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Original Reports

Corticomotor Depression is Associated With Higher Pain Severity in the Transition to Sustained Pain: A Longitudinal Exploratory Study of Individual Differences

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Abstract: **Aberrant motor cortex plasticity is hypothesized to contribute to chronic musculoskeletal pain, but evidence is limited. Critically, studies have not considered individual differences in motor plasticity or how this relates to pain susceptibility. Here we examined the relationship between corticomotor excitability and an individual's susceptibility to pain as pain developed, was sustained and resolved over 21 days. Nerve growth factor was injected into the right extensor carpi radialis brevis muscle of 20 healthy individuals on day 0, 2, and 4. Corticomotor excitability, pressure pain thresholds and performance on a cognitive conflict task were examined longitudinally (day 0, 2, 4, 6, and 14). Pain and disability were assessed on each alternate day (1,3...21). Two patterns of motor plasticity were observed in response to pain——corticomotor depression or corticomotor facilitation ($P = .009$). Individuals who displayed corticomotor depression experienced greater pain ($P = .027$), and had worse cognitive task performance ($P = .038$), than those who displayed facilitation. Pressure pain thresholds were reduced to a similar magnitude in both groups. Corticomotor depression in the early stage of pain could indicate a higher susceptibility to pain. Further work is required to determine whether corticomotor depression is a marker of pain susceptibility in musculoskeletal conditions.**

Perspective: ***This article explores individual differences in motor plasticity in the transition to sustained pain. Individuals who developed corticomotor depression experienced higher pain and worse cognitive task performance than those who developed corticomotor facilitation. Corticomotor depression in the early stage of pain could indicate a higher susceptibility to pain.***

Key Words: *Motor cortex plasticity, musculoskeletal pain, pain susceptibility, transcranial magnetic stimulation.*

The organization and function of the primary motor cortex is altered in the acute,[1] transitional,[2] and chronic stages of musculoskeletal pain and in chronic pain populations, altered motor cortex plasticity is associated with pain severity and impaired function.[3,4,5] These findings suggest that aberrant motor cortex plasticity may contribute to the development of chronic pain. However, direct evidence for a relationship between an individual's motor plasticity in response to pain and symptom severity is lacking. Critically, studies have examined only group level responses, without consideration of individual differences. This information is essential in order to understand why some people develop chronic pain while others do not, and to facilitate targeted, individualized treatment.

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Several studies have examined motor cortex plasticity in the transition to sustained pain with conflicting findings—2 studies demonstrate increased corticomotor excitability at the group level 4 days after pain onset[2,6] while another demonstrates decreased excitability.[7] One explanation for this discrepancy is that motor cortex plasticity in response to pain is not uniform across individuals. Although evidence for individual differences in the transitional stage of pain is absent, a recent study using a short-lasting experimental pain model (application of capsaicin; average pain duration 42 minutes) demonstrated reduced corticomotor excitability in some individuals but not others.[8] Individual differences in corticomotor excitability are hypothesized to reflect the emergence of distinct motor and cognitive strategies—some of which may be maladaptive and predispose to chronicity. For example, reduced corticomotor excitability is hypothesized to interfere with adaptive motor learning and contribute to poor recovery following an episode of musculoskeletal pain.[9,10] Similarly, the emergence of a cognitive passive coping strategy, characterized by the adoption of movement avoidance behaviors, is prognostic for poor outcome in subacute low back pain.[11] Despite this, there has been no investigation of individual differences in corticomotor excitability or how this relates to pain severity and cognitive response in the transition to sustained pain.

Intramuscular injection of nerve growth factor (NGF) is a clinically-relevant, human transitional pain model that induces progressively developing musculoskeletal pain lasting up to 21 days. Repeated injection of NGF at intervals of 48 hours results in symptoms that mimic those of persistent musculoskeletal conditions (eg, spreading hyperalgesia, pain with function, and distinct areas of referred pain) and injection of NGF has been shown to induce comparable functional limitation and pain after several days to patients with persistent lateral elbow pain who have had pain for approximately 26 weeks.[12] The use of the NGF model provides a unique opportunity to evaluate individual differences in corticomotor excitability and the relationship to pain severity and disability, as pain develops, is sustained and resolves over a 3-week period.

