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The Impact of a 20-Minute Animal-Assisted Activity Session on the Physiological and Emotional States in Patients With Fibromyalgia

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Abstract

Objective: To study the direct physiological and emotional impact of an animal-assisted activity (AAA) session (a form of complementary and integrative medicine) in patients with fibromyalgia (FM).

Patients and Methods: The study population consisted of 221 participants with FM who were attending Mayo Clinic's Fibromyalgia Treatment Program between August 5, 2017, and September 1, 2018. This was a randomized controlled trial. Participants were randomly assigned to either the treatment group (a 20-minute session with a certified therapy dog and handler) or the control group (a 20-minute session with a handler only). To gain a better understanding of the direct physiological and emotional effects of AAA in patients with FM, we used multiple noninvasive physiologic-emotional biomarkers, including salivary cortisol and oxytocin concentrations, tympanic membrane temperatures, and various cardiac parameters, in addition to standardized pain and mood-based questionnaires.

Results: Results show a decrease in heart rate, an increase in heart rate variability, an increase in well-being survey scores, an increase in salivary oxytocin, and subsequent tympanic membrane temperature changes, suggesting that participants in the treatment group were in a more positive emotional-physiologic state as a result of the AAA session compared with the control group.

Conclusion: Our results suggest that a 20-minute therapy dog visit in an outpatient setting can significantly and positively impact the physical and mental health of patients with FM.

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Fibromyalgia (FM) is a chronic centralized pain sensitivity disorder characterized by chronic widespread pain, fatigue, cognitive complaints, sleep disturbance, and psychological distress.[1] The estimated prevalence of FM is between 2% and 8%.[1] The National Fibromyalgia Association estimates that approximately 10 million Americans suffer from FM, many of whom are undiagnosed or misdiagnosed. The average financial costs associated with FM are two to three times higher compared with a healthy individual,[2] with indirect and direct costs totaling more than $4000 per month per individual.[2,3] This leads to an estimated $10 billion in total FM-related health care costs annually.[1,3,4]

The understanding of the pathophysiology of FM is complex and evolving; there is significant evidence-based support for the underlying/causal process of central sensitization (CS). CS is the pathophysiological dysregulation of the central nervous system (CNS) at numerous levels (structural/anatomic/functional brain and spinal cord changes, neurochemical concentration changes, CNS receptor concentration/functional changes, neuroplasticity of the CNS and peripheral nervous system, hypothalamic-pituitary-adrenal axis changes, sympathetic nervous system

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hyperactivity, and endogenous opioid system hyperactivity), collectively cascading into the amplification of ascending (excitatory/pain) signals and the reduction of descending (inhibitory/regulatory) signals. As CS is a centralized process, it can be more readily thought of as CNS dysregulation leading to CNS origination and amplification of various symptoms.[1,5-7]

There are many known risk factors associated with the development of FM, including female gender, first-degree family history, personal history of rheumatic disease (osteoarthritis, rheumatoid arthritis, or systemic lupus erythematosus), trauma (physical and emotional events), surgery, and infection.[1,5,8] Furthermore, there is strong evidence showing a very close association with concomitant mood disorders; 80% of patients with FM meet Diagnostic and Statistical Manual of Mental Disorders IV multiaxial system Axis I diagnostic criteria (depression or anxiety) whereas 30% of patients with FM meet Axis II criteria (personality disorders).[9]

The most common and effective treatment strategies for FM consist of a multimodal approach, including medication and non-medication treatment strategies,[1] with an overall aim to improve function and reduce symptom burden. Although there have been advances in treatment options, most individuals with FM continue to experience pain, suffering, and functional limitations; as a result, many have ventured beyond conventional treatment strategies to other complementary and integrative medicine (CIM) modalities for relief of various symptoms. According to a recent collaborative effort led by the US Department of Health and Human Services, CIM therapies continue to be commonly used; their use continues to increase in the United States, especially among those with musculoskeletal pain disorders.[10,11] Several studies have described the widespread use of CIM modalities and their clinical efficacy in patients with FM, showing promising results for various CIM modalities.[2,12-17]

Although not often studied in nor used for the treatment of FM, animal-assisted activity (AAA), as a form of CIM, has been shown to be extremely beneficial to those suffering from other chronic illnesses.[18] Numerous studies have previously shown the positive effects of human-animal interaction in alleviating pain, depression, anxiety,[19,20] dementia,[21] mental health symptoms,[22] and fear.[19] Marcus et al[23,24] studied the impact of therapy dogs in an outpatient pain clinic as well as investigated the impact of therapy dogs in patients with FM; the results supported that therapy dog visits could potentially reduce pain and emotional distress in both patients with chronic pain and their family members.

In general, these specific studies and most other therapy animal studies only collect self-reported subjective measures, such as pain, fatigue, and emotional state ratings via questionnaires and do not incorporate any physiological data to support or corroborate their claims. Given this limitation in the literature, the present study was designed to more thoroughly investigate the direct effects of AAA in patients with FM by using multiple, noninvasive physiological biomarkers, including salivary oxytocin and cortisol concentrations,[25] tympanic membrane temperatures,[26] and various cardiac parameters,[27] in addition to standardized pain and mood-based questionnaires.

These parameters were primarily selected due to being reliable physiologic indicators and surrogates of stress and well-being. Physiological stress can activate the adrenal cortex to increase production of cortisol[25]; as a result, cortisol concentration can be used as a surrogate to assess stress/well-being.[28] Oxytocin, a neuropeptide produced by the hypothalamus and released by the posterior pituitary,[29] is associated with social interaction[30] and can also be used as an indicator to assess the current state of stress and well-being. Moreover, it is generally accepted that emotional experiences lead to increased brain hemispheric activity for which the ipsilateral tympanic membrane temperature is directly correlated and can serve as a proxy measure.[26,31] Furthermore, fluctuations in tympanic membrane temperature can also serve as an indicator to reflect changes in the current emotional

state.[32] Lastly, cardiac parameters, such as heart rate (HR) and heart rate variability (HRV), can also be used as physiologic markers reflecting welfare and well-being.[27,33]

The authors of the present study collected the above-mentioned physiologic, noninvasive parameters (reflecting the physiologic well-being and emotional state), as well as pain, mood, and satisfaction questionnaires, to comprehensively evaluate the direct impact of AAA on patients with FM.

METHODS

General Methods

This study was part of a larger effort aimed at assessing the physiologic well-being and emotional state of both patients with FM and therapy dogs,[34] during and as a result of an AAA session. However, the focus of this paper will solely be on the impact of AAA on patients with FM. All study participants were patients with FM who were actively going through the Mayo Clinic Fibromyalgia Treatment Program (FTP). Halfway through the program, study members approached all participants and invited them for voluntary study participation. After obtaining consent, participants were asked to complete a demographic survey (age, sex, ethnicity, education level, marital status, and employment status), the Pet Attitude Scale, the Lexington Pet Attachment Scale, the Fibromyalgia Impact Questionnaire—Revised (FIQR), a numeric rating scale (NRS) for pain, and visual analog scales (VAS) for various emotions (Figure 1). The participants were then randomly assigned to either the treatment (a 20-minute session with a therapy dog and the handler) or control group (a 20-minute session with just the handler) (Table 1). After randomization, the participants were brought individually into an exam room where saliva was collected, bilateral tympanic membrane temperatures were taken simultaneously, and an HR monitor was placed by a study staff member. A study staff member then introduced the participant to the handler with or without the therapy dog. All study interactions took place in an exam room in Mayo Clinic's Fibromyalgia and Chronic Fatigue Clinic, which included a small exam table, four chairs, and a desk. Interactions were observed by a study staff member to ensure the proper functioning of HR monitors and observe and notate the therapy dog's behavioral response; otherwise, the observing study staff member was not allowed to interact. At the end of the 20-minute session, the handler with or without therapy dog left the room. The study participant, who was still in the room, had their post-session saliva and tympanic membrane temperatures collected and the HR monitor was removed. Next, the participants in both the treatment and control groups were asked to fill out post-session surveys (FIQR, VAS, and NRS). A 2-week follow-up satisfaction survey was sent to both groups, and a therapy dog satisfaction survey was also sent to the treatment (AAA) group.

