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Original Article

Effects of Nature-Based Multisensory Stimulation on Pain Mechanisms in Women with Fibromyalgia Syndrome: A Randomized Double-Blind Placebo-Controlled Trial

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ABSTRACT

Background: The term "nature-based sensory stimuli" refers to the sensory information produced by biotic and abiotic agents from natural environments. The literature has reported the beneficial effects of these agents on various pain dimensions in non-clinical populations.
Aims: To evaluate the potential analgesic effects of nature-based multisensory stimulation in women with fibromyalgia syndrome.
Methods: A randomized, double-blind, placebo-controlled, parallel-group trial with a 1:1 allocation ratio was conducted. Forty-two women with fibromyalgia syndrome interacted with either different plant species with flowers, stones, and soil organic matter or their synthetic imitations for 30 minutes. Outcome measurements were performed before and after the intervention, including clinical pain intensity using the Numeric Rating Scale, cold pain thresholds using the Cold Pressor Test, mechanical hyperalgesia and wind-up using a monofilament, and pressure pain thresholds using a pressure algometer.
Results: Analyses revealed group × time interactions for clinical pain intensity ($F = 7.915$, $p = .008$), cold-water immersion time ($F = 7.271$, $p = .010$), mechanical hyperalgesia ($F = 4.701$, $p = .036$), and pressure pain threshold ($p \leq .017$). Between-group differences were found in clinical pain intensity ($p = .012$), cold pain thresholds ($p = .002$), and pressure pain thresholds ($p < .05$). The experimental group exhibited reduced clinical pain intensity ($p = .001$) and increased pressure pain thresholds ($p \leq .034$).
Conclusions: Women with fibromyalgia syndrome may benefit from multisensory stimulation using biotic and abiotic agents from natural environments for 30 minutes. Interacting with flowering plants and soil components appears to induce analgesic effects.

Fibromyalgia syndrome (FMS) is a widespread pain disorder categorized under chronic primary pain, according to the International Classification of Diseases 11th Revision (Treede et al., 2015). This population experiences altered central pain processing, characterized by mechanical hyperalgesia, thermal hyperesthesia (Palmer et al., 2019), and abnormal wind-up (Staud et al., 2021). FMS is primarily prevalent in the female sex (Wolfe et al., 2018), and the current literature suggests two hypotheses to explain this: the effect of sexual dimorphism in the functioning of opioid receptors and the immune system on nociception (Meester et al., 2020; Sharp et al., 2022). Consequently, researchers believe that these sex-specific variations in physiologic functions cause differences in pain intensity and thresholds (Queme & Jankowski, 2019).

The need for developing new therapeutic approaches for FMS arises as recent meta-analyses report negligible efficacy (Bernardy et al., 2019; Kurian et al., 2019; Stockings et al., 2018)

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(i.e., internet-delivered psychological therapies, memantine, and cannabis and cannabinoids). In line with other meta-analyses, findings point to different levels of efficacy in improving pain symptoms, ranging from low with cognitive behavioral therapy, physical exercises, and mindfulness- and acceptance-based interventions (Bernardy et al., 2018; Ferro Moura Franco et al., 2021; Haugmark et al., 2019), to moderate with physical agent modalities, neurofeedback, and acupuncture (Honda et al., 2018; Patel et al., 2020; Zhang et al., 2019). Moreover, the quality of this evidence varies from low (Ferro Moura Franco et al., 2021; Honda et al., 2018; Kurian et al., 2019; Patel et al., 2020; Stockings et al., 2018), to moderate (Bernardy et al., 2018, 2019; Haugmark et al., 2019; Zhang et al., 2019). This is why a shift in focus from the individual to the contextual level could change the current rehabilitation paradigm for chronic pain patients (Johnson, 2019); hence, a new research line may emerge by integrating environmental and rehabilitation sciences. The World Health Organization (WHO) emphasizes the need for "significant implications for understanding the environment and health" and for "developing ideas or concepts concerning health, the environment, and their relationship" (World Health Organization, 2017).

Current therapeutic approaches for chronic pain include sensory stimulation through various pathways, which has been shown to positively affect central pain processing. For illustration, visual stimulation at 10 Hz was found to increase EEG alpha power significantly and reduce pain complaints (Arendsen et al., 2020); displaying pictures of landscapes decreased pain levels (Shaygan et al., 2017); viewing green paper relieved pain, unlike viewing reed paper (Kanai et al., 2017); and a 30-minute audiovisual stimulation program using flickering lights and gradually descending sound pulses alleviated pain symptoms (Tang et al., 2014). Tactile stimulation has been shown to mitigate pain and increase tactile acuity (Moseley et al., 2008), and two-point discrimination is inversely related to pain intensity and duration (Harvie et al., 2018). In chronic pain patients, the functioning of endogenous opioids during touch processing is altered (Case et al., 2016). Besides, congruent sensory information about the body contributes to somatosensory reorganization (Cardini & Longo, 2016), and light tactile contact and somatosensory attention directed toward the body may reduce pain (Kerr et al., 2007). Therefore, it could be promising to use sensory stimulation as a basis for developing new therapeutic approaches to improve central pain processing in chronic pain.

