The Role of Inhibitory Function in Pain

Authors: Liu Bo, Cheng Xiangjuan, Yue Heng, Bao Hugjiltu

Date: 2021-11-26T00:00:00+00:00

Abstract

Since the proposal of the biopsychosocial model, the utilization of psychological factors for pain prevention and treatment has attracted considerable attention. A growing body of research indicates that inhibitory function plays a pivotal role in both the development and recovery stages of pain. Pain-induced self-defense mechanisms impact inhibitory function by competing for cognitive resources; conversely, individuals with low inhibitory function demonstrate poorer performance in managing pain interference, which in turn influences pain expectation and learning. Current research on how inhibitory function affects pain has primarily relied on correlational designs, and future investigations should further elucidate the causal relationship between these two factors. A deeper understanding of the cognitive mechanisms underlying the interaction between pain and inhibitory function will help guide inhibitory function-targeted interventions for chronic pain.

Full Text

The Role of Inhibitory Function in Pain

Liu Bo[1], Cheng Xiangjuan[1], Yue Heng[1], Bao Hugejiletu[2]
([1] School of Psychology, Inner Mongolia Normal University, Hohhot 010022, China)
([2] School of Physical Education, Inner Mongolia Normal University, Hohhot 010022, China)

Abstract: Since the biopsychosocial model was proposed, using psychological factors to prevent and treat pain has attracted considerable attention. An increasing number of studies have demonstrated that inhibitory function plays a critical role in both the development and recovery stages of pain. Pain-induced self-defense mechanisms affect inhibitory function by competing for cognitive resources. Conversely, individuals with low inhibitory function perform poorly when coping with pain interference, which in turn influences pain expectation

and learning. Existing research on how inhibitory function affects pain has primarily employed correlational designs; future studies should further clarify the causal relationship between the two. A deeper understanding of the cognitive mechanisms underlying the interaction between pain and inhibitory function can help guide targeted interventions using inhibitory function for chronic pain.

Keywords: pain, chronic pain, inhibitory function, DLPFC

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Song et al., 2020). When pain persists for three months or longer, it develops into chronic pain (Treede et al., 2019). Chronic pain affects one-third of the global population, with a prevalence as high as 31.54% in China, and is often accompanied by depression, anxiety, sleep disorders (Zheng et al., 2020), and declines in executive function (Berryman et al., 2014). Notably, compared with emotional factors such as depression and anxiety, executive function is more closely linked to pain perception during chronic pain recovery (Elkana et al., 2020). Although opioid medications can directly alleviate pain perception, long-term use increases pain sensitivity and amplifies pain (Borsook et al., 2018; Stern & Roberts, 2016), leading to more negative emotions in chronic pain patients and even impairing their executive function (van Steenbergen et al., 2019). Therefore, intervening in chronic pain should not only focus on reducing pain perception but, more importantly, on functional reconstruction in chronic pain patients. The biopsychosocial model directs pain treatment toward psychological factors beyond medication, such as goal-directed higher-order executive functions.

The Cyclical Model of Chronic Pain, Executive Function, Emotion Management, and Self-Management (COPES) proposes that pain impairs executive function, which further affects self-management strategies when facing pain, and in turn, poor self-regulation of pain exacerbates the negative experience of chronic pain (Caes et al., 2020). Executive function, as a higher-order cognitive process, regulates lower-order cognitive processes in goal-directed behavior, including three sub-functions: updating, shifting, and inhibition. Inhibitory function refers to the suppression of conflicting information and dominant responses when necessary (Friedman & Miyake, 2017; Miyake et al., 2000). Some studies have shown a unique link between inhibitory function and pain sensitivity (Bjekić et al., 2018; Oosterman et al., 2010), a link not found for updating and shifting functions. Therefore, this paper focuses on the interaction between pain and inhibitory function, summarizing previous research on how pain affects inhibitory function and how inhibitory function affects pain, to highlight the important role of inhibitory function in pain chronification and the perpetuation of chronic pain. Analyzing the cognitive mechanisms of the interaction between pain and inhibitory function can facilitate targeted interventions using inhibitory function for chronic pain patients.