Here we aimed to examine individual differences in corticomotor excitability, and the relationship to pain, disability, and cognitive task performance, in the transition to sustained pain. Based on studies in acute pain models,[8] we hypothesized that some individuals would display corticomotor facilitation while others would display corticomotor depression. We additionally hypothesized that corticomotor depression would be associated with worse pain and disability and worse performance on a cognitive conflict task.

Materials and Methods

Participants

Twenty right-handed, healthy individuals (mean ± standard deviation age: 23 ± 4 years, 11 males) participated. While a previous study using the same NGF pain model showed changes in corticomotor excitability at the group level with a sample of 12 participants,[2] there have been no studies of individual variation in corticomotor excitability in the transition to sustained pain to inform a sample size calculation. Consistent with the exploratory aims of this study, we set our target sample size at 20. Handedness was assessed using the Edinburgh handedness questionnaire.[13] Participants with a history of neurological, psychiatric, musculoskeletal or upper limb conditions were excluded and a transcranial magnetic stimulation (TMS) safety screen was completed prior to study enrolment.[14] All participants provided written informed consent consistent with the Declaration of Helsinki. Experimental procedures were approved by the institutional ethics committee (H10184). Testing was undertaken in a University research laboratory between January and July 2017.

Experimental Protocol

Participants attended the laboratory on 5 occasions: Day 0, 2, 4, 6, and 14. Day 0 (pre-pain) outcome measures included pressure pain thresholds (PPTs), transcranial magnetic stimulation-derived motor cortical maps, and performance on the multisource interference task (MSIT).[15] The State-Trait Anxiety Inventory,[16] the Beck Depression Inventory[17] and the Pain Catastrophizing Scale[18] were also administered on day 0. Assessment of PPTs, motor cortical maps, and performance on the MSIT were repeated on Days 2, 4, 6, and 14. Nerve growth factor (NGF) was injected into the belly of the right extensor carpi radialis brevis (ECRB) muscle immediately following collection of all outcome measures on day 0, 2, and 4. No injection was given on day 6 or 14. Electronic pain diaries were administered on each alternate day from day 1 to day 21 (Day 1,3, 5...21) (Fig 1).

NGF-Induced Muscle Pain

Intramuscular injection of NGF in humans has been shown to induce progressively developing, clinically-relevant muscle pain that is sustained for up to 21 days and is accompanied by muscle hyperalgesia, movement-evoked pain, and reduced function.[12] After cleaning the skin with alcohol, a dose of 5 μg (0.2 ml) sterile, recombinant human NGF was given as a bolus injection into the muscle belly of ECRB using a 1 ml syringe with a disposable needle (27 G).[2]

Electronic Pain Diary

Pain was assessed using an 11-point numerical rating scale anchored with "no pain" at zero and "worst pain imaginable" at 10. The Patient-rated Tennis Elbow Evaluation Questionnaire was used to assess disability.[19] Scores for pain (sum of 5 items out of a maximum score of 50) and disability (sum of 10 items, divided by 2, out of a maximum score of 50) were combined to give a total score ranging from 0 (no pain and no functional impairment) to 100 (worst pain imaginable with significant functional impairment).

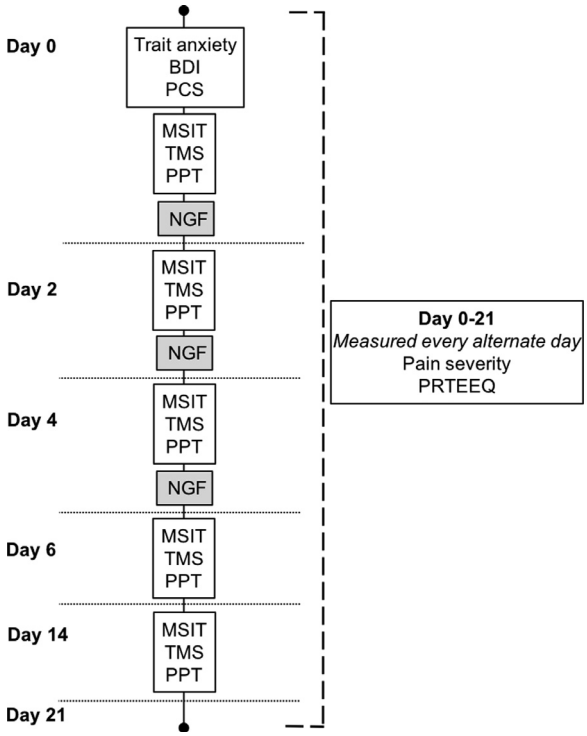

Figure 1. Experimental protocol. Abbreviations: BDI, Beck Depression Inventory; PCS, Pain Catastrophizing Scale; TMS, transcranial magnetic stimulation; PPT, pressure pain threshold; MSIT, multisource interference task; NGF, nerve growth factor; PRTEEQ, Patient Rated Tennis Elbow Evaluation Questionnaire.

