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# Extensive Sensorimotor Training Predetermines Central Pain Changes During the Development of Prolonged Muscle Pain

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**Abstract:** Repetitive movements (RM) are a main risk factor for musculoskeletal pain, which is partly explained by the overloading of musculoskeletal structures. However, RM may also drive brain plasticity, leading to maladaptive changes in sensorimotor areas and altered pain processing. This study aimed to understand whether individuals performing extensive RM (musicians) exhibit altered brain processing to prolonged experimental muscle pain. Nineteen healthy musicians and 20 healthy nontrained controls attended 3 sessions (Day 1–Day 3–Day 8). In each session, event-related potentials (ERPs) to non-nociceptive superficial and nociceptive intraepidermal electrical stimulation, reaction times, electrical detection thresholds, and pressure pain thresholds (PPTs) were recorded. In all participants, prolonged muscle pain was induced by intramuscular injection of nerve growth factor (NGF) into the right first dorsal interosseous muscle at the end of Day 1. Pain intensity was assessed on a numerical rating scale (NRS) and was lower in musicians compared to non-musicians ( $P < .007$ ). Moreover, in musicians, the higher amount of weekly training was associated with lower NRS pain scores on Day 3 to Day 8 ( $P < .037$ ). Compared with Day 1, NGF reduced PPTs on Day 3 to Day 8 ( $P < .001$ ) and non-nociceptive P200 and P300 ERP amplitudes on Day 8 ( $P < .044$ ) in both groups. Musicians compared to controls showed secondary hyperalgesia to electrical stimulation on Day 3 to Day 8 ( $P < .004$ ) and reduced nociceptive P200 ERP amplitudes on Day 8 ( $P < .005$ ). Across participants, ERP components correlated with pain detection reaction times, sensitivity (PPTs and electrical detection thresholds), and severity (NRS), (all  $P < .043$ ). These results show that repetitive sensorimotor training leads to brain changes in the processing of prolonged pain, biasing the cortical response to nociceptive inputs.

**Perspective:** Repetitive sensorimotor training may increase the responsiveness of nociceptive inputs during the development of prolonged muscle pain. These novel data highlight the role of repetitive sensorimotor practice as a source for interindividual variability in central pain processing.

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**Key words:** *Musculoskeletal pain, repetitive movements, sensorimotor training, chronic pain, use-dependent plasticity.*

## Introduction

Cohort studies have shown that people performing repeated movements (ie, sensorimotor training) for prolonged periods are more vulnerable to developing musculoskeletal pain syndromes.<sup>24</sup> This may partly be explained by overloading of musculoskeletal structures.<sup>4</sup> However, extensive sensorimotor training also plays a major role in the reorganization of sensory and motor cortical regions.<sup>8</sup> Certainly, extensive repetitive movements contribute to the genesis of adaptive and maladaptive neural plasticity,<sup>2</sup> which may be associated with the development of pain syndromes and focal dystonia.<sup>9</sup> However, the neural mechanisms by which extensive repetitive movements may affect pain processing remain unclear.

Invertebrate models show that repetitive mechanical stimulation generates a consistent afferent volley of information that may shape nociceptive responses over time.<sup>25,44</sup> In humans, the central integration of multiple innocuous stimuli amplifies oscillatory brain signals<sup>17,46,47,54</sup> and strengthens long-range functional connectivity.<sup>30,37,45,65</sup> Similar enhancements have been identified for noxious stimulation in trained musicians compared with nontrained participants, indicating that long-term sensorimotor training and its associated multisensory integration trigger task-specific adaptive neuroplasticity but may also modify nociceptive processing.<sup>66,68</sup> In particular, a recent study exploring the event-related potentials in response to nociceptive intraepidermal electrical stimulation showed that extensive sensorimotor training may be a contributing factor to the interindividual variability of pain processing.<sup>66</sup> This study evidenced that musicians compared to non-musicians showed a larger and longer N200 component, which was associated with higher activation of regions within the sensorimotor network. Moreover, nociceptive intraepidermal stimulation in non-musicians elicited an evoked cortical activity around 200 milliseconds (P200), which is normally concealed in response to the nociceptive stimulus.<sup>66</sup> Whether repetitive sensorimotor training also leads to neurophysiological changes during the development of prolonged pain is currently unknown.

Musicians represent a unique population as they perform an enormous amount of repetitive movements during music production (> 1,000 movements per minute in experts), which makes them ideal for studying skill training, motor learning, and the mechanisms of adaptive and maladaptive brain plasticity.<sup>2,23,27</sup> Moreover, musicians have an above-average prevalence (approx. 80%) of pain syndromes.<sup>32,34</sup> Thus, investigation of this unique population may unlock critical insights into conditions and triggers for maladaptive neuroplasticity and altered pain processing.<sup>66–68</sup>

In contrast to the phasic stimulations used to assess nociceptive and non-nociceptive sensitivity, no studies

explored the effects of prolonged experimental pain in musicians. Intramuscular injections of nerve growth factor (NGF) is a robust model for progressive experimental muscle pain, which leads to localized mechanical hyperalgesia, expanded pain distribution, and central modifications that can last up to 14 days in asymptomatic participants.<sup>3,11,52</sup>

By modelling the neural and behavioral responses to experimental pain as a function of extensive sensorimotor training (ie, musical practice), we may obtain insights into the neural mechanisms underlying repetitive movements as a risk factor for developing chronic musculoskeletal pain. Therefore, this study aimed to understand whether extensive multisensory training influences pain sensitivity and the cortical responses to noxious and non-noxious stimuli during the development of prolonged experimental pain. It was hypothesized that, after the intramuscular injection of NGF, pain-free musicians relative to non-musicians would demonstrate: 1) enhanced nociceptive and non-nociceptive evoked cortical responses in a phase of the development of prolonged experimentally-induced pain; 2) enhanced pain sensitivity (higher NGF-pain ratings, lower pain thresholds); and 3) that those musicians with a higher amount of musical practice would show higher pain sensitivity. We also aimed to determine how the cortical responses to nociceptive and non-nociceptive stimuli is linked to the individual's perception in this pain model. It was hypothesized that the amplitude of the modulated cortical responses would be associated with the individual's pain detection, pain sensitivity, and pain severity.

## Materials and Methods

### Participants

Thirty-nine healthy participants were recruited via adverts mainly at Aalborg University, Aarhus University, and The Royal Academy of Music, Aarhus/Aalborg. Nineteen of these were healthy musicians (6 females, mean age  $25.0 \pm 2.6$  years) consisting of 9 amateurs and 10 conservatory-trained instrumentalists (6 string, 6 keyboard, 2 woodwind, and 5 brass instruments). Amateur musicians included instrumentalists who started their musical training at  $13 \pm 6$  years and had an average accumulative experience of  $4,406 \pm 2,776$  hours and a mean daily practice of  $1.3 \pm 0.5$  hours. Conservatory-trained musicians included instrumentalists that started their musical training at the age of  $8 \pm 2$  years old, involving a total accumulative average of  $15,540 \pm 6,621$  hours of musical practice, and a daily practice average of  $3.9 \pm 2.1$  hours. The control group included 20 healthy non-musicians (9 females, mean age  $26.9 \pm 5.3$  years) without formal or informal music training who participated in a previous study.<sup>66</sup> Exclusion criteria

for all participants were neurological, cardiorespiratory, mental disorders, chronic pain, or pregnancy. The sample size was estimated using G\*Power<sup>16</sup> and based on previous publications using similar primary (ERPs) and secondary outcomes (pain ratings, PPTs, likert scores),<sup>11,53,66</sup> which ensure 80% power for detecting at least a medium effect size (Cohen's  $d \geq 0.6$ ) with a repeated measures ANOVA at an alpha level of 0.05. All participants received written and verbal information about the study and provided written consent. The study was performed in accordance with the Declaration of Helsinki,<sup>20</sup> and approved by the local ethics committee (Den Videnskabssetiske Komité for+67 Region Nordjylland, N-20170040).

### Psychological Measures

Anxiety was assessed using the State-Trait Anxiety Inventory (STAI)<sup>56</sup> before the experiment on Day 1 (state and trait anxiety) and during the induced muscle soreness on Day 3 and 8 (state anxiety). The STAI is a self-reported anxiety inventory that contains 2 separate 20-item multiple-choice subscales that measure trait (personal quality) and state (situational) anxiety and has good validity and reliability.

Catastrophizing was assessed using the Pain Catastrophizing Scale (PCS)<sup>58</sup> at the beginning of Day 1. The PCS is a reliable and valid instrument that assesses catastrophic thinking associated with pain in 3 subscales: rumination, magnification, and helplessness. Participants rated the extent to which they experienced these thoughts or feelings before the induction of prolonged pain.

Vigilance to pain was assessed by the Pain Vigilance and Awareness Questionnaire (PVAQ)<sup>38</sup> at the beginning of Day 1. This is a valid and reliable 6-point 16-item measure of attention to pain that assesses awareness, consciousness, and vigilance to pain. The PVAQ consists of 2 subscales: Attention to pain (eg, "I pay close attention to pain") and attention to changes in pain (eg, "I am quick to notice changes in pain intensity").

### Experimentally-Induced Prolonged Muscle Pain

Muscle pain and hyperalgesia were induced by intramuscular injections of NGF into the right first dorsal interosseous (FDI) muscle after all assessments at Day 1. Sterile solutions of recombinant human Beta-NGF were prepared by the pharmacy (Skanderborg Apotek, Denmark). The site of injection was cleaned with alcohol, and NGF solution (5 $\mu$ g/0.5 mL) was immediately injected into the muscles of the right hand.

Pain ratings in resting conditions were reported at the beginning of Day 3 and Day 8 using a Numeric Rating Scale (NRS) with 0 defined as "no pain" to 10 corresponding to "worst pain imaginable". In addition, NRS ratings for the worst, the least, and the average NGF-induced muscle pain during the entire week were reported on Day 8.

