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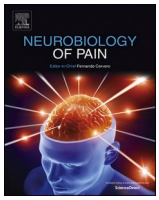

Neural indices of multimodal sensory and autonomic hyperexcitability in fibromyalgia

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ABSTRACT

Fibromyalgia (FM) is characterized by chronic widespread musculoskeletal pain and psychological distress. Research suggests people with FM experience increased somatosensory sensitization which generalizes to other sensory modalities and may indicate neural hyperexcitability. However, the available evidence is limited, and studies including measures of neural responsivity across sensory domains and both central and peripheral aspects of the neuraxis are lacking. Thirty-nine participants (51.5 ± 13.6 years of age) with no history of neurological disorders, psychosis, visual, auditory, or learning deficits, were recruited for this study. People with FM (N = 19) and control participants (CNT, N = 20) did not differ on demographic variables and cognitive capacity. Participants completed a task that combined innocuous auditory stimuli with electrocutaneous stimulation (ECS), delivered at individually-selected levels that were uncomfortable but not painful. Event-related potentials (ERPs) and electrodermal activity were analyzed to examine the central and sympathetic indices of neural responsivity. FM participants reported greater sensitivity to ECS and auditory stimulation, as well as higher levels of depression, anxiety, ADHD, and an array of pain-related experiences than CNT. In response to ECS, the P50 deflection was greater in FM than CNT participants, reflecting early somatosensory hyperexcitability. The P50 amplitude was positively correlated with the FM profile factor obtained with a principal component analysis. The N100 to innocuous tones and sympathetic reactivity to ECS were greater in FM participants, except in the subgroup treated with gabapentinoids, which aligns with previous evidence of symptomatic improvement with GABA-mimetic medications. These results support the principal tenet of generalized neural hyperexcitability in FM and provide preliminary mechanistic insight into the impact of GABA-mimetic pharmacological therapy on ameliorating the neural excitation dominance.

Introduction

Widespread musculoskeletal pain is the cardinal symptom of fibromyalgia (FM) which is additionally accompanied by fatigue, insomnia, depression, and anxiety (Arnold et al., 2016; Glass, 2008; Sluka and Clauw, 2016; Wolfe et al., 2016). FM is classified as a centralized chronic pain disorder without clear, causative peripheral pathology (Clauw, 2015; Petersel et al., 2011; Staud, 2002; Tennant, 2012), which presents a challenge for diagnosis and treatments (Kumbhare et al., 2018; Walitt et al., 2016). Another key symptom is central sensitization which is reflected in tactile hyperalgesia, exaggerated responsivity to pain, and allodynia, increased sensitivity to innocuous stimuli (Clauw et al., 2011; Desmeules et al., 2003; Latremoliere and Woolf, 2009; Meeus and Nijs, 2007). Indeed, lower pain thresholds for mechanical (pressure) and thermal (heat and cold) stimuli in participants with FM have been well-established (de la Coba et al., 2022; Desmeules et al., 2003; Plesner and Vaegter, 2018). Similarly, people with FM show increased sensitivity to electrical stimulation (Erturk Celik and Beyazova, 2020; Rhudy et al., 2013). Taken together, the evidence is indicative of deficient inhibitory top-down pain modulation pathways (Staud, 2006; Woolf, 2011). Anchored in the concept of central sensitization (Desmeules et al., 2003; Latremoliere and Woolf, 2009; Meeus and Nijs, 2007; Woolf, 2011), this model predicts generalized perceptual amplification across other sensory modalities in addition to somatosensory domain (Wilbarger and

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Cook, 2011), including lower tolerance to sounds (Geisser et al., 2008; McDermid et al., 1996; Staud et al., 2021) and visual stimuli (Harte et al., 2016). The framework has been termed generalized hypervigilance (McDermid et al., 1996).

Event-related potentials (ERPs) reflect postsynaptic currents directly (Nunez and Srinivasan, 2006), making them a preferred method for studying neural activity in real time (Luck, 2005). ERPs can capture early excitatory activation of the primary sensory areas (Allison et al., 1996; Yoshiura et al., 1996) and have confirmed a larger P50 deflection to nonpainful somatosensory stimuli in FM than control participants (Montoya et al., 2005), which aligns with the central sensitization model. In contrast, the supporting evidence for generalized hypervigilance in other modalities has been mixed. While some researchers report augmented early ERPs (Carrillo-de-la-Pena et al., 2006; Otsuru et al., 2022) and deficient habituation of the N100 to auditory stimuli (Choi et al., 2016), others have failed to find greater FM sensitivity to tones (Lorenz, 1998; Samartin-Veiga et al., 2020).

Neurotransmission has both, electrical and neurochemical aspects, which calls for complementary methods to examine FM's central tenet of hyperexcitability. Proton magnetic resonance spectroscopy (^{1}H-MRS) can provide a mechanistic insight into the concentration of GABA and glutamate, the principal inhibitory and excitatory neurotransmitters (Ende, 2015; Harris et al., 2017). The available ^{1}H-MRS evidence shows higher glutamate (Harris et al., 2009) and lower GABA levels in people with FM (Foerster et al., 2012) which correlates with pain. These findings suggest that increased neural excitability underlies central sensitization and the experience of pain (Meeus and Nijs, 2007; Petersel et al., 2011; Sluka and Clauw, 2016). Gabapentinoid medications are commonly prescribed for the treatment of FM (Cooper et al., 2017; Tzadok and Ablin, 2020). They provide pain relief which is associated with reduced neural excitability and brain activity to noxious as well as innocuous stimuli (Harris et al., 2013; Harte et al., 2016; Kim et al., 2013). In addition, GABA-mimetic medications have beneficial effects on sleep problems, fatigue, and depression (Arnold et al., 2018; Moore et al., 2014). While not acting on GABA receptors directly, gabapentinoids are structural analogues of GABA designed to suppress neural excitability (Cai et al., 2012). As would be expected, they exert effects on EEG signals, which should be considered in studies of patients receiving pharmacological treatment (Graversen et al., 2012).