The term "nature-based sensory stimuli" refers to sensory information produced by biotic and abiotic agents from natural environments. Biotic agents are considered living organisms, whereas abiotic agents are defined as non-living components of environments. Living organisms shape the surrounding environment, such as plants, bacteria, and animals. Non-living components in an ecosystem are physical and chemical factors such as soil composition, water, and sunlight (Molles & Sher, 2019). Natural environments are considered to be those that have not originated from or have not been significantly altered by human activity (Johnson et al., 1997). Pain processing is influenced by various physiological and psychological functions (pain correlates), including pro-inflammatory cytokines (Geiss et al., 2012), cortisol levels (Boakye et al., 2016), autonomic nervous activity (Hohenschurz-Schmidt et al., 2020), depression (Du et al., 2020), stress (Crettaz et al., 2013), and anxiety (Michaelides & Zis, 2019). Recent meta-analyses and systematic reviews have reported the role of nature exposure on these pain correlates (Antonelli et al., 2019; Gagliardi & Piccinini, 2019; Jo et al., 2019; Nicholas et al., 2019; Soga et al., 2017). In healthy populations, the ability of natural agents to positively modulate pain intensity and thresholds has been observed (Lohr & Pearson-Mims, 2000; Park et al., 2004). In acute pain conditions, a reduction in pain intensity after exposure to natural agents was reported (Khan et al., 2016; Park & Mattson, 2009). In chronic pain patients, four studies noted subjective reports of improvements in pain intensity and pain behavior after participating in forest therapy, forest bathing, and horticultural therapy (Han et al., 2016; Kang et al., 2015; Serrat et al., 2020; Verra et al., 2012). However, these studies combined multiple therapies, making it difficult to attribute the benefits to nature-based sensory stimuli alone. Thus, evaluating the isolated efficacy of the nature-based sensory stimuli is required for understanding their role in chronic pain management.

Given this background, there is a need to develop a novel non-pharmacological therapeutic intervention that is low-cost, easy to implement, environmentally friendly, and accessible worldwide. This study aims to evaluate the potential effects of multisensory stimulation resulting from exposure to both living (biotic) and non-living (abiotic) agents from natural environments on clinical pain intensity, cold pain thresholds, mechanical hyperalgesia, wind-up, and pressure pain thresholds in a sample of women with FMS. We hypothesize that nature-based multisensory stimulation may: (1) reduce the clinical pain intensity, mechanical hyperalgesia, and wind-up; and (2) increase the cold pain thresholds and pressure pain thresholds in a sample of women with FMS.

Methods

Design

The study was conducted as a randomized, double-blind, parallel-group, placebo-controlled trial. The CONSORT statement has been followed. All data collection and interventions were executed in the Hospital Neurotraumatológico de Jaén, Spain, from July 15 to August 31, 2021. The protocol was approved by the Ethics Committee for Provincial Research of Granada (CEI-Granada) with reference number 1509-N-21. This study was prospectively registered on ClinicalTrials.gov with identification number NCT05017220.

Randomization

Before data collection, participant identification numbers were randomly assigned in a 1:1 ratio to either an experimental group or a placebo control group, using a computer-generated random number sequence. An independent researcher, who was not involved in recruitment or intervention processes, conducted this task. The researchers randomly assigned individually numbered cards to the participants and placed them in closed sealed envelopes. A research assistant who was blinded to the baseline examination unveiled the cards. Finally, the researchers allocated the participants to their corresponding group.

Participants

This trial enrolled 42 female participants diagnosed with FMS. Before the recruitment, the participants were thoroughly informed about the objective and procedures of the study, and their written consent was obtained.

The inclusion criteria were: (1) female sex; (2) adults aged 18–65 years; (3) diagnosis of FMS by the regional health system based on the ACR 2016 criteria (Wolfe et al., 2016); (4) pain intensity of four or more on the Visual Analog Scale (Boonstra et al., 2014); and (5) ability to communicate in Spanish.

The exclusion criteria were: (1) co-occurrence of neuropathic or acute pain; (2) other disorders that can cause pain; (3) other serious or unstable medical conditions that may interfere with partici-

pation (e.g., cancer, airborne and direct contact diseases, asthma, unstable angina); (4) severe cognitive impairment (Mini-Mental State Examination score < 17 out of 30 points) (Tombaugh & McIntyre, 1992); (5) severe mental illnesses in the symptomatic phase; (6) behavioral disturbances that may interfere with their participation (e.g., anger expression and suicidal attempts) (Galvez-Sánchez et al., 2019); (7) diagnosis of severe intellectual disability as documented in the patient's health record; (8) pregnant or lactating; (9) if the administered analgesic or psychotropic medications have not been stabilized for a minimum of four weeks prior to enrollment; and (10) drug abuse in the previous year as reported by the participants or health professionals.

Sample Size

The sample size of the study was calculated by the G*Power 3.1.9.7 software, using the repeated-measures ANOVA between factors with a significance level of 5% and a power of 90%. The pressure pain threshold with the highest reported test-retest value ($r = .85$) among the primary outcomes of the study was considered for the sample size calculation (Russell, 1998). To achieve the minimum a priori determined variance (Cohen's $f = 0.5$) of the qualitative independent variable (factor or group) over the quantitative dependent variable (primary outcome), it is necessary to recruit 42 participants in total.