Pain distribution was assessed on Days 3 and 8 using the Navigate Pain app (Aglance Solutions ApS, Denmark) installed on a computer tablet (Samsung Galaxy note 10.1, 2014 Edition). Participants drew the area and location of the pain experienced on a high-resolution 3D body schema representing the hand and the wrist in palmar and dorsal views.<sup>6</sup> The number of pixels was extracted from the drawn areas in the body charts, including the different palmar and dorsal views, to calculate the size of pain areas.

Qualitative characteristics of NGF-induced pain were assessed using the McGill Pain Questionnaire<sup>39</sup> at the beginning of Days 3 and 8. For each subclass of words, participants were instructed to select 1 word that defined their pain. If none of the words described their pain, then no word was selected. Words chosen by at least one-third of the participants were used in data analyses.

Finally, muscle soreness was assessed daily during 14 days using a modified 7-point Likert scale. Each point of the scale represented: 0 = "a complete absence of soreness"; 1 = "a light soreness in the muscle felt only when touched/vague ache"; 2 = "a moderate soreness felt only when touched/a slight persistent ache"; 3 = "a light muscle soreness when lifting or carrying objects"; 4 = "a light muscle soreness, stiffness or weakness when moving the fingers without gripping an object"; 5 = "a moderate muscle soreness, stiffness or weakness when moving the fingers"; and 6 = "a severe muscle soreness, stiffness or weakness that limits the ability to move".<sup>11</sup>

### Pressure Pain Sensitivity

PPTs were recorded using a handheld pressure algometer (1-cm<sup>2</sup> probe, Somedic Electronics, Solna, Sweden) covered by a disposable latex sheath. Pressure was applied at a rate of 30 kPa/s perpendicular to the surface of the skin. The PPT was defined as the point at which a sensation of pressure changed to a sensation of pain. Participants were requested to push a button when the pressure sensation first became painful. Three readings at the PPT were made at 1-min intervals, at four sites: 1) right FDI muscle (injection site), 2) left FDI muscle, 3) right tibialis anterior muscle, and 4) left tibialis anterior muscle. For each site, the muscle belly was located and marked. The average PPT of the 3 measures for each site was used for statistical analysis.

### Sensitivity to Electrical Stimulation

Participants were seated in a comfortable chair and familiarized with the electrical test stimuli. To avoid excessive head and body movement, participants were instructed to fixate their gaze on a black cross (3  $\times$  3 cm) displayed 1.5 m in front of them for the entire duration of each stimulation block. The experiment consisted of 2 electrical stimulation blocks with a randomized sequence and counterbalanced across participants. Each block was comprised of 30 stimuli belonging to 1 of 2 types of electrical stimulation: 1) intraepidermal electrical (nociceptive) stimulation, which predominantly activates A $\delta$  nociceptors,<sup>41</sup> and 2) low-intensity

transcutaneous electrical (non-nociceptive) stimulation, which activates non-nociceptive A $\beta$  fibers.<sup>10</sup> To ensure that the stimulus remained selective for the respective fibers, the intensity was individually adjusted to twice the detection threshold.<sup>41</sup> Moreover, to ensure that each stimulus was perceived and to maintain vigilance across time, participants had to press a button immediately after the perception of each stimulus (reaction time). Detection thresholds were recorded for each stimulation modality at the beginning of each laboratory session.

Both nociceptive and non-nociceptive stimuli consisted of 2 rapidly succeeding constant-current square-wave pulses with a duration of 0.5 milliseconds each, an interpulse interval of 5 milliseconds, and an inter-stimulus interval that randomly varied between 8 and 10 seconds.<sup>42</sup> The electrical stimuli were controlled using custom-made software ("Mr. Kick", Aalborg University, Aalborg, Denmark), and delivered by a constant-current electrical stimulator (Digitimer DS5, Digitimer Ltd., Welwyn Garden City, UK).

Nociceptive stimuli were delivered using intraepidermal electrical stimulation.<sup>26</sup> Stimuli were delivered using a stainless steel concentric bipolar needle electrode developed by Inui et al,<sup>41</sup> consisting of a needle cathode (length: 0.1 mm,  $\varnothing$ : 0.2 mm) surrounded by a cylindrical anode ( $\varnothing$ : 1.4 mm). Gently pressing the device against the skin inserted the needle electrode into the epidermis of the dorsum of the right hand, which clearly elicited a burning/pricking sensation when stimulated. These stimuli, provided that low intensities are used, predominantly activate nociceptive A $\delta$  fibers.<sup>41</sup>

Non-nociceptive stimuli were elicited using low-intensity transcutaneous electrical stimulation. Stimuli were delivered through a pair of digital ring electrodes (Digitimer Ltd., Welwyn Garden City, UK) and applied to the first 2 phalanges of the right index finger (1-cm inter-electrode distance). These stimuli, provided that low intensities are used, predominantly activate non-nociceptive A $\beta$  fibers.<sup>10</sup>

Detection thresholds for nociceptive and non-nociceptive stimuli were estimated using a staircase procedure. The initial stimulus intensity was 30  $\mu$ A for the nociceptive and 100  $\mu$ A for the non-nociceptive stimulation, and the initial step sizes were 50  $\mu$ A and 500  $\mu$ A, respectively. After the first staircase reversal, step size was reduced to 10  $\mu$ A and 100  $\mu$ A, respectively. The procedure was interrupted after 3 staircase reversals at final step size. The detection thresholds were estimated by averaging the intensity of the stimuli at which these 3 reversals occurred.

## Electrophysiological Measures

Electroencephalographic (EEG) activity was recorded using an active electrode cap (g.SCARABEO, g.tec, Medical Engineering GmbH, Austria). The electrode montage included 64 electrodes consisting of the modified 10-20 system with a left earlobe (A1) reference. The ground electrode was placed at position AFz. The impedance of all electrodes was kept below 20 k $\Omega$  and assessed by the EEG system software (g.Recorder, g.tec, Medical Engineering

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GmbH, Austria). During recordings, the EEG signals were amplified and digitized using a sampling rate of 1200 Hz (g.Hlamp, g.tec, Medical Engineering GmbH, Austria).

Event-related potentials (ERPs) were analyzed offline using EEGLAB v.14.1.1<sup>12</sup> running under MATLAB (The Math-Works, Natick, USA). Data were first band-pass filtered (0.5–40 Hz), followed by an Infomax independent component analysis using the in-built EEGLAB function *runica* to identify and remove components associated with noise (eg, eye movement, eye blinks, cardiac, and muscle artefacts).<sup>28</sup> Continuous data were segmented into 1.5 seconds epochs, stimulus-locked from -500 to 1,000 milliseconds with time 0 corresponding to the stimulus onset. Baseline correction was made using the -500 to -10 milliseconds window. For each subject and stimulus type, baseline-corrected epochs were further averaged to extract the ERPs of interest.<sup>33,41</sup>

Nociceptive and non-nociceptive ERP components were defined and extracted on the basis of previous research.<sup>10,29,48,55,63</sup> For the ERPs in response to nociceptive stimulation, N100, N200, and P300 components were identified. The N100 component was defined as the first major negative deflection occurring within the 60 milliseconds time window preceding the N200 component, and measured with the recommended temporal–frontal montage (T7-Fz). The N200 and P300 components were identified with the recommended central-earlobe montage (Cz-A1): The N200 was defined as the first major negative deflection after stimulus onset, while P300 was defined as the first major positive deflection occurring after stimulus onset. For the nociceptive stimulation, moreover, an exploratory analysis was performed in a positive peak at the latency of 200 milliseconds (labelled P200) that is normally concealed in response to the nociceptive stimulus. The P200 was defined as the first major positive deflection occurring between N200 and P300.<sup>40</sup>

For the ERPs in response to non-nociceptive stimulation, the N140, P200, and P300 were determined using the midline Cz-A1 montage: the N140 was defined as the first major negative deflection after stimulus onset, the P200 was defined as the first major positive deflection occurring between N140 and P300, while P300 was defined as the first major positive deflection occurring after stimulus onset.

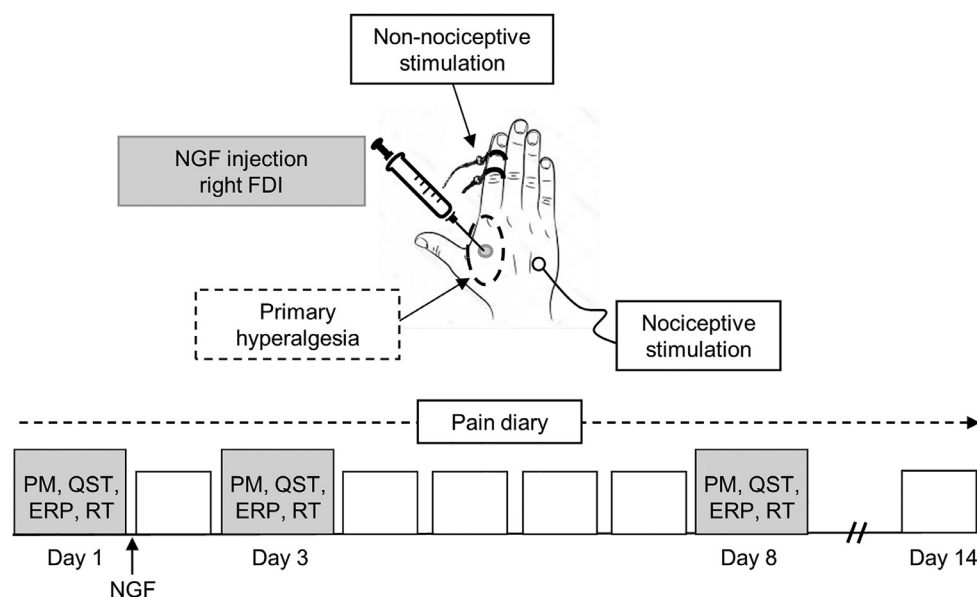
## Reaction Times

To explore the time until detection of the nociceptive and non-nociceptive stimuli used for ERP recordings, reaction times (RTs) were collected by instructing the participants to push a button held in the left hand as soon as they perceived the stimulus. The mean reaction time across the 30 stimulations in response to each kind of electrical stimulation was recorded relative to stimulus onset. RTs greater than 1000 milliseconds were considered as undetected.

