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Pain and the perception of space in OPEN fibromyalgia

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The Economy of action hypothesis postulates that bodily states rescale the perception of the individual's environment's spatial layout.The estimation of distances and slopes in navigation space (i.e. the space reachable by locomotion) is influenced by sensations relating to body condition and the metabolic cost of the actions.The results of the studies investigating the impact of pain on distance estimation remain inconclusive. 28 women suffering from chronic pain and fibromyalgia (FM), and 24 healthy women (HC) were assessed for musculoskeletal, neuropathic, and visceral pain by means of the Widespread Pain Index, the Symptom Severity Scale and an ad-hoc devised questionnaire for pain (theVerona Pain Questionnaire). In aVR-mediated task, they observed a 3D scenario and estimated the distance of a flag positioned at different distances (1, 2, 3, 4 or 5 m) on virtual ramps **with either a 4% or 24% inclination in two different conditions: sitting and standing. Overestimation of distances in the steeper ramp condition was expected, if participants executed the task by internally simulating the movement.The results showed a dissociation between the effects of musculoskeletal and visceral-neuropathic pain on distance estimations.While, according to the Economy ofAction hypothesis, the HCs estimated the distances as being farther away when the ramp was more inclined** (i.e. with a 24% inclination), there was no effect related to the different ramp inclinations in the FM **group. Furthermore, visceral and neuropathic pain were found to affect the performance of the FM group.These results suggest that chronic and widespread pain conditions, that typically characterize fibromyalgia, can affect space representations. In line with the Economy ofAction hypothesis, bodily based estimation of distances is compromised in these patients.**

Keywords Embodied cognition theories, Fibromyalgia, Space perception, Visceral pain, Neuropathic pain, Musculoskeletal pain

The role of the body and sensorimotor information in cognitive functions and social interactions represents the conceptual fulcrum of a set of theories gathered under the label of Embodied Cognition Theories (ECT^{[1](#page-11-0)}). This approach suggests that not only action representations but also higher-order processing, such as judgment capacities, the use of abstract concepts in language (e.g. metaphors^{[2](#page-11-1)}) or the creation of cultural artefacts, are grounded on the sensory and motor body/brain flow of information^{[3](#page-11-2)}. From this perspective, cognitive symbols are simulations of the bodily states built during previous sensorimotor experiences (the 'sensorimotor contingencies^{'[1](#page-11-0)}).

Within the ECT, the Embodied Perception Theory⁴ focuses on the perception of the external world, and states that the representation of objects and space is not a mere function of perceptual systems but rather involves adaptive processes emerging from the interdependent relationship between the state of the body and the environment^{[4](#page-11-3),[5](#page-11-4)}. In this sense, an individual's navigation space (i.e. the space within which individuals can move around to reach targets or explore the environment by locomotion) is the result of the integration of sensory information (i.e. from visual, auditory or tactile stimuli) and the internal mental simulation of the movement which is potentially to be performed (e.g. moving toward a distant target within the space).

In this process of internal simulation, the current state of the body impacts spatial perception and distance estimations. This has been studied by means of tasks requiring the estimation of the space to navigate in, while participants were in different states of metabolic consumption. For example, when carrying a heavy backpack, individuals tended to overestimate the distance of a target that they estimated correctly when they were not carrying the bag⁴. Indeed, according to the Economy of Action hypothesis⁴, when individuals are asked to

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estimate the distance to reach a specific target in navigation space, they automatically simulate the movement toward the target and for this, their perception of the distance is modulated by the effort potentially implied in the act of walking. As a consequence, perception adjusts spatial estimation to maintain body energy, with the result of overestimations that potentially discourage individuals from performing actions that are not energy-efficient^{[4](#page-11-3)}. Similar results have been found for other body conditions, for example when individuals' blood glucose levels are manipulated. In cases of low levels of glucose (i.e. low level of energy) overestimations of distances are recorded⁶. Thus, the hypothesis is that in representing navigational space, individuals activate the motor imagery (i.e. internal simulation) of the movement. Crucially, these effects are present only if individuals represent moving their bodies and not when they base their judgment exclusively on visual information. This seems to be also confirmed by studies on people suffering from motor deficits. In a virtual reality experiment involving individuals with complete traumatic paraplegia (i.e. paralysis of the lower body), we investigated whether being seated in their own wheelchair versus an unfamiliar, difficult-to-maneuver wheelchair would affect distance estimations. In an experimental paradigm very similar to that used in the current study, participants were asked to estimate the distance from a target positioned on a ramp with different degrees of inclination. When participants were sitting in their own wheelchair (i.e. in the condition they are used to move in space), their performances were consistent with predictions from the Embodied Perception Theory, i.e. the longer the distances and the steeper the ramp, the wider the estimation errors. In contrast, when seated in an unfamiliar wheelchair (i.e., a wheelchair that they do not consider as part of their body and that is not used daily to move), estimation errors were not influenced by the position of the target. This result suggests that in the latter condition, participants' perceptions are not shaped by the internal simulation of the movement required to reach the flag but rather rely on visual strategies⁷.

The aim of the current study is to understand the potential modulatory effects of pain on the perception and estimation of distances. Chronic pain is known to affect body representations in terms of action representations^{[8,](#page-12-0)[9](#page-12-1)} and motor imagery¹⁰, but its effects on the perception of navigation space are inconclusive^{[11–](#page-12-3)13}, probably because of the complex nature of pain. Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"¹⁴. This definition highlights the convergence of biological, psychological, and social factors, emphasizing that pain is always a uniquely personal experience, linked to body and action representation (see Ref.¹⁵ for a review). Pain can manifest in a variety of forms, including musculoskeletal pain (affecting bones, joints and muscles¹⁶), neuropathic pain (resulting from damage to the central or peripheral nervous system 17) and visceral pain (resulting from inflammation, disease or injury involving internal organs¹⁸). Pain can be acute or chronic, with chronic pain defined as pain that persists after an inciting event or the healing process and that lasts longer than 3 months (WHO, 2019/2021). Chronic pain is often associated with specific medical conditions, although transient pain is common in the general population. Musculoskeletal pain, for example, is reported by almost half of the general population (47%[16](#page-12-7)), while neuropathic pain is less common outside of diagnosed conditions $(7-8%$ in the undiagnosed population^{[19](#page-12-10)}). Visceral pain is also common, ranging from mild discomfort, such as indigestion, to severe pain, such as in renal colic¹⁸. Given the complexity of pain, it is likely that different types of pain affect spatial representation in different ways. Namely, each pain typology—whether musculoskeletal, neuropathic or visceral—has distinct characteristics and mechanisms that may influence spatial representation in specific ways.

