for improving of recovering health[3]. PMT provides an alternative approach to traditional therapy, in which participants engage in various activities involving plants as resources, such as gardening. This approach is based on the biophilia theory proposed by Wilson (1984)[4], which suggests that humans have an innate affinity for nature and natural elements. Recent studies have reported physiological and physical effects of PMT. Visual stimulation of green plants, tactile stimulation of natural elements such as grass and wood, and olfactory stimulation via herbal oils have been reported to induce physiological relaxation[5–7]. The effects of gardening have also been observed at

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the metabolic level. Older adults who participated in gardening activities expressed increased brain derived neurotrophic factor levels in blood serum, indicating improved cognitive function[8].

While most studies have focused on the mechanisms between people and plant interactions, few studies have focused on the relationship between people and the soil, along with its inhabitants. Soil microorganisms act as decomposers in the ecosystem by releasing inorganic nutrients into the soil to promote plant growth[9]. The species chain *Streptomyces* produces metabolites that promote plant growth and alleviate plant stress. *Streptomyces griseus* produces streptomycin, an antibiotic that removes pathogens from the soil and promotes soil health[10]. Microorganisms release various volatile organic compounds (VOCs) into the environment. Geosmin and 2-methylisoborneol, are released by *Streptomyces rimosus*, which gives off the distinct earthy musk of soil. Psychophysiological and metabolic differences have been observed when performing horticultural activities using soil inoculated with *S. rimosus* compared with sterilized soil[11].

Electroencephalography (EEG) analysis revealed activity related to psychophysiological comfort in the occipital lobe, and an increase in serotonin levels in the blood serum was also observed when conducting a short soil-mixing activity with soil inoculated with *S. rimosus*[12]. Serotonin is a neurotransmitter and one of the final products of tryptophan metabolism pathway. Although recent studies have suggested that serotonin and depressive disorders have little to no correlation[13], serotonin is also known to regulate mood and cognitive functions[14]. Low serotonin levels caused by tryptophan depletion cause acute depressive relapse in patients with remitted depression[15]. While other factors come into play, low serotonin levels can contribute to a lower or depressed mood state[14] and normalized serotonin levels may help alleviate depressive moods.

With the current population experiencing mental health issues, such as prolonged depressive mood and reluctance to seek professional assistance to alleviate these issues, an alternative non-clinical approach is needed to bridge this gap. Horticultural activities not only provide comfort to participants through interaction with plants and fulfillment of the innate affinity toward nature, but could also alleviate depressive moods via exposure to soil-derived metabolites. While the aforementioned studies suggest these effects, a clearer conclusion can be drawn by observing the effects on people experiencing depressive moods.

Therefore, this study aimed to observe the psychophysiological and metabolomic effects of horticultural activities in soil inoculated with *Streptomyces rimosus* in adults with depressive moods and anxiety.

Materials and methods

Participants

This study recruited adults aged 20–65 years. Left hand dominant participants were excluded from the study to avoid criteria that might have affected electroencephalographic data. Participants diagnosed with or prescribed medications for depression or other psychological disorders were also excluded from the study. Flyers, including the purpose of the study and recruitment requirements, were posted in libraries and community centers in G Province, Korea.

Participants who responded to the flyer were screened using the Korean version of the Beck's Depression Index I (K-BDI-I)[16,17] and the Korean version of the State-Trait Anxiety Inventory (K-STAI)[18,19]. Participants who scored > 10 on the K-BDI-I or > 37 on the K-STAI were included in the study. A total of 48 participants responded to the initial flyer, of whom 18 were screened for a final total of 30 participants (14 males and 16 females). Participants were asked to refrain from smoking for 3 h before the experiment to eliminate other physiological factors that may affect data collection. Participants were thoroughly informed on the contents and precautions of the experiment before proceeding, and voluntary written consent was obtained. Demographic data (sex, age, height, weight, and body mass index [IOI 353; Jawon Medical, Gyeongsan, Republic of Korea]) were recorded after obtaining informed consent. Olfactory function was assessed using the Scent Survey for Screening (SSS) test[20]. Participants received a small incentive of approximately 33 USD upon completion of the experiment. The protocol was designed in accordance with the Declaration of Helsinki, Bioethics and Safety Act of South Korea and the standard operating procedures of the Institutional Review Board of Konkuk University. The protocol and experimental guidelines were reviewed and approved by the Institutional Review Board of Konkuk University (7001355-2023-HR-642).

Experimental environment

An area (150 × 200 cm) within a room on the Konkuk University campus in Seoul was prepared for the experiment by installing ivory-colored curtains around a white desk (90 × 180 cm) to limit other visual stimuli. The average temperature was 25.25 ± 1.30 °C and the average humidity was 52.59 ± 9.00%. The environment was sterilized with alcohol and thoroughly ventilated for 10 min between each recording.

Preparation of the soil sample

Streptomyces rimosus Korean Agricultural Culture Collection (KACC) 20,082 was obtained from the KACC, Republic of Korea. *S. rimosus* was cultured on tryptic soy broth for 4 days at 27 °C by shaking (250 rpm). A total of two types of soil were used in this study, and the common mixed materials were peat moss (2000 mL), perlite (800 mL), and water (200 mL). To prepare samples in a sterile state, peat moss and perlite were autoclaved at 121 °C for 15 min. Culture medium (100 mL) without microorganisms was mixed with the soil mixture and used as the control group soil, whereas *S. rimosus* medium (100 mL) was added to the soil mixture and used as the experimental group soil.

Experimental protocol

Participants were asked to sit in an experimental environment facing forward and rest for 5 min. After resting, participants performed a horticultural activity for 20 min. The horticultural activity was a seed sowing activity divided into four parts (mixing soil, filling seeding tray with soil, sowing tray with white *Phaseolus vulgaris*

beans, and spraying with water) that lasted for 5 min each. The following activity was selected to avoid visual or emotional stimulation from green plants and maximize soil exposure[11]. Blood samples (5 mL) were collected from the brachial vein after the activity. Participants performed the activity with soil without microorganisms, which served as the control, and with soil with *S. rimosus*, which served as the experimental group. Participants performed horticultural activities with each case in a randomized crossover study, with at least a week apart from each recording. Total experimental time of each visit was approximately 50 min.