Participants

Two hundred twenty-one participants with FM were randomly assigned to either the treatment group (n=111) or the control group (n=110). Participants were between the ages of 18 and 76 years old, were formally diagnosed with FM (meeting the 1990 American College of Rheumatology diagnostic criteria and/or the 2010 American College of Rheumatology diagnostic criteria),[35,36] were not allergic to or fearful of dogs, and did not have a diagnosis of bipolar disorder, schizophrenia, or dementia. Participants were patients attending Mayo Clinic's FTP, a 1.5-day, multidisciplinary, outpatient treatment program staffed by physicians from the Mayo Clinic Division of General Internal Medicine. The FTP consists of individual and group sessions that are taught by a core group of general internists, registered nurses, physical therapists, occupational therapists, psychiatrists, psychologists, and ancillary staff. The primary aims of the FTP are to improve physical and mental health functioning, provide evidence-based treatment options, and create a lasting FM treatment regimen.[37,38] Mayo Clinic's Institutional Review Board committee approved this study (protocol number 16-006296).

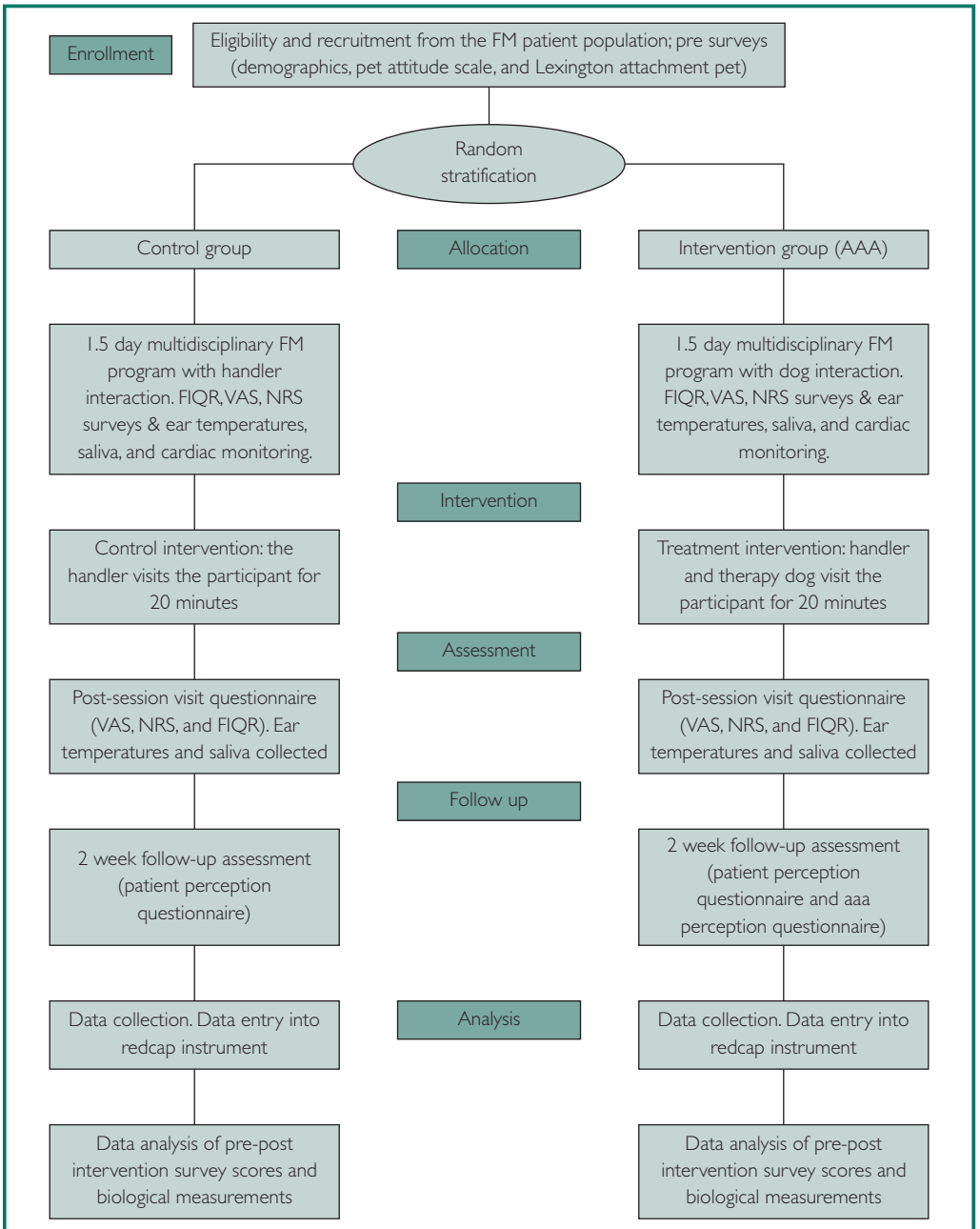

FIGURE 1. Study design showing animal-assisted activities in patients with fibromyalgia. AAA = animal-assisted activities; FIQR = Fibromyalgia Impact Questionnaire – Revised; FM = fibromyalgia; NRS = numeric rating scale; VAS = visual analog scale.

Canine Subjects and Handlers

This study used 19 therapy dogs that were part of Mayo Clinic's Caring Canine Program. The dogs were registered as therapy dogs with Alliance of Therapy Dogs, Pet Partners, Therapy Dog International, or Helping Paws. They were up to date on vaccines, deemed healthy by their veterinarian, at least 1 year of age, and were not fed a raw diet.[39,40] Of the therapy dogs, 13 were female and 6 were male. All dogs were spayed or neutered, and none were selected solely based on their breed. The dogs were always accompanied by their

TABLE 1. Outline of General Methods During a Randomized, Two-Arm, Animal-Assisted Activity Session

Event	Treatment group (handler and dog)	Control group (handler only)
Pre-session (observation room)	Pre-session surveys[a] were completed. Ear temperatures were collected simultaneously. Saliva samples were collected via passive drool method for cortisol and oxytocin concentrations. The participant was fitted with a cardiac monitor.	Pre-session surveys[a] were completed. Ear temperatures were collected simultaneously. Saliva samples were collected via passive drool method for cortisol and oxytocin concentrations. The participant was fitted with a cardiac monitor.
Interaction: 20-minute (observation room)	The participant was randomly assigned to a therapy dog and handler visit. The handler and dog entered the observation room where the participant was waiting. Dog was released from leash and allowed to move freely around. The participant could choose to interact with the dog. The participant could choose to sit in a chair or on the floor. A study staff member sat at a desk in the room and did not interact unless to fix the cardiac monitor. Continuous cardiac parameters were recorded throughout the entire interaction.	The participant was randomly assigned to a handler-only visit. The handler entered the observation room where the participant was waiting. The participant could choose to interact with the handler. The participant could choose to sit in a chair or on the floor. A study staff member sat at a desk in the room and did not interact unless to fix the cardiac monitor. Continuous cardiac parameters were recorded throughout the entire interaction.
Post-session (observation room)	At the 20-minute mark, the dog and handler exited the room. Saliva sample and ear temperatures were collected and the cardiac monitor was removed. Post-session surveys[b] were completed.	At the 20-minute mark, the handler exited the room. Saliva sample and ear temperatures were collected and the cardiac monitor was removed. Post-session surveys[b] were completed.
2-weeks post-session	Via e-mail, the participant received two surveys: satisfaction survey on the therapy dog visit and a satisfaction survey on their time at the fibromyalgia clinic.	Via e-mail, the participant received a satisfaction survey on their time at the fibromyalgia clinic.

[a]Pre-session surveys included, demographic survey (age, sex, ethnicity, education level, and martial and employment status), Pet Attitude Scale, Lexington Pet Attachment Scale, Fibromyalgia Impact Questionnaire—Revised (FIQR), numeric pain scale (NRS), and visual analog scales (VAS) for different emotions.
[b]Post-session surveys included, FIQR, NRS, and VAS for different emotions.

owners/handlers. A total of 19 handlers participated in the study; 15 women and 4 men. All of the therapy teams (dog-handler) volunteered at Mayo Clinic on a regular basis and participated in this study on a voluntary basis. The handlers were asked to conduct themselves in a professional manner and to uphold the Mayo Clinic Volunteer and Caring Canine program rules, including patient privacy, dressing professionally, and ensuring that their dog was properly groomed. In addition, the handlers were instructed to only talk about previously approved topics of conversation; a conversation starter list was provided to the handlers with potential topics including, weather, travel, hobbies, movies, and books. Conversations about the participant's FM or other medical conditions were not allowed. In the control group, conversation about pets was also not allowed. Each handler was asked to complete a total of 10 visits (five with his/her respective dog and five by him/herself).

