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ORIGINAL ARTICLE

Regional increases in brain signal variability are associated with pain intensity reductions following repeated eccentric exercise bouts

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Abstract

Background: Traditional pain interventions limit fluctuations in pain sensation, which may paradoxically impair endogenous pain modulatory systems (EPMS). However, controlled exposures to clinically relevant pain (e.g. delayed onset muscle soreness [DOMS]) may build capacity in the EPMS. Emerging evidence suggests that regional signal variability (RSV) may be an important indicator of efficiency and modulatory capacity within brain regions. This study sought to determine the role of RSV in both susceptibility to and trainability of pain response following repeated DOMS inductions.

Methods: Baseline and follow-up resting-state fMRI was performed on 12 healthy volunteers ~40 days apart. Between scanning visits, participants received four weekly DOMS inductions in alternating elbow flexors and were supplied seven days of post-induction pain ratings. Voxel-wise standard deviation of signal intensity was calculated to measure RSV. Associations among DOMS-related pain and RSV were assessed with regression. Relationships among baseline and change measurements were probed (i.e. susceptibility to DOMS; trainability following multiple inductions).

Results: Significant association between baseline RSV in left middle frontal gyrus (MFG) and right cerebellum and reductions in DOMS-related pain unpleasantness were detected. Furthermore, increases in RSV were associated with reduced DOMS pain intensity (left lingual gyrus, right MTG, left MTG, left precuneus) and unpleasantness (left MTG, right SFG).

Discussion: Findings suggest that RSV may be an indicator of EPMS resilience and responsivity to training, as well as an indicator that is responsive to training. Involved regions underlie cognitive, affective and representation processes. Results further clarify the potential role of RSV as an indicator of pain modulation and resilience.

Significance: Regional signal variability may be an important indicator of endogenous pain modulatory system *responsivity* to training following repeated bouts of clinically relevant pain and may in fact be *responsive* to training itself.

1 | INTRODUCTION

Pain is the primary reason patients seek medical care and is associated with significant morbidity and economic burden (Institute of Medicine, 2011). In conventional studies of pain treatments, successful interventions are often characterized by reduction of mean pain to the lowest level possible. However, although fluctuations in pain are common in individuals with and without chronic pain, this variability has generally not been considered as a treatment target. Physiological responses to momentary increases in pain are regulated by endogenous pain modulatory systems (EPMS). Evidence suggests that exposure to opioid analgesics can impair pain modulation (King, Ossipov, Vanderah, Porreca, & Lai, 2005; Rivat & Ballantyne, 2016), resulting in diminished pain modulatory capacity (PMC). Critically, preliminary evidence suggests that, like other physiological systems, EPMS may be trainable by stressing the system and allowing it an opportunity to adapt, thus increasing PMC and potentially pain resilience (Sevel, Boissoneault, Alappattu, Bishop, & Robinson, 2019).

Initial evidence suggests that regional signal variability (RSV; the voxel-wise standard deviation of BOLD % signal change) assessed during resting state functional magnetic resonance imaging (rs-fMRI) may reflect the capacity of brain regions to modulate activity and re-allocate resources to efficiently process tasks (Rogachov et al., 2016). In fact, several studies demonstrated that RSV reflects adaptive capacity within brain structures. For instance, greater RSV was associated with better memory performance and lower central pain sensitivity (Basalyga & Salinas, 2006; Garrett et al., 2013; Rogachov et al., 2016). Therefore, greater RSV in brain regions related to pain processing may also reflect greater resilience to pain challenges (i.e., faster resolution, lower pain severity, etc.).

Delayed onset muscle soreness (DOMS) is a clinically relevant laboratory-based musculoskeletal pain induction model with several advantageous characteristics when compared to other common experimental pain inductions. DOMS induction produces relatively long-lasting but inherently time-limited pain, typically resolving within 5–7 days; increases in negative affect; and functional limitation (Bishop, Horn, & George, 2011a; Bishop, Horn, George, & Robinson, 2011b; Dannecker, Hausenblas, Kaminski, & Robinson, 2005; Dannecker, Koltyn, Riley, & Robinson, 2002). Therefore, DOMS is an ideal model for testing hypotheses related associations between RSV and pain resilience. We previously reported that repeated exposure to DOMS in alternating elbow flexors over a period of approximately one month results in decreased DOMS severity following eccentric exercise challenge. These changes accompanied alterations in functional connectivity between pain modulatory brain regions (Sevel et al., 2019). Critically, connectivity changes between these regions correlated with reductions in negative affect associated with DOMS induction, including depression, anxiety, frustration, fear and anger.

In this secondary analysis of rs-fMRI data from the Sevel et al. (2019) study, we aimed to better characterize RSV in pain-related brain regions as an index of individual *sensitivity* to exercise-induced musculoskeletal pain (pain severity of initial exposure) and *trainability* of the EPMS (reduction in pain severity over repeated exposures). To this end, we tested three specific hypotheses: (1) greater RSV would be associated with lower susceptibility to DOMS at baseline, (2) greater RSV in pain-related regions would reflect greater trainability of the EPMS (i.e. reduction in DOMS pain intensity and unpleasantness from pre- to post-training), and (3) increases in RSV after the 30-day training period reflect greater trainability of the EPMS.