This study aims at investigating the effects of the different types of chronic pain on individual's perception of the navigation space. Pain has been found to be associated with motor imagery deficits. Specifically, imagining movement of painful body parts increases pain and swelling in patients with complex regional pain syndrome²⁰, and chronic pain in spinal cord injuries impairs motor imagery^{[21](#page-12-12)}. These findings suggest that motor simulation is more difficult for individuals with chronic pain, potentially creating an internal state comparable to that of high metabolic energy consumption. For this reason, we chose to interview participants who suffer from Fibromyalgia, and their responses were compared to those of a gender and age-matched control group. Fibromyalgia (FM) is a clinical condition characterised by widespread, chronic primary pain (ICD-11—code MG30.01^{22,23}). The prevalence of FM reaches 5.8% of the population in industrially developed countries²⁴⁻²⁶, and it is more frequent in women (8–10:1, female to male ratio). The pain that characterises FM is typically chronic and patients often report having experienced pain since childhood or youth, and that this has lasted over time with a certain degree of stability. Furthermore, other symptoms that make this syndrome a perfect model for the purposes of investigating the Economy of Action Hypothesis are the sense of chronic fatigue and sleep disorders, including non-restorative sleep. Physical exhaustion and cognitive difficulties, in particular involving memory²⁷, anxiety and depression^{[28](#page-12-18),29} have also been reported. FM was originally defined as a syndrome characterized by chronic, widespread musculoskeletal pain²⁷. However, a recent revision enlarges the focus behind musculoskeletal pain²², as FM is nowadays recognized as a "heterogeneous condition which has defied clear definition["23](#page-12-14). This is also confirmed by the current debate on nociplastic pain, i.e. pain that arises from altered nociception despite the absence of clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain (International Association for the Study of Pain (IASP)). This definition underlies the multidimensional nature of chronic pain in FM.

After the clinical data collection, FM and control participants were asked to perform a task in a virtual reality environment, and to estimate the distance between their body and a flag positioned at various distances on a virtual ramp presented with two different degrees of inclination. According to the Economy of Action Hypothesis, increasing flag distances, in particular when associated with steeper ramp inclination, should lead to an overestimation of distance. However, we postulated that this would also be influenced by the intensity and typology of pain and the sense of fatigue experienced by the participants. If internal simulation of the movement is adopted to estimate objects' distance, higher pain intensity should result in an overestimation of objects' distances depicted on a steeper ramp, while, in the case that pain prevents the use of internal motor simulation in favour of a purely visual estimation, the errors in estimation should not change for different slopes. Finally, there is the possibility that different typologies of pain (i.e. temporary and chronic pain, musculoskeletal, visceral and neuropathic pain) could impact in different ways on the performance.

Methods Participants

28 women suffering from fibromyalgia (FM, age= 48.4 ± 10.9 , years of education=12.3 \pm 3.6) and 24 healthy control participants (i.e. without diagnoses of neurological illness or other conditions associated with chronic pain, HC, matched for sex, age = 49.9 ± 10.2 and education = 14.8 ± 2.6) were recruited at the Analgesic Therapy Unit, Borgo Roma Hospital, Verona (Italy) and at the Rehabilitation Department in the IRCSS Sacro Cuore Hospital (Negrar, Verona, Italy) (Table [1\)](#page-2-0). The diagnosis of fibromyalgia was confirmed in the FM group by means of the combined scores on the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS)³⁰. The WPI is a self-reported pain index resulting from the number of painful regions out of the 19 regions considered in the Regional Pain Scale³¹ (score range = $0-19$). The SSS is the result (range $0-12$) of the sum of the severity scores of 3 symptoms (i.e. fatigue, waking unrefreshed, and cognitive symptoms, score range for each item=0–3), along with the sum of the number of other symptoms that might have co-occurred during the previous 6 months (i.e. headaches, pain or cramps in the lower abdomen, and depression—score 0–3)³⁰. A combination of WPI≥7 and SSS≥5 or WPI≥4 and SSS≥9 was considered as the two valid cut-offs for a diagnosis of FM. This means in fact that in the FM group, pain had been present in at least 4 or 5 regions for at least 3 months (with pain in the jaw and chest and abdominal pains not included in the list). It is to be noted that, following these diagnostic criteria 30 , a diagnosis of FM is considered to be valid irrespective of other diagnoses and does not exclude the presence of other serious clinical illnesses³⁰. The same scales were administered to the control group.

Based on the IASP and Nijs and collaborators criteria³², 14 patients presented with signs of probable nociplastic pain and 14 with signs of possible nociplastic pain in the FM group, while in the HC group there were no signs of nociplastic pain.The sample was consistent with an a-priori sample size that was computed by means of data simulations using a beta = 0.68 (Scandola, Togni and colleagues^{[7](#page-11-6)}, for the script see OSF repository at [https://osf.io/fmys5/\)](https://osf.io/fmys5/). According to the simulation, a minimum sample size of 24 participants per group was necessary to achieve a 95% credible interval of the posterior distribution completely outside, or completely within the Region of Practical Equivalence (the "range of parameter values that are equivalent to the null value for practical purposes["33](#page-12-23)). The participants read and signed the informed consent form. The study was approved

Table 1. Demographic data and clinical assessment of the two groups. *FM* fibromyalgia, *HC* healthy control (details for the diagnosis in the text), *WPI* Widespread Pain Index^{[27](#page-12-17)[,30](#page-12-20)}, *SSS* Symptom Severity Scale^{27,30}, *HADS* Hospital Anxiety-Depression Scale[34](#page-12-24), *VMIQ* Vividness of Motor Imagery Inventory[35,](#page-12-25) *EVI* Explicit Visual Imagery, *K* Kinaesthetic Imagery, Age and Education are reported in years. MAX=Maximum, $MIN = minimum$ and an Index (log[(maximum+1) \times (minimum+1)]) are reported for each typology of pain assessed by means of the Verona Pain Questionnaire (VPQ). The average between Visceral and Neuropathic pain is reported in the last three columns. See results (section Preliminary analysis of pain self-evaluations) for details, and Supplementary Materials SM1 for the table detailed at the single-participant level.

by the Ethics committee of the Province of Verona (Prot. N. 2147cesc) and was conducted in accordance with the Declaration of Helsinki (2013).