Pressure Algometry

Pressure was applied perpendicular to the surface of the skin using a hand-held pressure algometer with a 1 cm^2 probe (Force Ten, FDX Force Gage, Wagner instruments, Greenwich, CT). Three readings at the pressure pain threshold were made at 1-minute intervals at one local (right ECRB [injected site]) and 2 remote sites (left ECRB [matched to site of injection on right ECRB], and left tibialis anterior [10 cm distal from the tibial tuberosity]) to assess peripheral and central sensitivity. A tape measure was used to measure the position of each site (ECRB – distance [cm] distal to the lateral epicondyle and medial distance [cm]; Tibialis Anterior—distance [cm] distal from the base of the patellar tendon) and these values were recorded to ensure consistent positioning across measurement sessions. Participants were instructed to verbalize when the sensation of pressure first changed to pain. The average of the 3 recordings at each site was used for analysis.

Motor Cortical Maps

Electromyographic activity was recorded from right ECRB using bipolar Ag/AgCl surface electrodes (Medicotest 720-01-K, Ambu A/S, Ballerup, Denmark) positioned over the muscle belly. Electromyographic signals were amplified (1000 times), bandpass filtered between 20 and 1000 Hz and sampled at 2 kHz (CED 1401 AD, Cambridge Electronic Design, Cambridge, UK) using Signal acquisition software (CED, version 5.08 × 86).

A standard procedure for mapping the motor cortical representation of upper limb muscles was used.[2,4,20] Participants were fitted with a cap marked with a 1 cm x 1 cm grid and orientated to the vertex (point 0,0). A standard 70 mm figure-of-eight coil connected to a magnetic stimulator (Magstim 200, Magstim Co. Ltd. Dyfed, UK) was used to provide single-pulse TMS. The coil was positioned tangentially to the scalp with the handle pointing posterolateral at a 45° angle from the mid-sagittal plane. This orientation is optimal for the induction of posterior-to-anterior directed current for trans-synaptic activation of horizontal cortical connections in M1.[21] The optimal site ("hotspot") for eliciting motor evoked potential (MEP) responses from the relaxed ECRB muscle was determined by systematically moving the coil in 1 cm increments around the motor cortex. The site that evoked the largest responses at the lowest stimulator intensity was considered the hotspot. The stimulus intensity for mapping was set at 120% of resting motor threshold (rMT) on day 0, defined as the minimum stimulator intensity at which 5 out of 10 stimuli applied at the hotspot evoked a response with a peak-to-peak amplitude of at least 50 μV. To account for any changes in corticomotor excitability occurring in the presence of pain, the stimulus intensity determined at day 0 was also used for mapping on days 2, 4, 6, and 14. Single-pulse TMS was applied every 6 seconds with a total of 5 stimuli at each site. The number of scalp sites was pseudorandomly increased until no MEP was recorded (defined as less than 50 μV peak-to-peak amplitude in all five trials in all border sites). Participants were seated and instructed to keep their hand and forearm relaxed with the wrist pronated throughout the experiment. All TMS procedures adhered to the TMS checklist for methodological quality.[22]

The number of active map sites and map volume was calculated. A site was considered 'active' if the mean peak-to-peak amplitude of the five MEPs evoked at that site was greater than 50 μV. The mean peak-to-peak MEP amplitudes at all active sites were summed to calculate the map volume providing a measure of corticomotor excitability within the ECRB motor cortical representation.

MSIT

Participants performed the MSIT, which has been described in detail previously.[15,23-25] Briefly, 3 numbers were presented on a screen and the participant asked to identify the number that differed from the other 2. Two types of trials were displayed: easy trials consisted of the target number presented in the correct numerical position with the other 2 positions occupied by x's (ie, 1 x x, x 2 x, or x x 3, correct responses 1, 2, 3, respectively); difficult trials consisted of a target number in the wrong numerical position, with the other 2 positions occupied by another number (ie, 2 1 2, 3 3 2, 3 2 2, correct responses 1, 2, 3, respectively). Participants were given a 3-button keypad and instructed to press the number that corresponded to the number that was different than the other 2, responding as quickly as possible

without making errors. Four task blocks of 4 minutes were performed, in which a total of 288 easy and difficult trials were pseudorandomly presented with an interstimulus interval of 1500 msec. Conflict cost was calculated as the difference in reaction time between difficult and easy trials, in msec, for correct trials only.