The Overlap Between Pain and Inhibitory Function in the DLPFC

Pain is not a direct interpretation of nociceptive stimuli but rather a complex experience encompassing sensory, affective, motivational, and cognitive components that can trigger coordinated activation across multiple brain regions. Pain-related brain networks can be divided into two systems: the Neurologic Pain Signature (NPS) and the pain cognitive evaluation system (Woo et al., 2015). The NPS is closely linked to perceived pain intensity, demonstrating over 90% sensitivity and specificity in predicting experimentally induced physical pain, and includes regions such as the anterior cingulate cortex (ACC), insula (INS), and thalamus (THAL) (Wager et al., 2013). In contrast, the pain cognitive evaluation system serves as a neural signature independent of pain stimulus intensity (SIIPS1), primarily mediating top-down higher-order cognitive processing of pain information, with key brain regions including the dorsolateral prefrontal cortex (DLPFC) (Ong et al., 2019; Woo et al., 2017). From the reception of pain stimuli to the subsequent response, humans undergo three stages: unconscious sensation, conscious perception, and cognitive processing of pain information. The DLPFC begins to activate during the second stage and remains active throughout (Bastuji et al., 2016), indicating that the DLPFC is not involved in primary pain sensation but rather in cognitive processing within nociceptive processing and descending pain inhibitory systems. The DLPFC reduces the unpleasantness of pain by downregulating neural pathways from the midbrain to the thalamus, thereby influencing ACC activity (Lorenz et al., 2003). Additional research shows that during self-control of pain, negative connectivity between the DLPFC and INS significantly increases (Bräscher et al., 2016). Applications of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDS) to the DLPFC can not only alleviate chronic pain (Brighina et al., 2004; Short et al., 2011) and experimentally induced acute pain (Brighina et al., 2011; Deldar et al., 2018; Saldanha et al., 2020) but also improve negative emotions in social pain (Zhao et al., 2021).

Simultaneously, the DLPFC is a key region reflecting the developmental level of inhibitory function (Schroeter et al., 2004). TDS stimulation of the left DLPFC can significantly reduce error rates in incongruent conditions of inhibitory function tasks (Angius et al., 2019). Lee et al. (2015) found that compared with healthy individuals, chronic pain patients have thinner cortical thickness in the DLPFC and poorer inhibitory function, suggesting that alterations in the DLPFC may explain inhibitory function deficits in chronic pain patients. In studies examining pain stimuli applied after high-load inhibitory function tasks, inhibitory function consumes part of the neural network of the descending pain inhibitory system, resulting in a significant increase in NPS during pain processing. Moreover, activation of the anterior midcingulate cortex (aMCC) during inhibitory function tasks predicts activity in the aMCC and even the NPS during subsequent pain processing (Silvestrini et al., 2020). The partial overlap between inhibitory function and pain in neural circuits provides physiological

evidence for their relationship, further indicating that pain affects the execution of inhibitory function, and conversely, inhibitory function performance modulates pain experience.

Pain Affects Inhibitory Function

Both experimental and chronic pain lead to decreased inhibitory function in individuals (Bunk et al., 2019). Pain captures attention through both bottom-up and top-down processes (Sun et al., 2015), affecting individual performance in inhibitory function tasks. However, laboratory tasks used to measure inhibitory function include both information reception and information processing components. Therefore, the inhibitory function typically measured encompasses both monitoring and inhibition of conflicting information, with only the latter representing the motor system' s intrinsic inhibition of conflicting information (Chen et al., 2020). Consequently, inhibitory function itself, independent of laboratory tasks, emphasizes the top-down inhibition of conflicting information and dominant responses when necessary.