2 | METHODS

Participants were healthy adults over 18 years of age. Exclusion criteria included (a) previous participation in a conditioning program specific to the biceps in the past 6 months, (b) any report of wrist/hand, elbow or shoulder pain in the last 3 months, (c) any chronic medical conditions that may affect pain perception (e.g. diabetes, high blood pressure, fibromyalgia, headaches), kidney dysfunction, muscle damage or major psychiatric disorder, (d) consumption of any drugs (e.g. alcohol, theophylline, tranquilizers, antidepressants) that may affect pain perception or hydration status 24 hr before participation in the final testing session, (e) use of caffeine 4 or less hr before testing sessions, (f) use of any intervention (including but not limited to medication, massage and stretching) for symptoms induced by pain training for the duration of the study, (g) recent illness, and (h) positive result on pre-MRI metal screening or pregnancy test because of contraindication for the MRI environment. All study procedures were approved by the University of Florida Institutional Review Board, and informed consent was obtained prior to data collection. The current report represents a secondary analysis of data included in a prior report (Sevel et al., 2019). For brevity and clarity, methods described within this paper are restricted to those that are directly applicable to this analysis. For a complete description of study methods, see Sevel et al. (2019).

2.1 | Study design

Participants included in this analysis completed a total of five sessions. At the first session, participants provided demographic information and completed anatomical and functional MRI scanning. They then performed maximum voluntary contraction (MVC) testing and the DOMS induction protocol at

either their randomly determined dominant or non-dominant elbow flexors (biceps muscle group). Participants then repeated the DOMS induction protocol on the opposite elbow flexor muscles in an alternating pattern every 7–14 days for a total of four induction sessions. An alternating pattern was used to avoid strengthening the elbow flexors as a result of the DOMS induction paradigm. Finally, during Session 5, participants repeated MRI scanning and MVC assessment. For the 7 days following each session, participants completed daily pain measures that documented pain intensity and quality using the University of Florida (UF) Research Electronic Data Capture (REDCap) system (see Section 2.3 below) (Harris, Taylor, Minor, et al., 2019; Harris, Taylor, Thielke, et al., 2009). Mean reports of pain intensity and unpleasantness on the final day of rating (i.e. the 7th day following the 4th induction session) were minimal (5.16/100 and 5.58/100, respectively). Thus, although we did not assess pain intensity or unpleasantness prior to the final MRI session, we expect that any DOMS-related pain with movement or at rest would be either absent or inconsequential by this time. The overall study design is illustrated in Figure 1.

2.2 | MVC testing and delayed onset muscle soreness induction

MVC of the elbow flexors was tested using a Biodex System Isokinetic Dynamometer (Biodex Medical Systems). The participant was seated within the testing apparatus and moved through their available range of motion in elbow flexion and extension. The device was then locked at 90° of elbow flexion and the participant was instructed to pull as hard as possible on the Biodex grip handle for 3 s. The participant was allowed to relax in a neutral position after achieving peak and this was repeated two times, with the average MVC calculated. After resting for 60 s following the MVC test, the participant completed three sets of 15 repetitions of eccentric (elbow straightening/biceps lengthening) exercises to induce DOMS at the elbow flexors. Repetitions were performed at a speed of 60°/s. A licensed physical therapist (MJA) conducted the MVC test and DOMS induction protocol.

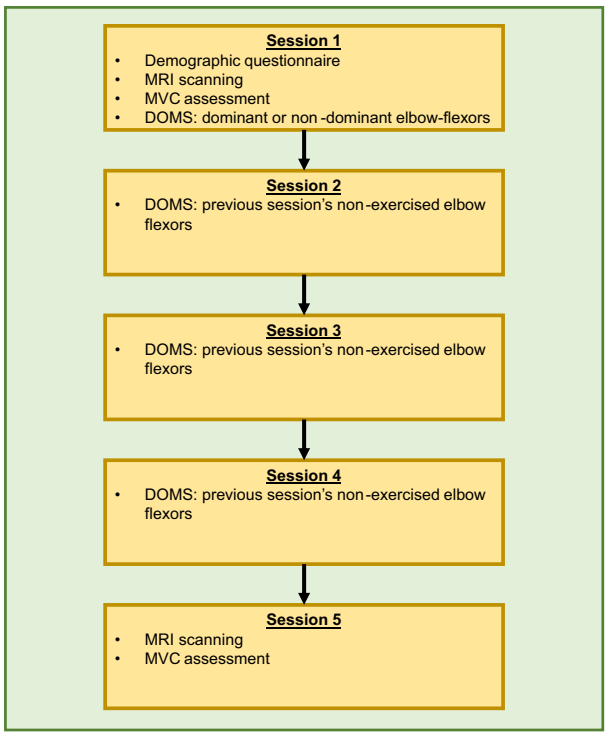

FIGURE 1 Subjects completed a total of five sessions with MRI scanning at the first and final session. The delayed onset muscle soreness (DOMS) induction protocol was completed in sessions 1–4

2.3 | Neuroimage acquisition

Structural MRI data were acquired with a research-dedicated whole-body Philips Achieva 3T scanner using a standard head 32-channel radiofrequency coil. High-resolution 3D anatomical images were collected using a T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) protocol (170 1 mm axial slices; repetition time = 8.1 ms, echo time = 3.7 ms, flip angle = 8°, matrix = 240 mm × 240 mm, field of view = 240 mm). Resting state functional images were collected using a T2-gradient echo planar imaging sequence capturing 33 contiguous axial slices of the whole brain parallel to the anterior commissure–posterior commissure plane (repetition time = 2000 ms; echo time = 30ms; flip angle = 80°; 80 × 80 matrix; field of view = 240 mm × 240 mm; 3 mm^3 isotropic voxels with 0 mm slice gap). A fixation cross was presented during resting state scans, and participants were instructed to keep their eyes open and focus on the cross, and to let their thoughts wander. Resting state scans were 6 min 20 s in duration (i.e. 190 dynamic volumes).