## Experimental Procedure

The experiment involved 3 sessions (Day 1, Day 3, and Day 8; Fig 1) over the course of 8 days, and daily diaries





**Figure 1.** Experimental procedure. The experiment involved 3 laboratory sessions (Day 1, Day 3, and Day 8) plus daily diaries about muscle soreness completed up to day 14. Psychological measures (PM) and corresponding self-reported pain measures in response to the nerve growth factor (NGF) injection, nociceptive and non-nociceptive event related potentials (ERPs) in response to intraepidermal and superficial electrical stimulation, respectively, quantitative sensory assessments (QST, electrical detection thresholds and pressure pain thresholds), and reaction times (RTs) were collected at each lab session. At the end of Day 1, NGF was injected into the right first dorsal interosseous (FDI) muscle to induce prolonged muscle pain.

about muscle soreness completed up to day 14. Participants were seated in a comfortable chair for the laboratory sessions. At the beginning of Day 1, participants reported their demographic characteristics and psychological measures (both state and trait anxiety, STAI; PCS, and PVAQ). Current pain ratings measured with an NRS were also collected on Day 1 to confirm that they did not suffer any form of acute pain at the beginning of the experiment. At the end of Day 1, all participants received an injection of NGF into the right FDI muscle to induce prolonged muscle pain for several days. At the beginning of Day 3 and Day 8, participants reported again their state anxiety (STAI) and current pain ratings (NRS), as well as the extent and distribution of the NGF-induced pain, and the qualitative characteristics (McGill Questionnaire). Moreover, on Day 8, participants reported pain ratings for the worst, least, and average NGF-induced pain during the last 7 days. All neurophysiological testing (nociceptive and non-nociceptive ERPs), pain sensitivity assessments (electric detection thresholds and pressure pain thresholds), and reaction times were registered on Day 1 (before the NGF injection), Day 3, and Day 8.

## Statistical Analysis

Data are presented as means and standard deviation in text and figures. Psychological, behavioral, and electrophysiological responses were statistically analyzed with SPSS for Windows (IBM SPSS Statistics 26; IBM, Armonk, NY) and screened for assumptions of normality, sphericity, homogeneity, and independent errors using descriptive plots and statistical tests. Demographic and psychometric data (PCS, T-STAI, and PVAQ), as well as worst, least, and average NRS pain ratings

were compared between groups (musicians vs non-musicians) using independent t-test. NGF-induced NRS pain ratings, state anxiety (S-STAI), behavioral data (RTs, detection thresholds) and electrophysiological data (latencies and amplitudes of ERP components) were compared across *Time* (Day 1, Day 3, and Day 8, except for NGF-induced pain NRS ratings that considered only Day 3 and Day 8; repeated measures) and *Groups* (musicians vs non-musicians; between group factor) using two-way repeated-measures analyses of variance (ANOVA). PPTs were analyzed using a three-way ANOVA to assess the within-subjects effects of *Time* (Day 1, Day 3, and Day 8), *Side* (lateral or contralateral), and the between-subjects effect of *Group* (musicians vs non-musicians). Finally, 7-point Likert Scale scores were also analyzed using an ANOVA over *Time* (Day 1–Day 14) as a repeated measure factor and *Group* (musicians vs non-musicians) as a between group factor. Significant main factors or interactions were analyzed post hoc using Bonferroni's procedure to correct for multiple comparisons.

Correlations were computed to investigate whether the electrophysiological responses to nociceptive stimulation could be associated with their respective stimulus detection thresholds, RTs, PPTs, and pain ratings across all participants. Based on previous studies indicating possible relationships between the main components of the ERPs and the characteristics related to pain perception, specifically detection and severity,<sup>36,60,66</sup> the following associations were assessed: 1) the amplitude of the non-nociceptive N140 and nociceptive N200 responses and their respective reaction times (ie, detection), 2) the amplitude of the nociceptive and non-nociceptive P200 responses and the nociceptive electrical detection thresholds and PPTs (ie, experimental

prolonged pain symptoms), and 3) the magnitude of the nociceptive and non-nociceptive P300 responses with the subjective severity reported with NRS scores for the individual days (ie, cognitive evaluation of pain). In musicians, it was furthermore tested if the accumulated sensorimotor training affected 1) the amplitude of the nociceptive ERPs components that were modulated by the NGF, and 2) their individual pain sensitivity (NRS scores, nociceptive detection thresholds, PPTs). Bootstrapping was used to estimate the correlations.<sup>51</sup> This is a nonparametric robust approach to hypothesis testing that does not make assumptions about the distribution of variables.<sup>14</sup> We used bias corrected and accelerated (BCa) 95% confidence intervals (CI) to test for significance, as they adjust for possible bias and skewness in the bootstrap distribution. If zero was not within the 95% confidence interval, it was concluded that the indirect effect was significantly different from zero at  $P < .05$ , two tailed.<sup>49</sup> For all tests used, the level for statistically significant difference was set at  $P < .05$ .

## Results

### Experimentally-Induced Prolonged Muscle Pain

The distribution of NGF-induced muscle pain was similar in both groups of participants ( $P = .61$ ). Pain was local to the injection site in the majority of participants on Days 3 and 8, affecting the dorsal and palmar regions of the hand (Fig 2A). Compared to Day 3, the pain area was reduced in all participants at Day 8 (Time effect;  $F_{1, 37} = 43.8$ ;  $P < .001$ ;  $\eta^2 = 0.54$ ).

The analysis of the NRS pain scores (Fig 2B) demonstrated a Time effect ( $F_{1, 37} = 13.2$ ;  $P = .001$ ;  $\eta^2 = 0.26$ ) with higher scores on Day 3 compared to Day 8. NGF-induced pain intensity scores, however, were significantly lower in musicians compared to non-musicians (Group effect;  $F_{1, 37} = 8.12$ ;  $P = .007$ ;  $\eta^2 = 0.18$ ). Finally, the interaction Time  $\times$  Group approached statistical significance ( $F_{1, 37} = 3.92$ ;  $P = .055$ ;  $\eta^2 = 0.09$ ).

The NRS pain scores assessing the worst (musicians:  $4.2 \pm 2.1$ ; non-musicians:  $4.7 \pm 1.6$ ), least (musicians:  $1.3 \pm 1.0$ ; non-musicians:  $1.7 \pm 1.8$ ), and average (musicians:  $2.7 \pm 1.5$ ; non-musicians:  $3.0 \pm 1.3$ ) NGF-induced pain intensity across all experimental days (reported on Day 8) were not significantly different (all  $P > .41$ ).

Likert scores of muscle soreness (Fig 2C) increased across days (Time effect;  $F_{4, 54, 167.88} = 83.56$ ;  $P < .001$ ;  $\eta^2 = 0.93$ ) and remained elevated during the 14 days. Compared to the second day, muscle soreness significantly increased on the third and fourth days ( $P < .001$ ), remained elevated until day 9 (all  $P > .185$ ), and started to decrease after the tenth day ( $P < .08$ ). Likert scores did not differ significantly between Groups, or for the interaction Group  $\times$  Time (all  $P > .24$ ).

On the McGill Pain Questionnaire, NGF-induced muscle pain was commonly described by musicians as annoying (74% of participants), sore (68%), pressing (53%), numb (47%), and/or tender (37%) on Day 3 and sore (68%), annoying (58%), tender (53%), and/or tiring

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(37%) on Day 8. Non-musicians described NGF-induced muscle pain as sore (70%), annoying (70%), and/or tender (40%) at Day 3 and sore (60%) and/or annoying (50%) on Day 8.

### Detection Thresholds

The ANOVA of nociceptive detection thresholds to intraepidermal electrical stimulation (Fig 3A) showed no significant Time effect ( $P = .138$ ) but a significant Group effect ( $F_{1, 36} = 9.368$ ;  $P = .004$ ;  $\eta^2 = 0.20$ ) and a significant interaction Time  $\times$  Group ( $F_{1, 57, 56.59} = 3.612$ ;  $P = .044$ ;  $\eta^2 = 0.09$ ). Musicians showed reduced nociceptive detection thresholds on Day 8 compared to Day 1 ( $P = .003$ ), and compared to non-musicians on Day 3 ( $P = .004$ ) and on Day 8 ( $P < .001$ ).

Non-nociceptive detection thresholds (Fig 3B) to superficial electrical stimulation over the last 2 distal phalanges of the right index finger were not significantly altered over Time or between Groups, and without significant Time  $\times$  Group interaction (all  $F < 2.9$  and  $P > .09$ ).

### Pressure Pain Thresholds

The 3-way ANOVA of the PPTs measured over the right and left FDI muscles (Fig 3C) demonstrated significant main effects of Time ( $F_{1, 71, 63.32} = 95.24$ ;  $P < .001$ ;  $\eta^2 = 0.72$ ), and Side ( $F_{1, 37} = 239.9$ ;  $P < .001$ ;  $\eta^2 = 0.86$ ) and a significant interaction Time  $\times$  Side ( $F_{2, 74} = 106.5$ ;  $P < .001$ ;  $\eta^2 = 0.74$ ). Post hoc analyses indicated that both right and left PPTs were significantly reduced on Day 3 ( $P < .001$ ) and Day 8 ( $P < .001$ ) compared with Day 1. PPTs were also more reduced in the right side (injection site) when compared to the left side on Day 3 ( $P < .001$ ) and Day 8 ( $P < .001$ ). There was a trend for PPTs to remain more reduced in musicians than in non-musicians (main effect of Group: ( $F_{1, 37} = 3.18$ ;  $P = .082$ ;  $\eta^2 = 0.08$ ). Finally, no significant interactions of Time  $\times$  Group nor Time  $\times$  Side  $\times$  Group were found (all  $P > .56$ ).