Interventions

Interventions were provided individually for each participant in a single session lasting 30 minutes. The length of the intervention was determined based on a similar study (Barton & Pretty, 2010). A longer period was avoided in order to prevent possible musculoskeletal fatigue and pain in the patients (Cook et al., 2012). Average room conditions included stable temperature, 50–60% humidity, 500 lx by artificial lighting (SCENIHR, 2012), and no artificial odor and noise. All participants continued to receive their usual pharmacological treatment previously prescribed by the Andalusian Public Health System throughout the recruitment (Sánchez Jiménez et al., 2016). It was not expected to have any serious adverse effects; although the participants were observed and inquired about the possible presence of adverse effects (Peryer et al., 2019).

The participants were informed that they were going to interact with objects from nature. To ensure participant blinding to group allocation, the material of these objects, whether real or artificial, was not specified in the informed consent. The information provided to participants regarding the interventions in both groups was as follows: "This study consists of two intervention groups. In both groups, regardless of the group you are allocated to, you will interact with elements and materials *related to* the natural environment (e.g., plants, soil, among others)". The word used to express the meaning "related to" was deliberately used to prevent participants from deducing which intervention they received.

Experimental Intervention Group

The intervention was based on multisensory stimulation involving interactive tasks with biotic and abiotic agents derived from natural sources. The biotic agents were represented by the following real plant species: sweet alyssum (*Lobularia maritima*), snapdragon (*Antirrhinum majus*), and pot marigold (*Calendula officinalis L.*). These plants were carefully selected to encompass the widest possible range of physical and chemical features, including color, size, shape, and smell. The abiotic agents were soil components, including humidity, air, stones, and soil organic matter. Soil organic matter is regarded as materials and substances that contribute to soil fertility by undergoing decomposition, such as plant and animal residues, microbial biomass, humus, and root exudates (Weil and Brady, 2016). These constituents were collected from the topsoil under the holm oaks (*Quercus ilex*) to a depth of about 5 cm within the diameter of the tree canopy. The soil had a moist texture and an earthy smell emitted by volatile organic compounds. Before the interaction, a comfortable chair was provided for the participant to sit in, having both feet in contact with the ground. Real natural agents were placed on a wooden desk, positioned 0.5 m away from the participant and approximately 0.3 m below shoulder level to prevent any musculoskeletal overload during the tasks.

The interaction tasks with the natural agents were based on transplanting plants from one pot to another. During the intervention, the participants were verbally guided and directed their attention to multisensory features of the flowers, plant stems, root balls, and soil components. The direction of attention was performed systematically: one sensory pathway at a time, sequentially. These features included visual (i.e., color, tone, shape, form, texture, and pattern), auditory (i.e., sounds resulting from touching the plants and soil), olfactory (i.e., smells of the plants and soil before and after transplanting), and tactile (i.e., humidity, temperature, friction, resistance, turgidity, and discrimination of different types of texture during static and dynamic touching) aspects. The activity was executed with the participants alternating between having their eyes open and closed for equivalent amounts of time, in sequence. The participants were instructed to contemplate variations in sensory perception from each pathway arising from closing and opening their eyes.

Placebo Control Group

This group adhered to the same procedures as the experimental intervention group. However, the interaction tasks in this group employed synthetic imitations of the biotic and abiotic agents instead of their genuine counterparts. The synthetic biotic agents were visually similar artificial plants with flowers, while the abiotic agents were plastic granules that closely resembled the color and grain size of the soil used in the experimental group. What differentiated the study groups was the distinct sensory information elicited by the different materials used. As compared to natural agents, plastic objects differ in terms of the sensory properties previously delineated in the experimental intervention group.

Outcome Measures

An evaluation protocol based on the consensus of the International Association for the Study of Pain was followed (Rolke et al., 2006). The primary outcomes were clinical pain intensity, cold pain thresholds, punctate mechanical hyperalgesia, wind-up, and pressure pain thresholds. The order of measurements was from the least painful to the most painful (Avellanal et al., 2020). A one-minute rest period was given between each measurement. Two evaluators blinded to participant allocation performed the measurements prior to and following the intervention. All procedures were implemented at the same time of day between 4 PM and 7 PM.

Clinical pain intensity

The 11-point Numeric Rating Scale (NRS-11) was used, with zero representing no pain and 10 representing the worst pain imaginable. This valid tool ($r = .81$) shows good test-retest reliability ($r = .77$) (Jensen & McFarland, 1993) and excellent concurrent

validity with the Visual Analog Scale (rho = .96, 95% CI .92–.97, $p < .001$) (Cheatham et al., 2018). Verbal ratings of ongoing pain intensity on the right and left sides of the body were obtained from the participants. In FMS, a raw score change of −1.74 points on the NRS-11 is considered a clinically important improvement (Farrar et al., 2001). Lower values indicated lower pain intensity at the moment.