2.4 | Neuroimage processing

SPM12 (Welcome Trust Centre for Neuroimaging) was used to preprocess and analyse fMRI data. Steps of preprocessing included slice-time correction, realignment, registration, normalization (MNI 2 mm^3 template) and spatial smoothing (8 mm^3 FWHM). The Artifact Detection Tool (ART) toolbox was used to detect motion and signal artefacts. Time points in which the global signal exceeded ±3 standard deviations from the mean of the previous image, translation exceeded 0.5 mm or rotation exceeded 0.02 radians from the previous image were identified as outliers. Outliers and rigid-body motion parameters calculated in the realignment step were included in denoising steps implemented using the CONN toolbox (Whitfield-Gabrieli &

Nieto-Castanon, 2012), including temporal bandpass filtering between 0.005 and 0.05 Hz (Rogachov et al., 2016) and component-based noise correction for physiological and other noise source reduction (CompCor). In this method, regression was used to remove the influence of nuisance variables derived from principal components decomposition (Behzadi, Restom, Liau, & Liu, 2007) and scrubbing-related confounds. These included five principal components identified through CompCor from signal within the lateral ventricles and deep cerebral white matter, the six parameters of translation and rotation and their first order derivatives, and the outlier data points identified with the ART toolbox. Consistent with previous reports (Rogachov et al., 2016), RSV was determined by calculating the standard deviation of voxel-wise signal intensity across the resting state scan.

2.5 | DOMS-related pain assessment

Once per day (prior to sleep), participants completed 10 cm visual analogue scales (VAS) of pain intensity and pain unpleasantness (anchored from "none" to "worst imaginable") for 7 days, beginning the day after each DOMS induction, to assess pain associated with the DOMS induction procedure. DOMS-related pain ratings typically peak 24–48 hr following induction before returning to baseline. The peak value for each measure for the Week 1 and Week 4 DOMS inductions was used as the dependent variable in voxel-wise regression analysis described below.

2.6 | Analysis strategy

To address our primary aims, we conducted a series of whole-brain voxel-wise regression analyses. First, we regressed baseline RSV on peak pain after the first DOMS induction to determine whether baseline RSV was associated with susceptibility to DOMS. Second, to assess whether baseline variability was associated with "trainability" (i.e. reduction in DOMS pain severity from pre- to post-training), baseline RSV was regressed onto change in peak DOMS pain from the first to the final induction. Finally, we tested whether training-related change in pain severity was associated with change in RSV by regressing change in RSV from the first to the second scan on change in peak DOMS severity from the first to the last induction. One-sided tests were used for each analysis given our a priori focus on repeated DOMS induction as a means of increasing PMC. Cluster size-based family-wise error (FWE) correction was implemented using SPM12 (cluster $p < .05$ [FWE], height $p < .001$ [uncorrected]). Given concerns regarding the potential effects of highly influential observations and outliers resulting from the study's small sample size, the REX toolbox was used to extract average RSV values from significant clusters so that the pattern of results could be manually checked.

TABLE 1 Participant characteristics

	Mean (*SD*) or %
Age	31.8 (16.5)
% Women	66.7
Race	
White	75
Asian	16.7
Other or multiple races	8.3
Ethnicity	
Hispanic or latino	8.3
Not hispanic or latino	91.7

3 | RESULTS

3.1 | Participant characteristics

Twelve healthy community-dwelling adults were assigned to and completed all five visits of the repeated DOMS induction protocol. Demographic characteristics of participants are displayed in Table 1. Pre- and post-training peak pain intensity and unpleasantness ratings are displayed in Table 2.

Hypothesis 1 *Association between RSV and susceptibility to DOMS-related pain.*

Voxel-wise regression analyses identified no significant clusters where baseline RSV correlated with DOMS-related pain intensity or unpleasantness following the first DOMS induction ($p_{FWE} > .05$).

Hypothesis 2 *Association between RSV and trainability of PMC.*

There were two clusters where stronger reductions in DOMS-related pain unpleasantness from pre- to post-training were associated with baseline RSV: left middle frontal gyrus (MFG; $p_{FWE} = .002$) and right cerebellum ($p_{FWE} = .03$; Figure 2; Table 3). Each 0.01 increment in baseline signal variability in these regions was associated with a predicted reduction in pain unpleasantness of 1.03 and 1.50 VAS units from pre- to post-training, respectively. There were no significant clusters where reductions in pain intensity from pre- to post-training was associated with baseline RSV ($p_{FWE} > .05$).

TABLE 2 Peak pain intensity and unpleasantness ratings pre- and post-training

Rating	Visit	Mean (*SD*)	*t*	*p*
Pain intensity	Pre-training	18.42 (17.00)	3.35	.006
	Post-training	11.08 (11.26)		
Pain unpleasantness	Pre-training	16.83 (13.56)	3.00	.012
	Post-training	9.33 (11.00)		

Note: Values represent the average peak pain rating in the week following the first and final delayed onset muscle soreness (DOMS) induction. *t* tests quantify the assessment of within-subjects difference in ratings from pre- to post-training.