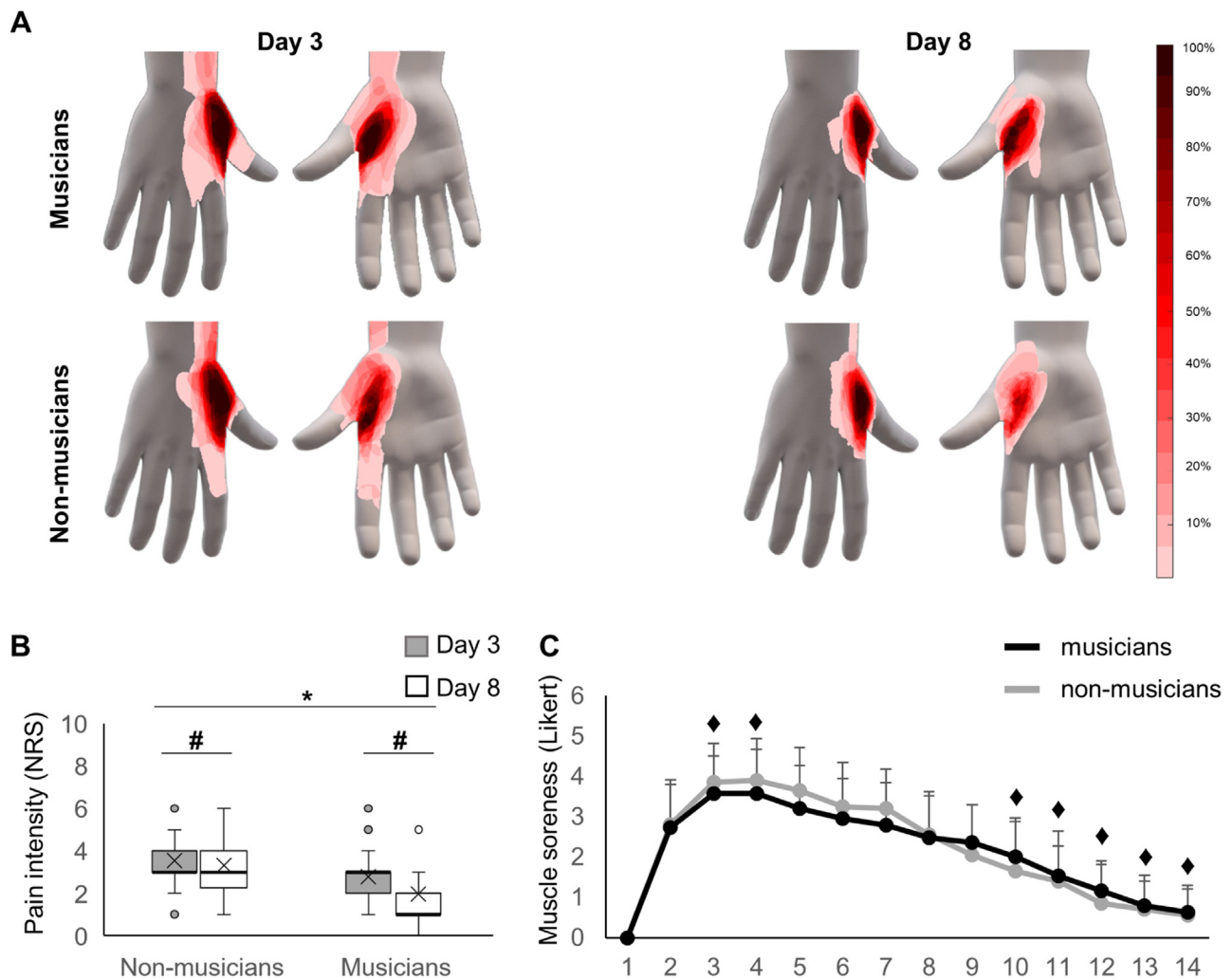
Bilateral PPTs over tibialis anterior muscles (Fig 3D) were similar across Time, Sides, and between Groups. No significant interaction of Time  $\times$  Side, Side  $\times$  Group, Time  $\times$  Group or Time  $\times$  Side  $\times$  Group were found (all  $P > .13$ ).

### Event-Related Potentials in Response to Nociceptive Stimulation

Nociceptive N100, N200, P200, and P300 ERP components elicited by intraepidermal electrical stimulation (Fig 4A and 4B, Table 1) were identified by visual inspection in all participants except for 2 non-musicians: 1 participant did not feel the nociceptive stimulation and, in another participant, the EEG recording of Day 2 failed. Those 2 participants were excluded from the analysis of nociceptive ERPs.

The N200 – P300 complex elicited a clear vertex potential constituted by a negative–positive biphasic wave in all participants with a scalp dominance at the central midline electrode. Visual inspection also





**Figure 2.** Effects of nerve growth factor (NGF) in pain distribution, pain intensity, and muscle soreness in musicians (black) and non-musicians (gray). (A) Distribution of NGF-induced pain at Day 3 and Day 8 in musicians and non-musicians. (B) Mean, median, and interquartile range of pain intensity (numerical rating scale, NRS) scores. (C) Mean (+ SD) of likert muscle soreness scores. #: Significantly different from Day 3. \*: Significantly different between groups. ♦: Significantly different from Day 2.

indicated a prominent positive component at 200 milliseconds. This nociceptive P200 component appeared immediately after N200 and before P300, and more notable and clearer in non-musicians than in musicians.

### N100 Amplitude and Latency

The ANOVA of the N100 peak amplitudes and latencies showed no significant effects of *Group*, *Time*, or the *Group x Time* interaction (all  $F < 0.93$  and  $P > .32$ ).

### N200 Amplitude and Latency

The N200 peak amplitudes and latencies analyses showed no significant effects of *Group*, *Time*, nor *Group x Time* interaction (all  $F < 1.22$  and  $P > .27$ ).

### P200 Amplitude

The P200 amplitudes analysis showed a main effect of *Group* ( $F_{1, 35} = 6.185$ ;  $P = .018$ ;  $\eta^2 = 0.15$ ) and a *Group x Time* interaction ( $F_{2, 70} = 3.345$ ;  $P = .041$ ;  $\eta^2 = 0.09$ ), but no main *Time* effect ( $F_{2, 70} = 2.425$ ;  $P = .096$ ;  $\eta^2 = 0.06$ ). Post hoc analysis indicated that musicians compared to

non-musicians showed lower P200 amplitudes at Day 8 ( $P = .005$ ), as well as reduced amplitudes at Day 8 compared to Day 1 ( $P = .042$ ).

### P200 Latency

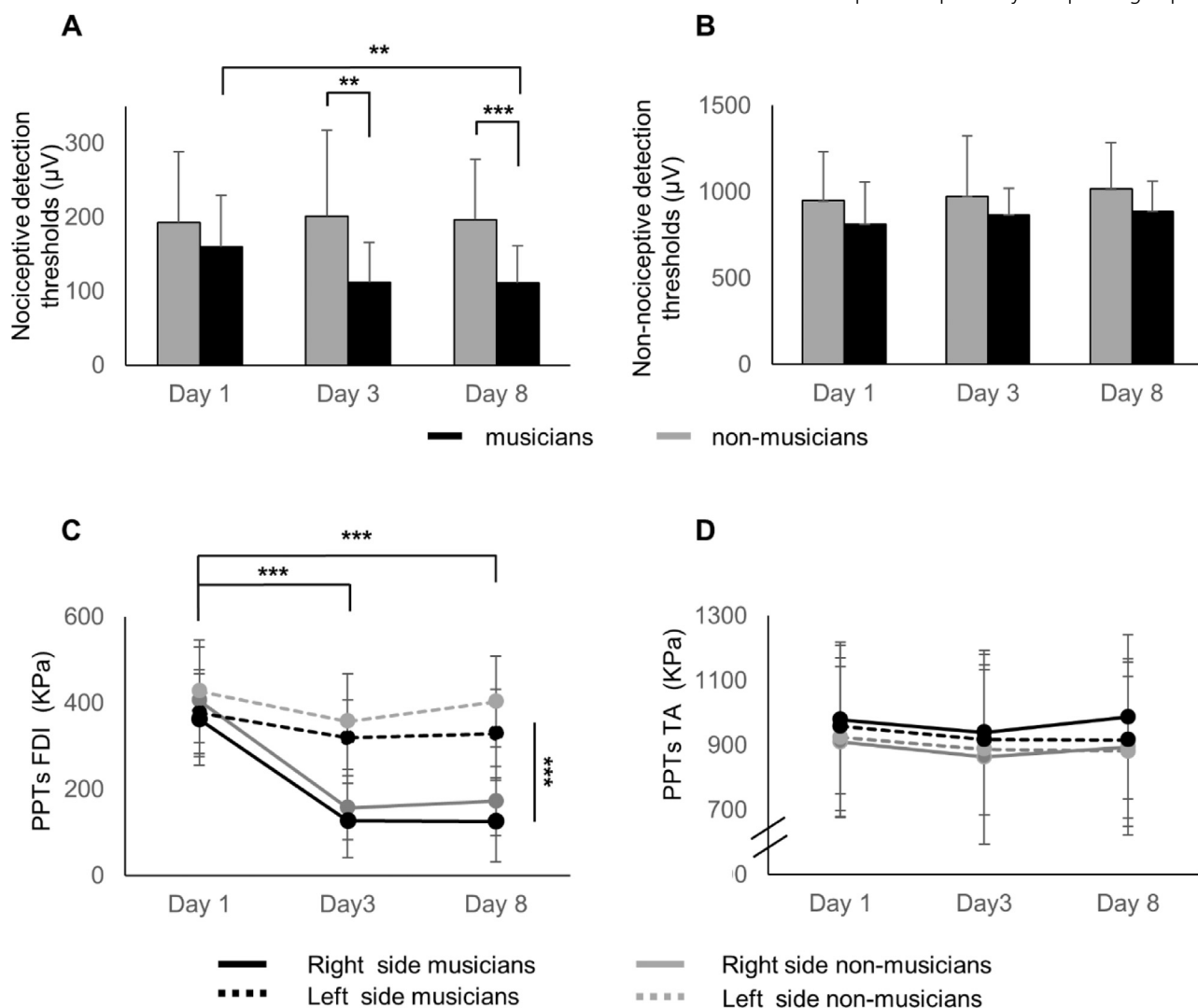
The P200 peak latency extracted at Cz showed no significant effects of *Group*, *Time*, nor *Group x Time* interaction (all  $F < 1.70$  and  $P > .19$ ).