Neural hyperexcitability extends to the autonomic nervous system. It can be expressed as sympathetic predominance in people with FM (Martinez-Lavin, 2007; Martinez-Martinez et al., 2014; Petzke and Clauw, 2000), raising a possibility that FM clinical features may be maintained through sympathetic hyperactivity (Martinez-Lavin, 2007; Solano et al., 2009; Zamuner et al., 2015). Electrodermal activity (EDA) reflects sympathetic arousal via innervation of eccrine skin glands (Boucsein, 2012) and is commonly measured as phasic skin conductance responses (SCR) and tonic skin conductance level (SCL) (Boucsein et al., 2012; Dawson et al., 2007). Sympathetic dominance is indicated by larger electrodermal activity in people with FM than in control participants (On et al., 2022; Qiao et al., 1991; Thieme et al., 2006; Thieme et al., 2016). However, there are also dissenting reports (Reyes Del Paso and de la Coba, 2020), calling for more experimental studies in FM.

In the present study, the neural indices of central and peripheral activity were used to examine whether people with FM show: a) greater sensitivity to electrocutaneous stimuli in the somatosensory domain; b) generalized hypersensitivity to auditory stimuli; and c) greater sympathetic activity, as a function of d) pharmacological treatment, than control participants. The stimuli were incorporated within a trace conditioning design with two tones serving as conditioned stimuli (CS+ and CS- respectively), while the electrocutaneous mini shocks served as unconditioned stimuli (UCS). Even though it has been established that trace conditioning with long trace gaps is rather ineffective (Sehlmeyer et al., 2009) and people with FM are deficient in contingency learning (Jenewein et al., 2013), the design provided an opportunity to additionally examine e) whether people with FM may be more likely to form an association in the context of their heightened sensitization (Chalaye et al., 2014; Meulders et al., 2015; Woolf, 2011).

Materials and methods

Participants

Thirty-nine right-handed participants ($M \pm SD = 51.51 \pm 13.61$ years of age, 37 females) were recruited for this study. They reported no history of neurological disorders such as stroke, brain, tumors, head injury, epilepsy, and no history of learning disorders or psychosis. All participants had normal or corrected-to-normal vision and no known visual or auditory deficits. Nineteen participants had previously received a physician's diagnosis of FM, which was confirmed with the Manual Tender Point Survey (MTPS) (Wolfe et al., 1990). They all reported persistent, widespread skeletal pain on both sides of the body, below and above the waist. The control group (CNT) comprised twenty additional participants who reported no chronic pain symptoms. The CNT did not differ from the FM group on demographic variables and cognitive capacity. To investigate potential impacts of pharmacotherapy on central and autonomic neural function measures, FM participants were additionally segregated into two subgroups. Participants who reported using medications known to suppress neural excitability including gabapentin (N = 4), pregabalin (N = 1), or fluoxetine (N = 1), were assigned to the FMG (FM GABA) group (N = 6). All other participants were assigned to the FMO (FM Other) group. Five FMO participants reported using antidepressants (SSRI/SRNI), and five additional FMO participants reported taking NSAIDs (N = 6) as needed. Four CNT participants reported taking antidepressants (SSRI/SRNI). Use of psychotropic medications was not considered exclusionary as they are commonly prescribed to women in this age range, so their exclusion would have rendered the CNT sample less representative of the broader population.

The San Diego State University Institutional Review Board approved the study's procedures. All participants provided informed consent and received monetary compensation for participating in the study.

Experimental protocol

Upon arrival at the lab, participants' cognitive abilities were evaluated with the Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005). All participants were administered the Manual Tender Point Survey (MTPS) (Wolfe et al., 1990), using the gold standard for FM diagnosis (Wolfe et al., 2016). A Demographic and Medical History Questionnaire (Oliver et al., 2001) was administered to obtain information about participants' demographics, medical history, and medication use. Subsequently, participants completed a battery of questionnaires probing different aspects of pain including the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995), the Pain Anxiety Symptoms Scale (PASS) (McCracken and Dhingra, 2002), while pain activity management was assessed with the Patterns of Activity Measure-Pain, (POAM-P) (Cane et al., 2013). Depression was assessed with the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001) and Generalized Anxiety Disorder 7-Item Scale (GAD-7) (Spitzer et al., 2006) was used to measure anxiety. FM shares clinical features with attention-deficit/hyperactivity disorder (Reyero et al., 2011), so those symptoms were evaluated with the Adult ADHD Self-Report Scale (ASRS) (Kessler et al., 2005). FM participants additionally rated their pain symptoms for severity and impact on functioning with the Fibromyalgia Impact Questionnaire-Revised (FIQR) (Bennett et al., 2009). Subsequently, all participants were fitted with an electrocap and underwent an EEG recording.

Somatosensory (electrocutaneous) and auditory stimuli

All participants completed a task that combined auditory and somatosensory stimuli and was designed as a trace classical conditioning

experiment. Electrocutaneous stimulation (ECS) in the form of mini shocks served as unconditioned stimuli presented at individually preselected levels. This was accomplished by delivering a low-level electric current with a linear isolated stimulator (STMISOLA, Biopac systems) via two Ag/AgCl electrodes (11 mm) attached to the participant's skin at the mid-level of the left tibia (shin bone). Participants selected their level of current, which was "uncomfortable but not painful, like a pinprick." The selection process began with a 0.3 mA current and proceeded in a stepwise manner. The current increased in steps of 0.5 mA until the participants reported feeling any sensation ("first felt") and continued until they selected their level of ECS. During the subsequent experiment, the ECS current was presented with a trace delay after a high (600 Hz) or low (300 Hz) tone, which was randomized across participants. Unbeknownst to the participants, only one tone was followed by the ECS. After the experiment, participants were asked about the association between the two tones and the ECS.