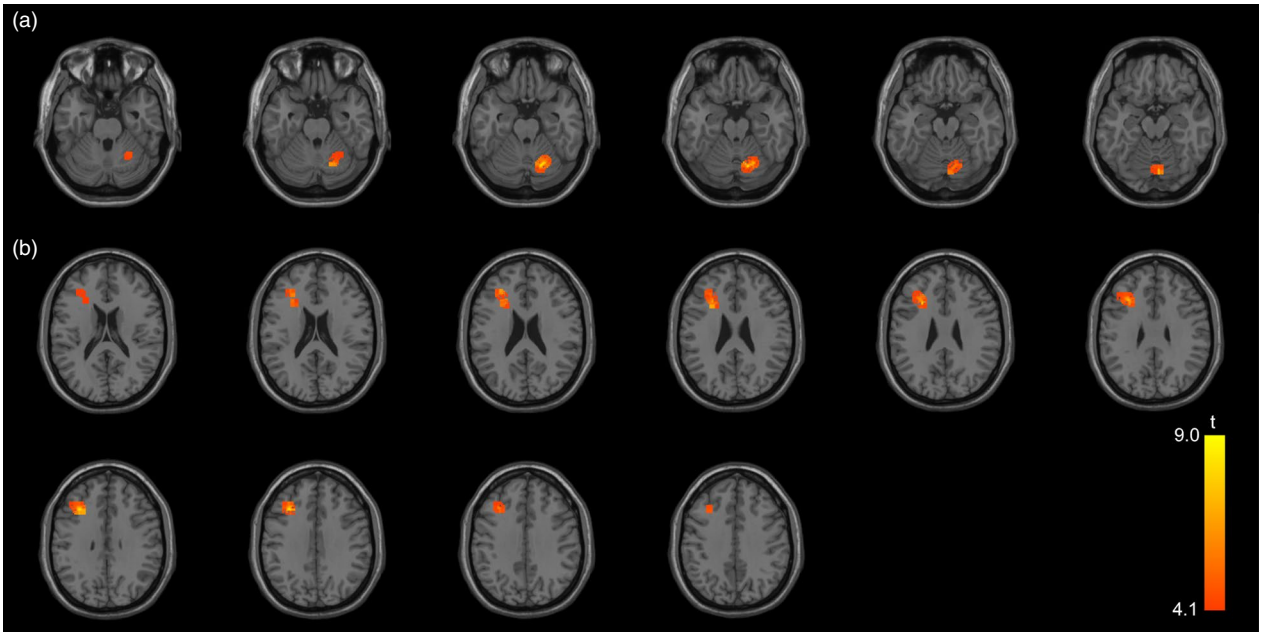

FIGURE 2 Clusters where baseline regional signal variability (RSV) predicted reduction in delayed onset muscle soreness (DOMS) pain unpleasantness from pre- to post-training, including (a) left middle frontal gyrus/dorsolateral prefrontal cortex; and (b) right cerebellum

TABLE 3 Clusters where baseline RSV was associated with reduced DOMS-related pain unpleasantness from pre- to post-training

	MNI coordinates					
Brain region	**X**	**Y**	**Z**	**k**	**Peak *t***	p_{FWE}
Left middle frontal gyrus	−32	22	32	169	8.43	.002
Right cerebellum	14	−70	−22	101	8.76	.03

Abbreviations: DOMS, delayed onset muscle soreness; RSV, regional signal variability.

Hypothesis 3 *Association between change in RSV and trainability of PMC.*

Reductions in DOMS pain intensity were associated with increases in RSV from pre- to post-training in several brain regions, including left lingual gyrus (p_{FWE} = .007), right middle temporal gyrus (p_{FWE} = .002), left middle temporal gyrus (p_{FWE} = .001) and left precuneus (p_{FWE} = .05; Figure 3). Each 0.01 increment in signal variability change from pre- to post-training in these regions was associated with predicted reductions in pain intensity of 0.74, 0.90, 0.76, and 0.60 VAS units, respectively. Similarly, reductions in DOMS-related pain unpleasantness were associated with increased RSV in left middle temporal gyrus (p_{FWE} = .003) and right superior frontal gyrus (p_{FWE} = .018; Figure 4; Table 4). Each 0.01 increment in signal variability change from pre- to post-training in these regions was associated with predicted reductions in pain unpleasantness of 0.81 and 0.55 units, respectively.