Questionnaires

Study participants were assigned an identification number and their status of participation was tracked in the research participant tracking software PTrax (Darlogix, Inc, Williamsville, NY). All participants were asked to fill out surveys pre-, immediately

post-, and 2 weeks post-session (Table 1 and Figure 1). The pre-session surveys included demographics (age, sex, ethnicity, education level, marital status, and employment status), pet attitude scale (PAS) (questions evaluating the attitude of humans towards pets), Lexington Pet Attachment Scale (LPAS) (questions assessing the emotional attachment an individual has with pets), FIQR (a 3-part questionnaire to assess the impact of FM symptoms and severity over the last 7 days), VAS (participants rate their positive and negative emotions as well as pain separately on a scale of 1 to 10, with 10 being the worst), and an NRS for pain (an average of the best, current, and worst pain scores over the last 24 hours, on a scale of 1 to 10, with 10 being the worst). Immediately after the session, participants were asked to complete the FIQR, VAS, and NRS again. Lastly, 2-week follow-up questionnaires were e-mailed to all participants; both groups (treatment and control) received an overall generalized perception survey of their time at the Fibromyalgia and Chronic Fatigue Clinic, whereas participants in the treatment (AAA) group also received a survey for their feedback on the AAA experience. All survey responses were collected and stored using the Research Electronic Data Capture software hosted by the Mayo Clinic Center for Clinical and Translational Science.

Salivary Cortisol and Oxytocin Concentrations

Pre- and post-session saliva were passively collected from participants over the course of 2 minutes. The samples were then aliquoted into separate tubes for cortisol and oxytocin analysis. Aliquots were stored in a −80°C freezer until shipped overnight on dry ice to the Nestlé Purina Research laboratory for analysis.

Salivary cortisol was analyzed on a cobas e411 (Roche Diagnostics, Indianapolis, IN). The electrochemiluminescence immunoassay Elecsys Cortisol Assay uses a competitive test principle in which a polyclonal antibody is specifically directed against cortisol. Untreated saliva samples are used following centrifugation. After the start of the analysis, an in-house assay verification was completed to evaluate the limit of quantification and dilution linearity. It showed that the lower limit of quantification for our laboratory was 0.130 μg/dL and dilution of saliva was linear with 106% linearity up to the limit of quanitification. Any value less than 0.130 μg/dL was noted. Samples that did not have enough volume for analysis were diluted with Roche Elecsys Diluent Universal. For those samples that required dilution, the final results took into account the dilution factor.

Salivary oxytocin was measured by a liquid chromatography—mass spectrometry platform containing a Nexera X2 ultra-high performance liquid chromatography (Shimadzu, Columbia, MD) and an AB Sciex 6500+ quadruple ion trap mass spectrometer (AB Sciex, Framingham, MA).[41] Briefly, 300 μL of calibration standard or saliva sample was mixed with 1.2 mL 80% aqueous acetonitrile containing oxytocin internal standard (oxytocin-d_5, 1 nmol/L) in a 2-mL Eppendorf tube. The mixture was vortexed for 30 seconds and then centrifuged at 15,000 × *g* under 4°C for 10 minutes. After the centrifugation, the supernatant was transferred into another 2-mL Eppendorf tube and dried using a miVac sample concentrator (SP Scientific, Stone Ridge, NY). After completely dried, the sample was reconstituted with 50 μL 50% aqueous acetonitrile. After another centrifugation at 15,000 × *g* under 4°C for 2 minutes, the supernatant was transferred to a high-pressure liquid chromatography vial. A portion (10 μL) of the aliquot-prepared sample was injected into the liquid chromatography—mass spectrometry for analysis. Quantification was performed by multiple reaction monitoring of the protonated precursor molecular ions $[M+H]^+$ and the related product ions. Chromatograms and mass spectral data were acquired and processed using Analyst 1.6.3 software (AB Sciex).

Tympanic Membrane Temperature

Tympanic ear thermometers (Braun ThermoScan PRO 6000 ear thermometer, Welch

Allyn, Skaneateles Falls, NY) were used to assess the temperature of both the left and right tympanic membranes, simultaneously.

Cardiac Activity

Cardiac activity was monitored using a Polar V800 device (Chicago, IL), which includes a receiver (watch) and a transmitter (soft elastic belt with electrodes imbedded in two sections). Water-based electrode lubricant was used to enhance conductivity. Continuous cardiac monitoring was maintained throughout each session. The recorded cardiac parameters included HR as well as measures of HRV, including high frequency (HF), low frequency (LF), very low frequency (VLF), LF/HF ratio, the percent of heart beats where differences between an RR interval and the previous RR interval is greater than 50 ms (PNN50), and the root square mean of the successive differences of RR intervals (RMSSD). Of these variables, the RMSSD is a good surrogate marker of the parasympathetic nervous system.[42]

Following the sessions, data were downloaded and exported from the receiver to a computer using the Polar Flow application for analysis (Polar Electro Öy, Kempele, Finland). The data was analyzed in 2-minute intervals via Kubios HRV Standard Version 3.1.0 (Kubios Oy). The analyzed cardiac parameters were at the beginning of the session (at minutes 3 and 4) and the end of the session (at minutes 17 and 18). These timeframes were selected to provide the cleanest 2-minute intervals for analysis, as this gave the participant and handler with or without dog time to settle at the beginning of the session and incorporated a standardized and consistent time point before the end of the session. Moreover, it has previously been shown that HRV that has an artifact correction factor greater than 10% cannot be calculated reliably[43]; therefore, any cardiac data that had an artifact correction of 10% or greater was not included in the analysis.

Statistical Analysis

A clinically meaningful difference on the VAS scales and NRS pain scale would be a half SD change (effect size = 0.50). With 86 eligible patients per group, there would be a 90% power to detect a mean difference of 1 on the scales, assuming an SD of 2 (effect size = 0.50) and a two-sided significance level of 0.05 (based on a 2-sample Student *t* test). Assuming a 15% drop out rate, we would plan to stratify a total of 200 total patients (100 per group).

The participants were randomized according to when they volunteered to participate and when they finished their preliminary questions/consent forms. Identical exam rooms were used for both groups (control and treatment). The handlers used an online volunteering website to randomly pick their five handler-only sessions and five dog visits. Demographic summaries of the participants can be found in Table 2. Two-week post-session survey responses were compared using a χ^2 test for categorical variables and Welch's two-sample t test for continuous variables.

For the continuous variables of FIQR, VAS, NRS, tympanic membrane temperature, salivary cortisol, salivary oxytocin, and HR outcomes, linear mixed models were ran for each outcome using the package lme4 in R. The model included fixed effects for treatment, time, and an interaction of treatment by time. Each participant completed two surveys which assessed their attitude towards pets, the PAS, and LPAS. To control for a participant's attitude towards pets, his/her average response on the PAS and LPAS were included as a fixed effect in the model where the average was computed for any individual who answered at least one question of either survey. The model included a random effect for participant and dog identification to account for repeated measures on patients and the same dogs being used in multiple sessions. Plots of residuals were used to check that model assumptions were satisfied. The Type III Sums of Squares (Type III SS) were used to test overall significance of a predictor. When a significant interaction was present according to the Type III SS, post hoc comparisons with a Tukey adjustment were made between groups at each

timepoint and between timepoints within each group. If there was no significant interaction but there was a significant time effect according to the Type III SS, post hoc comparisons with a Tukey adjustment were made between timepoints. Observed means were used to assess changes between pre- and post-session values for both groups. Outliers were identified if a value decreased above the mean + 3 SDs or below the mean - 3 SDs. Significance was set at $P \leq .05$.