As shown in Fig. 1, each trial began with a 200 ms tone. The 50 ms ECS was delivered with a stimulus-onset asynchrony (SOA) of 2500 ms. After a 1000 ms delay, two self-timed questions were consecutively shown on the screen, to which participants responded with a joystick on a visual analog scale. First, they were asked to rate how anxious the tone made them feel about the upcoming sensation from 0 (*not at all*) to 10 (*extremely*). Then they were asked to rate their discomfort level caused by the ECS from 0 (*no pain*) to 10 (*worst pain ever*). The subsequent trial began after a delay of 2000 ms. Forty-eight trials were presented in a randomized order with equiprobable high- and low-pitch tones that were presented at a comfortable level (65 dB). In addition, 24 trials with the ECS current lowered to the "first felt" level were presented, but the data obtained on these trials were not included in the analysis. All stimuli were presented with the Presentation software (Neurobehavioral systems Inc.).

Data acquisition and analysis

EEG and EDA signals were acquired simultaneously during the entire experiment with a BrainVision actiCHamp system (Brain Products GmbH, Germany). They were recorded continuously with a 500 Hz sampling rate and a low-pass filter at 200 Hz. EEG was recorded from a limited montage of electrodes embedded in an actiCAP which included Fz, F3, F4, Cz, C3, C4, Pz, Oz, TP9, TP10. Signals from the mastoids were averaged and served as the reference while the ground electrode was placed on the forehead. Electrode impedance was maintained below 5 kΩ. Analysis was conducted using MATLAB (Mathworks, Natick, MA) scripts that incorporated publicly available routines in the FieldTrip toolbox (Oostenveld et al., 2011) and EEGLab (Delorme and Makeig, 2004), as described in our previous publications (Holcomb et al., 2019; Huang et al., 2018). EEG data were epoched to the ECS (somatosensory) and the tones (auditory) stimuli from −300 to 800 ms relative to their onset. Epochs were down-sampled to 250 Hz and bandpass filtered 0.5 to 30 Hz, and those contaminated with large artifacts were removed from the analysis. Independent component analysis (ICA) was used to detect and remove eyeblinks and heartbeat artifacts (Makeig et al., 2004). EEG signals were averaged across trials into event-related potentials (ERPs). ERPs were then averaged across the central electrodes (Cz, C3, C4) and used in the analysis. Amplitudes and latencies of the early peaks were quantified with an automatic algorithm. The somatosensory P50 was defined as the highest peak within a 40 to 80 ms latency interval following each ECS. The auditory N100 was defined as the most negative peak within an 80 to 120 ms latency interval after the presentation of all tone stimuli since they elicited equivalent ERPs.

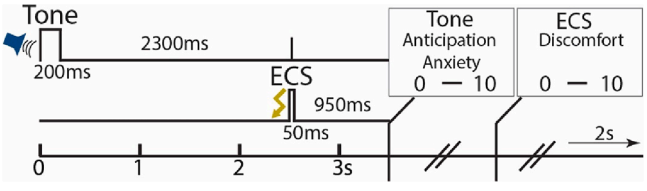

Fig. 1. Task design. The schematic includes the timing of tone and ECS presentation. At the end of each trial, participants indicated their responses to two questions on a visual analogue scale with a joystick. They rated the level of tone-evoked anticipatory anxiety from 0 (*not at all*) to 10 (*extremely*). They also rated their discomfort level caused by the ECS from 0 (*no pain*) to 10 (*worst pain ever*). Self-rating screens were presented until the participant gave a response. The next trial followed after a 2 s delay.

To measure EDA, Ag/AgCl skin electrodes were filled with BioPac isotonic electrode gel and attached to the volar surface of the distal phalanges of the index and middle fingers. The EDA signal was recorded with a BrainVision actiCHamp system (Brain Products GmbH, Germany) through a constant 0.5 V bridge circuit (Dawson et al., 2007; Marinkovic et al., 1989). EDA signals were low-pass filtered at 35 Hz, epoched from −1 to 10 s from the beginning of each trial. The data were quantified with respect to the tonic SCL baseline quantified at the start of each trial, as well as the peak SCR amplitude. All trials were visually inspected for artifacts to ensure a clean signal.

Statistical analysis

All self-reported and behavioral task-related variables were analyzed for CNT vs FM group differences with one-way between-subjects 2-tailed ANCOVAs with age as a covariate. Cohen's *d* was calculated to estimate effect sizes (Lakens, 2013). To account for small FMO and FMG sample sizes, statistical comparisons involving FM subgroups were conducted with the Mann-Whitney *U* test, as a nonparametric alternative to a *t*-test. In addition to p-values, effect sizes are reported as Hedges' g values, which is Cohen's d corrected for small sample sizes (Hedges and Olkin, 1985). The chi-square statistic was used to test group differences on categorical variables, including sex, ethnicity, and education.

Given that the questionnaire battery included several self-reported variables, a principal component analysis (PCA) with varimax rotation was conducted to examine the latent structure of the variance shared by all eight measures obtained from all participants (SPSS, 2017). The PCA included the number of tender points, average pain per tender point, and the scores on the questionnaires probing pain catastrophizing, pain anxiety, pain management, ADHD, depression, and anxiety. The first factor, termed "FM profile," had an eigenvalue of 6.20, which explained 77.55% of the variance. All other eigenvalues were below 1. The purpose of the PCA was to reduce the dimensionality of these variables and to examine correlations with ERPs and EDA measures. To accomplish that, each participant's factor score was calculated with the regression approach, and used in the correlation analysis.

Somatosensory P50, auditory N100, and EDA indices, including SCR and SCL, were analyzed using one-way ANCOVAs with age as a covariate. Overall group analyses were followed by pairwise comparisons conducted with nonparametric testing. Because of technical difficulties, one participant was removed from the analysis of P50 amplitude, two from the N100 analysis, and three from the EDA analysis.