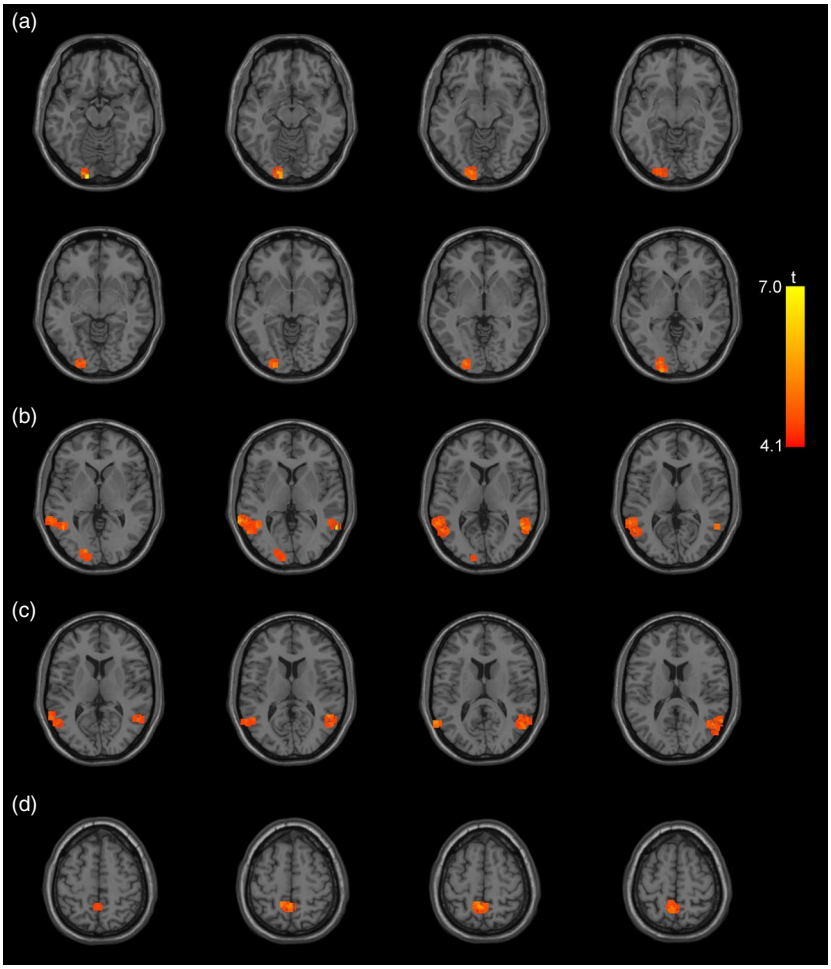

FIGURE 3 Clusters where increases in regional signal variability (RSV) predicted reduction in delayed onset muscle soreness (DOMS) pain intensity from pre- to post-training, including (a) left lingual gyrus; (b) right middle temporal gyrus; (c) left middle temporal gyrus; and (d) left precuneus

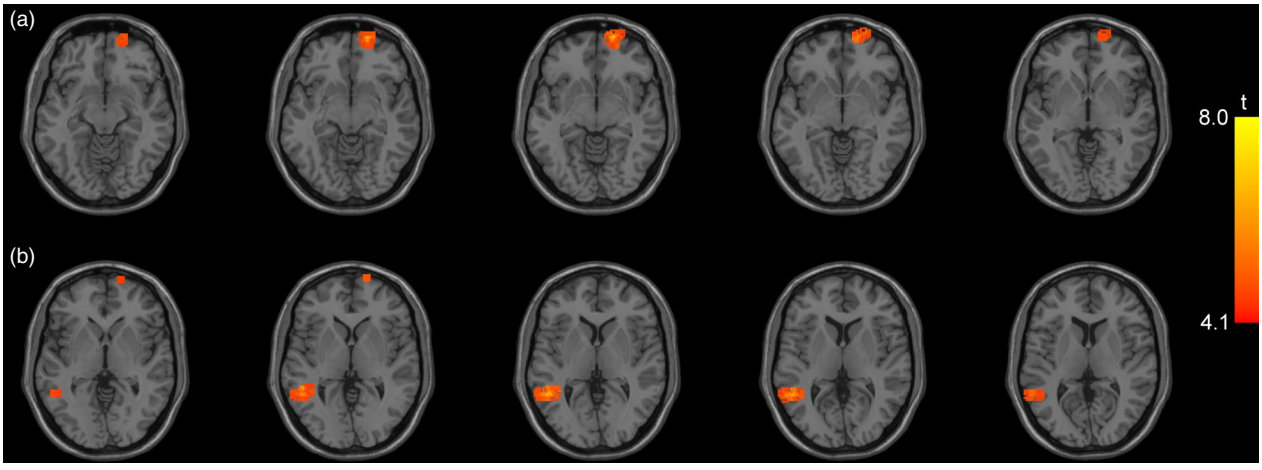

FIGURE 4 Clusters where increases in regional signal variability (RSV) predicted reduction in delayed onset muscle soreness (DOMS) pain unpleasantness from pre- to post-training, including (a) left middle temporal gyrus; and (b) right superior frontal gyrus

3.2 | Outlier/highly influential observation analysis

Examination of scatterplots of extracted RSV values from the above clusters plotted against pain intensity and unpleasantness revealed one participant who appeared to have substantially greater change in RSV from pre- to post-training than other participants (ranging from 2.3 to ~3 standard deviations, depending on region). As a result, correlation analyses between RSV within each cluster and DOMS-related pain outcome were run with and without the outlier participant. Within clusters identified from the previous

TABLE 4 Clusters where increased RSV was associated with reduction in DOMS pain intensity and unpleasantness from pre- to post-training

Brain region	MNI coordinates			k	Peak *t*	p_{FWE}
	X	Y	Z			
Pain intensity						
Left lingual gyrus	−18	−100	−16	106	6.66	.007
Right middle temporal gyrus	60	−56	2	136	6.23	.002
Left middle temporal gyrus	−48	−56	0	147	5.86	.001
Left precuneus	−4	−52	58	73	5.76	.05
Pain unpleasantness						
Left middle temporal gyrus	−52	−52	2	129	7.07	.003
Right superior frontal gyrus	18	64	−8	93	7.06	.018

Abbreviations: DOMS, delayed onset muscle soreness; RSV, regional signal variability.

whole-sample, voxel-wise analysis, exclusion of the outlier participant resulted in the loss of significance for a single association, between change in RSV in left middle temporal gyrus and change in pain unpleasantness (from $r = .87$ to $r = .56$, $p = .07$). Scatterplots demonstrating the influence of the outlier participant on all detected associations are depicted in Figures S1-S8.