Cold pain thresholds

The Cold Pressor Test (Wolf & Hardy, 1941) was used with the ascending method of limits. This test shows high correlations ($r = .70$) with the classic cold test with a Peltier thermode (Ruscheweyh et al., 2010). A 5.6-liter plastic container filled with a mixture of water and ice cubes was prepared to stimulate the C-fibers (Desmeules et al., 2003). The water temperature was maintained at approximately 3 °C. The participants were instructed to immerse both hands in the ice water bath and keep them submerged until the first pain was felt. The evaluator recorded the time in seconds using a stopwatch. Time elapsed until the pain was reported was registered as the cold pain thresholds. A longer latency period of withdrawal indicated higher cold pain thresholds, which can be interpreted as lower cold pain sensitivity (Wolf & Hardy, 1941).

Punctate mechanical hyperalgesia

A response-dependent procedure was implemented utilizing a Semmes-Weinstein monofilament (2940 mN pressure, 6.65 size, 0.1143 cm diameter; Aesthesio® Precise Tactile Sensory Evaluator, DanMic Global, LLC, San Jose, CA, USA) (Wasner et al., 2000). Application points were the upper border of the trapezius (10 cm away from the acromion) and the tibialis anterior (10 cm below the patella) on both sides of the body. The monofilament was applied perpendicularly to the same localized zone of one cm^2. The participants were asked to verbally rate the perceived pain intensity on the NRS-11, which was registered as punctate mechanical hyperalgesia. Lower scores were considered positive regulation of the pain inhibitory system (Blumenstiel et al., 2011).

Wind-up

The mechanical temporal summation was measured with a response-dependent procedure, utilizing the same monofilament as for the punctate mechanical hyperalgesia (Avellanal et al., 2020). This method shows good test-retest reliability (ICC = .74) in FMS patients (de la Coba et al., 2018). The same application points on both sides of the body as in the punctate mechanical hyperalgesia were selected. A single stimulus was applied to the specified points, and the participants were asked to rate the perceived pain intensity on the NRS-11. After an interval of 10 seconds, a train of 10 stimuli was applied to the same points with a mean cadence of three stimuli per second. This time, the participants were asked to rate the overall intensity of pain evoked by the stimuli series. The difference between the NRS-11 ratings of the stimuli series and single punctuation was registered as the wind-up. Lower values were considered a positive inhibition of ascending facilitatory mechanisms (Mackey et al., 2017).

Pressure pain thresholds

A hand-held dial pressure algometer with a circular flat probe of 1.4 cm diameter (Baseline Push Pull Force Gauge Model 12–0304, Fabrication Enterprises Inc., USA) was employed using the ascending method of limits. This device has shown excellent test-retest reliability ($r = .85$) in FMS patients (Russell, 1998). The pressure pain thresholds in nine body sites (the eighteen tender points) were measured bilaterally (Wolfe et al., 1990). The evaluator positioned the tip of the algometer perpendicularly to the test area and gradually incremented the pressure at a consistent rate of 50 kPa (~0.5 kg/cm^2) per second (Rolke et al., 2006). The participants were asked to report the initial moment of pain sensation to the evaluator. When the first pain was reported, the evaluator stopped the applied force. The values reached in kg were registered as the pressure pain thresholds. Higher values indicated higher pressure pain thresholds, which can be interpreted as lower sensitivity to pressure pain.

Statistical Methods

All data collected in the study were managed and analyzed using SPSS v26.0 for Windows (SPSS Inc., Chicago, IL, USA). All efficacy analyses were performed using the intention-to-treat approach (defined as all randomized patients). The data analyst was blinded for both groups. Descriptive analyses were performed to summarize the data, with continuous variables presented as mean ± standard deviation and categorical variables presented as absolute frequencies and percentages. Comparisons between groups for continuous and categorical variables were analyzed using the Pearson's χ^2 and Student t test, respectively. To assess the intervention effect over time, the repeated measures analysis of variance (ANOVA) with group (experimental versus control) and time (pre- and post-intervention) was used. Post-hoc analyses were conducted for between- and within-group comparisons using the Student's t test or the Mann–Whitney U test, depending on the relevant assumptions. The non-parametric test was used for the clinical pain intensity on both sides, cold pain thresholds, punctate mechanical hyperalgesia in the right tibialis anterior, wind-up in the tibialis anterior on both sides, and pressure pain thresholds in the left supraspinatus and medial knee on both sides. Effect sizes were calculated using Cohen's d.

Results

Forty-two women met the inclusion criteria and were randomly assigned to the experimental (n = 21) and placebo control (n = 21) groups. The participants were 54.6 ± 7.24 years old. A CONSORT flow diagram is depicted in Figure 1. No adverse effects have been reported.

The sociodemographic and clinical data showed no differences between the groups ($p > .05$) (Table 1). The baseline measures of the outcome variables showed no differences ($p > .05$), except for the pressure pain thresholds in the right low cervical ($t = -2.414$, $p = .02$), second rib ($t = -2.188$, $p = .035$), and left low cervical ($t = -2.108$, $p = .041$), lateral epicondyle ($t = -2.185$, $p = .035$), and gluteus ($t = -2.338$, $p = .027$), in favor of the experimental group. The pre- and post-treatment values, as well as post hoc results for each outcome measure, are presented in Tables 2 and 3.

Clinical Pain Intensity

A statistically significant group × time interaction was observed in the clinical pain intensity (Right $F = 7.915$, $p = .008$). The *post hoc* analysis showed a between-group difference at the post-treatment evaluation ($p = .012$). The within-group analyses revealed a reduction in pain intensity scores in the experimental group from pre- to post-treatment ($p = .001$).