Priority Processing of Pain Signals

When pain and inhibitory function occur simultaneously, why can' t we selectively ignore pain? As an alarm signal symbolizing bodily threat (Grayson, 2016), pain conflicts with humans' most fundamental survival needs. Pain is inherently threatening, novel, and unpredictable, inevitably interrupting cognitive functions and occupying absolute priority among cognitive objects (Eccleston & Crombez, 1999). Both visual search and dot-probe tasks demonstrate that pain signals can override other signals to be prioritized by the organism (Karsdorp et al., 2018; Notebaert et al., 2011). In chronic pain patients, long-term suffering from pain-induced fear and anxiety shifts patients' motivation from completing goal-oriented tasks to controlling pain (Becker et al., 2018). This motivational shift gives pain information input greater advantage, thereby increasing attentional bias toward pain information (Crombez et al., 2013; Todd et al., 2018). The special significance of pain to the organism overshadows other signals in the process of entering consciousness; perhaps only signals that similarly threaten basic bodily needs, such as hunger (Ponomarenko & Korotkova, 2018), can compete with it.

Pain-Evoked Self-Defense Mechanisms Compete with Inhibitory Function for Cognitive Resources

Survival depends on the organism' s dynamic equilibrium. As a salient sensory stimulus that disrupts this balance, pain evokes purposeful actions in the organism to maintain and restore equilibrium (Damasio & Carvalho, 2013). Significant increases in defensive reflexes such as skin conductance, heart rate, and eye blinking during pain (Bradley et al., 2008) symbolize pain' s function in activating individual self-defense mechanisms (Tabor et al., 2017). However,

defensive reflexes are not direct consequences of nociceptive stimuli but rather represent top-down cognitive control systems based on "self-protection" (Wallwork et al., 2017). The DLPFC serves as a node in multiple important networks and participates in top-down control of pain by the organism (Seminowicz & Moayedi, 2017). Conscious identification of pain stimuli subsequently triggers individual defense against pain. The DLPFC is only continuously activated after pain enters consciousness (Bastuji et al., 2016), indicating that the DLPFC is not involved in bottom-up pain input but rather in pain-evoked self-defense mechanisms. From an evolutionary perspective, DLPFC development originates from the motor system (Wood & Grafman, 2003), while inhibition of conflicting information in inhibitory function is driven by the motor system itself (Chen et al., 2020) and completed through the frontoparietal control network (Hung et al., 2018). Therefore, it can be argued that what affects inhibitory function is not the pain signal itself but rather the self-defense mechanisms evoked by pain.

Cognitive resource theory posits that human cognitive resources are limited, emphasizing competition for limited resources between dual tasks that share the same resources. Pain-evoked self-defense mechanisms and inhibitory function share top-down cognitive resources. When performing other inhibitory function tasks during pain, the motor system must inhibit pain information on one hand and conflicting information in the task on the other. Therefore, pain' s impact on inhibitory function stems from competition for cognitive resources between self-defense mechanisms and inhibitory function.

The Influence of Inhibitory Function on Pain

As the COPES model indicates, pain does not unidirectionally affect inhibitory function; inhibitory function can influence pain experience through the mediation of self-management. Longitudinal studies have shown that inhibitory function predicts the risk of developing chronic pain in healthy older adults five years later (Rouch et al., 2021). Inhibitory function emphasizes the inhibition of conflicting information and dominant responses (Miyake et al., 2000). Pain threatens individuals' needs for belonging, autonomy, and fairness (Karos et al., 2018). The conflict between escaping from pain and approaching goal-oriented tasks constitutes conflicting information. Moreover, the priority processing of pain signals determines that pain-evoked defense mechanisms represent a dominant response.

Inhibitory Function and Pain Sensitivity

Pain sensitivity represents vigilance to pain signals, facilitating increased processing of nociceptive input. Chronic pain patients exhibit significantly higher pain sensitivity than healthy individuals (Greenspan et al., 2011). In laboratory-induced acute pain, inhibitory function is closely linked to pain sensitivity. Specifically, higher inhibitory function is significantly associated with higher pain tolerance and endurance intensity, as well as lower pain thresholds (Bjekić

et al., 2018; Oosterman et al., 2010; Zhou, Kemp, et al., 2015). Transient decreases in pain sensitivity following exercise are also significantly correlated with inhibitory function (Gajsar et al., 2020). Facilitated perception of pain stimuli typically reflects the efficiency of endogenous pain inhibition, as endogenous pain inhibition may indicate fundamental changes in the pain perception system (Yarnitsky et al., 2014). Conditioned pain modulation (CPM) is commonly used as an indicator of individual endogenous pain inhibition. Compared with younger individuals, CPM efficiency declines in older adults (Tang et al., 2016). With increasing age, declining inhibitory function in older adults positively correlates with CPM, and this correlation remains significant after controlling for age (Marouf et al., 2014), indicating the stability of the relationship between inhibitory function and CPM. Further research in older adults has found that low cognitive function individuals exhibit poorer CPM compared to high cognitive function individuals including inhibitory function (Lithfous et al., 2019).