RESULTS

Participant Demographics

Control Group. The control group consisted of 110 participants, with 102 women and 8 men with a mean age of 43.99±14.72 years. Their ethnicities were white (n=103), Hispanic/Latino (n=2), African American (n=1), American Indian/Alaskan (n=1), and other (n=3). Their level of education ranged from post-graduate (n=24), 4-year university (n=25), some college (n=47), high school (n=13), and eighth grade education or less (n=1). Their marital status included married (n=63), single (n=28), divorced (n=16), widowed (n=2), and unknown (n=1). The control group employment status was employed (n=45), student (n=13), retired (n=13), full time homemaker (n=11), unemployed (n=10), work disabled (n=10), and self-employed (n=8).

Treatment Group. The treatment group consisted of 111 participants, with 102 women and 9 men with a mean age of 43.03±13.31 years. Their ethnicities were white (n=103), African American (n=3), Hispanic/Latino (n=2), American Indian/Alaskan (n=2), and other (n=1). Their level of education ranged from post-graduate (n=16), 4-year university (n=35), some college (n=49), and high school (n=11). Their marital status included married (n=64), single (n=32), divorced (n=13), widowed (n=1), and unknown (n=1). The treatment group employment status was employed (n=51), unemployed (n=14), work disabled (n=14), full time homemaker (n=10), retired (n=9), student (n=6), self-employed (n=6), and unknown (n=1).

Health Questionnaires

FIQR. The FIQR was administered immediately before and after the session. The FIQR is divided into three sections: function (9 questions), overall impact (2 questions), and symptoms (10 questions). The questions assess the impact of FM symptoms on a patient over the past 7 days and are captured on a 10-point scale (0 to 10 points) with 10 being the worst. The total FIQR is the sum of the function, overall impact, and symptom scores.

The total FIQR score can be further analyzed via different subcategories, including performance, function, and intensity. The performance FIQR subcategory had a significant group by time interaction (P=.01) (Table 3). There was no difference between treatment and control groups at either timepoint (pre- vs post-session); however, on average, both groups showed a decrease in score over the study session with the treatment group having a larger statistically significant decrease (-1.33) compared with the nonsignificant decrease in the control group (-0.40). The function FIQR subcategory had a significant time effect (P<.0001). On average, both the treatment (-1.55) and control (-0.89) groups showed a statistically significant decrease in score over the study session. The intensity FIQR subcategory had a significant group by time interaction (P=.005). There was no difference between treatment and control groups at either timepoint; however, on average, both groups showed a statistically significant decrease in scores over the session, with a bigger decrease for the treatment group (-4.51) compared with control group (-2.52). Overall, the total FIQR score had a significant group by time interaction (P=.003) (Figure 2A). There was no difference between the treatment and control groups at either timepoint; however, on average, both groups showed a statistically significant decrease in score over the study period, with a bigger decrease for the treatment group (-7.38) compared with the control group (-4.17).

TABLE 2. Demographics of the Control and Treatment Groups

	Control (n=110)	Treatment (n=111)
Sex		
Male	8	9
Female	102	102
Ethnicity		
White	103	103
Hispanic/Latino	2	2
African American	1	3
American Indian/ Alaskan	1	2
Other	3	1
Education		
Post-graduate	24	16
4-y university	25	35
Some college	47	49
High school	13	11
Eighth grade education or less	1	0
Marital status		
Married	63	64
Single	28	32
Divorced	16	13
Widowed	2	1
Unknown	1	1
Employment status		
Employed	45	51
Student	13	6
Retired	13	9
Full-time homemaker	11	10
Unemployed	10	14
Work disabled	10	14
Self-employed	8	6
Unknown	0	1

NRS—Pain. The pain NRS was administered immediately before and after the session. The pain NRS had a significant group by time interaction (P=.006) (Figure 2A). There was no difference between treatment and control groups at either timepoint. On average, both groups showed a nonsignificant decrease over the study session; however, the treatment group had a larger decrease in pain (-0.63) compared with the control group (-0.26).

VAS. The VAS (assessing various positive and negative emotions) was administered immediately before and after the session. For negative emotions, the Likert-scale was from 0 to 10 points, with 0 being not at all and 10 being the worst possible. The negative emotion responses had a significant group by time interaction for restlessness, fatigue, anxiety, depression, and stress (P=.04, .0004, <.0001, .01, and .0015, respectively) (Figure 2B). There were no differences between treatment and control groups at either of the timepoints. On average, both the treatment and control groups showed a statistically significant decrease in scores over the study session, with bigger decreases in the treatment group (-0.70, -1.61, -1.63, -1.13, and -1.96, respectively) compared with the control group (-0.19, -0.68, -0.39, -0.48, and -0.88, respectively).

The positive emotions were assessed on a 0- to 10-point Likert-scale, with 0 being the best possible and 10 feeling the worst. For positive emotions, there was a significant group by time interaction for happy, energetic, relaxed, calm, and well-being (P=.002, .04, .01, .02, and .002, respectively). There were no differences between treatment and control groups at either of the timepoints. On average, both the treatment and control groups showed a statistically significant decrease in scores over the study session with bigger decreases in the treatment group (-1.40, -1.54, -2.07, -1.68, and -1.72, respectively) compared with the control group (-0.53, -0.84, -1.13, -0.86, and -0.66, respectively).

Salivary Cortisol

There were no significant time (P=.45), treatment (P=.65), or treatment by time effects (P=.56) (Figure 2C) for salivary cortisol between the treatment and control groups.

Salivary Oxytocin

There was a significant group-by-time interaction for salivary oxytocin (P=.006) (Figure 2C). There were no differences between treatment and control groups at either timepoint; however, the treatment group showed a statistically significant increase (+0.09) in salivary oxytocin over the study

TABLE 3. Statistical Analysis of Collected Parameters[a]

Results Table											
		N		Mean			Type III SS *P* values				
Variable	Group	Pre-	Post-	Pre (SD)	Post (SD)	Post - Pre	Average LPAS	Average PAS	Time	TRT	TRT:time
FIQR											
Performance	CON	110	110	16.77 (6.85)	16.37 (6.90)	-0.40	.936	.820	< .001[b]	.638	.012[b]
	TRT	111	111	16.15 (7.62)	14.83 (7.51)	-1.33					
Functional	CON	110	109	13.16 (5.08)	12.28 (5.03)	-0.89	.898	.945	< .001[b]	.840	.123
	TRT	111	111	13.6 (5.43)	12.05 (5.57)	-1.55					
Intensity	CON	110	109	30.03 (8.04)	27.51 (8.25)	-2.52	.495	.567	< .001[b]	.812	.004[b]
	TRT	111	111	30.88 (8.52)	26.38 (9.24)	-4.51					
Total	CON	110	110	59.96 (17.02)	55.79 (17.02)	-4.17	.756	.863	< .001[b]	.673	.002[b]
	TRT	111	111	60.64 (18.58)	53.25 (19.39)	-7.38					
VAS											
Restlessness	CON	110	109	4.34 (2.54)	4.15 (2.49)	-0.19	.787	.358	< .001[b]	.081	.045[b]
	TRT	111	111	4.05 (2.83)	3.35 (2.81)	-0.70					
Fatigue	CON	110	109	7.42 (1.83)	6.74 (2.08)	-0.68	.625	.672	< .001[b]	.010[b]	< .001[b]
	TRT	111	109	7.29 (1.56)	5.68 (2.42)	-1.61					
Anxiety	CON	110	109	4.6 (2.66)	4.21 (2.82)	-0.39	.094	.671	< .001[b]	.912	< .001[b]
	TRT	110	111	5.17 (2.78)	3.54 (2.9)	-1.63					
Depression	CON	110	109	3.76 (2.67)	3.28 (2.54)	-0.48	.705	.412	< .001[b]	.942	.017[b]
	TRT	111	111	4.14 (3.12)	3.02 (2.9)	-1.13					
Stress	CON	110	109	5.53 (2.54)	4.65 (2.8)	-0.88	.488	.585	< .001[b]	.365	.001[b]
	TRT	110	111	5.8 (2.65)	3.84 (2.92)	-1.96					
Happy	CON	110	109	4.35 (2.13)	3.82 (2.07)	-0.53	.436	.932	< .001[b]	.495	.002[b]
	TRT	111	110	4.61 (1.99)	3.21 (2.42)	-1.40					
Energetic	CON	110	109	6.58 (2.15)	5.74 (2.25)	-0.84	.661	.555	< .001[b]	.378	.047[b]
	TRT	111	111	6.19 (2.54)	4.65 (2.56)	-1.54					
Relaxed	CON	110	109	5.51 (2.18)	4.38 (2.13)	-1.13	.902	.564	< .001[b]	.700	.010[b]
	TRT	111	111	5.62 (2.32)	3.55 (2.76)	-2.07					
Calm	CON	110	109	4.97 (2.27)	4.11 (2.17)	-0.86	.705	.939	< .001[b]	.075	.020[b]
	TRT	111	111	4.9 (2.39)	3.23 (2.59)	-1.68					
Well-being	CON	110	109	5.09 (2.35)	4.43 (2.29)	-0.66	.465	.987	< .001[b]	.203	.001[b]
	TRT	110	111	5.27 (2.35)	3.55 (2.60)	-1.72					
NRS											
	CON	109	108	5.46 (1.70)	5.19 (1.57)	-0.26	.763	.057[b]	< .001[b]	.897	.006[b]
	TRT	110	109	5.66 (1.57)	5.02 (1.62)	-0.63					
Salivary											
Cortisol	CON	69	70	174.83 (73.31)	173.76 (68.06)	-1.07	.075	.459	.447	.651	.564
	TRT	73	67	188.04 (68.04)	178.54 (68.22)	-9.50					
Oxytocin	CON	85	85	0.31 (0.16)	0.31 (0.17)	0	.784	.387	.006[b]	.849	.005[b]
	TRT	89	91	0.26 (0.13)	0.35 (0.20)	0.09					
Membrane temp											
R temp	CON	108	107	36.71 (0.39)	36.75 (0.37)	0.04	.135	.058	.002[b]	.988	.463
	TRT	110	110	36.69 (0.41)	36.76 (0.42)	0.07					
L temp	CON	109	108	36.7 (0.40)	36.72 (0.36)	0.01	.417	.005[b]	.006[b]	.387	.028[b]