Results

Demographic and self-reported variables

The FM and CNT groups did not differ on demographic variables or cognitive capacity, as estimated by MOCA (Table 1). FM participants had a higher body mass index, confirming previous reports (Neumann et al., 2008). As expected, the FM group had higher scores on all pain-related variables, including higher levels of reported pain, more tender points, greater pain-related catastrophizing, and more pain anxiety and avoidance symptoms. They also endorsed more depression, anxiety, and ADHD symptoms than the CNT group. FMO and FMG did not differ on any demographic or self-reported variables (Table 2).

As shown in Table 3, the PCA conducted on all eight variables

Table 1
Participant characteristics for CNT and FM groups.

	CNT (n = 20)	FM (n = 19)	F(1,36)/ χ^2	*p*	*d*
% Female (χ^2)	100%	89.47%	2.22	0.136	
% White/ Non-Hispanic (χ^2)	85%	84.21%	3.34	0.342	
% College Education (χ^2)	30%	47.37%	5.69	0.459	
Age	52.00 ± 11.61	50.79 ± 15.74	0.10	0.751	0.10
Cognition (MOCA)	27.45 ± 1.61	26.84 ± 1.95	1.35	0.253	0.37
Body Mass Index (BMI)	23.84 ± 4.80	29.19 ± 6.33	8.54	**0.006**	0.94
Manual Tend. Pt Survey (MTPS)					
# Tender Points	0.35 ± 0.88	16.00 ± 1.94	1039.47	**<0.001**	10.33
Avg. Pain per Tender Point	0.03 ± 0.09	4.78 ± 1.89	122.10	**<0.001**	3.54
Pain Catastrophizing (PCS)	7.05 ± 8.01	29.37 ± 9.51	61.14	**<0.001**	2.50
Pain Anxiety (PASS)	16.11 ± 15.64	59.50 ± 18.81	59.20	**<0.001**	2.46
Pain Management (POAM-P)	51.95 ± 21.96	75.28 ± 12.21	15.46	**<0.001**	1.26
Adult ADHD self-report (ASRS)	5.75 ± 3.82	13.58 ± 3.95	38.34	**<0.001**	1.98
Depression (PHQ-9)	1.35 ± 1.57	16.32 ± 5.49	133.00	**<0.001**	3.69
Anxiety (GAD-7)	1.20 ± 1.54	12.42 ± 5.67	70.66	**<0.001**	2.69
FM Impact (FIQ-R)		64.26 ± 16.15			

M ± SD were calculated for all measurements except sex, ethnicity, and education, which are represented as percentages. Group differences for these categorical variables were analyzed with chi-square tests and marked with χ^2. All other measures were analyzed using one-way ANCOVAs with age as a covariate. Effect sizes were calculated using Cohen's d. MOCA: Montreal Cognitive Assessment, MTPS: Manual Tender Point Survey, PCS: Pain Catastrophizing Survey, PASS: Pain Anxiety Symptoms Survey, POAM-P: Patterns of Activity Management-Pain, ASRS: Adult Attention Deficit/Hyperactivity Disorder Self Report, PHQ-9: Depression, GAD-7: Generalized Anxiety Disorder. FIQ-R: Fibromyalgia Impact Questionnaire Revised.

resulted in one strong factor representing the FM profile. Controlling for age, a two-way ANCOVA on the FM profile factor confirmed much higher scores in FM than in the CNT, $F(1, 36) = 221.98$, p <.001.

Task-related variables

As shown in Fig. 2a, the CNT and FM groups did not differ on the ECS threshold overall, $F(1, 36) = 2.75$, p =.11. However, the FMO subgroup showed a trend towards reaching an uncomfortable level sooner by selecting a marginally lower threshold than the CNT participants, $U = 82.5$, p <.08, but not compared to the FMG subgroup, $U = 55.5$, p =.15. However, the ECS threshold was equivalent between the FMG subgroup and the CNT participants, $U = 58$, p =.90.

Average ratings of tone-evoked anticipatory anxiety are presented in Fig. 2b. The FM group rated the tones as more anxiety-provoking than CNT, $F(1, 36) = 8.50$, p =.006. The FMO and FMG subgroups each gave higher anxiety ratings than the CNT to tones, $U = 188.5$p =.012, and $U = 99.5$. p =.006 respectively. The FMO and FMG subgroups' anxiety ratings did not differ, $U = 53$, p =.22. The anticipatory anxiety ratings correlated with the FM profile factor, $r = 0.52$, p =.001.

The FM group rated the ECS as more uncomfortable than the CNT, $F(1, 36) = 9.06$, p =.005 (Fig. 2c). This was confirmed by comparing each FM subgroup with CNT in turn. The FMO subgroup reported higher pain ratings than CNT, $U = 189$, p =.012, and so did the FMG subgroup, $U = 104$, p =.003. However, there was no difference in pain ratings between

Table 2
Participant characteristics for FMO and FMG subgroups.

	FMO (n = 13)	FMG (n = 6)	U/ χ2	*p*	*g*
% Female (χ2)	84.26%	100%	1.03	0.31	
% White/ Non-Hispanic (χ2)	76.92%	100%	1.64	0.44	
% College Education (χ2)	15.38%	83.33%	5.24	0.16	
Age	51.08 ± 14.90	51.17 ± 18.93	31	0.48	0.05
Cognition (MOCA)	26.62 ± 1.89	27.33 ± 2.16	45.5	0.56	0.35
Body Mass Index (BMI)	23.79 ± 6.94	30.05 ± 5.26	45.5	0.57	0.18
Manual Tend. Pt Survey. (MTPS)					
# Tender Points	16.38 ± 1.80	15.17 ± 2.14	24.5	0.19	0.61
Avg. Pain per Tender Point	4.92 ± 1.80	4.47 ± 2.23	32.0	0.54	0.22
Pain Catastrophizing (PCS)	28.92 ± 11.48	30.33 ± 2.73	40.5	0.90	0.14
Pain Anxiety (PASS)	58.58 ± 21.68	61.33 ± 12.77	36.5	0.96	0.14
Pain Management (POAM-P)	76.33 ± 13.61	73.17 ± 9.56	28.5	0.48	0.24
Adult ADHD self-report (ASRS)	13.62 ± 3.93	13.50 ± 4.37	37.0	0.86	0.03
Depression (PHQ-9)	16.92 ± 5.45	15.00 ± 5.83	32.0	0.54	0.33
Anxiety (GAD-7)	12.77 ± 6.02	11.67 ± 5.28	33.0	0.60	0.18
FM Impact (FIQ-R)	63.69 ± 18.60	65.50 ± 10.28	40.0	0.93	0.10