On the same day, but in a separated session, the participants responded to a questionnaire on body representations that was part of another study in another separated session 10 .

Materials and methods

Experimental task

Virtual reality scenarios

Two virtual reality (VR) scenarios were designed in 3DS max 2015 (Autodesk, Inc.), implemented in XVR2.0 and displayed through a head mounted display (HMD) Oculus Rift DK1.

The first scenario aimed at verifying the participants' general ability to estimate distances and controlling for any difference in sensitivities with regard to the perception of depth in a VR environment (baseline task). In this scenario, a flag was depicted in an open space in front of the participant, placed at various distances (from 0.5 to 8 m, with graduations of 0.5 m). The target distances used in the main task (i.e. 1, 2, 3, 4 and 5 m) were shown five times, while the other distances were shown only once with the mere purpose of reducing learning effects and habituation. A total of 36 stimuli were presented. The participants were requested to verbally estimate the distance of each flag from the perceived position of their own body. The data related to the target distances were then used to normalise the individual's perceptual errors in the main experimental task.

In the main experimental scenario, two features of the stimuli, previously found to impact the estimation of distances^{[4](#page-11-3)[,7](#page-11-6)}, were manipulated: (i) the distance of the target and (ii) the inclination of the surface. For this reason, this main scenario was identical to the baseline scenario, with the exception that in this case the flag was placed on a ramp shown in front of the participant. The stimuli thus differed in terms of the inclination of the ramp, that could be mild (4% corresponding to 7°) or steep (24%, i.e. [1](#page-3-0)3.5°, Fig. 1), as well as in terms of the distance of the flags from the participant (i.e. 1, 2, 3, 4 or 5 m). Each distance/inclination combination was presented 5 times in random order, for a total of 50 stimuli in each of the two experimental conditions (i.e. with the participant sitting or standing, see below). In both scenarios, each stimulus was shown for 1s.

Questionnaires

In addition to the measures collected during the experiment, data on the types of pain were recorded by means of a questionnaire²¹. Furthermore, due to the nature of the experimental task, the potential impact of the participants' motor imagery abilities was checked³⁵. Finally, as mood disorders have been reported in fibromyalgia patients²⁸, depression and anxiety were controlled³⁴.

Assessment of pain

In order to have a comprehensive evaluation of the different typologies of pain, the participants filled in the Verona Pain Questionnaire (VPQ[36](#page-12-26)), which comprises a scale which differentiates between musculoskeletal,

C) Ramp 4% - flag 5 m D) Ramp 24% - flag 5 m

Fig. 1. Graphical representation of the main experimental VR task. (**A**) mild ramp (4%) and shortest distance of the flag (1 m); (**B**) steep ramp (24%) and shortest distance of the flag (1 m); (**C**) mild ramp (4%) and longest distance of the flag (5 m); (**D**) steep ramp (24%) and longest distance of the flag (5 m).

visceral and neuropathic pain, the scores for which show a high degree of correlation with both the Brief Pain inventory³⁷ and the Douleur Neuropathique 4 scale¹⁹.

The VPQ provides an assessment of pain by qualitatively categorising its source into musculoskeletal, neuropathic and visceral pain and considering the participants symptoms over the past two weeks. Based on IASP descriptions, when the source of pain was clearly identifiable and associated with damage or overuse of structures such as bones, ligaments, muscles, intervertebral discs, and facet joints, it was classified as musculoskeletal pain^{[16](#page-12-7)}. When the pain was not clearly identifiable as nociceptive and described using terms such as sharp, shooting, electric, burning, or stabbing, it was classified as neuropathic pain³⁸. Pain identified in the abdominal region, and characterized by dullness, poor localization, cramping, and related to visceral function or pathology (without evidence of visceral pathology), was classified as visceral pain³⁹.

For each type of pain reported by the participants, they were asked to rate the frequency of the painful sensation (from constant to rare) and to indicate the highest and lowest intensity of pain experienced over the past 2 weeks (on a numerical scale from $0 =$ no pain to $10 =$ worst pain imaginable)^{[21](#page-12-12)}. In addition, participants were asked to rate each specific qualitative characteristic of each pain type, such as for example 'is it a dull pain' for musculoskeletal pain and 'is it a burning pain' for neuropathic pain. For the full scale, see^{[21](#page-12-12)}.

Assessment of motor imagery

To estimate Motor Imagery abilities, two subscales of the Visual Motor Imagery Questionnaire-2 (VMIQ^{35,40}) were used. The subscale External Visual Imagery (VMIQ-EVI) asks the participants to imagine themselves performing 12 actions as if they are looking at themselves from a third-person perspective ("as if you were watching yourself from an external position"). The Kinaesthetic Imagery subscale (VMIQ-K) requires participants to imagine the somatosensory feelings associated with the execution of the same actions. In both conditions, the actions are not actually performed but only imagined. Thus, the two subscales involve different cognitive processes, specifically visual imagery in the former and the simulation of bodily sensations in the latter^{[21,](#page-12-12)[41](#page-12-31)[,42](#page-12-32)}. Furthermore, it was observed that Kinaesthetic Imagery is associated with corticomotor activation, whereas External Visual Imagery is not^{[43](#page-12-33)}. The participants are asked to estimate the vividness of each action imagined, on a 5-point Likert scale (with 1 = perfectly vivid imagined action and 5 = not imagined at all). The sums of the scores are considered as the final scores for each subscale (score range=12–60, with lower scores indicating better motor imagery). Specifically, in the VMIQ-EVI subscale, vividness pertains to imagining oneself from a third-person perspective, while in the VMIQ-K subscale, vividness relates to imagery of the somatosensory sensations associated with performing actions.

Assessment of anxiety and depression

To control for the potential effects of mood on the two groups' performances, the Hospital Anxiety and Depression Scale $(HADS³⁴)$ $(HADS³⁴)$ $(HADS³⁴)$ was used. The questionnaire, which provides a scale that gives scores for anxiety and depression, consists in 14 multiple-choice questions investigating the frequency $(1 =$ never, $5 =$ always) with which a specific mood occurs (e.g. "I feel agitated and tense"; "I feel in a good mood").

Procedure

Participants sat in a comfortable chair and were interviewed by the examiner in order to fill in the preliminary questionnaires (VPQ, VMIQ, HADS). After this, they wore the HMD and anti-noise headphones to isolate them from the environment. In a preliminary phase, they freely explored the VR environment.