Continued on next page

TABLE 3. Continued

Results Table

Variable	Group	N Pre-	N Post-	Mean Pre (SD)	Mean Post (SD)	Post - Pre	Type III SS *P* values Average LPAS	Average PAS	Time	TRT	TRT:time
	TRT	109	109	36.69 (0.39)	36.79 (0.36)	0.10					
L temp − R temp	CON	107	109	-0.01 (0.32)	0 (0.30)	0	.290	.656	0.338	0.975	.403
	TRT	109	111	-0.02 (0.29)	0.02 (0.29)	0.04					
Heart rate variables											
HR	CON	91	89	78.65 (12.58)	77.28 (11.8)	-1.37	.972	.597	.019[b]	.927	.575
	TRT	78	81	77.37 (10.52)	76.3 (10.84)	-1.07					
RR	CON	90	88	769.97 (119.57)	782.83 (118.82)	12.86	.562	.322	.016[b]	.715	.511
	TRT	79	81	785.27 (105.28)	799.84 (109.7)	14.57					
RMSSD	CON	90	89	33.02 (20.88)	30.01 (17.74)	-3.01	.064	.430	.809	.441	.070
	TRT	79	79	33.9 (18.77)	35.4 (20.20)	1.50					
PNN50	CON	90	89	10.49 (11.04)	9.67 (11.49)	-0.82	.050	.261	.115	.125	.006[b]
	TRT	78	81	11.95 (12.42)	14.8 (16)	2.85					
VLF	CON	90	87	119.96 (120.13)	132.06 (157.61)	12.10	< .001[b]	.007[b]	.416	.225	.868
	TRT	72	80	139.75 (159.53)	149.43 (143.89)	9.68					
LF	CON	91	90	1058.24 (944.42)	974.81 (805.31)	-83.43	.025[b]	.088	.905	.297	.297
	TRT	77	81	1104.83 (912.63)	1137.46 (941.26)	32.63					
HF	CON	90	88	458.94 (524.52)	309.15 (380.99)	-149.79	.067	.233	.080	.507	.029
	TRT	76	77	487.86 (494.39)	498.33 (514.57)	10.48					
LF/HF ratio	CON	89	86	4.21 (3.52)	4.64 (3.85)	0.43	.593	.236	.542	.031[b]	.576
	TRT	79	80	3.52 (2.57)	3.47 (2.78)	-0.05					

[a]CON = control; FIQR = Fibromyalgia Impact Questionnaire—Revised; HF = high frequency; HR = heart rate; L = left; LF = low frequency; LPAS = Lexington Pet Attachment Scale; NRS = numeric rating scale; PAS = pet attitude scale; Post = post-session; PNN50 = percent of heart beats where differences between an RR interval and the previous RR interval is greater than 50 ms; Pre = pre-session; R = right; RMSSD = root square mean of the successive differences of RR intervals; TRT = treatment; Type III SS = type III sums of squares; VAS = visual analog scale; VLF = very low frequency.

[b]Statistically significant ($P<.05$).

session, whereas the control group showed no change (0.00).

Tympanic Membrane Temperatures

Right tympanic membrane temperatures had a significant time effect ($P=.003$). On average, post-session right tympanic membrane temperature values were higher than pre-session values (treatment: +0.07; control: +0.04) (Figure 2C). Left tympanic membrane temperatures had a significant group-by-time interaction ($P=.03$). There were no differences in left tympanic membrane temperature between treatment and control groups at either timepoint; however, the treatment group showed a statistically significant increase over the study session (+0.10) whereas the control group remained largely unchanged (+0.01).

Cardiac Activity

There was a significant time effect for HR values ($P=.02$). On average, the HR values decreased over the study session for both treatment (-1.07) and control groups (-1.37) (Figure 2D). Additionally, there was a significant time effect for RR values ($P=.02$) (Figure 2D). On average, the RR values increased over the study session for both groups (treatment: +14.57; control: +12.86). The LF/HF ratio had a