Statistical Analyses

A one-way repeated-measures analysis of variance was first performed for map volume on data from the whole sample with factor Time (days 2, 4, 6, and 14). Consistent with our hypothesis, participants were then divided into 2 groups based on whether they showed facilitation or depression of corticomotor excitability in response to pain (calculated as the average map volume across days 2, 4, 6, and 14 as a proportion of day 0). A mixed model analysis of variance was performed for each independent variable with the between-subjects factor of group (facilitator, depressor) and the within-subjects factor of time (Days 1, 3, 5,. . ..21 for pain and disability; days 0, 2, 4, 6, and 14 for resting motor threshold, map volume, PPTs, and MSIT). As we were interested in differences occurring between groups over time, and not at specific Days, post-hoc testing, and subsequent adjustment for multiple comparisons, was not required and only main effects are reported. To account for any influence of depression, anxiety, pain catastrophizing, or age on corticomotor excitability, the model for map volume was repeated with these factors included as covariates. In addition, depression, anxiety, catastrophizing and age were compared between individuals who displayed corticomotor depression and those who displayed corticomotor facilitation using 2-tailed independent samples t-tests. Effect sizes were calculated using Cohen's d (where .2 = small effect, .5 = medium effect, >.8 = large effect). Significance was set at $P < .05$.

Results

All participants completed all test sessions and diaries in full. No adverse events were reported in relation to the injection of NGF. When examined across the whole sample, corticomotor excitability was unaltered over time (map volume $F_{2.5,47} = 1.8$, $P = .17$). However, when the individual response was considered, 2 distinct patterns of corticomotor excitability were observed - facilitation (n = 8, 24 ± 4 years, 5 males) or depression (n = 12, 22 ± 4 years, 7 males) of corticomotor excitability in response to pain (Fig 2). A statistical manipulation check confirmed the 2 groups were significantly different for map volume ($F_{1,18} = 8.6$, $P = .009$; Cohen's $d = 1.3$) over time but did not differ at day 0 (facilitators: 9.2 ± 3.4, depressors 10.3 ± 3.0, $F_{1,18} = .98$, $P = .34$). On average, individuals in the facilitator group displayed an increase in map volume from baseline of 47% at day 2, 56% at day 4, 20% at day 6, and 65% at day 14, while individuals in the depressor group reduced map volume by 22% at day 2, 40% at day 4, 50% at Day 6, and 30% at day 14. All participants had at least a 20% change in map volume over time with the exception of 2 individuals—one in the depressor group (average change of 4%) and one in the facilitator group (average change of 3%). However, both individuals displayed changes in map volume on single days of >10% of baseline in the direction in which they were grouped.