The procedure was the same for both the baseline and the experimental tasks, with the only difference being that the baseline task was executed with the participant sitting in a comfortable chair, while the experimental task consisted of two conditions: a Standing condition (in which the participants had to complete the task while standing) and a Sitting condition (in which the task was executed with the participant sitting in a comfortable chair). These two conditions served to control the effects of any feelings of fatigue associated with the execution of the task and were presented in a counterbalanced order across participants. The stimuli in the baseline and experimental tasks were shown in random order for 1s. For each stimulus, the participants were requested to estimate the distance of the flag from themselves in centimetres and respond verbally. There were no time constraints.

After the baseline task and the main task in each of the two conditions (i.e. sitting and standing), the participants were asked to evaluate their current level of fatigue and pain on a visual analogue scale (10cm long VAS, from "no pain" or "no fatigue" to "maximum pain" or "maximum fatigue").

Data handling and statistical analyses

Preliminary analyses: localised v. widespread pain and differences between musculoskeletal, visceral and neuropathic pain

One of the key features of pain in FM (that also represents a diagnostic criterion) is that it is not localised, but spread, involving different body parts³⁰. Thus, in order to confirm a difference in the degree of pain spread between the two groups, the WPI scores of FM and HC participants were compared by means of a Bayesian Linear Model with Group as independent variable.

Another preliminary analysis regarding the typologies of pain was carried out. Notwithstanding the fact that the diagnosis of FM is based on musculoskeletal pain, other typologies of pain (i.e. neuropathic and visceral pain) are often reported by FM patients^{44–46}. For this reason, since the study focuses on the potential effects of pain on distance estimation, a preliminary analysis was performed to check whether differences might arise with respect to the typology of pain in the two groups. An index of pain was calculated for each type of pain, accounting for both the minimum and maximum pain intensity: $log[(maximum+1) \times (minimum+1)]$, ranging between 0 (no pain) and 4.79 (worse minimum and maximum pain, both scored 10). A Bayesian Linear Model was used, with Group and Type of Pain (musculoskeletal, visceral and neuropathic) as independent variables and slope of Type of Pain grouped by participant as a random effect in order to control for within-subjects variability. The prior distributions were two Gaussian distributions (mean=0, sd=1 for the regressors and mean=0, sd=5 for the intercept) which were chosen as they have a good sensitivity with regard to the differences between the various types of pain and the groups (the regressors), but a wide overall mean range (the intercept). A series of five models were fitted, starting from a null model (i.e. only intercept, no regressors) to the saturated model (i.e. all regressors and interactions). The model that best represented the data was chosen by means of posterior probabilities based on marginal likelihoods^{[47](#page-12-36)}. An additional preliminary analysis was conducted to examine the types of pain experienced over the past two weeks, suggesting an absence of differences between Visceral and Neuropathic pain which were then averaged in the subsequent analyses (see ["Results](#page-6-0)" section).

The experimental virtual reality task: distance estimation

An analysis of the baseline task was carried out to confirm that the distances used in the task were perceived by the participants as being progressively farther away (see Supplementary Materials, SM2). Bayesian analyses with non-informative priors were used to analyse the errors in estimating the distances and the VASs of current fatigue and pain. The inference was based on 89% Highest Posterior Density Intervals (89%HPDI) of posterior distributions[48](#page-12-37) and the Region of Practical Equivalence (ROPE, Kruschke & Liddell, 2018). ROPEs were computed as the range for a negligible effect size⁴⁹, namely the interval within $-0.1 \times SD$, +0.1 $\times SD$ (note that the intervals of computed ROPEs will be reported at the beginning of each analysis). This means that when the 89% HPDI is completely outside the ROPE, the null hypothesis can be rejected.

In the analysis of the distance estimations, the dependent variable was the Error in estimation, calculated as the difference between the actual and estimated distances of the flag, and converted into a z-score by means of an established procedure^{[7](#page-11-6)}, using as a reference the mean and standard deviations for each distance in the baseline task (see SM2 for the analysis of the raw data of baseline estimations that confirm that participants were able to discriminate different levels of depth; see Eq. ([1](#page-5-0)) for the formula used to compute the z-scores). The use of this index allowed us to limit potential biases within the sample (i.e. heteroskedasticity, extreme values) and to standardize depth perception, that in a virtual reality environment can largely vary⁵⁰.

$$
z_{exp,distance=d_i,subj=s_j} = \frac{err_{exp,distance=d_i,subj=s_j} - M(err_{baseline,distance=d_i,subj=s_j})}{S(err_{baseline,distance=d_i,subj=s_j})}
$$
(1)

Computation of z-scores of the main experiment. The subscript "exp" indicates the "main experiment", "baseline" the "baseline task", "distance" refers to a particular distance *di* (the computation was executed for all distances one by one), "subj" represents a specific participant *sj* (the computation was executed for all participants one by one), 'M' stands for the mean function, and 'S' represents the standard deviation function.

The fixed effects of the Bayesian Linear Model were the Condition (Seated, Standing), the inclination of the Ramp (4%, 24%), the Group (FM, HC), and the Distance of the flag (1, 2, 3, 4 or 5 m). Since the distance from the flag might impact evaluations linearly or non-linearly, polynomial contrasts were used to capture non-linear relations (linear, quadratic, cubic and fourth order).

Moreover, the index of musculoskeletal pain and the average index of visceral and neuropathic pain were used as covariates in interaction with the other fixed effects. As random effects, we used the intercept of the individual participant and the intercept of the interaction between the participant and all of the within-subject factors (Condition, Ramp and Distance) in order to avoid pseudo-replication biases 51 .

Moreover, to determine whether the hypothetical effects on the estimation of distances were specifically related to pain or influenced by other factors, such as abilities in motor imagery and mood variables²⁸, two further models were fitted, using as covariates the scores in the VMIQ subscales and the Anxiety and Depression subscales of the HADS, respectively.

To analyse any changes in fatigue and pain (i.e. The VAS estimations) after the Baseline task, and in the Standing and Sitting conditions of the experimental paradigm, a Bayesian Linear Model was used with the Group and the Condition as fixed effects, and the intercept of the participants and the intercept of the interaction between the participants and the within-subjects factor Condition as random effects.