Measurements

EEG measurement

EEG data were recorded during each horticultural activity to measure psychophysiological responses according to exposure to soil microorganisms. A 20-channel wireless dry-electrode electroencephalograph device (Quick-20; Cognionics, San Diego, CA) was used during this experiment. The left earlobe (A1) served as the reference. EEG data were collected from electrodes corresponding to the frontal (Fz, F3, F4, F7, and F8) and prefrontal cortex (Fp1 and Fp2). Data from the frontal cortex have been observed in several studies showing significant activity in the frontal region after exposure to olfactory stimulation[21,22]. EEG activity according to olfactory stimulation was also observed in the prefrontal cortex in a previous study[7], and prefrontal cortex EEG activity also served as a potential non-invasive biomarker for depression[23].

Extraction and analysis of S. rimosus VOCs

Headspace solid-phase microextraction (HS-SPME) was performed on three biological replicates of tryptic soy broth and *S. rimosus* bacterial suspension. *S. rimosus* was cultured in a baffled flask (125 mL) on tryptic soy broth (50 mL) with 1% (v/v) inoculation for 4 days at 27 °C by shaking (250 rpm). After cultivation, 8 mL of broth and bacterial suspension was transferred into a 20 mL headspace vial with a PTFE septum and screw cap. To profile VOCs, each vial was maintained at 50 °C for 30 min. Subsequently, VOCs from the headspace of each vial were collected using a 50/30 µm DVB/CAR/PDMS (divinylbenzene/carboxen/polydimethylosiloxane) -coated SPME fiber (Sigma-Aldrich, St. Louis, MO) using an L-PAL3 autosampler (LECO Corporation).

Before exposure, the SPME fiber was preheated at 250 °C for 30 min, injected into the SPME vial and exposed to the headspace of the samples at 50 °C for 30 min with 250 rpm for emission of the VOCs. The fiber containing the VOCs was then automatically injected into an Agilent 7890 A GC system (Agilent Technologies, Palo Alto, CA) coupled with a Pegasus HT TOF-mass spectrometry (MS) (LECO Corp., St. Joseph, MI) for desorption for 5 min. Chromatographic separation was conducted using an Rtx-5MS column (30 m × 0.25 mm, 0.25 µm particle size; Restek Corp., St. Joseph, MI) with helium as the carrier gas at a flow of 1.0 mL/min. After desorption, the oven temperature was initially held at 40 °C for 3 min, further increased to 150 °C at a rate of 4 °C/min and held for 1 min, and further increased to 250 °C at a rate of 8 °C/min and held for 2 min. The transfer line temperature was 260 °C and the mass spectra were scanned from 33 to 300 m/z at a rate of 10 scans.

Measurement of serum metabolites

Blood samples (5 mL) were collected before and after each horticultural activity. Trained professionals collected the blood samples, placed them in ice packs, and transported them to the analysis site. Serum samples were maintained at room temperature for 20 min and then separated by centrifugation at 1000 x g for 10 min at 4 °C. Aliquots were then stored in a deep freezer at -70 °C. Serum metabolite extraction and gas chromatography/time-of-flight (GC-TOF) MS analysis were conducted. Human serum sample (100 µL) was transferred into a 2 mL Eppendorf tube and 600 µL of cold methanol including internal standard (2-chlorophenylalanine, 10 mg/L in methanol) was added to the tube, and the mixture was vortexed for 1 min. The mixture was homogenized for 10 min at 30 Hz using a mixer mill (MM400; Retsch, Haan, Germany) and sonicated for 10 min. After homogenization, the suspension was stored at -20 °C for 60 min. It was then centrifuged at 13,000 rpm at 4 °C for 10 min, and the supernatant was filtered through a 0.2 µm polytetrafluoroethylene filter and completely evaporated using a speed vacuum concentrator.

The final concentration of each sample was dissolved to 5 mg/mL with methanol for MS analysis. For derivatization, 100 µL of the 5 mg/mL sample extract was collected in 1.5 mL Eppendorf tubes and completely dried using a speed vacuum concentrator. The derivatization reaction involved oximation and silylation. For oximation, 50 µL of methoxyamine hydrochloride (20 mg/mL in pyridine) was added to the dried extract, and the mixture was incubated for 90 min at 30 °C. Next, silylation was performed by adding 50 µL of N-methyl-N-(trimethylsilyl) trifluoroacetamide to the mixture, followed by incubation for 30 min at 37 °C. All derivatized samples were filtered using a 0.2 µm polytetrafluoroethylene filter prior to instrument analysis, and 1 µL of the derivatized samples were injected into the GC-TOF-MS instrument. An Agilent 7890 B GC system (Agilent Technologies, Palo Alto, CA) comprising an Agilent 7693 autosampler coupled with a TOF Pegasus BT mass spectrometer (LECO, St. Joseph, MI), was used for GC–TOF-MS analysis. An RTX-5MS column (30 m × 0.25 mm, 0.25 µm particle size; Restek Corp., Bellefonte, PA) was used, with helium as the carrier gas at a flow rate of 1.0 mL/min. The samples were injected at a split ratio of 15:1. The oven temperature was initially held at 75 °C for 2 min, then further increased to 300 °C at a rate of 15 °C/min and held for 3 min. The transfer line temperature was 250 °C and the mass spectra were scanned from 50 to 600 m/z at a rate of 10 scans.

Data analysis

EEG data analysis

EEG data were recorded, processed, and analyzed using Bio-scan (Bio-Tech, Daejeon, Republic of Korea).

Demographic information and descriptive statistics of the means and standard deviations of all collected data, along with a paired t-test of the EEG data, were calculated using SPSS (version 26 for Windows; IBM, Armonk, NY). The significance level was set at $p < 0.05$.