The relationship between inhibitory function and CPM seems to partially explain the high risk of chronic pain in older adults; however, contradictory results also exist. Even though white matter connectivity between the DLPFC and periaqueductal gray (PAG) can explain variance in CPM, inhibitory function shows no significant correlation with CPM (Bunk et al., 2020). Similarly, contradictory results exist in the relationship between inhibitory function and exercise-induced reductions in pain sensitivity (Gajsar et al., 2021). Inconsistent results are often explained by different experimental paradigms, but more importantly, they suggest weak associations between inhibitory function and both CPM and pain sensitivity (Bunk et al., 2019). This indicates that other moderating variables may exist between inhibitory function and pain sensitivity, or that inhibitory function may be more involved in other top-down pain control systems (Verhoeven et al., 2014).

Inhibitory Function and Distraction Analgesia

Distraction analgesia can shift partial attention away from pain toward a distraction task. As the difficulty of the distraction task increases, the perceived pain intensity gradually decreases (Buhle & Wager, 2010; Rischer et al., 2020; Verhoeven et al., 2011), and the effect of distraction analgesia significantly correlates with inhibitory function (Rischer et al., 2020). Inhibitory function may be involved in the process of shifting attention from pain to the distraction task, as in younger individuals, the P3(Cz) component during the later inhibition process of inhibitory function tasks significantly correlates with the degree of pain neglect, a relationship not observed in older adults (Zhou, Després, et al., 2015). This result may be due to abnormal inhibitory function in older adults that prevents effective pain inhibition during tasks. Furthermore, distraction analgesia can reflect not only the degree of pain avoidance and shift to distraction tasks but also the interference of pain on cognitive tasks. When using a tone detection task as the distraction task, inhibitory function significantly positively correlates with performance on the tone detection task (Karsdorp et

al., 2014; Verhoeven et al., 2011). Even in studies where inhibitory function is not associated with pain perception, inhibitory function can still predict performance on the tone detection task (Verhoeven et al., 2014), indicating that high inhibitory function individuals experience less pain interference compared to low inhibitory function individuals.

Further research indicates that other moderating variables exist between inhibitory function and distraction task performance, such as pain-related fear. When pain-related fear is low, inhibitory function can predict hit rates in distraction tasks, but this predictive relationship is not significant when pain-related fear is high (Karsdorp et al., 2014). Two explanations exist for this result: first, higher pain-related fear promotes greater pain escape rather than top-down pain inhibition; second, higher pain-related fear evokes another automatic pain inhibition system that compensates for the role of inhibitory function. Interestingly, higher inhibitory function can accelerate the extinction of pain-related fear (Niederstrasser et al., 2017), indicating that inhibitory function can reduce pain interference in cognitive tasks by inhibiting pain-related fear. In addition to pain-related fear, pain catastrophizing also moderates the relationship between inhibitory function and distraction analgesia effects. Under low pain catastrophizing conditions, the relationship between inhibitory function and pain intensity reduction through distraction is not significant, whereas under high pain catastrophizing conditions, inhibitory function significantly positively correlates with reduced pain intensity (Rischer et al., 2020). Reduced pain intensity facilitates better cognitive performance. Pain catastrophizing increases pain' s capture of attention, and the correlation between inhibitory function and analgesic effects only under high pain catastrophizing conditions demonstrates the unique role of inhibitory function in distraction analgesia, with the DLPFC also showing specificity in distraction analgesia (Zhao et al., 2021).