Cold Pain Thresholds

A statistically significant interaction effect was observed between group and time in the cold pain thresholds ($F = 7.271$, $p = .01$). The values obtained from the experimental and placebo control groups differed at the post-treatment evaluation ($p = .002$).

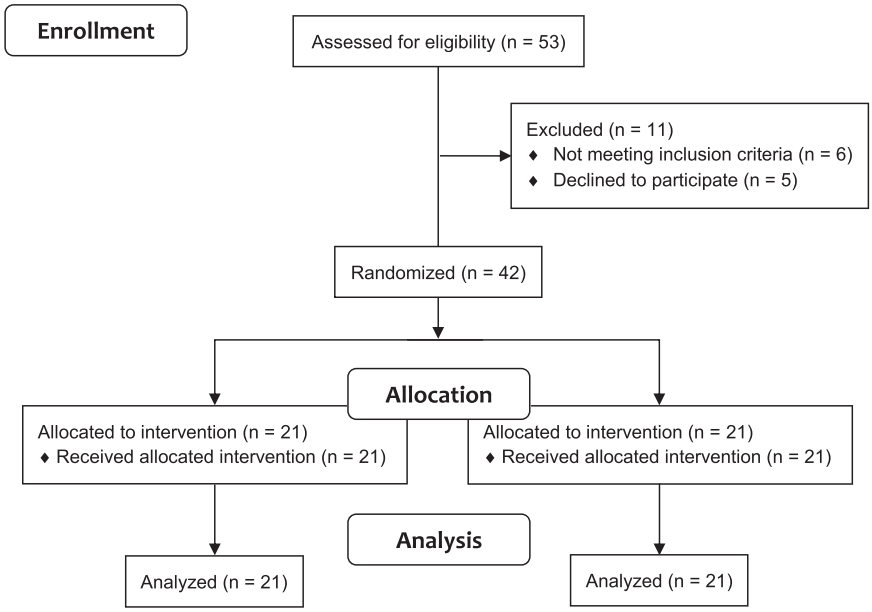

Figure 1. CONSORT 2010 flow diagram of the study participants.

Table 1
Sociodemographic and Clinical Characteristics of the Study Participants.

Sociodemographic and Clinical Characteristics	Nature-Based Multisensory Stimulation Group (n = 21) Mean ± SD or n (%)	Placebo Control Group (n = 21) Mean ± SD or n (%)	*p*
Sex, female	21 (100)	21 (100)	1.000
Age, years	54.38 ± 7.46	54.81 ± 7.19	.851
Employment			.122
Unemployed	9 (42.9)	3 (14.3)	
Employed	10 (47.6)	15 (71.4)	
Pensioner	2 (9.5)	3 (14.3)	
Education			.578
Incomplete	1 (4.8)	0 (0)	
Primary	14 (66.7)	12 (57.1)	
Secondary	2 (9.5)	2 (9.5)	
Tertiary	4 (19)	7 (33.3)	
Marital status			.116
Married	19 (90.5)	15 (71.4)	
Divorced	2 (9.5)	6 (28.6)	
Number of pregnancies	2.10 ± 0.70	1.81 ± 0.68	.187
Onset of symptoms, years	8.62 ± 3.72	9.62 ± 3.79	.393
Diagnosis, years	4.81 ± 3.59	6.14 ± 3.24	.214
Pain medication users	21 (100)	18 (85.7)	.072
Paracetamol	3 (14.3)	3 (14.3)	
NSAIDs	8 (38.1)	5 (23.8)	
Anticonvulsants	7 (33.3)	3 (14.3)	
Weak opioids	3 (14.3)	5 (23.8)	
Potent opioids	4 (19)	5 (23.8)	
Antidepressant users	19 (90.5)	17 (81)	.378
SSRIs	10 (47.6)	10 (47.6)	
SNRIs	7 (33.3)	7 (33.3)	
TCAs	1 (4.8)	0 (0)	
Atypical	3 (14.3)	1 (4.8)	

SD = standard deviation; NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin and norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants.

The within-group analyses showed a pre-post decrease in the cold-water immersion time in the placebo control group ($p = .001$).

Punctate Mechanical Hyperalgesia

A statistically significant group × time interaction was observed in the tibialis anterior (Right $F = 4.701$, $p = .036$). However, there was no significant difference between the groups at the post-treatment evaluation ($p > .05$).

Wind-Up

No significant group × time interaction was observed in the wind-up ($p > .05$).

Table 2
Pre-Post Differences in the Clinical Pain Intensity, Cold Pain Thresholds, Punctate Mechanical Hyperalgesia, and Wind-Up Between and Within Groups.