Only the effects that show 89% HPDI (thus making it possible to reject the null hypothesis) are reported. However, the complete list of results is shown in the Supplementary Materials (Table SM3—for the analysis with musculoskeletal and visceral-neuropathic pain as covariates, Table SM4—for the analysis with motor imagery scores as covariates and Table SM5—for the analysis with depression and anxiety scores as covariates), including the Gelman–Rubin convergence diagnostic (\hat{R}^{52} \hat{R}^{52} \hat{R}^{52}), the Bulk and Tail Estimated Sample Size (ESS⁴⁶), the Posterior Predictive Checking⁵³, (in all cases, $\overrightarrow{R} \le 1.01$, ESS > 500, and Posterior Predictive Checking show that the fitted models are compatible with the data).

In order to check the robustness of the results of this analysis, we also carried out the analysis by grouping the distances into a two-levels factor (near=1 and 2 m, far=3, 4 and 5 m). The results are shown in SM6. To further verify the robustness of our findings, we conducted an additional Bayesian linear model (detailed in Table SM7) excluding participants in the control group who reported baseline pain levels of 40 or above in the Visual Analog Scale collected after the baseline assessment.

All the Bayesian models were fitted with 4 chains with 1000 warmup iterations and 1000 sampling iterations, for a total of 4000 iterations.

The statistical analyses were conducted on R 4.2.2⁵⁴, using brms 2.18.0⁵⁵ and emmeans⁵⁶ for post-hoc testing.

Results

Preliminary analyses: widespread v. localised pain and comparisons among musculoskeletal, visceral and neuropathic pain

In order to confirm that pain sensations were more spread in the FM group than in the HC group, the WPI scores were analysed. This analysis confirmed that pain was more spread in the FM group than in the HCs as there was a difference in the number of painful body regions between the groups $(M=0.71, 89\% \text{ HPDI} = 0.62,$ 0.80, ROPE = $-$ 0.61, 0.61). The mean number of painful areas in the FM group was 13.47 (SD \pm 3.87), while the HCs reported on average 3.23 areas of pain (± 2.34) . Full details are in the Supplementary Materials SM8 and SM9.

Visceral and neuropathic pain are more frequently reported as chronic in FM compared to HC participants (M=3.57, 89% HPDI=0.81, 7.96, ROPE=− 0.1, 0.1; M=0.115, 89% HPDI=0.07, 0.22, ROPE=− 0.04, 0.04). Specifically, 11 FM participants reported visceral pain as chronic, and 8 reported neuropathic pain as chronic, whereas no HC participant reported chronicity in either pain type. In contrast, no significant difference was found between FM and HC participants regarding musculoskeletal pain (M=0.31, 89% HPDI=− 0.005, 0.61, ROPE=− 0.1, 0.1).As far as the typology of pain is concerned, the analyses of the indexes of pain intensity experienced by the participants showed that the model with both main factors (Group and Type of Pain), but not their interaction, was the best model (Table [2A](#page-6-1)). In particular, the results showed higher pain levels in the FM group (2.66 ± 1.42) than in the HCs (1.08 ± 1.29) , without any differences between the types of pain experienced. By analysing the main effect of the typologies of pain (Table [2B](#page-6-1)), we found that visceral (1.58 ± 1.55) and neuropathic pain (1.28 ± 1.56) could be merged into a unique pain evaluation (see Table [2B](#page-6-1)), while musculoskeletal pain (2.74 ± 1.16) was more severe (i.e. higher scores) than the former pain sensations. Considering these results, the visceral and neuropathic pain evaluations were then averaged in the subsequent analyses.

The experimental virtual reality task: distance estimation

Distance estimation and pain were analysed for the main task in a single model (see "Data handling and statistical analysis"). However, to simplify the explanation of the results, the effects will be reported separately.

The ROPE for this analysis was between − 0.10 and 0.10.

The estimation of distances in Healthy Controls and Fibromyalgia patients

The results showed the main effects of Linear Distance ($M=1.83$, 89%HPDI=1.73, 1.92) and the interaction between Group and Quadratic Distance (M=0.25, 89%HPDI=0.15, 0.34) indicating different non-linear trends in the two groups. Furthermore, an interaction between Ramp Inclination, Group and Linear Distance (M=− 0.25, 89%HPDI=− 0.37, − 0.11) was found. No conclusive effects were observed for Condition (sitting/ standing) and its interactions (see the Supplementary Materials Table SM3).

The post-hoc analysis of the Ramp:Group:Distance interaction was performed in two steps. First, we tested for differences in performance between the 4% and 24% ramps within each distance and group. Then, we examined whether there were differences between the HC and FM groups at each ramp and distance.

In the HC group, significant differences between the 4% and 24% ramps were observed at 3 m (M=− 0.42, 89% HPDI = − 0.75, − 0.102) and 5 m (M = − 0.84, 89% HPDI = − 1.16, − 0.51), where steeper ramps were associated with larger overestimation errors, meaning that distances were perceived as farther. At 4 m, the difference was inconclusive, as the 89% HPDI overlapped the Region of Practical Equivalence (ROPE)

Table 2. Comparisons between Bayesian Linear Models on the index of pain. The posterior model probability is an index in a 0–1 range that allows Bayesian model comparison. (A) comparison among models with different regressors. Comparison between "Type of Pain+Group" and "Type of Pain * Group" models show a Bayes Factor = 12.4 in favour of the former model; (B) Comparisons among models where it was tested if specific pain sensations have identical scores. Comparison between the "(Visceral=Neuropathic)≠Musculoskeletal" and "Neuropathic≠Visceral≠Musculoskeletal" models show a Bayes Factor=3.36 in favour of the "(Visceral=Neuropathic) \neq Musculoskeletal" model. The mean, median and standard deviation values for the two groups are shown in Table [1.](#page-2-0)

Fig. 2. Median and 89%HPDI of the posterior distributions of the interaction between Inclination, Group and Distance. ≠stands for comparisons for which a difference not overlapping the ROPE was found.

Table 3. Mean and standard deviations of the z-scores of the Errors in the estimation of distances, computed using as normative values the scores from the baseline scenario, divided by Group (FM=Fibromyalgia participants, HC=Healthy Controls), Distance (1 m, 2 m, 3 m, 4 m and 5 m) and Ramp (4% and 24%).

(M=− 0.31, 89% HPDI=− 0.63, 0.02). However, with 94% of the posterior distribution below zero, this result hints at a trend toward overestimation, consistent with the observed results at 3 m and 5 m.