Although numerous studies indicate that better inhibitory function improves pain experience and reduces pain interference, regrettably, because inhibitory function as an individual trait variable is difficult to manipulate, most research remains correlational. Future studies need to control inhibitory function (e.g., through cognitive training to enhance inhibitory function) to clarify the causal relationship between inhibitory function and different aspects of pain.

The Role of Inhibitory Function in Pain Chronification and the Perpetuation of Chronic Pain

Many chronic pain conditions have no clear etiology, with the only explanation being tissue damage in a body part resulting from previous acute pain. How acute pain transforms into chronic pain remains an unresolved question. Borsook et al. (2018) propose that the development of chronic pain involves changes in brain network efficiency, connectivity, and strength. Repeated episodes of pain, accompanied by emotional and cognitive changes, drive gradual quantitative changes in individual brain networks toward chronic pain, with the final qualitative change making chronic pain possible. Thinner DLPFC can increase

the risk of chronic pain, and during chronic pain, the DLPFC exhibits persistent structural and functional deficits, which can be reversed upon chronic pain recovery (Seminowicz & Moayedi, 2017; Seminowicz et al., 2011; Čeko et al., 2015). The entire process from acute to chronic pain and recovery is accompanied by DLPFC changes, indicating that top-down pain control systems play an important role in pain chronification and the perpetuation of chronic pain.

Pain Expectation is Accompanied by DLPFC Activation

Frequent pain experiences endow pain with special meaning, and cognition can manipulate the final output of pain perception. Expectation is a precursor to pain perception. Pain stimuli contrast with pain expectations; when consistent, existing pain meaning is maintained, but when inconsistent, learning updates pain meaning to form expectations for the next pain occurrence (Wiech, 2016). Using placebos to manipulate pain expectations significantly activates bilateral DLPFC, and this activation negatively correlates with subsequent pain reduction intensity (Wager et al., 2004). Both high and low expectations of pain intensity significantly activate the DLPFC, with activation significantly higher for high expectations than for low expectations (Lobanov et al., 2014). This result suggests that when the DLPFC encodes pain expectations, if the impending pain is anticipated to be high-intensity, it evokes a higher degree of pain descending inhibitory systems, as DLPFC activation also signifies increased self-control over pain (Wiech et al., 2006). Moreover, DLPFC activation is higher when pain stimuli and expectations are inconsistent compared to when they are consistent (Henderson et al., 2020), indicating that more inhibitory function is needed to suppress conflicting information arising from inconsistency between pain stimuli and expectations.

Although no direct evidence points to inhibitory function, the role of the DLPFC in pain expectation suggests that the emergence of pain expectation spontaneously activates inhibitory function to prepare for suppressing impending pain information. When pain stimuli and expectations are inconsistent, inhibitory function suppresses inconsistent information to align pain stimuli with expectations, thereby reducing the deterioration of subsequent pain expectations. Pain expectations are updated from previous to subsequent occurrences through learning, making the role of inhibitory function particularly important in pain learning processes.

High Inhibitory Function Reduces Pain Interference

The new generation fear-avoidance model (Crombez et al., 2012) emphasizes the motivational function of pain. Acute pain only briefly interferes with daily activities without affecting individuals' motivation to pursue other goal-oriented tasks. In contrast, persistent pain continuously affects daily activities, with motivation to complete daily activities being chronically hindered by motivation to avoid pain. Moreover, chronic interference of daily activities by pain intensifies individuals' aversion and fear of pain, thereby increasing expected

pain intensity when pain next occurs. When individuals perceive pain as highly threatening, pain-related fear enhances motivation to avoid pain, further interfering with daily activities to a greater extent (Vlaeyen et al., 2016). Therefore, pain interference with daily activities is an important factor in maintaining and developing chronic pain, to the extent that chronic pain can be redefined as chronic interference (Eccleston & Crombez, 1999).