Outcome Measure	Areas		Nature-Based Multisensory Stimulation Group (n = 21)					Placebo Control Group (n = 21)					Between-Group Differences		
			Pre M ± SD	Post M ± SD	*t*/*Z*	*p*	Cohen's *d*	Pre M ± SD	Post M ± SD	*t*/*Z*	*p*	Cohen's *d*	*t*/*Z*	*p*	Cohen's *d*
Clinical pain intensity		R	8.36 ± 1.15	6.50 ± 2.90	−3.343	.001	0.843	8.24 ± 1.95	8.19 ± 1.66	−0.184	.854	0.028	−2.517	.012	0.715
		L	8.21 ± 1.25	7.07 ± 2.16	−3.165	.002	0.646	7.90 ± 2.47	7.76 ± 2.23	−0.362	.717	0.059	−1.567	.117	0.314
Cold pain thresholds			9.55 ± 6.94	9.89 ± 4.82	1.475	.140	0.057	10.32 ± 11.99	7.65 ± 12.37	−3.360	.001	0.219	3.056	.002	0.239
Punctate mechanical hyperalgesia	Trapezius	R	4.90 ± 2.68	5.10 ± 2.32	−0.400	.693	0.080	5.05 ± 3.11	6.29 ± 3.44	−2.515	.021	0.378	1.315	.196	0.406
		L	4.90 ± 2.70	4.57 ± 2.93	0.602	.554	0.117	5.10 ± 2.62	6.33 ± 3.09	−2.087	.050	0.429	1.898	.065	0.585
	Tibialis	R	3.52 ± 3.08	2.95 ± 3.06	−1.489	.137	0.186	3.90 ± 3.74	4.71 ± 3.18	1.263	.207	0.233	−1.622	.105	0.564
	anterior	L	3.76 ± 2.95	3.10 ± 2.91	1.299	.209	0.225	4.43 ± 3.71	4.76 ± 3.13	−0.627	.538	0.096	1.786	.082	0.549
Wind-up	Trapezius	R	1.71 ± 2.08	1.43 ± 0.98	0.662	.516	0.172	2.19 ± 2.06	1.86 ± 2.29	0.632	.534	0.152	0.790	.437	0.244
		L	2.05 ± 2.33	2.14 ± 1.98	−0.266	.793	0.042	2.29 ± 2.10	1.86 ± 2.33	0.779	.445	0.194	−0.428	.671	0.130
	Tibialis	R	1.86 ± 2.33	1.71 ± 2.22	−0.635	.526	0.066	1.62 ± 2.31	2.05 ± 2.89	0.426	.670	0.164	−0.180	.857	0.132
	anterior	L	1.38 ± 2.33	1.38 ± 1.88	−0.212	.832	0.000	2.10 ± 2.77	2.10 ± 2.72	0.186	.852	0.000	−0.468	.639	0.308

n = sample size; M = mean; SD = standard deviation; R = right; L = left; *t* = Student's *t*-distribution; *Z* = standard normal distribution.

Table 3
Pre-Post Differences in the Pressure Pain Thresholds Between and Within Groups.

Outcome Measure	Areas		Nature-Based Multisensory Stimulation Group (n = 21)					Placebo Control Group (n = 21)					Between-Group Differences		
			Pre M ± SD	Post M ± SD	*t*/*Z*	*p*	Cohen's *d*	Pre M ± SD	Post M ± SD	*t*/*Z*	*p*	Cohen's *d*	*t*/*Z*	*p*	Cohen's *d*
Pressure pain thresholds	Occiput	R	1.38 ± 0.75	1.42 ± 0.62	−0.382	.707	0.058	1.15 ± 0.43	0.81 ± 0.41	3.084	.006	0.809	−3.725	.001	1.161
		L	1.38 ± 0.73	1.42 ± 0.57	−0.354	.727	0.061	1.14 ± 0.46	0.82 ± 0.44	3.967	.001	0.711	−3.805	< .001	1.178
	Trapezius	R	1.48 ±0.73	1.60 ± 0.76	−0.839	.411	0.161	1.34 ± 0.72	1.02 ± 0.65	3.088	.006	0.467	−2.659	.011	0.820
		L	1.54 ± 0.71	1.66 ± 0.77	−1.175	.254	0.162	1.36 ± 0.58	1.04 ± 0.61	2.736	.013	0.538	−2.904	.006	0.893
	Supraspinatus	R	1.69 ± 0.71	1.79 ± 0.77	−0.959	.349	0.135	1.48 ± 0.58	1.18 ± 0.67	3.403	.003	0.479	−2.752	.009	0.845
		L	1.80 ± 0.86	1.92 ± 0.80	1.047	.295	0.144	1.41 ± 0.67	1.09 ± 0.54	−3.296	< .001	0.526	3.645	< .001	1.216
	Low cervical	R	0.89 ± 0.50	0.94 ± 0.43	−0.588	.563	0.107	0.59 ± 0.28	0.48 ± 0.26	1.859	.078	0.407	−4.216	< .001	1.295
		L	0.85 ± 0.39	0.93 ± 0.42	−1.353	.191	0.197	0.62 ± 0.32	0.60 ± 0.34	0.231	.820	0.061	−2.763	.009	0.864
	Second rib	R	1.28 ± 0.52	1.38 ± 0.57	−1.367	.187	0.183	0.98 ± 0.36	0.92 ± 0.34	0.851	.405	0.171	−3.119	.004	0.980
		L	1.27 ± 0.53	1.37 ± 0.64	−1.596	.126	0.170	1.04 ± 0.35	0.93 ± 0.37	1.149	.264	0.305	−2.707	.011	0.842
	Lateral	R	1.36 ± 0.67	1.47 ± 0.69	−0.886	.386	0.162	1.06 ± 0.59	0.87 ± 0.45	2.010	.058	0.362	−3.322	.002	1.030
	epicondyle	L	1.38 ± 0.61	1.56 ± 0.70	−1.801	.087	0.274	1.00 ± 0.52	0.90 ± 0.41	0.909	.374	0.214	−3.728	.001	1.151
	Medial knee	R	1.78 ± 0.83	2.10 ± 1.04	2.195	.028	0.340	1.72 ± 0.86	1.44 ± 0.83	−2.601	.009	0.331	2.585	.010	0.701
		L	1.87 ± 0.86	2.13 ± 0.97	1.817	.069	0.283	1.88 ± 1.11	1.49 ± 0.94	−3.105	.002	0.379	2.545	.011	0.670
	Gluteal	R	2.61 ± 1.29	3.06 ± 1.29	−2.949	.021	0.348	1.74 ± 0.74	1.72 ± 0.98	0.142	.888	0.023	−2.994	.006	1.170
		L	2.57 ± 1.03	2.89 ± 1.03	−2.147	.069	0.310	1.79 ± 0.71	1.79 ± 1.08	−0.028	.978	0.000	−2.469	.020	1.042
	Great	R	1.95 ± 1.01	2.18 ± 1.09	−2.276	.034	0.218	1.97 ± 0.88	1.61 ± 0.65	2.918	.009	0.465	−2.042	.048	0.635
	trochanter	L	1.95 ± 0.85	2.28 ± 1.02	−2.584	.018	0.351	2.06 ± 0.72	1.71 ± 0.95	3.422	.003	0.415	−1.882	.067	0.578