Included are the M ± SD values for all measurements except for the categorical variables which are represented as percentages, and which were analyzed with chi-square tests (χ^2). All other measures were analyzed using the Mann-Whitney test, a nonparametric alternative to a *t*-test. Effect sizes were calculated using Hedges' g, which provides a correction for Cohen's d for small sample sizes. Full names of all the standardized questionnaires are listed in the legend for Table 1.

Table 3
PCA Factor "FM Profile" - Loadings and Communalities.

	Factor Loading	Communality
Tend. Point Survey. (MTPS)		
# Tender Points	0.935	0.875
Avg. Pain per Tender Point	0.904	0.817
Pain Catastrophizing (PCS)	0.919	0.844
Pain Anxiety (PASS)	0.919	0.844
Pain Management (POAM-P)	0.597	0.357
ADHD (ASRS)	0.837	0.701
Depression (PHQ-9)	0.958	0.919
Anxiety (GAD-7)	0.921	0.848

Principal component analysis factor loadings and communalities for the factor titled "FM Profile". It included the following variables: MTPS: Manual Tender Point Survey, PCS: Pain Catastrophizing Survey, PASS: Pain Anxiety Symptoms Survey, POAM-P: Patterns of Activity Management-Pain, ASRS: Adult Attention Deficit/Hyperactivity Disorder Self Report, PHQ-9: Depression, GAD-7: Generalized Anxiety Disorder.

the FMO and FMG subgroups, $U = 57$, p =.11. The ECS discomfort ratings correlated with the FM profile factor, $r = 0.59$, p <.001.

Somatosensory Domain: P50

Group average ERPs for the three groups are presented in Fig. 3a (see the supplementary Fig. 1S for other electrodes). A main effect of group indicated that higher peak P50 amplitude was observed in FM than CNT participants $F(1, 35) = 9.31$, p =.004 (Fig. 3b). This was true for each FM subgroup as the FMO participants showed higher P50 amplitudes relative to CNT participants, $U = 176$, p =.029. Similarly, the FMG

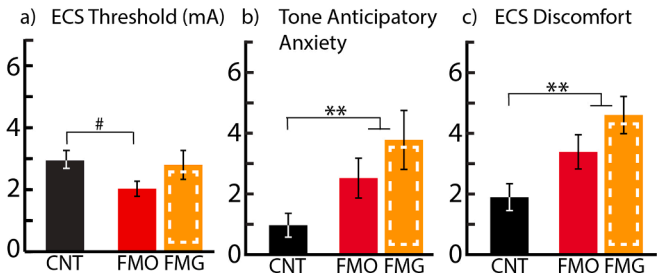

Fig. 2. Task-related variables. Histograms depicting group averages ± SEMs for a) electrocutaneous stimulation (ECS) threshold (in mA), b) tone anticipatory anxiety, and c) ECS-evoked discomfort, both on the scale from 0, not at all, to 10, extremely. # p <.08, **p <.01.

participants exhibited higher P50 amplitude than CNT, $U = 102$, p =.01, but the two FM subgroups did not differ, $U = 44$, p =.45. Across all groups, the P50 amplitude correlated with the FM profile factor, $r = 0.45$, p =.007. Among FM participants, P50 also marginally correlated with FIQ-R scores $r = 0.46$, p =.053.

The P50 peak latency tended to be shorter by ~ 5 ms for the CNT group (62.3 ± 7 ms) compared to the FMO group (67 ± 8 ms), U = 167, p =.063. However, the latency did not differ between the CNT and FMG group (62.7 ± 9 ms), U = 59.5, p =.98, nor between the two FM subgroups, U = 26.5, p =.37.

Auditory domain: N100

Group average ERPs to tones are presented in Fig. 4a (other electrodes are shown in the supplementary Fig. 1S). No main effect of group was detected for N100 amplitudes between FM and CNT participants overall, $F(1, 34) = 1.97$, p =.17 (Fig. 4b). However, the FMO subgroup had a more negative N100 peak than both CNT, $U = 61$, p =.025, and FMG participants, $U = 65$, p =.023. No difference in N100 amplitude was found between FMG and CNT groups, $U = 61$, p =.64.

Electrodermal sympathetic responsivity to ECS

Group average EDA responses are presented in Fig. 5a. The FM and CNT groups did not differ overall on SCR amplitudes $F(1, 33) = 2.21$, p =.15. However, the FMO subgroup showed larger SCR amplitudes relative to CNT participants, $U = 149$, p =.025, and the FMG subgroup, U = 12, p =.035 (Fig. 5b). No differences were found between the FMG and CNT groups, $U = 43$, p =.46. SCR amplitudes correlated with the FM profile factor, $r = 0.34$, p =.04 (Fig. 5c).

Analysis of the tonic SCL replicated these results with higher SCLs recorded in the FMO subgroup than in CNT participants, $U = 166$, p =.014. The FMG subgroup showed no difference from the CNT, $U = 46$, p =.59, in the absence of the overall FM vs CNT group differences, $F(1, 33) = 2.24$, p =.14. The two FM subgroups did not differ, $U = 19$, p =.11. Tonic SCL correlated with the FM profile, $r = 0.35$, p <.04, and with tone anticipatory anxiety ratings, $r = 0.33$, p =.05.