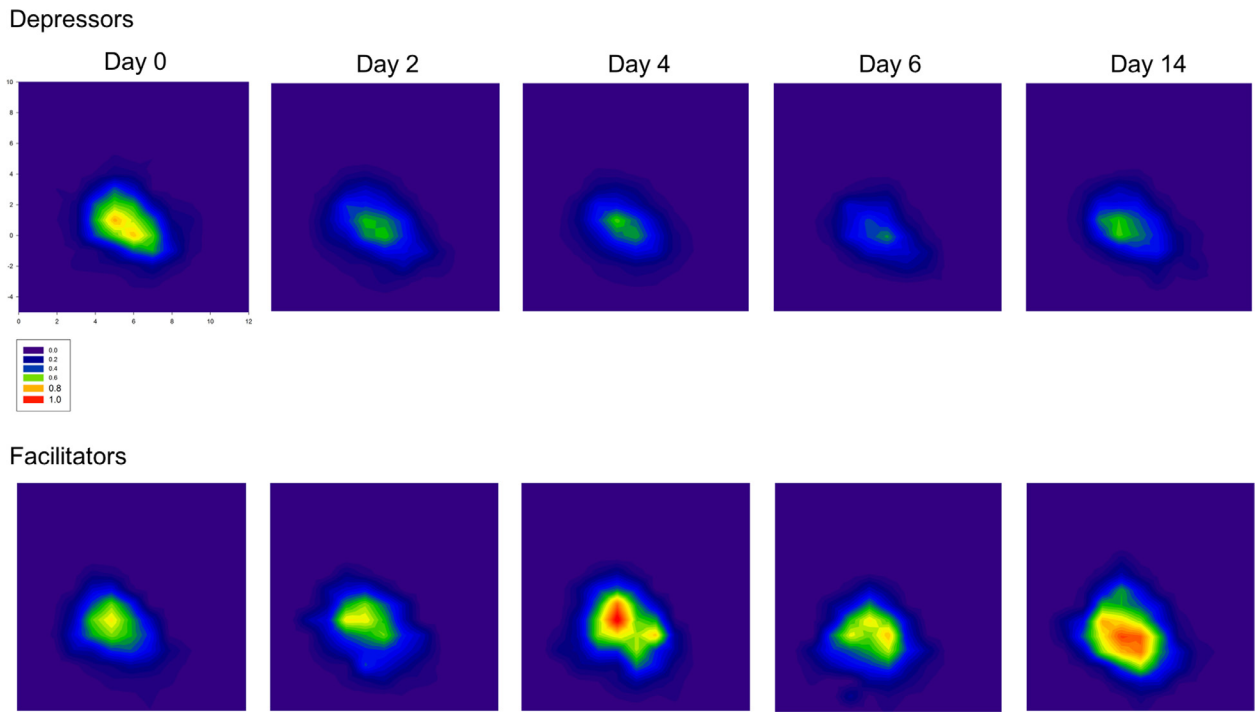

Figure 2. Motor cortex maps (group average) for the ECRB muscle in depressors (n = 12, top) and facilitators (n = 8, bottom) in response to NGF-induced sustained muscle pain. Map volume is normalized to day 0 for each participant. Warmer colours represent greater excitability (proportion of the motor evoked potential response at day 0, mV).

Resting motor threshold was stable over time ($F_{4,72} = 1.2$, $P = .34$) but differed between groups, with a lower resting motor threshold in those who displayed facilitation of corticomotor excitability ($F_{1,18} = 5.7$, $P = .028$; Cohen's $d = 1.06$). Group mean and individual data for map volume and resting motor threshold are shown in Fig. 3A and 3B. There were no differences between groups for age ($t_{18} = .98$, $P = .34$), depression ($t_{18} = 0.04$, $P = .97$), anxiety ($t_{18} = 1.7$, $P = .11$), or pain catastrophizing ($t_{18} = .73$, $P = .76$) and when these factors were included as covariates in the statistical model, the difference in corticomotor excitability remained ($F_{1,14} = 7.5$, $P = .016$).

Pain was greater in individuals who displayed corticomotor depression than in those who displayed corticomotor facilitation ($F_{1,18} = 5.8$, $P = .027$, Cohen's $d = .81$; Fig 4A) and disability showed a similar trend ($F_{1,18} = 3.8$, $P = 0.066$; Cohen's $d = .74$; Fig 4B, Supplementary Table 1). PPTs at the site of injection ($F_{2.2,39} = 50.2$, $P < .0001$; Fig 4C), but not the remote tibialis anterior site ($F_{2.9,56} = 0.98$, $P = .42$), decreased following NGF injection in both groups ($F_{1,18} = 0.23$, $P = .64$). Although both groups improved performance on the cognitive task over time ($F_{1.7,4} = 23.6$, $P < .001$), individuals who displayed corticomotor depression exhibited worse performance (greater conflict effects) on the cognitive task than those who displayed corticomotor facilitation ($F_{1,17} = 5.1$, $P = .038$; Cohen's $d = .84$; Fig 4D).

Discussion

This preliminary study is the first investigation of individual differences in corticomotor excitability, and how these differences relate to pain severity, disability, and performance on a cognitive task, in the transition to sustained pain. Using a clinically-relevant model of sustained pain, we show that individuals who develop corticomotor depression in the transition to sustained pain experience higher pain severity and worse cognitive task performance than those who develop corticomotor facilitation. Interestingly, although depressors experienced worse pain, measures of peripheral, and central sensitivity were similar between groups.