n = sample size; M = mean; SD = standard deviation; R = right; L = left; *t* = Student's *t*-distribution; *Z* = standard normal distribution.

Pressure Pain Thresholds

Statistically significant group × time interactions were observed in the following tender points: occiput (Right $F = 6.148$, $p = .017$; Left $F = 7.188$, $p = .011$), trapezius (Right $F = 6.420$, $p = .015$; Left $F = 8{,}024$, $p = .007$), supraspinatus (Right $F = 9.029$, $p = .005$; Left $F = 10.326$, $p = .003$), medial knee (Right $F = 15.401$, $p < .001$; Left $F = 13.909$, $p = .001$), and greater trochanter (Right $F = 13.683$, $p = .001$; Left $F = 17.338$, $p < .001$). The between-group analyses showed differences in the aforementioned tender points on both sides of the body at the post-treatment evaluation ($p < .05$), except in the greater trochanter (Left $p > .05$). The within-group analyses showed pre-post increases in the medial knee (Right $p = .028$) and greater trochanter (Right $p = .034$) in the experimental group and decreases in the occiput (Right $p = .006$; Left $p = .013$), trapezius (Right $p = .006$; Left $p = .013$), supraspinatus (Right $p = .003$; Left $p < .001$), medial knee (Right $p = .009$; Left $p = .002$), and greater trochanter (Right $p = .009$) in the placebo control group.

Discussion

The objective of this trial was to evaluate the potential effects of multisensory stimulation using biotic and abiotic agents from natural environments on the clinical pain intensity, cold pain thresholds, mechanical hyperalgesia, wind-up, and pressure pain thresholds in women with FMS. The findings of this study showed that: (1) the clinical pain intensity was reduced following multisensory stimulation using natural agents; (2) the cold pain thresholds were maintained after the experimental intervention, while they decreased after the placebo intervention using sham biotic and abiotic agents made of synthetic materials; and (3) the pressure pain thresholds increased and remained similar levels across various body areas in the experimental group, whereas they decreased in some areas in the placebo control group. The effect observed following the placebo intervention may have potentially resulted from central sensitization temporarily induced during the pain evaluation procedure.

These findings suggest the arousal of a diffuse analgesic response. It can be argued that nature-based sensory stimuli might reduce pain by modulating several neurobiological functions involved in chronic pain processes. These functions include cerebral activity and neurocardiovascular, neuroimmune, neuroendocrine, and neurochemical functions. Research has shown that sensory stimulation using natural agents induces changes in cerebral activity in pain-related neural networks in healthy populations (Jo et al., 2019). According to a recent meta-analysis (Ideno et al., 2017) and a systematic review (Jo et al., 2019), both indoor and outdoor exposure to natural agents lead to decreases in blood pressure levels. Some authors have found a correlation between lower blood pressure levels and decreased pain sensitivity among individuals with chronic pain (Makovac et al., 2020; Saccò et al., 2013). Additionally, both natural scenery viewing and blood pressure-related hypoalgesia appear to activate the same cerebral area (i.e., superior parietal gyrus) (Kim et al., 2010; Ottaviani et al., 2018). Therefore, reduced pain sensitivity may arise from cerebral activation elicited by the visualization of natural scenes. On the other hand, studies have reported that exposure to nature positively affects pain-related neuroimmune and neuroendocrine functions such as the regulation of pro-inflammatory cytokines (Im et al., 2016; Mao et al., 2012) and cortisol levels (Twohig-Bennett & Jones, 2018). Moreover, elevated glutamate levels are associated with the FMS (Peek et al., 2020; Pyke et al., 2017), which is an excitatory neurotransmitter increased under chronic stress conditions (Pal, 2021). As natural agents have been reported to reduce stress biomarkers, they may thus potentially lower glutamate levels, which could help ease the symptomatology of FMS.