### P300 Amplitude and Latency

The P300 peak amplitudes and latencies showed no significant main effect of *Group*, *Time*, nor *Group x Time* interaction (all  $F < 1.80$  and  $P > .17$ ).

### Event-Related Potentials in Response to Non-Nociceptive Stimulation

Non-nociceptive N140, P200, and P300 ERP components elicited by superficial electrical stimulation (Fig 5A and 5B, Table 1) were clearly identified in all participants except for 1 non-musician, where the EEG recording of



**Figure 3.** Effects of NGF in pressure pain thresholds (PPTs) and nociceptive and non-nociceptive detection thresholds in musicians and non-musicians. (A) Mean ( $\pm$  SD) of detection thresholds following nociceptive stimuli elicited by intraepidermal electrical stimulation over the right hand. Musicians showed reduced nociceptive detection thresholds at Day 8 compared to Day 1, as well as compared to non-musicians at Day 3 and at Day 8. (B) Mean ( $\pm$  SD) of detection thresholds following non-nociceptive stimuli elicited by superficial electrical stimulation over the right hand. (C) Mean ( $\pm$  SD) of PPTs over the right and left first dorsal interosseous (FDI) muscle. Compared to Day 1, both right and left PPTs were reduced at Day 3 and Day 8, as well as PPTs were more reduced in the right side (injection site) when compared to the left side. (D) Mean ( $\pm$  SD) of PPTs over the right and tibialis anterior (TA) muscle. (\*,  $P < .05$ ; \*\*,  $P < .005$ ; \*\*\*,  $P < .001$ ).

Day 1 failed. The N140 component exhibited a clear negative wave with a maximum scalp-dominance at left (contralateral) central and midline Cz electrodes. The P200 component exhibited a clear positive wave immediately after the N140 with a maximum scalp-dominance at midline Cz and CPz electrodes. The P300 component exhibited a prominent positive wave with a maximum scalp-dominance at central midline PCz and Pz electrodes.

### N140 Amplitude and Latency

The ANOVA of the N140 amplitudes and latencies showed no significant effects of *Group*, *Time* nor *Group x Time* interaction (all  $F < 1.30$  and  $P > .28$ ).

### P200 Amplitude

A main effect of *Time* ( $F_{2, 72} = 4.336$ ;  $P = .017$ ;  $\eta^2 = 0.17$ ) was found, indicating that P200 amplitudes

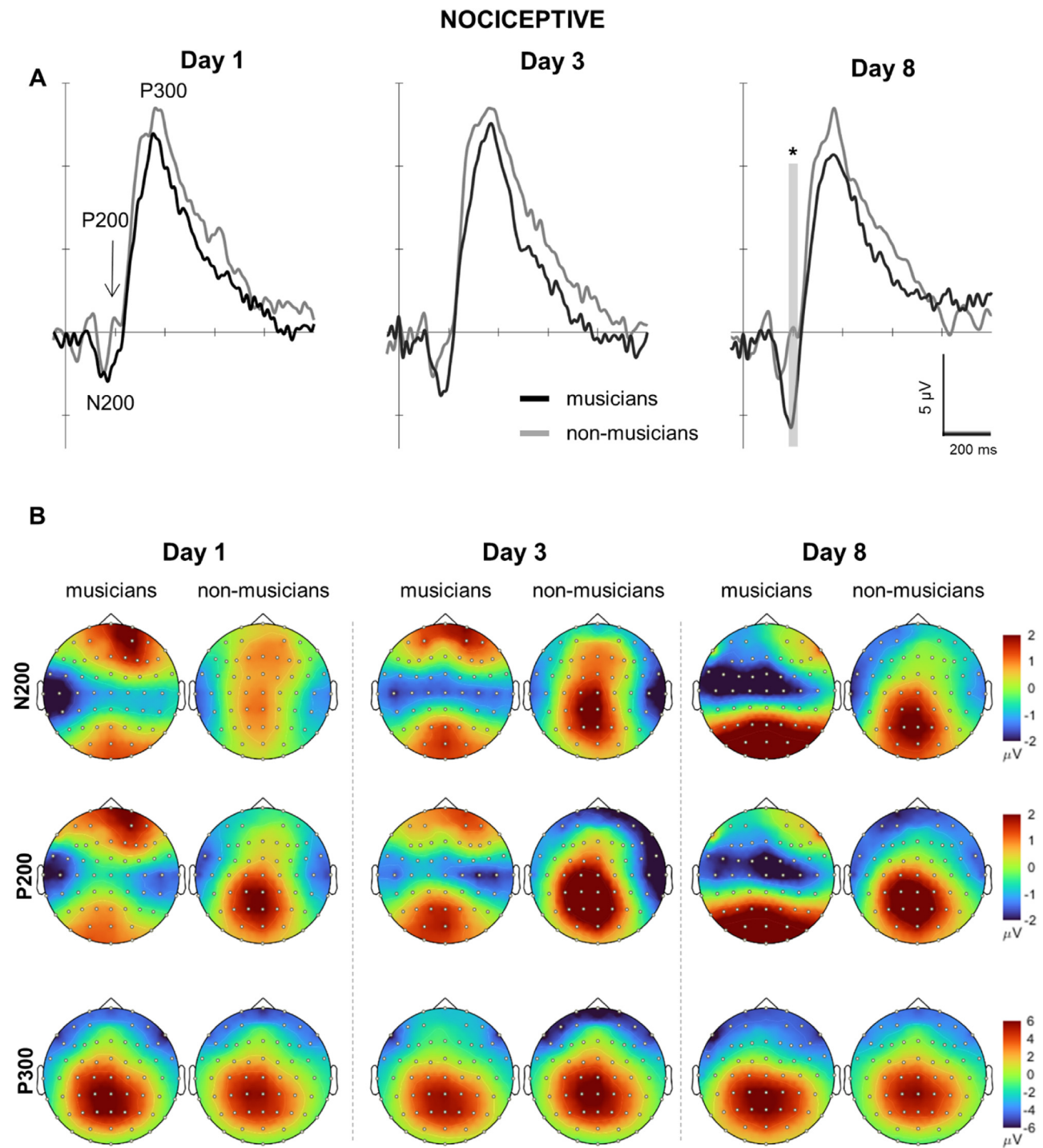
were reduced at Day 8 compared to Day 1 ( $P = .044$ ). No significant effects of *Group* or *Group x Time* interaction were found for non-nociceptive P200 (all  $P > .05$ ).

### P200 Latency

Extracted at Cz this latency did not show significant effects of *Group*, *Time*, nor *Group x Time* interaction (all  $F < 1.64$  and  $P > .20$ ).

### P300 Amplitude

The ANOVA of P300 amplitudes demonstrated a main effect of *Time* ( $F_{2, 72} = 7.562$ ;  $P = .001$ ;  $\eta^2 = 0.17$ ). Post hoc analyses showed that P300 amplitudes were reduced at Day 8 compared to Day 1 ( $P = .002$ ) and Day 3 ( $P = .010$ ). No significant effects of *Group* or *Group x Time* interaction were found for P300 (all  $F < 1.73$  and  $P > .18$ ).



**Figure 4.** Brain responses and scalp topographies to nociceptive stimuli. A) Grand-averaged event related potentials elicited by nociceptive intraepidermal electrical stimulation at the hand and illustrated at Cz in musicians (dark lines) and non-musicians (gray lines) at Day 1, Day 3, and Day 8 following induction of prolonged pain in the right hand muscle. Peak amplitudes indicate the appearance of a prominent P200 component, as well as the N200 and P300 component. Compared to non-musicians and Day 1, musicians showed lower P200 amplitudes at Day 8 when assessing maximum peak values (\*,  $P < .05$ ). Negative is plotted downward. B) Amplitude scalp topography of each nociceptive component in musicians and non-musicians across days. Scalp topographies shown are generated at 175 ms (N200), 200 ms (P200), and 350 ms (P300).

### P300 Latency

The P300 latency extracted at Cz showed a significant *Group*  $\times$  *Time* interaction ( $F_{2, 72} = 4.137$ ;  $P = .020$ ;  $\eta^2 = 0.10$ ). However, pairwise comparison comparing

Day 8 versus Day 1 in musicians did not achieve significance ( $P = .064$ ). No main effects of *Time* or *Group* were found for P300 latencies (all  $F < 0.92$  and  $P > .34$ ).