When pain is short-lasting (minutes to hours) systematic review evidence demonstrates corticomotor depression during and immediately after the resolution of pain that is thought to reflect a protective motor strategy that limits movement and protects against further pain or injury.[1] However, when pain is sustained for days or weeks, the persistence of corticomotor depression is hypothesized to be maladaptive, underpinning the adoption of simplified movement strategies, altered tissue loading and potentially pain chronicity.[26,27] Further, corticomotor depression is suggested to interfere with beneficial motor learning and may negatively impact on the success of rehabilitation.[8-10] In contrast, corticomotor facilitation several days after pain onset is interpreted as an adaptive response, reflecting the search for a new motor strategy that utilizes synergies with surrounding muscles to reduce loading, minimize pain or the threat of pain, and maximize task performance.[2,28] The current data provide longitudinal evidence in support of these hypotheses. Indeed, individuals who displayed corticomotor depression several days after pain onset experienced worse pain than those who displayed corticomotor facilitation.

Currently, the best-known predictor of chronicity is high pain severity in response to the initial injury[29,30] yet screening tools that capture this information have poor discrimination performance,[31-34] resulting in misclassification of a large proportion of individuals.[35] Indeed, in-depth analysis of these tools suggests no net benefit of screening over and above a "treat all" approach.[33] The identification of markers that can discriminate between those likely to develop high pain severity with greater accuracy than currently available tools would be of clinical value. The current data provide preliminary evidence of an association between corticomotor excitability and high pain severity that could provide an early marker for those at risk of

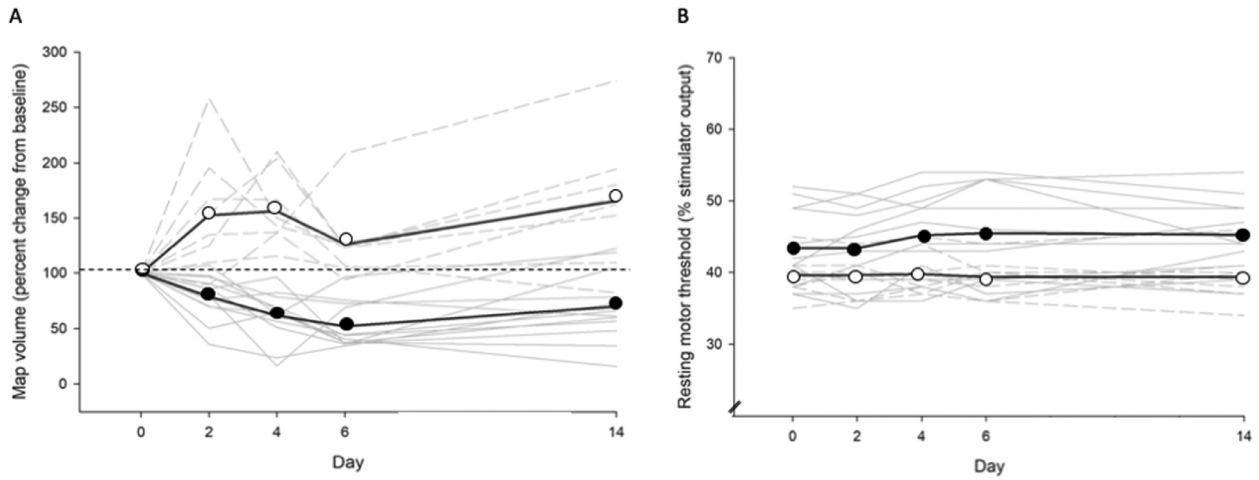

Figure 3. Individual and group data for **(A)** map volume over time (percent change from day 0), and **(B)** resting motor threshold (percent of stimulator output). Black lines represent the group mean for depressors (filled circles) and facilitators (open circles). Gray lines show individual data for all participants (solid gray lines—depressors; dashed gray lines—facilitators). Map volume ($P = .09$) and resting motor threshold ($P = .028$) differed between depressors and facilitators over time.