4 | DISCUSSION

Response variability in numerous physiological systems is linked to resilience in the face of stressors and is associated with salutary health outcomes (e.g. heart rate variability; Thayer, Yamamoto, & Brosschot, 2010). Recent research suggests that RSV among pain modulatory regions may be associated with endogenous pain modulation (Rogachov et al., 2016). Furthermore, our prior work showed that functional capacity of the PMC may be increased following successive and controlled exposures to clinically relevant pain (i.e. DOMS; Sevel et al., 2019). As such, this study sought to clarify the role of neurophysiological variability, RSV, in terms of both susceptibility to clinically relevant pain and its association with increases in PMC. Results suggested that baseline levels of RSV were linked with trainability of the negative appraisal of pain (i.e. pain unpleasantness) and that, following a period of training, increases in RSV were significantly associated with concurrent reductions in DOMS-related pain intensity and unpleasantness.

Notably, we found RSV in regions related to cognitive and affective aspects of the pain experience were associated with pain reductions following training. Reductions in pain unpleasantness were associated with baseline RSV in regions involved in cognitive and affective modulation of pain and sensory processing (the left middle frontal gyrus and right cerebellum), respectively (Derbyshire, Whalley, Stenger, & Oakley, 2004; Eippert et al., 2009; Lebel et al., 2008; Wiech et al., 2005). Interestingly, reductions in pain intensity and unpleasantness were also associated with co-occurring changes in RSV. Reductions in pain intensity were linked to changes in RSV among the left lingual gyrus, right and left middle temporal lobes and left precuneus, all of which are involved in processes linked to visual representation of painful experiences and movement in self and others, and cognitive modulation of pain via visual or cognitive cues (Corradi-Dell'Acqua, Hofstetter, & Vuilleumier, 2011; Kong et al., 2013; Meier et al., 2015; Price, Craggs, Verne, Perlstein, & Robinson, 2007; Shimo et al., 2011; Van Der Meulen, Allali, Rieger, Assal, & Vuilleumier, 2014).

Similarly, regions in which concurrent changes in RSV were associated with reductions in pain unpleasantness were those associated with internal representations of pain in self and others and expectation-related pain modulation such as the left middle temporal and right superior frontal gyri (Atlas et al., 2012; Guo et al., 2011; Lamm, Nusbaum, Meltzoff, & Decety, 2007; Lötsch et al., 2011; Simon, Craig, Miltner, & Rainville, 2006; van der Heiden, Scherpiet, Konicar, Birbaumer, & Veit, 2013). Although we advise caution in interpretation of these regional findings given the current sample size and potential for undue influence of outlier observations (as in left middle temporal gyrus), these results suggest that trainability of pain modulation following multiple pain exposures may depend on changes in pain appraisal, underpinned by brain regions associated with cognition and pain representational processes. These results extend our previous work in this area, which highlighted the role of central adaptation in affective and sensory functional networks following repeated bouts of DOMS networks, to include the role of RSV in largely cognitive and representation areas in pain modulatory trainability.

The present findings provide unique insights regarding the potential roles of RSV in pain adaptation. Presently, RSV was more strongly associated with *trainability* of the EPMS in response to multiple DOMS bouts rather than *susceptibility* to pain following a single bout.

Consistent with work on the role of RSV in pain modulation (Rogachov et al., 2016), this finding further suggests that pain-related RSV may be an indicator of EPMS resilience rather than risk. We also found that the degree to which an individual adapted to the pain training paradigm was related both to baseline levels of RSV and inter-individual differences in RSV change from pre- to post-training, indicating that RSV may be a marker of *responsivity* to training and a neural indicator that is *responsive* to training. Future studies are encouraged to investigate the role of RSV in the context of pain modulation and resilience to pain chronicity using both cross-sectional and longitudinal approaches.

Although the present findings are novel and have important implications for pain research, we recognize a number of potentially influential limitations. Our results were not supportive of certain hypothesis (e.g. that greater baseline RSV would be associated with susceptibility to pain following a single DOMS induction). It is nonetheless possible that while RSV in a pain-free individual is not strongly associated with initial susceptibility to exercise-induced musculoskeletal pain, RSV reflects capacity of the EPMS to adapt to subsequent pain challenges.