When distances were grouped into "near" (less than 3 m) and "far" (3-5 m), a significant difference between the two ramps was found in the HC group for the "far" distances (M=− 0.526, 89% HPDI=− 0.773, − 0.292), supporting the hypothesis that steeper ramps led to greater overestimation in the HC group. This trend was absent in the FM group, either using the 5 distances separately or grouping them into two (far and near) distances. In both analyses, all HPDIs overlapped the ROPE, indicating inconclusive results for ramp effects on distance estimation in this group.

When comparing the two groups, differences emerged for the steeper ramp (24%) at the 3 m ($M = -0.79$, 89% HPDI=− 1.15, − 0.49), 4 m (M=− 0.61, 89% HPDI=− 0.93, − 0.27), and 5 m distances (M=− 0.42, 89% HPDI=− 0.78, − 0.12). In these cases, the HC participants overestimated distances more than the FM participants. A reverse pattern appeared on the 4% ramp at the 5 m distance, where HC participants made smaller errors than the FM group ($M=0.49$, 89% HPDI = 0.13, 0.82).

Overall, distance estimates in the HC group differed between the 4% and 24% ramps, with steeper inclines leading to larger overestimation. In contrast, the FM group's estimates were not affected by the ramp inclination. All the other comparisons between the groups were inconclusive.

For a graphical representation, see Fig. [2](#page-7-0) and Table [3,](#page-7-1) and Table SM3 in the Supplementary Materials for the inconclusive effects.

Fig. 3. Graphical representation of the interaction between Distance and the Visceral-Neuropathic Pain Index. The points represent the average errors per participant, while the line is the overall linear regression. * stands for a regression coefficient not overlapping the ROPE.

The effects of pain on distance estimation

Considering the participants as a whole (both FM and HC), it was found that the intensity of visceral-neuropathic pain (as quantified in the pain index) impacted distance estimations. In particular, this index covaried with Distance $(M=0.21, 89\%HPDI=0.14, 0.28)$, thus indicating that the more severe the pain reported, the farther away the flags were perceived to be.

A post-hoc analysis showed that only the errors made at the 5 m distance covaried with the visceral-neuropathic pain index, with a direct relationship (M=0.27, 89%HPDI=0.17, 0.37) (see Fig. [3,](#page-8-0) Table SM3 for the inconclusive results). However, although this effect was present in the HC group at 5 m (M=0.41, 89%HPDI = 0.23, 0.60), the errors made by the FM group overlapped with the ROPE ($M=0.11$, 89%HPDI = 0.05, 0.23). In order to determine whether this effect was related to visceral or neuropathic pain in the HC group, explorative correlations between the distance estimations and the neuropathic and visceral pain indexes were computed. The correlation between visceral pain and erroneous estimations at the 5 m distance was rho=0.32, while the correlation between neuropathic pain and erroneous estimations was $rho=0.19$, suggesting that the effect was mainly linked to visceral pain in HC.

The effects of body positions on fatigue and pain

The VAS measuring Pain and Fatigue revealed a difference between the two groups (Pain: M=21.22, 89% HPDI=15.78, 27.63, ROPE=− 3.42, 3.42; Fatigue: M=21.59, 89% HPDI=15.96, 27.77, ROPE=− 3.64, 3.64), with the FM group always suffering from fatigue (FM=63.06 \pm 34.48, HC=19.84 \pm 22.36) and from Pain (FM=53.61±31.55, HC=11.14±18.48) more than the HC group. Inconclusive effects were observed for Condition (i.e. sitting or standing) and for the Group:Condition interaction in both VAS analyses. No modulation of the feelings of pain or fatigue due to the body position was found.

Effects of motor imagery and mood

Neither the model analysing the erroneous distance estimations using the VMIQ subscales as covariates nor the model using the Anxiety and Depression subscales of the HADS as covariates revealed any effects of motor imagery or mood on the estimations. The complete results are reported in Tables SM4 and Table SM5.

No differences between the HC and FM groups in their self-evaluations of Anxiety and Depression were observed (Anxiety: M=− 0.24, 89% HPDI=− 0.96, 0.96, ROPE=− 0.35, 0.35; Depression: M=0.68, 89% $HPDI = -0.06, 1.28, ROPE = -0.33, 0.33$.

A difference in Motor Imagery was found between the two groups in both the VMIQ-EVI (M=6.82, 89% HPDI=4.49, 9.26, ROPE=− 1.33, 1.33) and VMIQ-K (M=6.37, 89% HPDI=3.80, 9.08, ROPE=− 1.39, 1.39) subscales, with the FM group performing worse than the HCs. For the descriptive statistics, see Table [1.](#page-2-0)

Discussion

The study tested the hypothesis of the potential role of pain and sense of fatigue in the representation of navigation space (i.e. the space within which individuals move around to reach targets or explore the environment) and compared a clinical sample of women suffering from fibromyalgia to a control group. The participants performed a task requiring them to estimate the distance of a target (a flag) that was positioned on an inclined ramp. The inclination was either mild (4%) or steep (24%). The presence of pain was not excluded in the control group, but while the FM group was characterised in most of the cases by highly-frequent, chronic, widespread pain, the control sample only reported specific conditions of localised pain (Tables SM8 and SM9 for details). We anticipated that the presence of pain would impact the distance estimations, in particular resulting in overestimations of the greater distances and when the ramp was steeper. This hypothesis would be in accordance with the Embodied Perception Theory, according to which greater distances and steeper inclinations are imagined to require greater efforts when individuals mentally travel through space to reach a target⁵⁷. In order to induce a sense of fatigue, the experimental task was executed in two conditions, one in which the participants were seated and another in which they were standing. However, these two conditions did not impact the results, although the FM group always reported greater levels of fatigue than the control group.

The results revealed that, although a general effect of overestimation of distances was present in both groups, a dissociation emerged with regard to their responses. Specifically, while in the case of the HC group the steeper inclination (i.e. 24%) was associated with larger overestimations than the mild inclination (i.e. 4%) over longer distances (i.e. when the flag was at 3 m and 5 m), as expected according to the Economy of Action theory, this did not occur in the FM sample, for which no conclusive difference was observed.