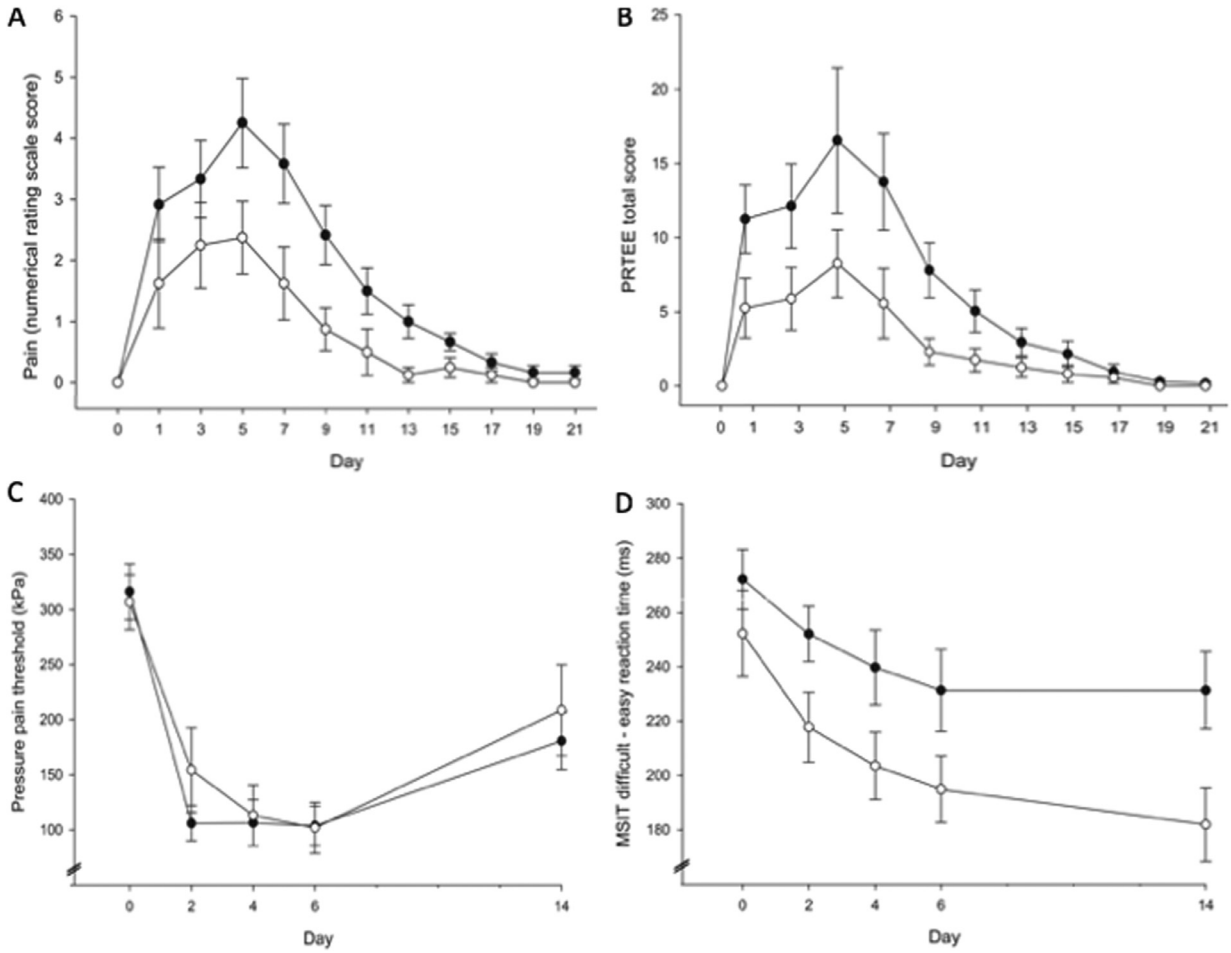

Figure 4. Group data (mean ± standard error) in depressors (filled circles) and facilitators (open circles) for: **(A)** pain severity (numerical rating scale); **(B)** disability (patient rated tennis elbow evaluation questionnaire total scores, PRTEEQ); **(C)** pressure pain thresholds (kPa); **(D)** performance on the multisource interference task (MSIT). Depressors developed more pain (P= .027) with a similar trend for disability (P = .066), and had worse task performance (P = .038) than facilitators (greater conflict effects, based on the difference in reaction time between difficult and easy trials, in milliseconds) but did not display greater sensitivity to pressure (P = .64).

developing chronic pain. However, the current study design does not allow exploration of causation and findings should be interpreted with caution. Further investigation is required to determine whether altered corticomotor excitability is a useful marker of pain severity or an epiphenomenon with no causal relationship to pain.