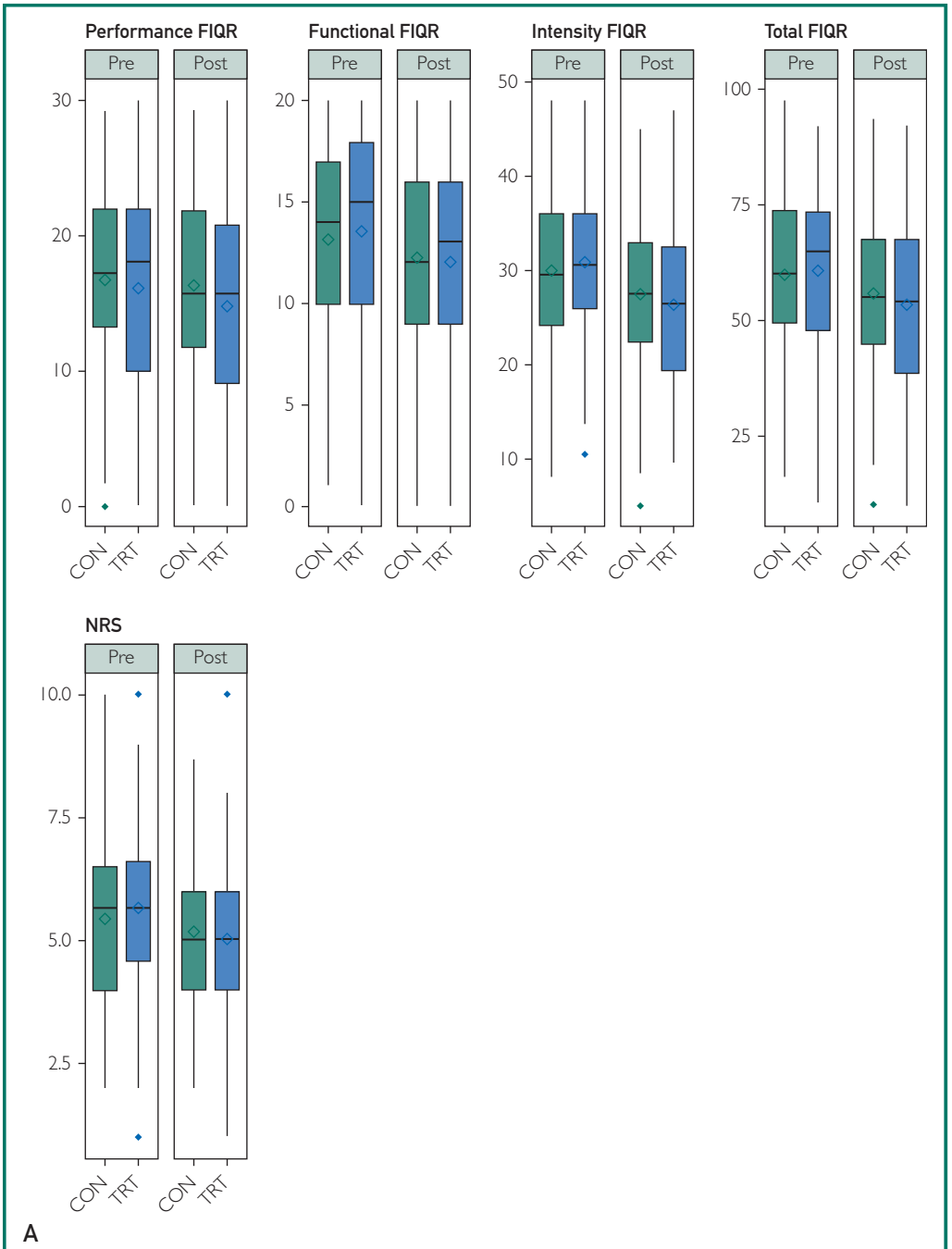

FIGURE 2. Survey and biological graphs for control and treatment groups comparing pre and post means. *A*, Fibromyalgia Impact Questionnaire – Revised and pain numeric rate scale. *B*,Visual analog scale. *C*, Tympanic membrane temperatures and salivary cortisol and oxytocin. *D*, Heart rate variability. CON = control; FIQR = Fibromyalgia Impact Questionnaire – Revised; HF = high frequency; HRV = heart rate variability; LF = low frequency; NRS = numeric rating scale; PNN50 = percent of heart beats where differences between an RR interval and the previous RR interval is greater than 50 ms; RMSSD = root square mean of the successive differences of RR intervals; TRT = treatment; RR = RR interval; VLF = very low frequency.

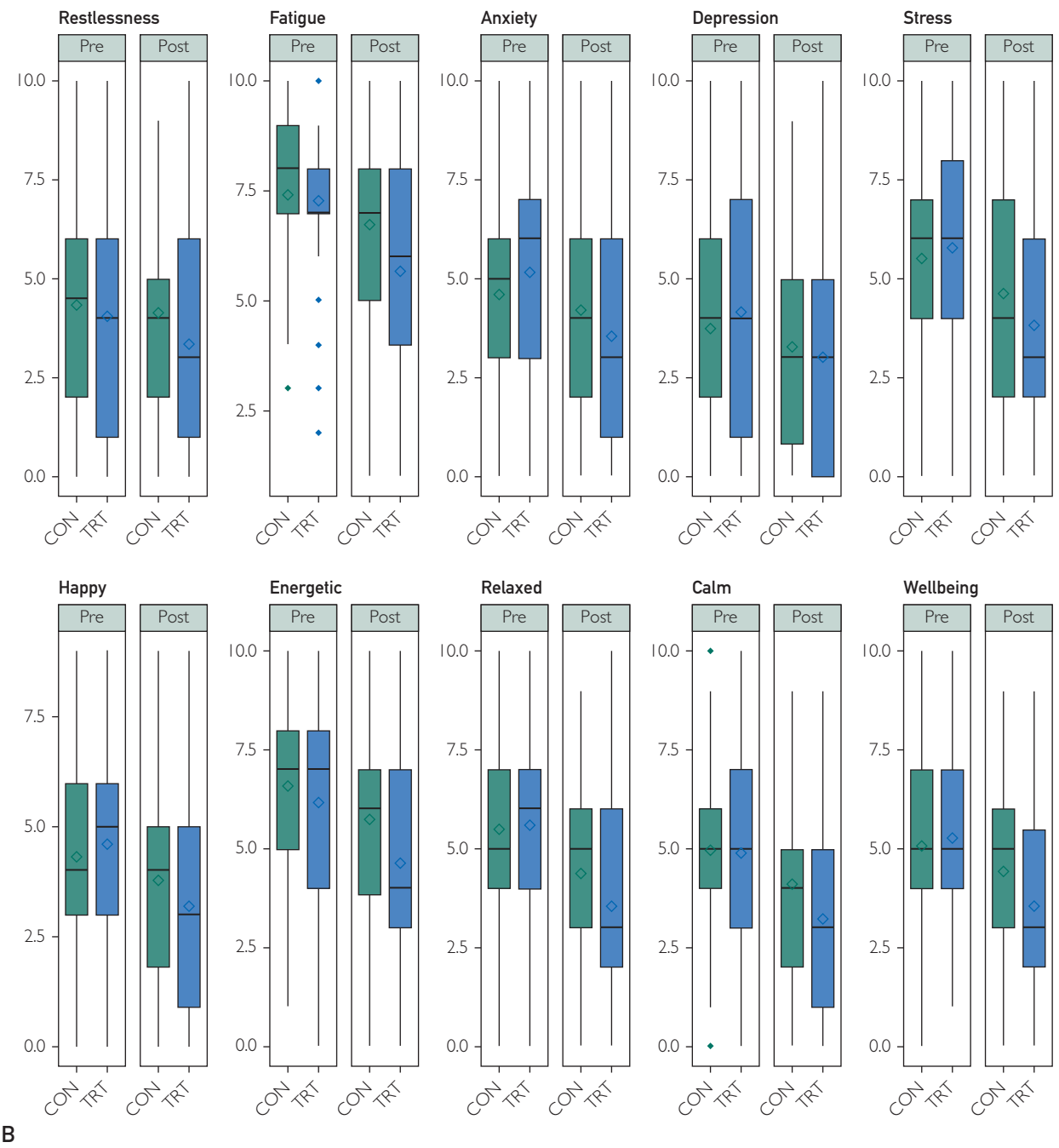

FIGURE 2. continued

significant treatment effect (P=.03). The control group had on average higher LF/HF ratio values than the treatment group (control−treatment pre-session: +0.69; post-session: +1.17). RMSSD had a marginal (although nonsignificant) group-by-time interaction (P=.07). PNN50 and HF had significant group-by-time interactions (P=.006 and P=.03, respectively). For RMSSD and PNN50, the treatment group showed a statistically significant increase on average over the study session (+1.50 and +2.85,