Performance on distraction tasks in distraction analgesia studies can measure the degree of pain interference in individuals, with better distraction task performance indicating less pain interference. Numerous studies have found that inhibitory function positively correlates with distraction task performance (Karsdorp et al., 2014; Verhoeven et al., 2014; Verhoeven et al., 2011), indicating that chronic pain patients with high inhibitory function can better suppress pain interference with daily activities. Reduced pain interference can decrease subsequent negative expectations of pain, thereby reducing inconsistency between pain stimuli and expectations. In this case, pain meaning will be redefined, and learning new pain meaning will help prevent pain chronification and the perpetuation of chronic pain. Conversely, when reduced pain interference increases positive expectations of pain, it facilitates chronic pain recovery.

Summary

[Figure 1: see original paper] The Interaction Between Pain and Inhibitory Function
Note: "-" indicates decrease, "+" indicates increase.

Based on the COPES model framework, the interaction between pain and inhibitory function (as shown in Figure 1) is an important factor in pain chronification and the perpetuation of chronic pain. On one hand, pain evokes individual self-defense mechanisms that compete with inhibitory function for cognitive resources in top-down pain control. Pain signals threaten basic human survival needs, making it unavoidable to prioritize pain inhibition when inhibiting pain and other tasks occur simultaneously, thus pain inevitably interferes with inhibitory function. On the other hand, inhibitory function also affects pain experience. High inhibitory function individuals exhibit lower pain sensitivity, and more importantly, inhibitory function influences pain interference with daily activities. Compared with low inhibitory function individuals, high inhibitory function individuals demonstrate higher efficiency in coping with pain interference, thereby reducing negative experiences caused by pain interference. Learning from reduced negative experiences can update pain meaning and increase positive expectations for the next pain occurrence.

Clinical Application of Inhibitory Function Interventions for Chronic Pain

Young people currently experiencing chronic pain or who have recovered from chronic pain exhibit significantly higher inhibitory function than young peo-

ple who have never experienced chronic pain (Hollins et al., 2020). Stronger frontal lobe function in young people enables inhibitory function training during chronic pain, whereas older adults with poorer frontal lobe function cannot reverse inhibitory function during chronic pain. This result not only explains why older adults have higher chronic pain risk than young people but also highlights the special significance of inhibitory function training for treating chronic pain in elderly patients. Pharmacological treatment increases drug dependence in chronic pain patients, which is particularly detrimental for older adults with already declining physical function (Zhang et al., 2021), whereas inhibitory function training directly targets functional reconstruction in chronic pain patients. Clinical research can combine inhibitory function with other effective interventions such as exercise, music, and optimism to a greater extent reduce drug dependence and pain experience in chronic pain patients, enabling them to autonomously control pain through their own capacity rather than relying on passive pharmacological control.

The difficulty of experimentally controlling inhibitory function has resulted in numerous correlational studies, leaving the cognitive mechanisms through which inhibitory function affects pain experience unclear. Although longitudinal studies show that inhibitory function can predict chronic pain (Rouch et al., 2021), pain chronification encompasses multiple complex experiences including sensory, cognitive, affective, and motivational components, making it impossible to specify the uniqueness of inhibitory function in predicting chronic pain. DLPFC changes accompanying pain expectation indirectly reflect the relationship between inhibitory function and pain expectation, but substantial research is still needed to directly investigate the role of inhibitory function in pain expectation. The relationship between inhibitory function and pain interference demonstrates stability. Research shows that trait anxiety and trait mindfulness moderate the trade-off between pain perception and pain interference (Tabry et al., 2020), but whether they moderate the relationship between inhibitory function and pain interference requires further investigation. Exploring moderating factors in the relationship between inhibitory function and pain interference can deepen understanding of the cognitive mechanisms and individual differences in how inhibitory function affects pain interference. In summary, future research should employ methods to control inhibitory function to clarify causal relationships between inhibitory function and pain, which will facilitate targeted clinical interventions using inhibitory function for chronic pain.