This study provides insight into individual adaption occurring across both motor and cognitive domains in the transition to sustained pain. Specifically, we demonstrate that individuals who display corticomotor depression also perform worse on a cognitive conflict task. Previous studies have shown that individuals select one of 2 cognitive response strategies to cope with pain 1) passive disengagement, characterized by a cognitive focus on pain and the adoption of escape or avoidance behaviors, or 2) active engagement, characterized by a cognitive focus on task completion and active problem solving. When performing a cognitive, attention demanding task (counting Stroop) while simultaneously experiencing pain, participants spontaneously adopt one of these 2 strategies to cope with pain and perform the task.[36] In participants who select a passive coping strategy, pain dominates and reaction times increase (performance worsens). Conversely, participants who select an active coping strategy focus on task completion and reaction times decrease (performance improves).[36] This finding has been replicated in several studies.[37-39] Our data suggest that those who display corticomotor depression also exhibit a passive cognitive coping strategy.

Although individuals who displayed corticomotor depression experienced worse pain than those who displayed facilitation, measures of peripheral (local PPTs) and central (remote PPTs) sensitization were similar between groups. These data suggest that motor cortex plasticity early in the transition to sustained pain may be independent of peripheral and central sensitization mechanisms. This is perhaps not surprising in the context of central sensitization which is typically observed in chronic, long-lasting pain conditions (pain lasting >3 months) and likely takes time to evolve.[40] Indeed, our data provide no evidence of central sensitization (when assessed using PPTs from the remote tibialis anterior

muscle) at any time-point in the early transition to sustained pain. However, comprehensive assessment of central sensitization is needed before definitive conclusions can be drawn. In addition, further research is needed to determine how alterations in corticomotor excitability interact with mechanisms of central sensitization once pain has become chronic.

Repeated intramuscular injection of NGF provides a clinically relevant model to investigate the transition from a no pain baseline to sustained muscle pain and to identify mechanisms that may be relevant to clinical musculoskeletal pain conditions. Although our findings require confirmation in clinical populations to determine whether corticomotor excitability predicts pain chronicity, we have recently shown that individuals with clinical low back pain who display low sensory and anterior cingulate cortex excitability in the acute stage of pain (first 4 weeks after pain onset) have greater pain severity (numerical rating scale: low excitability 4.0 $\pm$ 1.6; high excitability 2.9 $\pm$ 1.9) and worse outcome at 6 months follow-up (low excitability 25% recovered, high excitability 75% recovered) than individuals who display high sensory and anterior cingulate cortex excitability.[41] As previous studies have shown that primary sensory and motor cortex excitability are comodulated in response to acute experimental pain,[42] it is plausible that sensorimotor cortex excitability in the early stages of pain could be a marker of clinical outcome. Of interest, the proportion of individuals who display low sensorimotor cortex excitability in response to pain is consistent across studies. In the current study, 60% of individuals developed corticomotor depression compared with 66% of individuals with acute low back pain who displayed low sensorimotor cortex excitability,[41] and 66% of individuals who reportedly developed corticomotor depression in response to capsaicin-induced pain.[8]

Several limitations should be considered. First, although this study uses a robust longitudinal repeated-measures design, with 5 test sessions for each individual and 21-day follow-up of pain and disability, the sample size was small and further testing in a sample powered to detect individual differences is needed to confirm our findings. Second, we divided participants into 2 groups based on their average map volume across days 2 to 14 (as a proportion of baseline). As the corticomotor response to pain was large (average change of 40−50% of baseline in all but two individuals) and relatively consistent over time within an individual (Fig 3), dividing the data based on a single day (eg, day 2, 4, or 6) would not have altered the results of the current study. However, future large-scale studies are needed to determine the performance characteristics and range of normative values for corticomotor excitability in response to pain in order to determine the most appropriate cut-off between groups. This study did not include monitoring of participant activity (eg, exercise or activities of daily living) in response to NGF-induced pain and it is unknown whether the degree of activity adopted by each individual may have influenced the corticomotor response. Future studies should include monitoring of physical activity, in addition to more specific measures of motor adaptation, to more clearly elucidate the relationship between movement, corticomotor excitability and pain. Finally, our findings require replication in clinical pain populations before the feasibility and clinical utility of corticomotor depression as a marker for pain severity and chronicity can be determined.

Conclusions

These data demonstrate individual differences in corticomotor excitability that are related to symptom severity in the transition to sustained pain. Specifically, individuals who develop corticomotor depression in the transition to sustained pain experience greater pain severity and worse cognitive task performance than those who develop corticomotor facilitation. Our preliminary findings suggest that corticomotor depression in the early stage of pain could indicate a higher susceptibility to pain. Further studies are warranted to confirm and extend these findings.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2019.06.005.

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