Interestingly, in the HC group, visceral and neuropathic pain had an effect on participants' perception of distances in the case of the farthest flag (i.e. 5 m), indicating a direct relationship between overestimation errors and greater levels of visceral-neuropathic pain. It is worth noting that, although also HC reported some degree of pain, none of them was identified as presenting with nociplastic pain. Furthermore HC pain was localised and not as widespread as in the FM group, seeTables SM8 and SM9., and visceral and neuropathic pain, when present, was always reported as temporary in the HC group. Overall, the results suggest a difference in the impact of temporary compared to chronic, highly-frequent and widespread pain on distance estimations. Furthermore, they suggest the possibility that the perception of internal bodily states (i.e. interoception) could impact space representation. Indeed, in this study, the predictions of the Embodied Perception Theory about the impact of pain on distance estimation were confirmed only in the case of temporary, but not chronic and highly-frequent visceral or neuropathic pain. The overestimation of distances, which is consistent with higher metabolic costs relating to the effort of imagining actions, seems to be mainly associated with the moment-bymoment, perceived internal states of the body rather than with a stable condition of chronic and highly-frequent musculoskeletal pain. Our results suggest that chronic, widespread pain induces a change in the cognitive strategies used to estimate distances, preventing the process of internal simulation of the movement to reach the target. Without this simulation process, the task is carried out by means of different strategies, possibly visual spatial representation strategies, with errors in estimations that are not influenced by distances and ramp inclination. These results could provide evidence of the role of the current internal states of the body in space representation in the presence of different typologies of pain, thus supporting previous studies on healthy and deafferented populations^{[58](#page-13-0)-60}.

The effects of temporary pain on distance estimations

The results pertaining to the group of healthy participants support the Economy of Action hypothesis^{[4](#page-11-3)}. This theory claims that the perception that people have of their navigation space changes not only depending on variations in the characteristics of the environment but also on the current condition of their body. These factors affect their automatic, implicit estimate of the metabolic costs of moving within the environment. It has been hypothesised that this effect is advantageous from an evolutionary point of view since preserving metabolic energy might make a difference in an individual's chance of survival (i.e. Economy of Action^{[4](#page-11-3)}). Previous studies have demonstrated that this body/space link is present not only when locomotory movements actually occur, but also when these movements are implicitly represented, as in the task used in the present study. For example, a series of experiments has shown that when people feel fatigued or physically unfit, they tend to overestimate slopes⁶¹. The same happens with ageing or declining health⁶¹. In contrast, motor expertise in sports or physical exercise influences and ameliorates a person's visual perception of objects that have a crucial role in the sport they practise, for example, the hole in the course for golfers⁶² or the ball for baseball players⁶³. Furthermore, temporary changes in bodily states may modulate space perception, as shown by the results of a seminal study which provided evidence that wearing a heavy backpack makes people perceive a target as being farther away than it is^{[64](#page-13-5)} and the inclination of a slope as steeper than in reality⁶¹. The results of the HC group in this study confirm the effects of the inclination of the ramp on estimations of distance and suggest that transitory conditions of pain, in particular visceral and neuropathic pain (i.e. pain associated with internal states of the body), may modulate distance estimations.

Interestingly, there were no effects resulting from the position of the participants (i.e. sitting or standing) or other variables such as mood, thus excluding the possibility that participants' anticipation regarding the expected responses was biased by the experimental paradigm or the response requests 66 .

Two factors (which are not mutually exclusive) potentially explain the lack of difference related to the body position. The first possibility is that the two conditions do not differ in terms of the metabolic cost of the actions considered, and thus, asking participants to stand while executing the task is not enough to induce a sense of fatigue. The second possibility is that sitting does not impact the implicit mental representations of the actions required to move towards a target in the navigation space. This seems to be in contrast with a previous study⁷ that compared the performance of a group of healthy subjects with a group of paraplegic participants using the same task described in this study. In particular, the paraplegic participants performed according to the Economy of Action principle when they were sitting on their own wheelchair (i.e. increasing errors with steeper ramps). In contrast, when they were seated on an unfamiliar wheelchair that was difficult-to-manoeuvre, they used only visual strategies and showed a different response pattern (i.e. their errors did not change with the increase in distance). This evidence seems not to be confirmed in FM by the present study, as the position does not impact the results. It is noteworthy that while in spinal cord injured people changing the wheelchair on which they sit could impact on their possibility to move, in FM movement remains possible in both the positions.

Chronic, highly-frequent pain and navigation space

While the effects of temporary pain in undiagnosed participants support the Embodied Perception Theory, suggesting that a feeling of pain can turn into a cost for the body in terms of energy, conditions of highly-frequent, chronic and widespread pain do not seem to have similar effects. Indeed, the FM group did not overestimate distances like the control group, as the inclination of the ramp (with the steeper gradient implying a greater effort and cost to the body) did not affect their performance. This is an apparently counterintuitive result: indeed, while more severe pain was expected to be associated with more overestimation errors 67 , the present study revealed that the severity of pain in the FM group did not impact on their performance.

One possible explanation for this peculiar result is related to the adaptation processes that come into play when the pain continues over time, with the consequence that several strategies are activated in order to deal with cognitive tasks²¹ and, among these, the estimation of distances that move from a motor toward a visual strategy. Following the Embodied Perception Theory, estimating distances requires motor simulation⁶², and, similarly to actual movement, imagining movement of painful body parts increases pain and swelling in patients with complex regional pain syndrome^{[20](#page-12-11)}. Thus, it might be that adaptive processes take over and are effective when patients are engaged in a particular action that might potentially worsen the pain level, even though they may stay still. In this sense, the use of visual strategies could be seen as a failure of motor simulation, which is affected by pain. It is well known that pain is a multidimensional experience that impacts the physiological and psychological states of individuals. Contrary to common belief, pain also involves cognitive processing and is not simply a sensory phenomenon, and as a result, it affects each individual differently⁶⁸. Previous studies have shown that chronic pain affects several aspects of cognition, such as attention⁶⁹, memory⁷⁰, and decision making 71 .

Moreover, pain also affects action representation and perception, and this supports the embodied cognition approach. Using the Hand laterality task⁷², Coslett and colleagues^{[8](#page-12-0)} recorded slower reaction times in people suffering from chronic pain as compared to the controls, but only when the hands were rotated 180°. The authors concluded that a mental representation of hand rotation is more difficult for participants with chronic pain, reflecting the fact that it would, in effect, take longer for them to actually perform a rotation. Similar results were found in paraplegics, showing that the differences in response times between 180° and 0° rotated images are reduced for images of feet (but not hands) as a consequence of deafferentation/deafferentation, even if the performance may ameliorate with motor rehabilitation⁷³.