Metabolite data analysis

MS data processing and multivariate statistical analyses were performed, as previously described. For MS data processing, the raw data obtained from GC-TOF-MS were converted to netCDF (*.cdf) format using LECO Chroma TOF software (version 4.44, LECO Corp., St. Joseph, MI). Subsequently, peak selection, retention time, and peak alignment were determined using MetAlign software (RIKILT-Institute of Food Safety, Wageningen, The Netherlands). Alignment data were exported to Microsoft Excel. Multivariate statistical analyses were performed using SIMCA-P + ver. 12.0 software (Umetrics, Urea, Sweden). Orthogonal partial least squares-discriminant analysis (OPLS-DA) was performed to compare different metabolites. The significance of the OPLS-DA model was determined by an analysis of variance (ANOVA) of cross-validated predictive residuals using the SIMCA-P + program. Different metabolites were selected based on their variable importance in the projection (VIP) value of the OPLS-DA model. In addition, a significance test ($p < 0.05$) between replicates was performed using ANOVA and Duncan's multiple-range tests using Predictive Analytics SoftWare (PASW) Statistics 18 (SPSS, Inc., Chicago, IL). The metabolites were identified by comparing their retention time and mass fragment data (through MS) with available databases such as the Human Metabolome Database (2023), National Institute of Standards and Technology database (version 2.0, 2011; FairCom, Gaithersburg, MD), Wiley 9 database (Wiley VCH, Weinheim, Germany), and our in-house library of standard compounds. A correlation map was obtained using PASW (SPSS Inc., Chicago, IL). Pathway analysis was conducted to identify altered metabolic pathways using MetaboAnalyst 6.0 (https://www.metaboanalyst.ca/), and the Kyoto Encyclopedia of Genes and Genomes database[24] was used as the reference metabolic pathway.

Results

Demographic information

Demographic information is shown in Table 1. The average age of participants was 25.00 years. The average height, weight, and body mass index of male and female participants complied with those of the Korean population. The average SSS score was 88.10, indicating that all participants had normally functioning olfactory systems and had no difficulty smelling or recognizing odors. The average BDI-I and STAI scores were 15.23 and 50.40, respectively. Scores above 11 on the BDI-I indicate a depressive mood, while a score above 38 on the STAI indicates a state of mild anxiety. Through this screening process, participants experiencing depressive mood and anxiety were recruited.

Volatilome profiling of *S. Rimosus*

VOCs with VIP values > 1.0 were selected and identified through the OPLS-DA model (Supplementary Figure S1) comparing the broth and *S. rimosus* bacterial suspension. A total of 22 compounds were identified in the VOCs of *S. rimosus* using HS-SPME-GC-TOF-MS (including 10 sesquiterpenes, 3 monoterpenes, 2 organosulfur compounds, 3 hydrocarbons, and 4 others), with sesquiterpenes and monoterpenes being the major compound classes (Table 2). The compound 2-methylisoborneol (2-MIB) exhibited the highest relative content (37.74%), making it the most prominent compound, followed by geosmin (23.55%), which is also a major component. Other compounds include 2-methyl-2-bornene (16.66%) and 3-caren-10-al (10.63%).

Psychophysiological response

Relative theta (RT), relative alpha (RA), relative slow alpha (RSA), ratio of sensorimotor rhythm mid beta to theta (RSMT), and ratio of alpha to high beta (RAHB) power spectra in the central frontal lobe (Fz) were significantly higher when performing horticultural activities with soil inoculated with *S. rimosus* than when using sterilized soil ($p < 0.05$), while relative beta (RB), relative high beta (RHB), relative gamma (RG) power spectra in the same channel was significantly lower ($p < 0.05$) (Table 3). RA and RSA are indicators of relaxation and passive attention, respectively[25]. RSMT is widely considered an indicator of neurophysiological concentrations[26,27]. RAHB is an indicator of relaxation and recovery from stress[28]. Spectral edge frequency 50% (SEF50) and 90% (SEF90) indices in the central frontal lobe (Fz) were significantly lower for soil inoculated with *S. rimosus*. SEFs are indicators of overall brain activation and are used as indices of brain stress[29,30].

Metabolite analysis of serum after horticultural activity

Based on the VOCs from *S. rimosus*, GC-TOF-MS-based metabolite profiling was conducted to assess the metabolite levels in serum samples after horticultural activity in the experimental (SRI) group compared with

	Total ($N = 30$)	Male($n = 14$)	Female($n = 16$)
Age (years)	25.00 ± 6.55	24.79 ± 4.46	25.19 ± 8.10
Height (cm)	166.23 ± 6.55	172.51 ± 5.53	160.73 ± 4.25
Weight (kg)	62.91 ± 11.45	71.24 ± 9.25	55.63 ± 6.61
BMI[1] (kg/cm^2)	22.51 ± 2.69	23.49 ± 2.67	21.66 ± 2.47
SSS[2]	88.10 ± 9.39	90.29 ± 8.13	86.19 ± 10.23
BDI-I[3]	15.23 ± 10.45	12.86 ± 8.47	17.31 ± 11.80
STAI[4]	50.40 ± 9.73	50.57 ± 10.50	50.25 ± 9.35

Table 1. Demographic information of participants. [1]Body mass index; [2]Scent screening survey; [3]Beck's Depression Index I; [4]State-Trait Anxiety Index.