We believe that the cluster size-based significance threshold used in this study is an appropriate method of FWE correction for our analyses because it maximizes our ability to identify regions where RSV may reflect trainability of the EPMS. However, it should be noted that such an approach involves some compromises when compared to voxel height-based thresholds, including low sensitivity to statistically large but spatially limited effects. In addition, because this was a preliminary study of RSV as reflective of resilience to musculoskeletal pain in healthy individuals, our sample size was relatively small. This small sample size limited statistical power, allowing us to find only the strongest effects. Although small sample size may make findings vulnerable to the effects of movement confounds, post-hoc correlational analyses showed no relationship between observed RSV and mean framewise displacement within significant clusters (Figure S9). In addition, resting state scans in this study were somewhat brief in duration (~6.5 min). Recent studies suggest that statistical power and reliability, at least in functional connectivity analyses, increase as a function of scan duration (Birn et al., 2013; Caparelli, Ross, Gu, & Yang, 2019). It seems likely that similar considerations may apply in RSV analyses. Considering both sample size and scan duration, we may not have been sufficiently powered to identify more nuanced associations while also maintaining rigorous controls for multiple comparisons. As a result, it is possible that additional regions related to the supported hypotheses were not identified in this analysis. That being said, our analyses revealed seemingly substantial associations between inter-individual differences in RSV and pain reduction (e.g. nearly double RSV when comparing individuals with greatest and least pain reduction, see Figure S1). In the absence of established norms for RSV and in light of the study's sample size, we are cautious to overinterpret these findings. The magnitude of such associations clearly warrants clarification from subsequent investigations of RSV in pain processing. Finally, future studies are suggested to obtain larger samples based upon these effects with a meaningful control group (e.g. individuals that receive only a single bout of DOMS during the study period), and to characterize RSV in pain-related regions as a determinant of risk for pain chronification.

5 | CONCLUSIONS

Resilience to environmental challenges is related to response variability among numerous physiological systems. The current findings suggest that the same may be true for pain modulatory neural systems—both that baseline RSV and inter-individual differences in RSV alterations are related to EPMS trainability following repeated exposures to clinically relevant pain. These results further clarify the role of RSV in pain modulation and resilience, identifying targets for both future investigations of pain adaptation and potential interventions for chronicity.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

JB, LS, MA, MB and MR contributed to the conception and design of the study, and acquisition of the data. All authors contributed to the analysis and interpretation of the data. All authors contributed to the drafting of the article and critical

revisions and approved submission of the manuscript for consideration.

REFERENCES

Atlas, L. Y., Whittington, R. A., Lindquist, M. A., Wielgosz, J., Sonty, N., & Wager, T. D. (2012). Dissociable influences of opiates and expectations on pain. *Journal of Neuroscience*, *32*(23), 8053–8064. https://doi.org/10.1523/JNEUROSCI.0383-12.2012

Basalyga, G., & Salinas, E. (2006). When response variability increases neural network robustness to synaptic noise. *Neural Computation*, *18*, 1349–1379. https://doi.org/10.1162/neco.2006.18.6.1349

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042

Birn, R. M., Molloy, E. K., Patriat, R., Parker, T., Meier, T. B., Kirk, G. R., … Prabhakaran, V. (2013). The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *NeuroImage*, *83*, 550–558. https://doi.org/10.1016/j.neuroimage.2013.05.099

Bishop, M. D., Horn, M. E., & George, S. Z. (2011a). Exercise-induced pain intensity predicted by pre-exercise fear of pain and pain sensitivity. *Clinical Journal of Pain*, *72*(5), 398–404. https://doi.org/10.1097/AJP.0b013e31820d9bbf

Bishop, M. D., Horn, M. E., George, S. Z., & Robinson, M. E. (2011b). Self-reported pain and disability outcomes from an endogenous model of muscular back pain. *BMC Musculoskeletal Disorders*, *12*, 35. https://doi.org/10.1186/1471-2474-12-35

Caparelli, E. C., Ross, T. J., Gu, H., & Yang, Y. (2019). Factors affecting detection power of BOLD signal in resting-state fMRI using high resolution Echo-Planar Imaging. *Brain Connectivity*, *9*(8), 638–648. https://doi.org/10.1089/brain.2019.0683

Corradi-Dell'Acqua, C., Hofstetter, C., & Vuilleumier, P. (2011). Felt and seen pain evoke the same local patterns of cortical activity in insular and cingulate cortex. *Journal of Neuroscience*, *31*(49), 17996–18006. https://doi.org/10.1523/JNEUROSCI.2686-11.2011

Dannecker, E. A., Hausenblas, H. A., Kaminski, T. W., & Robinson, M. E. (2005). Sex differences in delayed onset muscle pain. *Clinical Journal of Pain*, *21*(2), 120–126. https://doi.org/10.1097/00002508-200503000-00002

Dannecker, E. A., Koltyn, K. F., Riley, J. L., & Robinson, M. E. (2002). The influence of endurance exercise on delayed onset muscle soreness. *Journal of Sports Medicine and Physical Fitness*, *42*(4), 458–465.

Derbyshire, S. W., Whalley, M. G., Stenger, V. A., & Oakley, D. A. (2004). Cerebral activation during hypnotically induced and imagined pain. *NeuroImage*, *23*(1), 392–401. https://doi.org/10.1016/j.neuroimage.2004.04.033

Eippert, F., Bingel, U., Schoell, E. D., Yacubian, J., Klinger, R., Lorenz, J., & Büchel, C. (2009). Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron*, *63*(4), 533–543. https://doi.org/10.1016/j.neuron.2009.07.014

Garrett, D. D., Samanez-Larkin, G. R., MacDonald, S. W., Lindenberger, U., McIntosh, A. R., & Grady, C. L. (2013). Moment-to-moment brain signal variability: A next frontier in human brain mapping? *Neuroscience and Biobehavioral Reviews*, *37*, 610–624. https://doi.org/10.1016/j.neubiorev.2013.02.015

Guo, X., Zheng, L. I., Zhang, W., Zhu, L., Li, J., Wang, Q., … Yang, Z. (2011). Empathic neural responses to others' pain depend on monetary reward. *Social Cognitive and Affective Neuroscience*, *7*(5), 535–541. https://doi.org/10.1093/scan/nsr034

Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., … Duda, S. N. (2019). REDCap Consortium, The REDCap consortium: Building an international community of software partners. *Journal of Biomedical Informatics*. https://doi.org/10.1016/j.jbi.2019.103208

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377–381.