A dissociation between the visual perception of an action and the extraction of relative somatosensory information has been demonstrated in patients with chronic pain who accurately recognise the patterns of point-lights resembling biological motion but show significant impairment when asked to estimate the weight of invisible objects based on the point-light patterns they see. Crucially, this dissociation is only found when the movements shown involve painful body parts[74.](#page-13-14) The differences with respect to the results from the task used in the present study are probably due to the localisation of symptoms that are specific to certain body parts as in these previous studies but are widespread in FM patients. Indeed, localised pain allows a precise somatotopic representation that can modulate the body representation in a specific location and specific functions, impairing but also preserving or even enhancing body representation in specific conditions¹⁵. On the other hand, widespread pain has not a well localised body location and, therefore, might not be limited to specific body functions.

According to the Embodied Perception Theory, the representation of space and of action are intimately connected^{[57](#page-12-46)} and it is reasonable to assume that chronic pain impacts the representation of the navigation space within which individuals imagine themselves moving. However, to date, it remains unclear whether chronic pain is associated with the metabolic cost of the action represented. Our results do not support this notion (but rather suggest a change from motor to visual strategy to carry out the task) and previous studies have also been unable to offer conclusive evidence^{[11](#page-12-3)}. Witt and colleagues¹³ used a distance perception task to compare a group of participants affected by chronic pain in their lower back and legs and a control group. Although the participant sample was small (8 participants suffering from pain and 7 healthy controls), the results indicate a general overestimation of distances in the group of patients suffering from chronic pain, but this did not apply to the controls. In contrast, a study with a larger sample (36 chronic pain sufferers with different diagnoses and 36 controls⁷⁵) did not find any difference between the participants suffering from pain and the controls¹¹. These inconsistent results might reflect not only the differences in the sample size, but also the heterogeneity of the nature and location of the pain (i.e. there were various locations and aetiologies in the study carried out by Tabor and colleagues⁷⁵ and both lower back and leg pain in the Witt and colleagues' study¹³). Our results extend previous evidence and also indicate a dissociation between temporary and widespread, highly-frequent and chronic pain. Indeed, while the HC group was sensitive to the steeper ramps (with increasing overestimations), the FM group consistently increased their overestimation errors for farther distances, without being influenced by the inclination of the ramp. This behaviour is more consistent with a visual strategy rather than with motor simulation. According to the Economy of action hypothesis, it is possible to conclude that in the presence of temporary pain, people continue to estimate distances in an embodied way (with an internal simulation of a metabolic cost in the presence of inclined ramps), while chronic pain affects Embodied Perception, affecting internal motor simulation.

Motor imagery differences

Motor Imagery scores suggest worse imagery abilities in FM than HC participants both in the Kinesthetic Motor Imagery and in the External Visual Motor Imagery. These could indicate a general difficulty in the representation of actions, rather than a difficulty in representing the internal sensations associated with self-movement; alternatively, this could reflect a more general difficulty in cognitive performance^{[76](#page-13-16)}. Given that the scores on these two sub-scales do not affect the performance on the study task (see SM4), which requires some degree of motor simulation, the hypothesis of a general cognitive difficulty in mental imagery may be supported.

The influence of task request

Some effects observed in experimental paradigms designed to test the Embodied Perception Theory might be influenced by the task requests. For example, Durgin and colleagues $(^{65}$, see also⁷⁷ for a review) showed that Economy of Action effects might be explained in terms of participant bias (i.e. consciously or unconsciously acting in a way they believe the researcher wants them to, rather than responding naturally). However, if the task requests influenced participants in the current study, one should expect finding differences in the most obvious manipulated variable, which is the body position (i.e. Standing/Sitting), which indeed does not show any effects.

Limitations

The empirical results reported herein should be considered in the light of some limitations.

More control for comorbid difficulties would have been useful. While participants were tested for anxiety and depression, it is worth noting that people with FM have been reported to show difficulties in proprioception, balance^{[78](#page-13-19),79} and spatial memory⁸⁰. Unfortunately, these aspects have not been specifically assessed in the current study. In the perspective of the Embodied Perception theory, proprioceptive and balance difficulties should be associated with lower performances in the Standing condition with respect to the Sitting one. Our results may be due to the fact that the Standing position could have not be challenging enough for our sample of FM patients. Another aspect that might have affected the performance on the task is the spatial memory deficit, that might be present in FM⁸⁰. However, the task in the present study did not require remembering complex 3D spaces and multiple objects.

Moreover, the physical activity of the participants should have been controlled, as it might influence motor simulation 81 .

Finally, the participants were not directly tested for nociplastic pain with a specific tool, but the IAPS criteria⁸² and the derived Clinical decision-making tree³² were used based on the available clinical data. Unfortunately at the moment of data collection, a specific tool to assess this aspect (e.g. the Central Sensitization Inventory) was not in use in the hospitals where the study has been carried out.

Conclusions

The results of this experimental study indicate that in the HC group steeper ramps are perceived as farther, in line with the Economy of Action hypothesis. In contrast, in the FM group, ramp steepness did not affect distance estimations. Additionally, the findings suggest that transient neuropathic-visceral pain may influence distance perception. Indeed, HC participants showed that more severe transient painful sensations are linked to a perceptual scaling of distances, as predicted by the Economy of Action hypothesis. Conversely, highly-frequent and chronic pain seems to lead to relative insensitivity to conditions characterised by different metabolic costs. This might be explained by the presence of adaptive processes, or an impairment in the body-based estimation of the metabolic cost of an action. Although further studies are needed to explore the relationship between pain and Embodied perception, this study sheds new light on the potential cognitive effects of chronic and transient pain and how they might impact the perception of navigational space.

Data availability

Both the data and the script for the statistical analyses are available at: [https://osf.io/fmys5/.](https://osf.io/fmys5/)

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M.S.: conceptualization; data curation; formal analysis; investigation; methodology; writing—original draft; writing—review and editing. M.B.: investigation; writing—original draft; writing—review and editing. E.P.: investigation. G.P.: investigation. E.R.: investigation. V.S.: conceptualization; methodology; project administration; resources; supervision; writing—review and editing. V.M.: conceptualization; funding acquisition; methodology; project administration; resources; supervision; writing—original draft; writing—review and editing.

Competing interests

The authors declare no competing interests.

Additional information

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