No.	Tentative identification[a]	RT (min)[b]	VIP	Unique mass(m/z)	Mass fragmentation(m/z)	ID[c]	Relative content (%)[d]	Similarity[e]
	Sesquiterpenes							
1	α-Cubebene	24.21	1.05	119	119, 105, 81, 91, 161, 55, 65, 77, 43, 107	MS	0.04	865
2	β-Elemene	25.60	1.07	81	93, 67, 79, 81, 68, 91, 41, 107, 53, 105	MS	0.04	892
3	Geosmin	25.95	1.10	112	112, 55, 41, 43, 67, 111, 97, 69, 81, 79	MS	23.55	885
4	Germacrene D	26.44	1.07	161	91, 105, 79, 161, 41, 120, 133, 92, 93, 119	MS	0.02	833
5	γ-Elemene	27.62	1.09	107	79, 107, 93, 91, 105, 77, 67, 55, 41, 94	MS	0.10	836
6	Dihydroagarofuran	27.88	1.09	81	81, 43, 41, 79, 207, 67, 95, 93, 55, 107	MS	0.70	794
7	Ledene	28.22	1.08	107	107, 91, 41, 105, 79, 93, 81, 55, 77, 53	MS	0.04	783
8	γ-Gurjunene	28.91	1.07	107	107, 79, 91, 105, 93, 41, 81, 77, 67, 119	MS	0.19	837
9	Calamenene	29.64	1.06	129	159, 129, 131, 128, 115, 160, 142, 141, 91, 77	MS	0.11	829
10	Elemol	33.10	1.08	79	59, 43, 67, 79, 93, 91, 81, 82, 41, 105	MS	0.14	778
	Monoterpenes							
11	3-Caren-10-al	11.04	1.10	107	107, 79, 91, 93, 41, 77, 67, 105, 39, 121	MS	10.63	833
12	2-Methyl-2-bornene	12.25	1.10	107	79, 107, 91, 93, 94, 41, 77, 95, 135, 39	MS	16.66	842
13	2-Methylisoborneol	18.48	1.10	95	95, 107, 43, 79, 41, 91, 108, 93, 67, 39	MS	37.74	879
	Organosulfur compounds							
14	S-Methyl butanethioate	6.32	1.03	71	43, 71, 41, 48, 47, 39, 75, 45, 118, 49	MS	0.02	854
15	Dimethyl trisulfide	10.52	1.07	126	126, 79, 45, 47, 64, 80, 46, 111, 61, 128	MS	0.86	958
	Hydrocarbons							
16	5-Undecen-3-yne	12.62	1.10	80	80, 79, 77, 71, 41, 43, 91, 107, 55, 93	MS	0.10	755
17	1,3-Dimethyladamantane	20.68	1.10	149	149, 93, 81, 91, 79, 107, 67, 77, 41, 105	MS	0.58	835
18	3-Decen-5-yne, 2,2-dimethyl-	20.90	1.09	93	93, 108, 67, 79, 91, 77, 121, 109, 81, 41	MS	0.87	811
	Etcs.							
19	1,3-Di(propan-2-yl)cyclopenta-1,3-diene	10.83	1.10	107	107, 91, 135, 93, 79, 77, 105, 122, 41, 39	MS	5.03	837
20	(2,2,6-Trimethyl-bicyclo[4.1.0]hept-1-yl)-methanol	18.57	1.10	86	81, 107, 43, 41, 69, 79, 80, 71, 85, 86	MS	0.23	751
21	1 H-Indene, 1-ethylideneoctahydro-7a-methyl-, cis-	19.50	1.10	149	149, 67, 81, 79, 93, 91, 109, 107, 77, 41	MS	0.23	821
22	1,1,4,4-Tetramethyl-2,6-bis(methylene)cyclohexane	20.28	1.10	149	93, 79, 67, 91, 149, 108, 81, 107, 77, 121	MS	2.09	838

Table 2. The main volatile organic compounds of *Streptomyces rimosus* based on HS-SPME-GC-TOF-MS. [a]Identified compounds based on HS-SPME-GC-TOF-MS; [b]Retention time; [c]MS, mass spectrum compared with the National Institute of Standards and Technology (NIST) database; [d]Relative content has been calculated as the ratio between the area of the specific compound and the sum of the areas of all identified peaks in the chromatogram; [e]A number defined by the NIST search algorithm that is between zero and 999 describing how well the library hit matches the peak using all masses.

		RT[1]	RA[2]	RSA[3]	RFA[4]	RB[5]	RHB[6]	RG[7]	RSMT[8]	RAHB[9]	SEF50[10]	SEF90[11]
		Mean ± SD[12]										
Fz[13]	CON	0.24 ± 0.07	0.17 ± 0.04	0.11 ± 0.02	0.06 ± 0.01	0.33 ± 0.04	0.18 ± 0.03	0.26 ± 0.07	1.05 ± 0.17	1.03 ± 0.32	16.70 ± 4.15	40.82 ± 2.37
	SRI	0.30 ± 0.08	0.19 ± 0.04	0.13 ± 0.02	0.06 ± 0.02	0.31 ± 0.04	0.15 ± 0.03	0.20 ± 0.07	1.24 ± 0.28	1.33 ± 0.44	13.99 ± 3.91	38.04 ± 3.84
	p-value	0.007**	0.016*	0.012*	0.073^{NS}	0.021*	0.006**	0.006**	0.002**	0.003**	0.012*	0.001***
F3[14]	CON	0.26 ± 0.08	0.18 ± 0.04	0.12 ± 0.03	0.06 ± 0.01	0.32 ± 0.04	0.17 ± 0.04	0.24 ± 0.08	1.12 ± 0.26	1.13 ± 0.44	16.13 ± 4.69	39.92 ± 3.52
	SRI	0.29 ± 0.08	0.18 ± 0.03	0.12 ± 0.03	0.06 ± 0.01	0.30 ± 0.04	0.16 ± 0.03	0.22 ± 0.08	1.24 ± 0.28	1.27 ± 0.48	14.70 ± 4.29	38.88 ± 3.67
	p-value	0.109^{NS}	0.512^{NS}	0.358^{NS}	0.914^{NS}	0.092^{NS}	0.127^{NS}	0.261^{NS}	0.317^{NS}	0.267^{NS}	0.222^{NS}	0.267^{NS}
F4[15]	CON	0.23 ± 0.07	0.17 ± 0.03	0.11 ± 0.03	0.06 ± 0.01	0.33 ± 0.03	0.18 ± 0.03	0.26 ± 0.07	1.02 ± 0.17	0.98 ± 0.31	17/43 ± 4.27	41.04 ± 2.37
	SRI	0.26 ± 0.05	0.17 ± 0.03	0.12 ± 0.02	0.06 ± 0.01	0.32 ± 0.02	0.17 ± 0.02	0.25 ± 0.06	1.07 ± 0.15	1.05 ± 0.35	16.09 ± 3.57	40.42 ± 2.33
	p-value	0.119^{NS}	0.461^{NS}	0.463^{NS}	0.557^{NS}	0.127^{NS}	0.094^{NS}	0.266^{NS}	0.981^{NS}	0.318^{NS}	0.192^{NS}	0.339^{NS}