Institute of Medicine (2011). *Relieving pain in America: A blueprint for transforming prevention, care, education, and research*. Washington, DC: National Academies Press.

King, T., Ossipov, M. H., Vanderah, T. W., Porreca, F., & Lai, J. (2005). Is paradoxical pain induced by sustained opioid exposure an underlying mechanism of opioid antinociceptive tolerance? *Neurosignals*, *14*(4), 194–205. https://doi.org/10.1159/000087658

Kong, J., Jensen, K., Loiotile, R., Cheetham, A., Wey, H.-Y., Tan, Y., … Gollub, R. L. (2013). Functional connectivity of the frontoparietal network predicts cognitive modulation of pain. *Pain*, *154*(3), 459–467. https://doi.org/10.1016/j.pain.2012.12.004

Lamm, C., Nusbaum, H. C., Meltzoff, A. N., & Decety, J. (2007). What are you feeling? Using functional magnetic resonance imaging to assess the modulation of sensory and affective responses during empathy for pain. *PLoS ONE*, *2*(12), e1292. https://doi.org/10.1371/journal.pone.0001292

Lebel, A., Becerra, L., Wallin, D., Moulton, E. A., Morris, S., Pendse, G., … Borsook, D. (2008). fMRI reveals distinct CNS processing during symptomatic and recovered complex regional pain syndrome in children. *Brain*, *131*(7), 1854–1879. https://doi.org/10.1093/brain/awn123

Lötsch, J., Walter, C., Felden, L., Preibisch, C., Nöth, U., Martin, T., … Oertel, B. G. (2011). Extended cortical activations during evaluating successive pain stimuli. *Social Cognitive and Affective Neuroscience*, *7*(6), 698–707. https://doi.org/10.1093/scan/nsr042

Meier, M. L., Stämpfli, P., Vrana, A., Humphreys, B. K., Seifritz, E., & Hotz-Boendermaker, S. (2015). Fear avoidance beliefs in back pain-free subjects are reflected by amygdala-cingulate responses. *Frontiers in Human Neuroscience*, *9*, 424. https://doi.org/10.3389/fnhum.2015.00424

Price, D. D., Craggs, J., Verne, G. N., Perlstein, W. M., & Robinson, M. E. (2007). Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *Pain*, *127*(1–2), 63–72. https://doi.org/10.1016/j.pain.2006.08.001

Rivat, C., & Ballantyne, J. (2016). The dark side of opioids in pain management. *PAIN Reports*, *1*(2), e570. https://doi.org/10.1097/PR9.0000000000000570

Rogachov, A., Cheng, J. C., Erpelding, N., Hemington, K. S., Crawley, A. P., & Davis, K. D. (2016). Regional brain signal variability: A novel indicator of pain sensitivity and coping. *Pain*, *157*(11), 2483–2492. https://doi.org/10.1097/j.pain.0000000000000665

Sevel, L., Boissoneault, J., Alappattu, M., Bishop, M., & Robinson, M. E. (2019). Training endogenous pain modulation: A preliminary investigation of neural adaptation following repeated exposure to clinically-relevant pain. *Brain Imaging and Behavior*, https://doi.org/10.1007/s11682-018-0033-8

Shimo, K., Ueno, T., Younger, J., Nishihara, M., Inoue, S., Ikemoto, T., … Ushida, T. (2011). Visualization of painful experiences believed to trigger the activation of affective and emotional brain regions in subjects with low back pain. *PLoS ONE*, *6*(11), e26681. https://doi.org/10.1371/journal.pone.0026681

Simon, D., Craig, K. D., Miltner, W. H., & Rainville, P. (2006). Brain responses to dynamic facial expressions of pain. *Pain*, *126*(1–3), 309–318. https://doi.org/10.1016/j.pain.2006.08.033

Thayer, J. F., Yamamoto, S. S., & Brosschot, J. F. (2010). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology*, *141*(2), 122–131. https://doi.org/10.1016/j.ijcard.2009.09.543

Van der Heiden, L., Scherpiet, S., Konicar, L., Birbaumer, N., & Veit, R. (2013). Inter-individual differences in successful perspective taking during pain perception mediates emotional responsiveness in self and others: An fMRI study. *NeuroImage*, *65*, 387–394. https://doi.org/10.1016/j.neuroimage.2012.10.003

Van Der Meulen, M., Allali, G., Rieger, S. W., Assal, F., & Vuilleumier, P. (2014). The influence of individual motor imagery ability on cerebral recruitment during gait imagery. *Human Brain Mapping*, *35*(2), 455–470. https://doi.org/10.1002/hbm.22192

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity*, *2*(3), 125–141, https://doi.org/10.1089/brain.2012.0073

Wiech, K., Seymour, B., Kalisch, R., Stephan, K. E., Koltzenburg, M., Driver, J., & Dolan, R. J. (2005). Modulation of pain processing in hyperalgesia by cognitive demand. *NeuroImage*, *27*(1), 59–69. https://doi.org/10.1016/j.neuroimage.2005.03.044

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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