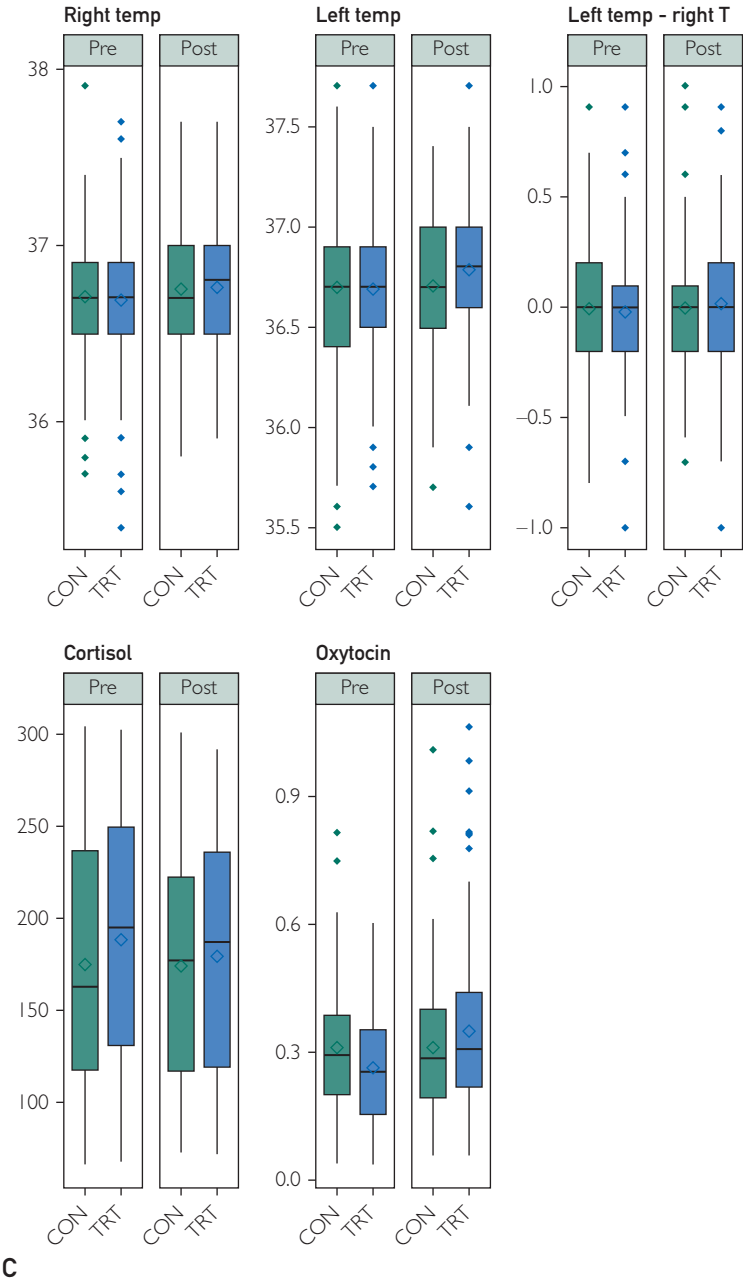

FIGURE 2. continued

respectively), whereas the control group showed a statistically significant decrease in values over the study session (-3.01 and -0.82, respectively). For HF, the treatment group showed a nonsignificant increase, on average, over the study session (+10.48) whereas the control group had a statistically significant decrease over the study session (-149.79). For VLF and LF, there were no significant time (P=.42 and .91, respectively), treatment (P=.23 and .30, respectively), or treatment-by-time effects (P=.87 and .30, respectively). There were no differences between treatment and control groups at either timepoint for RMSSD, PNN50, or HF.

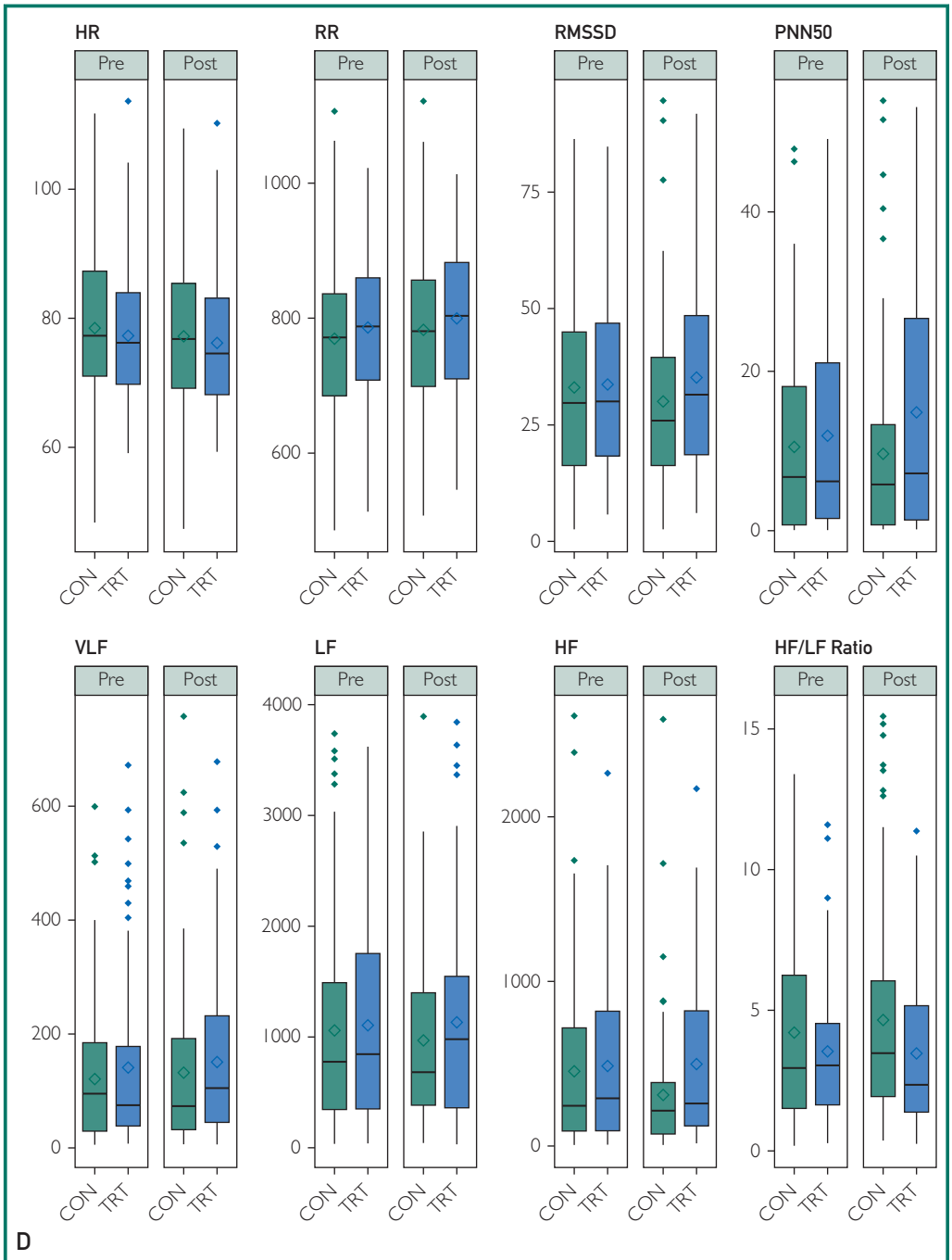

FIGURE 2. continued

Patient Satisfaction Surveys

Control Group. Of the 110 control group participants, 92 (83.6%) responded to the two-week post-session satisfaction survey. When asked to rank their overall satisfaction with their experience at the Mayo Clinic FTP, on a scale of 1-5, with 5 being highly satisfied, the average was 4.39±SD=0.55.

Treatment Group. Of 111 treatment group participants, 65 (58.6%) responded to the 2-wk post-session satisfaction survey. When

asked to rank their overall satisfaction with their experience at the Mayo Clinic FTP, on a scale of 1 to 5, with 5 being highly satisfied, the average was 4.52±0.47. Control and treatment groups were compared for overall satisfaction and there was no significant difference between groups (P=.12). Furthermore, the treatment group was asked to fill out an additional survey on overall satisfaction with the AAA visit. Of the 111 treatment group participants, 89 (80.2%) completed the AAA satisfaction survey. When asked if the AAA met their expectations, 49 (55.0%) strongly agreed and 29 (33.0%) agreed. Forty-nine (55.1%) participants strongly agreed that the AAA was helpful during their time at the clinic and 25 (28.1%) agreed. Sixty-one (68.5%) participants strongly agreed and 22 (24.7%) agreed that the therapy dog behaved appropriately. Furthermore, 60 (67.4%) participants strongly agreed and 21 (23.6%) agreed that they would recommend AAA to other patients.

DISCUSSION

Outcome Summary

The present study aimed to answer the following question: What is the emotional and physiological impact of AAA in patients with FM after a 20-minute session? We attempted to close this literature gap by using standard survey techniques in addition to the innovative use of multiple, noninvasive biomarkers to further assess the objective physiological response of the participants as a result of an AAA. Moreover, we attempted to further close the literature gap by including a control (handler-only) group, given that most previous studies either lack a control group altogether or simply combine the dog and handler as a single variable. This is a major limitation in the current literature due to the fact that there can be a human-human as well as a human-animal impact that could affect outcomes. Overall, the study showed that a 20-minute human-animal interaction (treatment group) as well as a human-human interaction (control group) could improve the emotional and physiological state of patients with FM; however, those who interacted with a therapy dog showed a more robust improvement.

Demographics

According to past literature, the prevalence of FM is higher in white, married, middle-aged females, with an average age of 47.3±10.56 years.[44] These demographics were similar to the demographics of our study population. This study does clearly represent the intended target patient population and thus should have strong applicability and generalizability.