Long-gap trace conditioning paradigm was ineffective in forming a CS-UCS association

To examine possible associations between the CS+ and UCS, participants were asked at the end of the experiment whether they noticed any link between a tone and the ECS. Only a minority of participants, 31.6% FM and 40% CONT, noticed a contingency association, with no difference between the two groups, X^2 (1) = 0.30, p =.58. Similarly, the two FM subgroups did not differ, X^2 (1) = 0.01, p =.91, with only 30.7% FMO and 33.3% FMG participants displaying CS-UCS contingency awareness.

Discussion

Combining central and peripheral indices of neural excitability with behavioral measures, the findings from this study have confirmed enhanced generalized hypersensitivity in people with FM, which was partly ameliorated by GABA-mimetic medications. The principal results can be summarized as follows: compared to a CNT group, 1) FM participants reported higher sensitivity to both electrocutaneous (ECS - tactile) and auditory stimulation (Fig. 2), as well as higher levels of self-reported pain-related experiences, depression, anxiety, and ADHD, as shown in Table 1. 2) FM participants showed greater P50 to ECS reflecting early somatosensory hyperexcitability, (Fig. 3), which

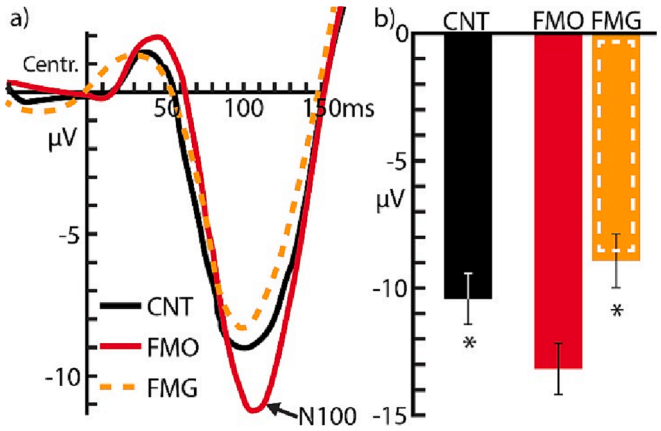

Fig. 4. ERPs: Auditory domain. a) Auditory ERPs to innocuous tones averaged over the central electrodes for all three groups. The N100 deflection is marked. Negative is down. Histogram shows mean ± SEM N100 amplitudes for all three groups. *p <.05.

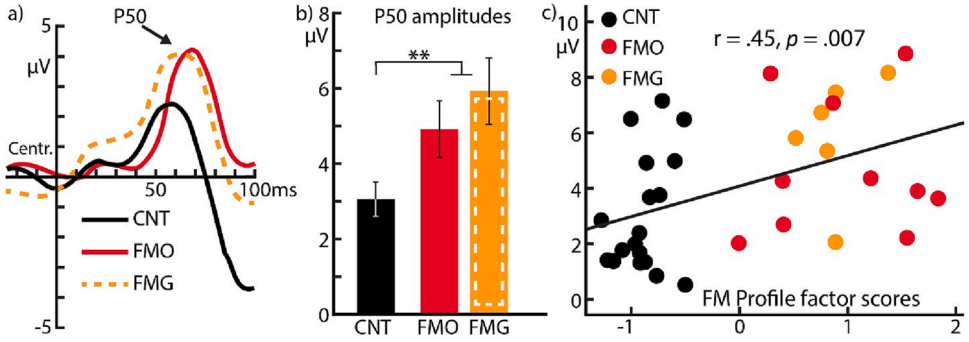

Fig. 3. ERPs: Somatosensory domain. a) Somatosensory ERPs to the ECS averaged over central electrodes for all three groups. The P50 deflection is marked. Negative is down. b) Histograms display mean ± SEM P50 amplitudes. c) Scatterplot shows correlation between P50 amplitudes and the FM profile PCA factor. **$p \leq 0.01$.

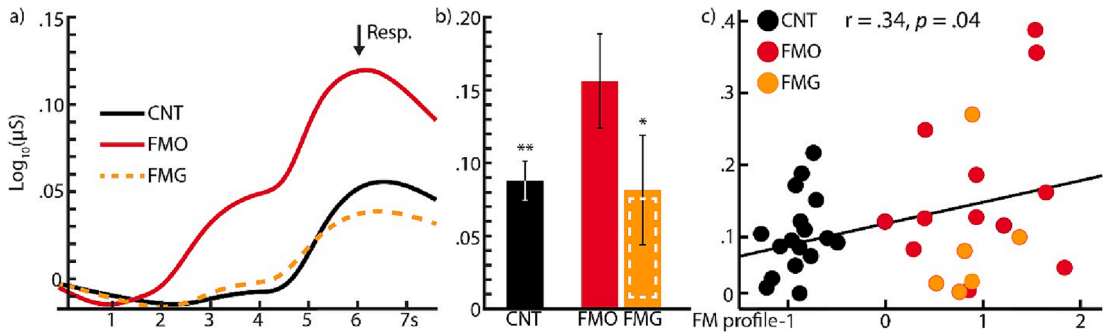

Fig. 5. Electrodermal Activity. a) Averaged phasic skin conductance responses (SCRs) for all three groups. b) Average ± SEM SCR amplitudes for all three groups. c) SCR amplitudes correlated with FM Profile factor scores. $^{**}p \leq 0.01$.

correlated with a PCA-derived "FM profile" factor (Table 3); 3) the N100 to innocuous tones was greater in FM participants, except in the subgroup treated with GABA-mimetic medications (Fig. 4). 4) Similarly, sympathetic reactivity to ECS was greater in FM participants except those on GABA analogs, with the overall effect correlating with the FM profile (Fig. 5). While confirming the principal tenet of central hyperexcitability to tactile stimuli in FM, the results indicate that the hyperexcitability generalizes to the auditory domain and sympathetic reactivity. This finding is indicative of excitation/inhibition imbalance reflected in downregulated inhibition and is consistent with other evidence of impaired endogenous pain inhibition mechanisms (Desmeules et al., 2003; Julien et al., 2005; Latremoliere and Woolf, 2009). In a subset of FM participants treated with gabapentinoids, the N100 and the sympathetic reactivity did not differ from CNT, which is aligned with the evidence of symptomatic improvement with GABA-mimetic medications and reduced neural activity (Derry et al., 2016; Harris et al., 2013; Harte et al., 2016; Kim et al., 2013; Petersel et al., 2011). 5) A long-delay trace conditioning paradigm was ineffective in forming the CS-UCS associations, which was not unexpected.