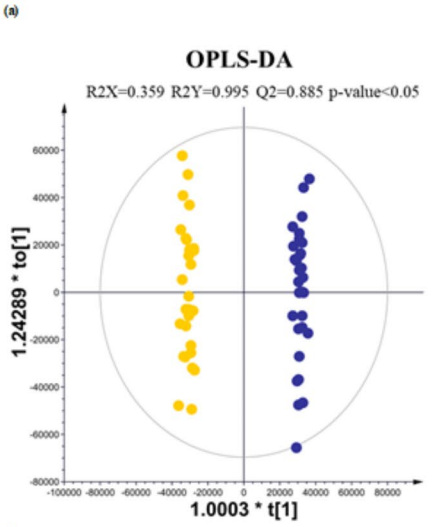
Table 3. Electroencephalography results of the frontal lobe. Analysis by independent *t*-test (^{NS} not significant; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). [1] relative theta. [2] relative alpha. [3] relative slow alpha. [4] relative fast alpha. [5] relative beta. [6] relative high beta. [7] relative gamma. [8] ratio of sensorimotor theta to high beta rhythms [9] ratio of alpha to high beta. [10] spectral edge frequency 50%. [11] spectral edge frequency 90%. [12] standard differentials. [13] central frontal lobe. [14] left frontal lobe. [15] right frontal lobe.

the control (CON) group. The OPLS-DA score plot for the serum dataset showed a clear difference between the CON and SRI groups ($p < 0.05$) (Fig. 1a). A validation plot was constructed with a 200-time permutation test to evaluate the goodness of fit of the model (Fig. 1b). The OPLS model showed perfect goodness of fit, where R2Y [cum] > 0.9 and good predictive quality Q2 [cum] > 0.8. The permutation results showed that the Y-intercept R2 and Q2 values were 0.952 and 0.44, respectively. These results indicate that OPLS was valid and did not overfit, exhibiting good predictive abilities. According to the OPLS-DA model, discriminant metabolites were selected between the CON and SRI groups with VIP values > 1.0 and $p < 0.05$. A total of 44 metabolites were identified (3 carbohydrates and derivatives, 5 carboxylic acids and derivatives, 5 amino acids and derivatives, 13 fatty acids and derivatives, 9 lipids and derivatives, 3 alcohols, and 6 others), and 4 metabolites were unknown (Supplementary Table S1). To visualize all the metabolites, they were plotted on a heat map (Fig. 1c).

According to the heat map analysis, most of the carbohydrates and derivatives, carboxylic acids and derivatives, amino acids and derivatives, fatty acids and derivatives, and lipids and derivatives, except for glucose, 2,3-dihydroxybutanoic acid, methyl stearate, and 2-palmitoylglycerol, were relatively higher in the SRI group than in the CON group. Collectively, most of the metabolites exhibited higher levels in the SRI group.

Pathway analysis and correlation analysis of serum metabolites after horticultural activity

The altered metabolites in the serum samples were subjected to metabolic pathway analysis using MetaboAnalyst 6.0. Important pathways affected by SRI treatment were identified and are shown in Fig. 2. The results showed that



(c)

No.	Tentative identification[a]	SRI/CON[b]
	Carbohydrates and derivatives	
1	Glyceric acid	1.46
2	Arabinose	1.44
3	Glucose	0.80
	Carboxylic acids and derivatives	
4	Glycolic acid	1.27
5	Acetic acid	1.56
6	Carbamic acid	1.65
7	Benzoic acid	1.32
8	Succinic acid	3.40
	Amino acids and derivatives	
9	Carnitine	1.64
10	N-Methyl-L-glutamic acid	2.07
11	Pyroglutamic acid	1.27
12	Threonine	1.97
13	Proline	1.63
	Fatty acids and derivatives	
14	Octanoic acid	2.27
15	Valeric acid	1.38
16	Nonanoic acid	2.58
17	Capric acid	3.32
18	Lauric acid	3.27
19	Myristic acid	1.55
20	Palmitic acid	1.22
21	Stearic acid	1.24
22	Arachidonic acid	1.20
23	2-Hydroxy-2-methylbutyric acid	1.37
24	2,3-Dihydroxybutanoic acid	0.79
25	2-Hydroxy-3-methylpentanoic acid	3.36
26	Erythronic acid	2.12
	Lipids and derivatives	
27	Methyl stearate	0.56
28	Hexadecanamide	1.19
29	Oleamide	1.21
30	Monomyristin	1.21
31	Monopalmitin	1.05
32	2-Palmitoylglycerol	0.89
33	2-Stearoylglycerol	1.12
34	Glycerol monostearate	1.10
35	Glyceryl monolinolenate	1.39
	Alcohols	
36	Ethylene glycol	0.73
37	Propylene glycol	0.61
38	Glycerol	1.15
	Ethers	
39	Ethoxylamine	0.92
40	Hydroxylamine	0.92
41	Nicotinic acid	1.18
42	Dodecane	1.31
43	Phosphoric acid	1.67
44	3-Hydroxybutyryl carnitine	2.26
	N.I.D.[c]	
	N.I.D. 1	0.63
	N.I.D. 2	2.44
	N.I.D. 3	1.57
	N.I.D. 4	1.55

Fig. 1. (a) Orthogonal partial least squares-discriminant analysis (OPLS-DA) score plot derived from the GC-TOF-MS datasets for serum samples. CON (control; soil treated with culture media (yellow circle), SRI (treatment; soil treated with *Streptomyces rimosus* (Violet circle). (b) Validation plot obtained from 200 permutation tests of the predictive OPLS-DA model. (c) Heat map analysis of the relative abundance of different serum metabolites derived from the GC-TOF-MS analysis. The colored squares (blue to red) indicate fold changes that are normalized by the CON group. [a]Identified compounds based on the VIP value (> 1.0) and p (< 0.05) from the OPLS-DA model in Fig. 1a; [b]SRI/CON, change trend in the SRI group compared with the CON group; [c]N.I.D., not identified.

citrate cycle (TCA cycle), glycine, serine and threonine metabolism, glyoxylate and dicarboxylate metabolism, galactose metabolism, glycerolipid metabolism, fatty acid biosynthesis, arachidonic acid metabolism, and starch and sucrose metabolism had pathway impact > 0.1 or -log10(p) > 5 and the metabolic pathways showing 0.0 pathway impact were excluded. The results of pathway topology analysis are presented in Table 4.