**Table 1. Mean ( $\pm$  SD) Reaction Times and Peak Latencies and Amplitudes of Each Event Related Potential (ERP) Component Elicited by Nociceptive (ie, Intra-Epidermal) and Non-nociceptive (ie, Superficial) Electrical Stimulation (Right Hand) Before (Day 1) and After (Day 3 and 8) NGF-Induced Pain in the Right FDI Muscle.**

	MUSICIANS ( <i>N</i> = 19)			NON-MUSICIANS ( <i>N</i> = 20)		
	DAY 1	DAY 3	DAY 8	DAY 1	DAY 3	DAY 8
<b>Reaction times (ms)</b>						
Nociceptive	369 $\pm$ 85 <sup>‡</sup>	340 $\pm$ 65 <sup>‡</sup>	333 $\pm$ 55 <sup>‡,§</sup>	433 $\pm$ 139 <sup>‡</sup>	387 $\pm$ 109 <sup>‡</sup>	367 $\pm$ 71 <sup>‡,§</sup>
Non-nociceptive	269 $\pm$ 42	265 $\pm$ 45	265 $\pm$ 53	315 $\pm$ 89	293 $\pm$ 92	309 $\pm$ 101
<b>Amplitude ERP (<math>\mu</math>V)</b>						
<i>Nociceptive</i>						
N100	-7.0 $\pm$ 4.3	-6.0 $\pm$ 3.4	-6.7 $\pm$ 4.0	-6.3 $\pm$ 3.1	-6.2 $\pm$ 2.4	-6.3 $\pm$ 4.9
N200	-8.4 $\pm$ 8.4	-7.7 $\pm$ 6.8	-8.8 $\pm$ 6.5	-5.4 $\pm$ 4.9	-6.6 $\pm$ 5.6	-6.7 $\pm$ 5.4
P200	2.2 $\pm$ 6.7	-0.6 $\pm$ 7.0	-1.9 $\pm$ 7.6 <sup>‡,§</sup>	4.5 $\pm$ 3.5	3.0 $\pm$ 5.8	5.5 $\pm$ 7.1 <sup>‡</sup>
P300	15.9 $\pm$ 7.3	15.7 $\pm$ 8.3	14.3 $\pm$ 10.6	16.0 $\pm$ 6.5	17.3 $\pm$ 8.3	15.8 $\pm$ 6.8
<i>Non-nociceptive</i>						
N140	-10.8 $\pm$ 10.6	-11.9 $\pm$ 11.5	-11.0 $\pm$ 10.6	-7.2 $\pm$ 7.1	-8.6 $\pm$ 8.7	-9.7 $\pm$ 10.1
P200	9.2 $\pm$ 10.3	7.0 $\pm$ 9.7	5.1 $\pm$ 8.8 <sup>‡</sup>	9.7 $\pm$ 7.5	9.8 $\pm$ 8.3	7.9 $\pm$ 6.1 <sup>‡</sup>
P300	21.2 $\pm$ 10.1	18.0 $\pm$ 9.9	15.9 $\pm$ 7.4 <sup>‡,§</sup>	20.3 $\pm$ 7.6	20.6 $\pm$ 9.8	17.8 $\pm$ 9.2 <sup>‡,§</sup>
<b>Latency ERP (ms)</b>						
<i>Nociceptive</i>						
N100	135 $\pm$ 37	130 $\pm$ 27	126 $\pm$ 41	132 $\pm$ 35	129 $\pm$ 30	121 $\pm$ 23
N200	172 $\pm$ 42	180 $\pm$ 33	180 $\pm$ 31	175 $\pm$ 36	168 $\pm$ 35	169 $\pm$ 33
P200	231 $\pm$ 33	216 $\pm$ 24	220 $\pm$ 33	228 $\pm$ 35	223 $\pm$ 33	221 $\pm$ 36
P300	349 $\pm$ 59	356 $\pm$ 57	357 $\pm$ 59	347 $\pm$ 44	338 $\pm$ 57	367 $\pm$ 51
<i>Non-nociceptive</i>						
N140	140 $\pm$ 14	148 $\pm$ 20	146 $\pm$ 18	141 $\pm$ 13	145 $\pm$ 23	145 $\pm$ 23
P200	199 $\pm$ 13	198 $\pm$ 18	200 $\pm$ 19	192 $\pm$ 11	203 $\pm$ 22	200 $\pm$ 19
P300	314 $\pm$ 38	310 $\pm$ 42	297 $\pm$ 32	294 $\pm$ 42	294 $\pm$ 36	301 $\pm$ 37

<sup>‡</sup>Significantly different from Day 1.

<sup>§</sup>Significantly different from Day 3.

<sup>‡§</sup>Significantly different between groups within the day.

## Correlations

### Nociceptive N200 and Non-Nociceptive N140 Amplitudes Correlate With Reaction Times

Across all participants, nociceptive reaction times across days correlated with their respective nociceptive N200 peak amplitudes (Day 1:  $r = 0.46$ ,  $P = .004$ ,  $BCa\ CI = 0.26$  to  $0.66$ ; Day 3:  $r = 0.34$ ,  $P = .041$ ,  $BCa\ CI = 0.07$  to  $0.56$ ; Day 8:  $r = 0.39$ ,  $P = .017$ ,  $BCa\ CI = 0.06$ – $0.68$ ). Likewise, non-nociceptive reaction times were correlated with their respective non-nociceptive N140 peak amplitudes (Day 1:  $r = 0.46$ ,  $P = .004$ ,  $BCa\ CI = 0.25$ – $0.63$ ; Day 3:  $r = 0.45$ ,  $P = 0.005$ ,  $BCa\ CI = 0.21$ – $0.65$ ; Day 8:  $r = 0.45$ ,  $P = 0.005$ ,  $BCa\ CI = 0.19$ – $0.64$ ).

### Nociceptive and Non-Nociceptive P200 Components Correlate With the Individual's Pain Sensitivity

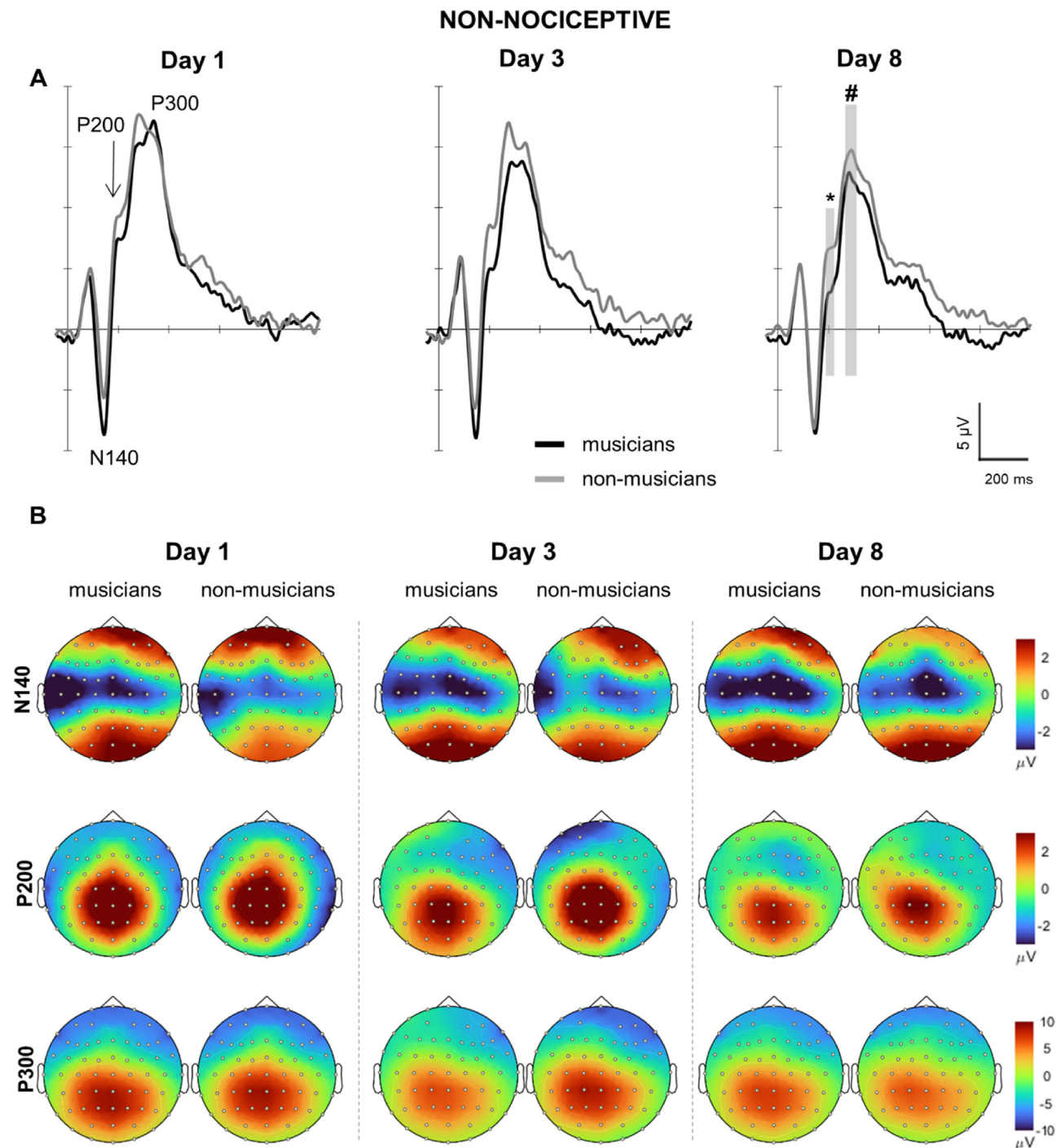
The daily nociceptive P200 peak amplitudes (Fig 6A) were correlated with their daily nociceptive electrical detection thresholds across all participants (Day 1:  $r = 0.33$ ,  $P = .043$ ,  $BCa\ CI = 0.26$ – $0.59$ ; Day 3:  $r = 0.49$ ,  $P = .002$ ,  $BCa\ CI = 0.20$ – $0.70$ ; Day 8:  $r = 0.41$ ,  $P = .011$ ,  $BCa\ CI = 0.14$ – $0.65$ ). Across all participants (Fig 6B), nociceptive

P200 amplitudes at Day 1 correlated with the PPTs measured at Day 3 (right hand:  $r = 0.40$ ,  $P = .013$ ,  $BCa\ CI = 0.13$ – $0.63$ ) and at Day 8 (right hand:  $r = 0.45$ ,  $P = .005$ ,  $BCa\ CI = 0.19$ – $0.68$ ; left hand:  $r = 0.35$ ,  $P = .035$ ,  $BCa\ CI = 0.10$ – $0.63$ ). The non-nociceptive P200 peak amplitudes were also correlated with the nociceptive electrical detection thresholds at Day 1 ( $r = 0.33$ ,  $P = .043$ ,  $BCa\ CI = 0.04$ – $0.59$ ) and Day 8 ( $r = 0.39$ ,  $P = .016$ ,  $BCa\ CI = 0.04$ – $0.69$ ). No significant correlation was found between non-nociceptive electrical detection thresholds with their respective non-nociceptive P200 ERP components (all  $P > .05$ ).