Tactile hyperexcitability in FM: P50

To examine behavioral and physiological indices of central sensitization, ECS was delivered to participants' tibia (shin bone) at individually-selected levels and was paired with innocuous tones (Fig. 1). FM participants perceived the ECS as more uncomfortable than the CNT group (Fig. 1c), which replicates previous reports (Desmeules et al., 2014; Erturk Celik and Beyazova, 2020; Rhudy et al., 2013). Importantly, in comparison to CNT participants, the FM group showed greater P50 to ECS, which correlated with the FM profile (Fig. 3). This finding aligns with previous reports of a larger P50 deflection to non-painful pressure stimuli in people with FM (Montoya et al., 2005). Since the P50 reflects excitatory thalamic input to the primary somatosensory area (Allison et al., 1991; Hari et al., 1993), its greater amplitude is indicative of excitation/inhibition imbalance in FM at a point of cortical entry and is consistent with neural hyperexcitability (Clauw, 2015). Furthermore, the P50 does not habituate in a paired-stimulus paradigm in people with FM, suggesting reduced gating of the P50 amplitude to both pneumatic (Montoya et al., 2006) and electrical stimulation (Lim et al., 2015). Our results further contribute to this line of evidence by suggesting that clinical pain is associated with hyperexcitability of the primary somatosensory cortex (Fig. 3) (Lim et al., 2015). Consequently, it has been proposed that increased neural excitability and deficient inhibitory modulation reflected in central sensitization play a pathogenic role in FM pain (Petersel et al., 2011; Sluka and Clauw, 2016; Woolf, 2011). Broadly converging evidence has been provided by neuroimaging studies reporting greater activation of the primary somatosensory cortex to noxious stimuli in patients with postherpetic neuralgia (Li et al., 2022).

Generalized hyperexcitability in FMO: Auditory N100

Impaired descending inhibitory pathways reflected in neural hyperexcitability may also generalize to other sensory modalities. In addition to nociception, people with FM show amplified sensitivity to visual (Harte et al., 2016) and auditory stimuli which has been termed generalized hypervigilance (Geisser et al., 2008; McDermid et al., 1996; Staud et al., 2021). In the present study, the N100 to innocuous auditory stimuli was greater in the FMO participants (Fig. 4) in support of this phenomenon. Evidence from other studies is partly consistent with auditory hypersensitivity in FM. Carrillo-de-la-Pena and colleagues (Carrillo-de-la-Pena et al., 2006) examined auditory ERPs to a range of tone intensities and reported greater N1-P2 amplitudes and shorter latencies to very loud tones (105 dB) in FM participants compared to the CNT group, but did not replicate this finding in a follow-up study (Samartin-Veiga et al., 2020). Converging support for cross-sensory hypervigilance has been provided by a recent study in healthy participants (Otsuru et al., 2022), which reported a significant association between auditory change-related ERPs and attention and sensitivity to pain. This aligns with deficient habituation of the auditory N100 in FM participants reported in one study (Choi et al., 2016), but another one failed to show this effect (Montoya et al., 2006). The N100 is a large auditory ERP generated in the primary and associated auditory cortices in the superior temporal cortex, as reported by studies using intracranial and scalp EEG, and MEG (Godey et al., 2001; Tzourio et al., 1997; Yoshiura et al., 1996).

In the present study, GABA-mimetic medications normalized the N100 in the FMG group, confirming their inhibitory effects on cortical circuitry. Indeed, the N100 amplitude is sensitive to excitation/inhibition balance, as shown by pharmacological manipulations of glutamate and GABA signaling. For instance, while GABA agonists decrease the N100 amplitude (Holliday et al., 2018), the application of GABA antagonists increases the N100 amplitude (Kurt et al., 2008) in animal models. This was confirmed in a human study that combined MEG and ^{1}H-MRS, which reported that the auditory N100 amplitude tended to be higher in individuals with higher excitatory (glutamate/glutamine) neurotransmitter concentration (Soros et al., 2006). Even though gabapentinoids do not bind to GABA receptors, they exert their analgesic effects by suppressing neural excitability via calcium channels (Patel and Dickenson, 2016). The present study provides additional support for the excitation-dominant state of the neural system characterizing FM that generalizes beyond somatosensory to other sensory domains.

Hyperexcitability in FMO generalizes to electrodermal indices of sympathetic arousal

In addition to the central indices of somatosensory and auditory activity, we measured sympathetic arousal in response to ECS in the present study. EDA provides excellent insight into sympathetic activity since the eccrine sweat glands are sympathetically regulated (Dawson

et al., 2007). As shown in Fig. 5, the FMO group had larger phasic SCRs than the CNT and FMG participants. The SCRs correlated with the FM profile factor, confirming greater sympathetic arousal in FM participants. Similarly, tonic SCL was also higher in the FMO group than in CNT participants, which was associated with FM symptomatology. Our results are well aligned with a recent study that reported greater SCRs and SCL to electrical stimulation in people with FM (On et al., 2022). Greater arousal reflected in larger SCRs has been observed in FM participants in response to stress manipulation (Thieme et al., 2006), acoustic stimulation and cold pressor test (Qiao et al., 1991). Higher baseline SCL has also been reported during the social conflict, cognitively demanding, and relaxation tasks in people with FM (Thieme et al., 2016). In contrast, other researchers have reported no group differences in SCRs to laser stimulation (de Tommaso et al., 2017).