To identify the compounds that contributed to EEG activity, we conducted a correlation analysis between EEG activity and significantly altered serum metabolites (Fig. 3). In particular, glucose, glycolic acid, succinic acid, octanoic acid, capric acid, lauric acid, arachidonic acid and glycerol, which were the metabolites involved in important pathways affected by SRI treatment, were significant ($p < 0.05$).

Discussion

This study was conducted to investigate the effects on the psychophysiology and metabolic response of individuals with depression when performing horticultural activities using soil inoculated with soil microorganisms, focusing on VOCs derived from *S. rimosus*. The experiment examined changes based on bacterial inoculation during short-term horticultural activities, assuming that the differences between the CON and SRI groups could be attributed to variations in *S. rimosus* due to the presence or absence of bacteria, leading to olfactory stimulation.

EEG analysis revealed significant changes in the frontal lobe during horticultural activities using soil inoculated with *S. rimosus* compared with using sterilized soil. The frontal lobe is responsible for many functions including cognitive thinking, memory, speech, and motivation[30]. Frontal lobe activity is correlated with many psychological disorders such as depression and dysphoria[31,32].

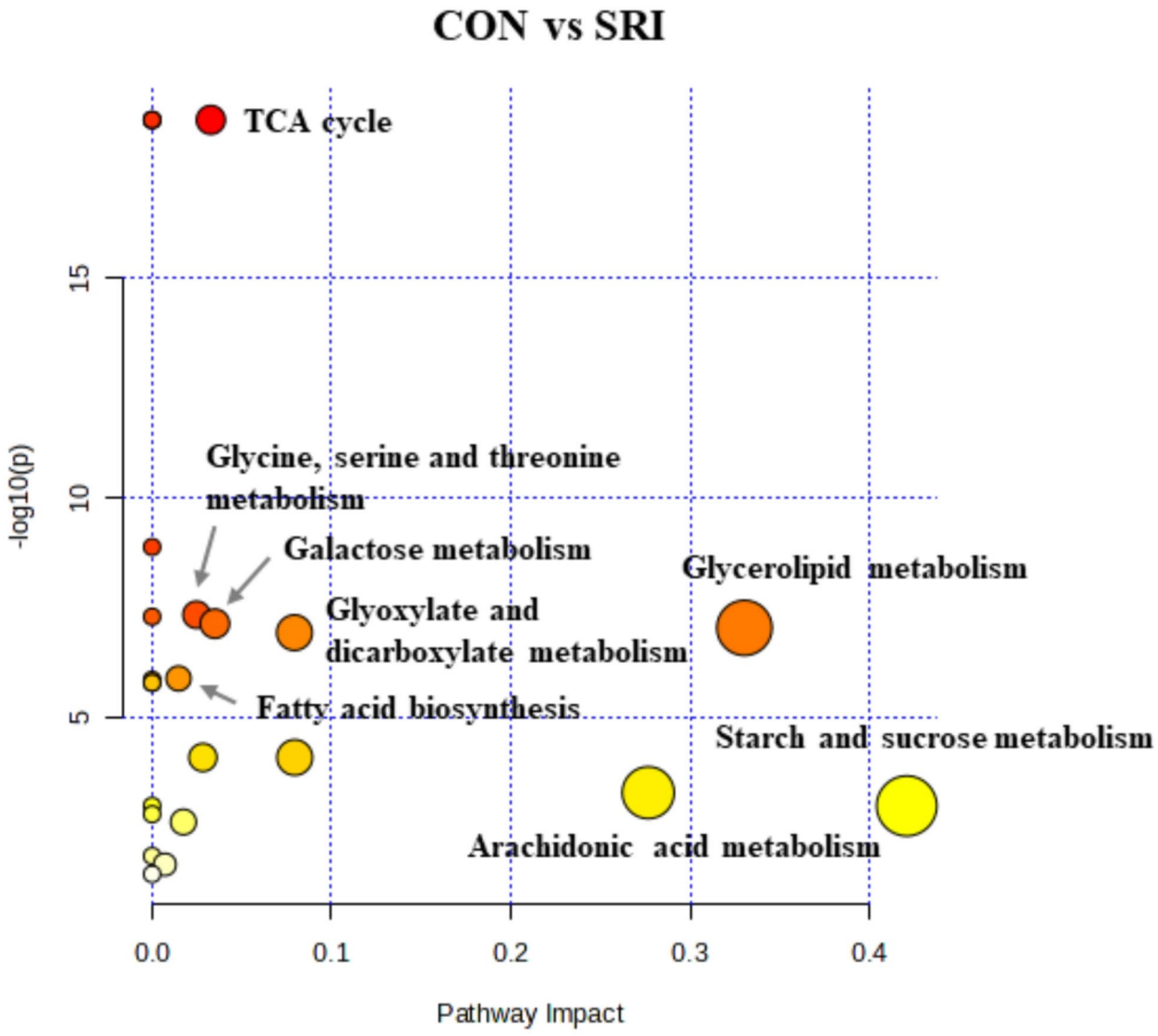


Fig. 2. Pathway analysis of the altered metabolites in the serum based on KEGG pathway networks.