### Nociceptive and Non-Nociceptive P300 Amplitudes Correlate With the Prolonged Pain Severity

Across all participants, the worst pain NRS scores of the prolonged experimental pain model until Day 8 were correlated with the magnitude of the nociceptive P300 amplitudes (Day 1:  $r = -0.37$ ,  $P = .021$ ,  $BCa\ CI = -0.63$  to  $-0.06$ ; Day 3:  $r = -0.37$ ,  $P = .024$ ,  $BCa\ CI = -0.61$  to  $-0.10$ ; Day 8:  $r = -0.37$ ,  $P = .023$ ,  $BCa\ CI = -0.62$  to  $-0.08$ ). Likewise, across all participants intensities of worst pain NRS ratings were correlated with the magnitude of the non-nociceptive P300 amplitudes at Day 3 ( $r = -0.35$ ,  $P = .031$ ,  $BCa\ CI = -0.05$  to  $-0.17$ ).





**Figure 5.** Brain responses and scalp topographies to non-nociceptive stimuli. **A)** Grand-averaged event related potentials elicited by non-nociceptive electrical stimulation at the right index finger and illustrated at Cz in musicians (dark lines) and non-musicians (gray lines) at Day 1, Day 3, and Day 8 following induction of prolonged pain in the right hand muscle. Peak amplitudes indicate that P200 and P300 amplitudes were reduced at Day 8 and at Day 3 and 8, respectively, compared to Day 1 when assessing maximum peak values. \*: Significantly different from Day 1. #: Significantly different from Day 1 and Day 3.  $P < .05$ . Negative is plotted downward. **B)** Amplitude scalp topography of each non-nociceptive component in musicians and non-musicians across days. Scalp topographies shown are generated at 140 ms (N140), 200 ms (P200), and 300 ms (P300).

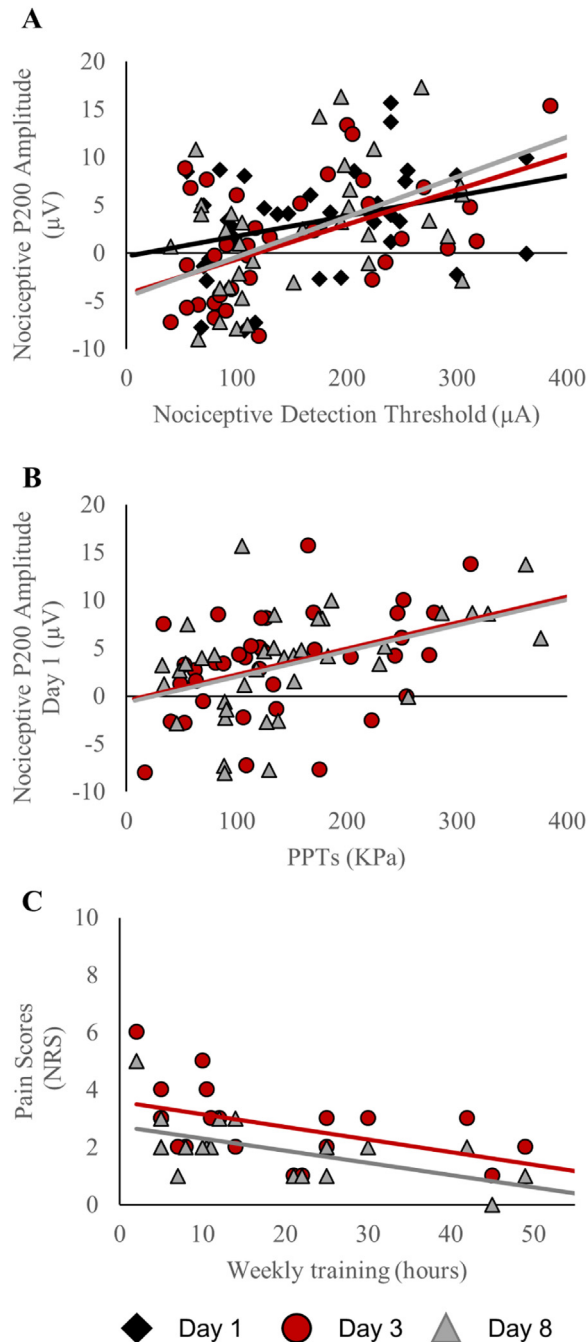
### In Musicians, the Weekly Training Time Correlate With Pain Severity

In musicians, the weekly training (Fig 6) inversely correlated with the severity of the induced pain (NRS ratings) at Day 3 ( $r = -0.48$ ,  $P = .037$ , BCa CI =  $-0.72$  to  $-0.11$ ) and Day 8 ( $r = -0.57$ ,  $p = 0.011$ , BCa CI =  $-0.78$  to  $-0.30$ ).

### Reaction Times

For nociceptive stimuli (Table 1), the ANOVA of reaction times revealed a main effect of *Time* ( $F_{1,60} = 5.883$ ;  $P = .008$ ;  $\eta^2 = 0.14$ ) and *Group* ( $F_{1,36} = 4.137$ ;  $P = .049$ ;  $\eta^2 = 0.10$ ). Post hoc analysis indicated faster reaction times at Day 8 compared to Day 1





**Figure 6.** Significant correlations of nociceptive event related potentials, pain sensitivity, and weekly practice. A) The daily nociceptive P200 peak amplitudes correlated with their respective daily nociceptive electrical detection thresholds across all participants. Day 1 correlation is represented by black rhombus, Day 3 by red dots and Day 8 by gray triangles. B) The nociceptive P200 amplitudes at Day 1 correlated with the PPTs measured at Day 3 (red dots) and Day 8 (gray triangles) across all participants. C) In musicians, the amount of hours of weekly practice correlates with the intensity of the induced pain (NRS ratings) at Day 3 (red dots) and Day 8 (gray triangles). Fit lines indicate correlations between respective variables.

( $P = .022$ ) across all participants, as well as faster RTs in musicians compared to non-musicians ( $P = .049$ ). No significant interaction *Time*  $\times$  *Group* was found ( $P = .583$ ).

Reaction times for non-nociceptive stimulations (Table 1) showed no significant effects of *Time* nor

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interaction (all  $P > .30$ ). However, there was a weak indication that musicians had faster reaction times compared to non-musicians (Group effect:  $F_{1, 37} = 3.225$ ;  $P = .081$ ;  $\eta^2 = 0.08$ ).

### Psychological Measures Between Groups

The PCS (Table 2), PVAQ, and trait STAI were not significantly different between groups (all  $P > .40$ ). Likewise, the state anxiety (S-STAI) at Day 1, Day 3, and Day 8 did not differ neither between Groups, across Time, nor yielded any significant interaction *Group*  $\times$  *Time* (all  $P > .16$ ).

### Discussion

Using a multi-modal neurophysiological approach, we here show that long-term sensorimotor training (ie, extensive repetitive movements) may facilitate central pain mechanisms, as evidenced by electrical secondary hyperalgesia and altered cortical evoked responses after experiencing prolonged pain for several days. These responses were characterized by reduced nociceptive P200 amplitudes in musicians as compared to non-trained controls. However, subjective ratings of NGF-induced muscle pain were reduced in musicians compared to untrained participants. Moreover, musicians with higher weekly training reported lower pain ratings. Interestingly, the induction of experimental muscle pain for several days reduced the non-nociceptive P200 and P300 amplitudes across all participants. Furthermore, the amplitude of each nociceptive ERP component correlated with the individual's pain detection, sensitivity, and severity during the effects of the prolonged pain. More specifically, daily nociceptive N200 amplitudes were associated to their respective reaction times, the magnitude of nociceptive P200 reflected the increment of pain sensitivity to pressure and electrical stimulation, and the nociceptive P300 showed an association with the worst pain intensity. Altogether, this work expands our knowledge about the temporal transition from acute to prolonged pain and provide novel findings of how long-term sensorimotor training may enhance the behavioral and neural response to pain during the development of prolonged pain in individuals performing extensive repetitive movements.