FM is characterized by autonomic dysfunction across different peripheral response domains (Martinez-Lavin, 2007; Solano et al., 2009). The evidence favors sympathetic system predominance (Martinez-Martinez et al., 2014), which has led to proposals that sympathetic hyperactivity may partly underlie FM-related clinical features (Martinez-Lavin, 2007; Zamuner et al., 2015). However, in the present study, sympathetic hyperactivity was observed only in the FMO group, while the participants receiving GABA-mimetic medications (the FMG group) did not differ from CNT (Fig. 5). It has been shown that GABA exerts an inhibitory influence on sympathetic hypothalamic outflow (Li et al., 2006), and modulates higher brain areas involved in EDA generation such as the insula (Critchley, 2002; Harris et al., 2013; Harte et al., 2016; Kim et al., 2013). Diazepam, an allosteric GABA agonist, lowers EDA and exerts anxiolytic effects by increasing inhibitory signaling (Frith et al., 1984).

Generalized hyperexcitability in FM: Deficient descending inhibitory modulation

Our findings confirm that FM is associated with neural hyperexcitability across sensory and autonomic domains, providing support for generalized central sensitization (Carrillo-de-la-Pena et al., 2006; Latremoliere and Woolf, 2009; McDermid et al., 1996). This is consistent with suggestions that generalized hypervigilance may result from deficiencies in descending inhibitory pathways (Petersel et al., 2011). Imaging studies have reported lower activation and reduced functional connectivity of the brain areas implicated in descending pain inhibition (Flodin et al., 2014; Harris et al., 2013; Harte et al., 2016; Jensen et al., 2009). This low-level neural dysregulation may be associated with other pain conditions characterized by overlapping symptoms, including fatigue, cognitive dysfunction (“brain fog”), insomnia, etc. (Maixner et al., 2016; Veasley et al., 2015). Thus, central sensitization reflected in neural hyperexcitability may be a common pathogenic mechanism underlying these similar phenotypes (Arnold et al., 2016; Harte et al., 2018; Latremoliere and Woolf, 2009; Staud, 2011).

^{1}H-MRS studies have reported elevated glutamate (Harris et al., 2009; Harte et al., 2013; Pyke et al., 2017) and lower GABA levels in FM (Foerster et al., 2012), in association with pain sensitivity. Such mechanistic evidence provides insight into the underlying neurochemistry of FM and confirms the importance of top-down inhibition exerting analgesic effects (Jasmin et al., 2003). Furthermore, GABA-mimetic medications show clinical efficacy in reducing pain (Maneuf et al., 2003) and reducing neural activity (Harris et al., 2013; Harte et al., 2016; Kim et al., 2013) along with beneficial effects on sleep, anxiety, fatigue, and tactile sensitivity (Baidya et al., 2011; Murasawa et al., 2020). Indeed, even though the sample of the participants on GABA-mimetic medications (the FMG group) was very small, they tended to have higher pain thresholds (i.e., lower sensitivity) than those on other non-GABA-related medications. Furthermore, their N100 to innocuous tones and the EDA indices of sympathetic arousal were normalized.

Long-gap trace conditioning is unreliable in inducing associative learning

With the primary aim of examining the tenets of the generalized hypersensitive framework in people with FM, the stimuli were presented within a trace conditioning design. We used a long trace interval (2.3 sec), which is known to have detrimental effects on the strength of conditioning (Raybuck and Lattal, 2014; Sehlmeyer et al., 2009). Nonetheless, it was deemed of some interest to additionally examine potential group differences in acquiring the CS-UCS association, given the generalized hypersensitivity characterizing people with FM (Chalaye et al., 2014; Meulders et al., 2015; Woolf, 2011). Since only a minority of participants noticed the CS-UCS contingency, the finding that the conditioning paradigm was ineffective was not unexpected. Evidence based on our work (Marinkovic et al., 1989) and numerous other studies (Dawson and Schell, 1987; Klucken et al., 2009; Lovibond et al., 2011; Lovibond and Shanks, 2002; Mitchell et al., 2009; Weidemann and Antees, 2012) indicated that differential conditioning was successful only in the participants that were aware of the CS-UCS contingency. This pertains particularly to trace conditioning (Knight et al., 2006; Li, 2009; Mitchell et al., 2009) since it relies on the hippocampo-cortical circuitry (Clark et al., 2002; McGlinchey-Berroth et al., 1997), known to be critically involved in memory.

Limitations and future directions

There are limitations to the current study that should be addressed by future researchers. The sample size is small, which limits the generalizability of the study findings. Thus, the results should be treated as explorative until replicated in larger cohorts. While the CNT group comprised only female participants, there were two males in the FMO group. However, the results did not change after excluding the two participants. While preliminary, the findings support the principal tenet of generalized neural hyperexcitability in FM and provide preliminary mechanistic information about the impact of GABA-mimetic pharmacological therapy on restoring the excitation/inhibition balance. The findings from the present study also demonstrate the importance of analyzing EEG-based signals as a function of pharmacological therapy, given its compelling effects on direct measures of neural function. Future researchers should focus on mechanistic studies of possible interventions that could be tested to determine whether they could reduce hyperexcitability among people with FM.

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CRediT authorship contribution statement

Ksenija Marinkovic: Conceptualization, Investigation, Resources, Supervision, Project administration, Funding acquisition. **Denali Woodruff:** Investigation, Data curation, Formal analysis. **David R. White:** Data curation, Formal analysis, Investigation. **Morgan M. Caudle:** Investigation. **Terry Cronan:** Funding acquisition, Project administration, Supervision, Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynpai.2023.100140.

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