Metabolic pathway	Implicated metabolites	Total[a]	Hits[b]	Raw p[c]	-log10(p)	Holm p[d]	FDR p[e]	Impact[f]
Citrate cycle (TCA cycle)	Succinic acid	20	1	2.55E-19	18.593	5.87E-18	1.47E-18	0.03273
Glycine, serine, and threonine metabolism	Glyceric acid, Threonine	33	2	4.47E-08	7.349	8.05E-07	1.63E-07	0.02475
Glyoxylate and dicarboxylate metabolism	Glycolic acid, Glyceric acid, Acetic acid	32	3	6.59E-08	7.181	1.06E-06	1.82E-07	0.15874
Galactose metabolism	Glucose, Glycerol	27	2	7.13E-08	7.147	1.07E-06	1.82E-07	0.03499
Glycerolipid metabolism	Glycerol, Glyceric acid	16	2	8.88E-08	7.052	1.24E-06	2.04E-07	0.33022
Fatty acid biosynthesis	Palmitic acid, Myristic acid, Lauric acid, Capric acid, Octanoic acid	47	5	1.25E-06	5.902	1.63E-05	2.58E-06	0.01473
Arachidonic acid metabolism	Arachidonic acid	44	1	0.0004929	3.307	0.0034504	0.0006669	0.27659
Starch and sucrose metabolism	Glucose	18	1	0.000985	3.007	0.0059103	0.0011924	0.4207

Table 4. Results of the pathway analysis of differential metabolites. [a] Total number of compounds in the pathway; [b] Number of matched metabolites involved in the metabolic pathway; [c] Original p value calculated from the pathway analysis; [d]p value adjusted by Holm-Bonferroni method; [e]p value adjusted using False Discovery Rate; [f] Pathway impact value calculated from pathway topology analysis.

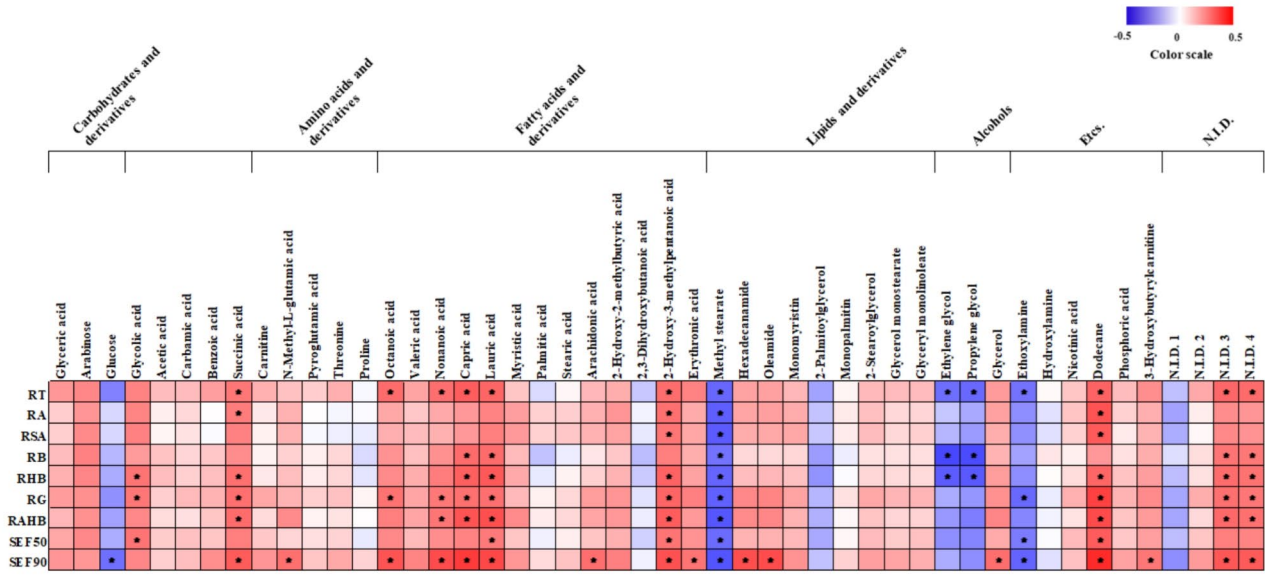


Fig. 3. Correlation map between EEG activity and metabolite levels according to Pearson's correlation coefficient. Each square indicates Pearson's correlation coefficient values (r). Red and blue represent positive ($0 < r < 0.5$) and negative ($-0.5 < r < 0$) correlations, respectively. To ensure visual consistency, the values for RB, RHB, RG, SEF50, and SEF90 have been reversed. Asterisks indicate $p < 0.05$.

VOC analysis revealed volatile terpenes (sesquiterpenes and monoterpenes as the major compound classes) as the primary secondary metabolites produced by *S. rimosus*. Streptomyces belongs to a class of actinomycetes, which produces volatile terpenoids[33–37]. Monoterpenes are generated from geranyl diphosphate and sesquiterpenes from farnesyl diphosphate by terpene cyclase[37–39]. As the major VOCs of *S. rimosus*, 2-MIB and geosmin are responsible for the typical musty and earthy odors. Both the compounds have low odor thresholds, indicating that they can strongly stimulate the human sense of smell, even at low concentrations[37,39–42]. In addition, 2-methyl-2-bornene is a homo-monoterpenoid side product of 2-MIB synthase[38,43]. Through horticultural activities, humans can inhale 2-MIB and geosmin, VOCs produced directly from *S. rimosus*, and provide olfactory stimulation, affecting the human brain by increasing alpha waves in the frontal lobe[44]. Moreover, VOCs emitted from soil play a significant role in alleviating inflammation and stress, mitigating sleep disturbances, and regulating the immune system[45,46].

In a previous study, participants with psychopathological diseases were excluded and gardening activities were conducted using *S. rimosus*. Changes in the occipital lobe were observed, along with a decrease in most amino acids and C6 sugar monomers and an increase in serum lipid levels[11]. In contrast to the previous study that excluded individuals with depression, the current study specifically included participants with depressive mood. Consequently, differences were observed in both psychophysiological and metabolomic outcomes compared with those in the previous study. While it can be interpreted that the observed outcomes are the results of the horticultural activity itself, due to the study design, where both cases performed the same activity, exposure to VOCs emitted from *S. rimosus* is estimated as the main differing factor between the two cases.