Regarding the clinical pain intensity, the experimental group demonstrated a clinically important improvement (a decrease of 1.86 points on the NRS-11) with a large effect size (Farrar et al., 2001). A recent study evaluating the effectiveness of a 12-week multicomponent treatment incorporating nature-based activities in FMS patients (Serrat et al., 2020) reported significant pain relief. A similar investigation that implemented a forest camping program (Han et al., 2016) also reported significant reductions in pain intensity. Likewise, another research evaluating the efficacy of walking in the forest for 2 hours a day for 7 days in patients with chronic posterior neck pain (Kang et al., 2015) reported a significant decrease in pain levels. Nonetheless, the results of the aforementioned studies cannot be attributed solely to the benefits of the natural environments because the interventions implemented were multimodal. The therapeutic strategies included, in addition to the multisensory stimulation, different unimodal therapeutic approaches. These approaches alone have been shown to be effective in patients with pain such as physical exercise (Ferro Moura Franco et al., 2021), psychological interventions (Bernardy et al., 2018; Haugmark et al., 2019), or physical activity (O'Connor et al., 2015).

As for the pain thresholds, FMS patients experience sensitization instead of the natural habituation process to cold pain (Smith et al., 2008). The results of the current study indicate that multisensory stimulation using biotic and abiotic agents from nature may suppress this sensitization. The experimental group was able to keep their hands submerged in the cold water without pain for a period similar to that of the baseline evaluation, whereas this duration significantly decreased in the placebo control group. As there was a between-group difference in the predicted direction, the hypothesis of the present study regarding the cold pain thresholds was therefore only partially supported. Moreover, the pressure pain thresholds increased in the right medial knee and greater trochanter tender points after the experimental intervention. To the authors' knowledge, there is no literature regarding the effects of nature-based multisensory stimulation on cold or pressure pain thresholds. On the other hand, the effects observed in the placebo control group might be due to a central sensitization state provoked by the painful stimuli at the pre-intervention measurement. According to the literature, this sensitization is often maintained for several hours after the induction of a painful stimulus (Latremoliere & Woolf, 2009). As the experimental and placebo interventions lasted 30 minutes, it is possible that the central sensitization might have led to the worsening of the baseline situation in both groups. Thus, one could argue that the effect of the natural agents had a positive effect by maintaining the pre-intervention values in certain outcome measures and improving others. In contrast, the effect of the synthetic imitations was absent for most of the variables, hence the exacerbation of some symptoms post-intervention.

This study exhibits the potential benefits of exposure to nature-based sensory stimuli on pain mechanisms in chronic pain. By virtue of a single-session intervention, the sustainability of the effects was predicted to be short-lasting; thus, follow-up evaluations were not included. This study contributes to the literature by increasing knowledge about the potential benefits of multisensory stimulation using natural agents on pain and confirming its relevance and clinical importance for women with FMS.

Limitations

Several limitations should be considered when interpreting the results of the present study: (1) the use of algometry with the

method of limits is open to the "halo effect" bias (Gracely et al., 2003); (2) as the study is based on the female population, the findings should interest this particular demographic cohort; and (3) the fact that the study hypothesis was known by the therapist who implemented the intervention, namely the intervention with real natural agents was expected to yield greater benefits, could imply a possible flaw; nevertheless, a protocol was established in advance to prevent possible differences in outcome expectations between the groups.

Conclusions

In conclusion, interacting with real plants and moist soil through a transplanting activity appears to improve the clinical pain intensity, cold pain thresholds, and pressure pain thresholds in women with FMS. Therefore, this population may benefit from multisensory stimulation using biotic and abiotic agents from natural environments for 30 minutes. A previous study investigated the incorporation of natural agents' exposure as a component of a multimodal intervention of 12 weeks in fibromyalgia patients (Serrat et al., 2020). The intervention program comprised pain neuroscience education, exercise therapy, cognitive-behavioral therapy, and mindfulness along with nature exposure through activities such as yoga, Nordic walking, nature photography, and Shinrin-yoku. Both studies contribute substantially to advancing our understanding of the therapeutic implications of nature-based multisensory stimulation.

Implications for Nursing Research and Practice

This randomized controlled trial provides evidence supporting the pain-relieving effects of nature-based multisensory stimulation. The current therapeutic approach uses visual, auditory, olfactory, and tactile stimuli produced by biotic and abiotic agents, including plants and moist soil. This therapeutic intervention is available for clinicians as a pain relief strategy. Future studies may focus on clarifying the underlying mechanisms by examining physiological stress responses in chronic pain populations following the implementation of this intervention. Further research is required to explore the effects of nature-based multisensory stimulation on core outcome measures for chronic pain clinical trials, such as sleep domains and emotional functioning.

Ethical Statement

The protocol was approved by the Ethics Committee for Provincial Research of Granada (CEI-Granada) with reference number 1509-N-21.

Declaration of Competing Interest

None.

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