### Hyperalgesia and Central Changes Induced by Experimental Muscle Pain

NGF-induced experimental muscle pain is based on a robust and long-lasting sensitizing effect on the nociceptive system.<sup>21,59</sup> Accordingly, the present study showed that prolonged pain evoked by an NGF injection into the right FDI muscle induced a long-lasting primary mechanical hyperalgesia and an increment of self-reported pain intensity in all participants, which were evident on Day 3 and Day 8, confirming the robustness of the NGF as a reliable model to induce prolonged muscle (hand) pain. Similar to findings in clinical studies<sup>22</sup> and previous research using this pain model,<sup>52</sup>

**Table 2. Mean ( $\pm$  SD) of Spontaneous Pain Intensity Induced by the Intramuscular Injection of the NGF at the Lab Sessions (Day 3 and Day 8) and Mean ( $\pm$  SD) of the Worst, Least, and Average NGF-Induced Pain Intensity Across all Experimental Days (Reported on Day 8)**

	MUSICIANS			NON-MUSICIANS		
	DAY 1	DAY 3	DAY 8	DAY 1	DAY 3	DAY 8
PCS	14.1 $\pm$ 8.6	-	-	14.9 $\pm$ 10.2	-	-
PVAQ	28.1 $\pm$ 12.7	-	-	26.6 $\pm$ 11.3	-	-
T-STAI	23.8 $\pm$ 8.3	-	-	26. $\pm$ 8.1	-	-
S-STAI	9.2 $\pm$ 6.3	10.3 $\pm$ 2.5	10.2 $\pm$ 2.1	11.7 $\pm$ 8.6	11.4 $\pm$ 2.7	11.3 $\pm$ 3.0

mechanical hyperalgesia is apparent, albeit less intense, in the non-injected contralateral hand after 3 and 8 days. One explanation of these contralateral findings may be mechanical sensitization induced by repeated pressure assessments. However, the neurophysiological cortical changes observed after eight days of prolonged pain in this study, characterized by an inhibition of the nociceptive P200 and the non-nociceptive P200 and P300 cortical responses, support the implication of supraspinal mechanisms during the transition to prolonged muscle pain.

The P200 somatosensory component has been directly linked to body awareness and the sense of agency,<sup>1,5,7,50,61</sup> reflecting the processing of bottom-up somatosensory and proprioceptive inputs. The P300 component, on the other hand, is associated with attentional orienting, as well as cognitive evaluation of the stimulus.<sup>31,48</sup> It has been argued that cognitive processes related to attention may modulate the P200 and P300 responses. However, since reaction times and electrical thresholds to non-nociceptive stimulation in the current study were not altered across days, the reduction of P200 and P300 is unlikely to be caused by a lack of attention, a reduction in salience detection, or habituation. This notion is supported by the lack of modulation of the N140 across days. The N140, which is associated with the activation of regions within the salience network,<sup>66</sup> was not significantly different across days and positively correlated with the respective reaction times. This indicates that several days of prolonged experimental muscle pain did neither modulate non-nociceptive salience detection nor attentional processes. On the other hand, non-nociceptive P200 and P300 amplitudes were associated with the individual's pain sensitivity, linking lower non-nociceptive P200 magnitudes with more hyperalgesia and lower non-nociceptive P300 amplitudes with enhanced severity. Altogether it suggests that the modulation of non-nociceptive P200 and P300 may be better explained by the presence of experimental prolonged pain.

An inhibition of the non-nociceptive P200 magnitude has been observed during the phenomenon of sensory attenuation (ie, the top-down filtering of afferent information)<sup>50</sup> and during the processing of somatosensory stimuli when another task requires higher attention.<sup>57</sup> Similarly, a P300 inhibition has been related to higher cognitive demands due to evaluation and comparison

processes of several stimuli within the same environment.<sup>31,48</sup> Therefore, it is possible that the reduction of somatosensory P200 and P300 components in this study reflects not only bottom-up processing but also a top-down cognitive "conflict". This top-down cognitive conflict might result from the evaluation process of the upstream signals produced by the electrical somatosensory stimuli and the ones caused by the NGF-induced muscle pain, which probably demands higher allocation resources and interferes with decision-making processes.

### **Brain-Based Pain Facilitation as a Function of Extensive Sensorimotor Training**

The used experimental prolonged muscle pain caused secondary hyperalgesia in individuals with long experience in performing sensorimotor training compared to controls. This distinct profile was also observed at the neural level, where only trained individuals showed temporal modifications of nociceptive brain responses characterized by an inhibition of nociceptive P200. Thus, both behavioral and neural results indicate between-group heterogeneity in the mechanisms driving these pain indices, and suggest that extensive sensorimotor training is an important factor for driving peripheral as well as central changes in pain processing.

Recent reports using experimental pain models provide evidence of central adaptations related to corticomotor excitability, sensorimotor integration, and sensory discrimination.<sup>11,21,52</sup> The fact that non-nociceptive electrical perception thresholds remained unchanged throughout sessions and between groups suggests that neither intramuscular NGF into the right hand nor extensive sensorimotor training elicited changes on the somatosensory system (ie, tactile receptors and dorsal column-lemniscal pathway). Instead, this lack of modulation reinforces the hypothesis that the observed changes in nociceptive processing of trained participants may be supported by brain-associative neurophysiological changes between pain and extensive sensorimotor training, as suggested in previous studies with musicians<sup>65–67</sup> and demonstrated in animals models.<sup>9</sup>

Electrophysiological pain studies typically measure the N200 and P300 (N2/P2) components by quantifying the individual and/or the peak-to-peak amplitude.<sup>10</sup> In the present study, the N200, associated with the activation of regions within the salience and sensorimotor networks,<sup>35,66</sup> and the P300, associated with the activation of regions related to recognition and evaluation,<sup>48,66</sup> were not significantly modulated as a function of prolonged pain over several days. Such lack of modulation of N200/P300 might indicate that prolonged muscle pain does not alter the neural responses to nociceptive salience detection or recognition. However, individual inspection and analysis of the subjects' responses evidenced that the N200 component in musicians compared to non-musicians was concatenated with the reduction of the nociceptive P200 (190–220 milliseconds), a positive component between the N200–P300 peaks that was only evidenced in non-musicians and which is generally concealed in response to the nociceptive stimulus.<sup>40,66</sup> As this component is not always uncovered in pain-related studies, its specific function and mechanistic pathways remain unclear. Potential reasons for its intermittent appearance may include the high degree of between-subject variability in response to the same painful stimulation, wherein a sensory response may or may not even be produced in some individuals.

In a recent study in which the nociceptive pathways of healthy participants were explored as a function of extensive repetitive movements (ie, use-dependent plasticity), the presence of this P200 component was notably more prominent in those participants who did not perform repetitive training.<sup>66</sup> In the current work, a nociceptive P200 component was again observed as a function of extensive sensorimotor training, and subsequently uniquely decreased after 8 days of prolonged muscle pain. One explanation could be that facilitation of central pain mechanisms due to NGF-induced pain engaged with the neuroplasticity processes associated with sensorimotor training. Although speculative, this interaction might involve heterosynaptic plasticity in the nociceptive pathways, leading to the enhancement of central responses after several days of low-moderate prolonged muscle pain. Notably, the nociceptive P200 amplitude was associated with the corresponding electrical hyperalgesia across days. Moreover, the P200 baseline amplitude correlated with the response of the mechanical hyperalgesia on Days 3 and 8, indicating a possible predictability value of sensitization. Although this temporal profile requires further investigation, the current findings imply that the nociceptive P200 in response to intraepidermal electrical stimulation may behave as a relevant marker of an individual's pain behavior and cortical reorganization during the transition to prolonged pain.

### ***Perceived Pain as a Function of Extensive Sensorimotor Training***

It must be highlighted that, although musicians experienced secondary hyperalgesia and temporal

Use-dependent plasticity and prolonged pain

modifications of nociceptive brain responses, ratings of NGF-induced muscle pain were reduced in musicians compared to untrained participants. Moreover, musicians with higher accumulated training reported lower pain ratings. These results indicate that musicians down-regulated the response to pain, evidencing two largely dissociated neural processes mediating bottom-up perception (ie, stimulus-driven) and top-down cognitive control (ie, driven by experience, expectations, and/or motivations) of pain.<sup>62,64</sup> High-performing musicians describe pain as inherent to practice and inevitable,<sup>13,18</sup> being the most common physical complaint of performing musicians.<sup>32</sup> Despite these potential health and performance challenges, neuroimaging studies showed that elite musicians display decreased insula connectivity and experience lower pain-related inferences with daily activities compared to chronic pain non-musicians.<sup>67</sup> Although the design of the present study cannot provide a causal explanation of the lower pain scores in high-performing musicians compared to untrained individuals, this altered pain perception may reflect the necessity of musicians to tolerate pain to keep training and maintain performance levels throughout their careers.<sup>19,43</sup> Therefore, it is likely that individuals who routinely perform repetitive training under high physical and psychological demands may control and cope prolonged with pain in a unique way compared to untrained people.<sup>15,67</sup>

### ***Limitations***

A number of limitations need to be highlighted. First, the effects might differ depending on the kind of sensorimotor training. Although musicians are a well-known model of use-dependent plasticity, their high-volume training regimens focus on instrument-specific sensorimotor routines that may differ from individuals performing other repetitive and stereotyped movements. To address this question, future studies should investigate other forms of homogenous and stereotyped repetitive movements, with performance quantity as a variable of interest. Second, the present study's design is not suitable to establish the nature of the underlying mechanisms responsible for modulating the facilitated responses in musicians. This limits our conclusions of the neurobiological mechanisms by which repetitive movements may contribute to modulating pain perception. Similarly, the present experiment cannot provide a causal explanation of the lower pain scores in high-performing musicians compared to untrained individuals; it is therefore suggested that top-down modulation mechanisms may be investigated in future studies.

### ***Conclusion***

These data provide important information to elucidate the underlying neural mechanisms by which extensive repetitive movements are associated with the vulnerability towards developing prolonged pain and hyperalgesia. Particularly, the appearance of secondary hyperalgesia and a reduction of nociceptive P200

amplitudes in musicians relative to non-trained controls indicate that repetitive sensorimotor training contribute to altering the pain processing during the development of prolonged muscle pain. This work also expands prior findings on cortical responses to nociceptive and non-nociceptive stimulation and the individual's pain features during prolonged muscle pain. Especially, it

highlights the presence of small amplitude cortical evoked activity (approx. latency 200 milliseconds) that represents well the temporal aspects of pain developing over several days, and holds some predictive value as well. Altogether, this study opens up new avenues to understand general principles of musculoskeletal pain and its relationship to use-dependent plasticity.

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