Olfaction, the sense of smell, is first processed in the olfactory bulb, which is located in the frontal part of the brain. The olfactory bulb also extends its neural connections directly to areas of the brain that support cognition[47]. This connection allows olfactory stimulation to affect the activity of these areas more directly than other senses that pass through the thalamus before processing at their respective locations. A review study showed that olfactory training, a practice that exposes patients to odorants repeatedly over time to recover olfactory ability, is "associated with improved global cognition, and in particular, verbal fluency and verbal learning/memory"[47]. Although the olfactory bulb is located in the inner part of the brain, it is close to the Fz channel, which may explain the results of the current study. A study that observed EEG responses to olfactory stimulation found similar results for the F3 and F4 channels[48].

RA is often correlated with feelings of content and comfort. One study showed that individuals with depression and depressive mood have significantly lower alpha waves in the brain during the resting state than healthy individuals[49]. Frontal alpha asymmetry is viewed as a possible marker for diagnosing depression[50]; however, alpha asymmetry was not considered in the current study because of its design, and the results of the current study suggest that prolonged exposure to soil inoculated with *S. rimosus* could alleviate depressive mood and be used as a preventive measure for depression.

RB and RHB are considered states of high tension, nervousness, and cognitive stress[51]. RG is also high when individuals are under a lot of stress[52]. The results of the present study suggested that exposure to *S. rimosus* can lower physiological stress in the frontal lobe via olfactory stimulation. The SEF results suggested similar effects. A high SEF generally correlates with a state of alertness and stress in individuals[31]. The current study showed a significant decrease in both SEF50% and SEF90%, suggesting that individuals generally felt less stressed and less alert during horticultural activities using soil inoculated with *S. rimosus*.

Increases in RT waves and RSMT suggested that while individuals felt less alert, the overall concentration increased when exposed to soil inoculated with *S. rimosus*. Theta waves and RSMT are generally used as markers to measure a person's attentiveness and concentration during tasks[27]. Although states of intense concentration can lead to stress[53], a decrease in beta and gamma waves suggests that participants were mostly in a state of content concentration.

In addition, serum metabolomics of individuals with depression during horticultural activities with *S. rimosus* revealed changes in metabolite levels. Metabolites of the altered TCA cycle and glyoxylate and dicarboxylate metabolism participate in the energy metabolism pathway. The TCA cycle is a key metabolic pathway involved in energy metabolism in humans[54]. It is closely related to glyoxylate and dicarboxylate metabolism, which shares some metabolites with the TCA cycle. Therefore, changes in both pathways are closely linked to energy metabolism. In individuals with depression, energy deficiency leads to reduced activity, which downregulates energy metabolism[54,55]. In this study, metabolites involved in the TCA cycle and glyoxylate and dicarboxylate metabolism (succinic acid, glycolic acid, glyceric acid, and acetic acid) showed higher levels in the SRI group. An abnormal increase in glucose, which serves as the primary energy source, signifies a disruption in energy metabolism[56]. Glucose exhibited a decreasing trend in the SRI group, indicating increased energy metabolism, as indicated by both glucose consumption and elevated levels of metabolites linked to the TCA cycle and glyoxylate and dicarboxylate metabolism. Based on the contact time with soil and inhalation of key VOCs from *S. rimosus*, specifically 2-MIB and geosmin, the results indicate that horticultural activities using *S. rimosus* enhance energy metabolism in individuals with depression. Additionally, succinic acid, glycolic acid, and glucose were significant ($p < 0.05$) in the correlation map between EEG activity and metabolites.

Alterations in fatty acid levels may contribute to depression through various mechanisms such as biological stress, cell membrane structure, and inflammatory responses[57]. Fatty acids, serving as the major source of energy via β-oxidation and energy storage, also contribute to ATP production in the TCA cycle through the generation of acetyl-coenzyme A units[54,58]. In the blood of patients with major depressive disorder compared with that of the controls, fatty acid biosynthesis was significantly altered due to the downregulation of fatty acids[59]. The alleviation of depression was suggested by the increase in metabolites such as palmitic acid, myristic acid, lauric acid, capric acid, and octanoic acid in the SRI group, which influenced changes in fatty acid biosynthesis. Among these, lauric acid, capric acid, and octanoic acid levels were significantly correlated with EEG activity ($p < 0.05$).

Conclusion

The VOCs emitted by *S. rimosus* were identified, with 2-MIB and geosmin as the main volatile terpenes contributing to the musty, earthy odor. EEG results indicated that participants experienced psychophysiological relaxation and reduced stress in the frontal lobe, particularly with increased alpha wave activity in the regions near the olfactory lobe. Additionally, serum analysis revealed increased levels of metabolites, such as succinic acid, glycolic acid, glyceric acid, acetic acid, palmitic acid, myristic acid, lauric acid, capric acid, and octanoic acid, along with decreased glucose levels. These metabolic changes suggest an enhancement in energy metabolism. The observed psychophysiological and metabolomic responses imply that the inhalation of VOCs emitted from *S. rimosus* during horticultural activities may help alleviate depressive mood.

This study identified VOCs that were assumed to be emitted during the metabolic processes of *S. rimosus*, which could influence olfactory stimulation. This complements prior research by confirming that in individuals with depression, the inhalation of VOCs from soil and soil microorganisms contributes to psychological stability. However, because this study constitutes basic research, its generalizability is limited because of its small sample size. Future research should aim to gather data from a broader population by using more specific and objective criteria. Although this study identified the substances released by microorganisms during metabolic processes, it remains unclear which specific substances are responsible for the observed psychophysiological and metabolic differences.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

R. K. and S.-A. P. conceived the experiments, R. K performed EEG analysis and S. Y. performed metabolomics analysis. R. K. and S. Y. conducted data acquisition, analysis, and interpretation. R. K. and S. Y wrote the main manuscript. C. H. L and S.-A. P. reviewed and edited the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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