FIQR

In this study, we observed a decrease in the three subcategories of FIQR (performance, function, and intensity) as well as total FIQR score, with the treatment group having a larger decrease in comparison to the control. The human-human and human-animal interaction both had positive impacts. We hypothesize that this could be due to the social interaction, emotional connection, spiritual connection, or social support that was experienced during the encounter.[45] In a previous study, Montoya et al (2004)[46] assessed the impact of a social interaction on the severity of tender points in individuals with FM. Similar to our NRS pain findings, they observed that after a social interaction, the self-reported severity of tender points had decreased when compared with controls.

Other studies[47,48] have also noted that mood can directly affect the perceived severity of various symptoms. Overall, our data suggests that the human-human and the human-animal interactions were experienced positively for both groups and thus led to mood improvement, which in turn led to FM-related symptom improvement. However, visits with a therapy dog resulted in a likely stronger association and thus a greater decrease in FM-symptom intensity.

VAS

Positive feelings became stronger and negative feelings lessened more so in the treatment group in comparison to the control group, suggesting that the participants who

had a 20-minute visit with a therapy dog and handler were in an overall better mood. Studies have shown that dogs can decrease people's anxiety,[49] depression,[50] fear,[19] loneliness,[51] and stress.[52] Given the significantly high concomitant rates of mood disorders in patients with FM, morale and emotions are often down. Our results suggest that having a 20-minute session with a therapy dog can help to decrease negative feelings and increase positive feelings. AAA could serve as an effective and cost-effective complementary therapeutic option in this setting.

NRS-Pain

Pain scores were significantly lower in each group after the 20-minute session; however, the treatment group had a larger decrease in pain. We noted that the average pain score for the treatment group improved from "severe pain" (NRS scores 5.5 to 7.5) to "moderate pain" (NRS scores 3.5 to 5.5). Given that individuals with FM suffer pain chronically, this reduction, even if numerically minimal, could help to provide symptomatic relief and quality of life improvement.

Our results are similar to previously published literature which suggests that therapy dog visits can improve pain scores in people with chronic pain in an outpatient setting. One such study, which observed 235 therapy dog visits in an outpatient setting, noted a significant decrease in perceived pain on a numerical pain scale, concluding that a therapy dog visit could be used to temporarily reduce pain in people with chronic pain.[24] Not only has this association been documented in adults, but an additional study observed a similar statistically significant decrease in perceived physical pain after a therapy dog visit in children.[53] In an era of ever-increasing rates of FM and other chronic pain conditions and the shift away from opioids and other potentially harmful medication strategies, health care providers should consider using AAA as an additional CIM option.

Salivary Cortisol

We did not observe significant changes in salivary cortisol concentration in the study participants. It has been previously hypothesized that significant changes in salivary cortisol could have a lag time of up to 45 minutes after an intervention/session.[54] Our methodology may have prevented us from observing changes in salivary cortisol. Future studies should examine the potential effect of the time of collection of salivary cortisol post-intervention.

Salivary Oxytocin

Salivary oxytocin increased post-session in the treatment group, suggesting that the participants were in a more positive state of well-being. Changes in oxytocin concentrations during human-animal interactions have been studied previously due to their role in social interaction and in moderating stress.[29,55,56] In a recent study,[57] it was observed that both dogs and owners had an increase in oxytocin concentration after a visit, suggesting a more positive emotional state as a result of the human-animal interaction. Similar findings of increasing OT concentration in humans and dogs due to an interaction have been shown.[55,58] Our results similarly suggest a more positive emotional state in patients with FM after a 20-minute therapy dog interaction.

Tympanic Membrane Temperatures

Activity changes in the hemispheres of the brain (measured indirectly by temperature changes in the ipsilateral tympanic membrane) provide useful information for evaluating an individual's emotional state and well-being.[59] Past studies have shown that a higher right tympanic membrane temperature is associated with negative emotions,[32] such as anger.[26] Thus, a decrease in right hemisphere activity (and a resultant decrease in right tympanic membrane temperature) suggests that the individual may be in a more positive emotional state. Conversely, a higher left tympanic membrane temperature is associated with a more positive state.[32,59] Gunner and Donzella (2004)[32] also noted that an increase in temperature laterality (the difference between left and right tympanic membrane temperature) was associated with a more positive emotional state.

In our study's treatment group, both the left and right tympanic membrane temperatures increased from pre- to post-session, but the left increased more so than the right. Furthermore, the treatment group's tympanic membrane temperature laterality (the difference between left and right tympanic membrane temperatures) was greater (from pre- to post-session) compared with the control group. Taken together, our results suggest that the participants in the treatment group were in a more relaxed state post-session compared with pre-session. This conclusion fits cohesively with the results of the other studied physiologic parameters, suggesting that the treatment group was more relaxed than the control group after their 20-minute intervention.

Cardiac Activity

HRV changed in both groups post-session; however, the treatment group had lower HR and higher RR, RMSSD, HF, LF/HF, and PNN50, signifying a more positive emotional-physiologic state as a result of the 20-minute session with the therapy dog. HRV is influenced by the autonomic nervous system and can be used as a quantifiable, noninvasive surrogate for well-being.[60] When an individual is calm, the parasympathetic nervous system is more active leading to a decrease in HR; conversely, in a state of mental or physiological stress, the sympathetic nervous system is more active, increasing the HR accordingly.[60,61] A 2013 study observed that individuals who were experiencing negative emotions (aggression, anxiety, and stress) had decreased RMSSD, HF, and PNN50.[59] Additionally, individuals who suffer from depression or are in a depressed state have lower HRV parameters.[62] Our results, which showed an increase in HRV parameters and a decrease in HR, suggest that participants in the treatment group were in a more positive emotional-physiologic state after the 20-minute AAA.

Study Limitations

There are several limitations in our study. First, the study was performed in a tertiary academic medical center; this could have created a selection bias for patients that were of higher socioeconomic status, higher educational backgrounds, and more familiar with or open to the concept of complementary and integrative medical modalities. Second, it has been shown that in FM there is evidence of sympathetic nervous system hyperactivity; this could impact the balance between the sympathetic and parasympathetic systems, which in turn could have affected our HR and HRV results. Third, we did not control for the breed of the therapy dogs. From the participants' feedback, a theme of dog breed preference did arise; one may postulate that having the opportunity to interact with a dog from a preferred breed could have arguably increased the positive effects of AAA. In our study, therapy dog assignment was randomized, reflecting how therapy dog visits are scheduled at Mayo Clinic's Caring Canine Program where specific breeds cannot be requested. Fourth, we used self-reported surveys, which may create recall bias[63] or evasion bias.[64] However, the participants' survey responses were well aligned with their collected biological parameters, supporting our conclusions. Fifth, we indirectly measured the emotional and physiological impact of an AAA session in patients with FM by using several evidence-based surrogate markers; as these are still evolving tools, there could have been unexpected variances in our results due to random chance, the collection time window, or the nature of the surrogate markers themselves.

CONCLUSION

Our results suggest that a 20-minute AAA in an outpatient setting can significantly and positively impact the physical and mental health of patients with FM. The noninvasive physiological measures (salivary cortisol, salivary oxytocin, tympanic membrane temperatures, and cardiac parameters) used for this study acted cohesively and further support our conclusion. Although both groups experienced changes in most measured parameters, the treatment group (therapy dog and handler) had larger and more positive changes post-session than the control group

(handler only). As a result, health care professionals should strongly consider using AAA in the care of their patients with FM. Future studies should continue with the concurrent use of multiple noninvasive physiological measures to help advance our understanding of the impact of AAA in other health conditions.

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Abbreviations and Acronyms: **AAA** = animal assisted activity; **CIM** = complementary and integrative medicine; **CNS** = central nervous system; **CS** = central sensitization; **FIQR** = fibromyalgia impact questionnaire – revised; **FM** = fibromyalgia; **FTP** = fibromyalgia treatment program; **HF** = high frequency; **HR** = heart rate; **HRV** = heart rate variability; **LF** = low frequency; **LF/HF ratio** = low frequency/high frequency ratio; **LPAS** = Lexington pet attitude attachment scale; **NRS** = numeric rating scale; **PAS** = pet attitude scale; **PNN50** = percent of heart beats where differences between an RR interval and the previous RR interval is greater than 50 ms; **RMSSD** = root square mean of the successive differences of RR intervals; **VAS** = visual analog scale; **VLF** = very low frequency

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