Exploring the Role of Inhibitory Function in Pain Fear Extinction

Pain-related fear can strengthen the connection between conditioned and unconditioned stimuli, leading to generalization of pain fear and further deteriorating pain perception and psychological experience in chronic pain patients (Su et al., 2016; Zheng et al., 2016). High and low inhibitory function individuals show no difference in the intensity of pain fear generalization, but low inhibitory function individuals extinguish pain fear generalization more slowly than high

inhibitory function individuals (Niederstrasser et al., 2017). When fear of equal intensity emerges, low inhibitory function individuals have difficulty inhibiting fear responses, resulting in longer-lasting fear than in high inhibitory function individuals. Since current psychological-behavioral therapies for pain fear extinction show unstable effects (Wang et al., 2017), further exploring the role of inhibitory function in pain fear extinction can enhance intervention effectiveness. Similar to pain fear extinction, whether the extinction speed of pain perception and pain catastrophizing processes is affected by inhibitory function, and the relationship between DLPFC changes during pain relief and inhibitory function, remain questions for future research to clarify.

References

Song, X.J., Fan, B.F., Wan, Y., Zhang, D.Y., Lv, Y., & Han, J.S. (2020). Brief analysis of the new definition of pain revised by the International Association for the Study of Pain. *Chinese Journal of Pain Medicine*, 26(9), 641–644.

Su, L., Yang, Z., Todd Jackson, Chen, H., & Huang, C.Z. (2016). The formation of pain fear and its impact on pain perception. *Advances in Psychological Science*, 24(8), 1228–1236.

Sun, Z.K., Wang, J.Y., & Luo, F. (2015). The interaction between pain and attention: Bottom-up capture effect and top-down modulation. *Advances in Psychological Science*, 23(12), 2096–2106.

Tang, Y., Tang, D.D., Peng, W.W., & Hu, L. (2016). "Pain inhibits pain" : Conditioned pain modulation. *Chinese Science Bulletin*, 61(6), 642–653.

Wang, X.L., Tang, D.D., Jin, Q.Q., Peng, W.W., & Hu, L. (2017). Neural mechanisms of pain fear and its extinction. *Advances in Psychological Science*, 25(10), 1758–1768.

Zhang, L.B., Lv, X.J., & Hu, L. (2021). Cognitive neuroscience of pain development: Current status and future trends. *Scientia Sinica (Vitae)*, 51(6), 641–652.

Zheng, P.P., Lv, Z.Y., & Todd Jackson. (2016). The formation, generalization, and extinction of pain fear. *Advances in Psychological Science*, 24(7), 1065–1076.

Angius, L., Santarnecchi, E., Pascual-Leone, A., & Marcora, S. M. (2019). Transcranial direct current stimulation over the left dorsolateral prefrontal cortex improves inhibitory control and endurance performance in healthy individuals. *Neuroscience*, 419, 34–45.

Bastuji, H., Frot, M., Perchet, C., Magnin, M., & Garcia-Larrea, L. (2016). Pain networks from the inside: Spatiotemporal analysis of brain responses leading from nociception to conscious perception. *Human Brain Mapping*, 37(12), 4301–4315.

Becker, S., Navratilova, E., Nees, F., & Van Damme, S. (2018). Emotional and motivational pain processing: Current state of knowledge and perspectives in translational research. *Pain Research & Management*, 2018, Article 5457870. https://doi.org/10.1155/2018/5457870

Berryman, C., Stanton, T. R., Bowering, K. J., Tabor, A., McFarlane, A., & Moseley, G. L. (2014). Do people with chronic pain have impaired executive function? A meta-analytical review. *Clinical Psychology Review*, 34(7), 563–579.

Bjekić, J., Živanović, M., Purić, D., Oosterman, J. M., & Filipović, S. R. (2018). Pain and executive functions: A unique relationship between Stroop task and experimentally induced pain. *Psychological Research*, 82(3), 444–453.

Borsook, D., Youssef, A. M., Barakat, N., Sieberg, C. B., & Elman, I. (2018). Subliminal (latent) processing of pain and its evolution to conscious awareness. *Neuroscience and Biobehavioral Reviews*, 88, 1–15.

Bradley, M. M., Silakowski, T., & Lang, P. J. (2008). Fear of pain and defensive activation. *Pain*, 137(1), 156–163.

Brighina, F., De Tommaso, M., Giglia, F., Scalia, S., Cosentino, G., Puma, A., ···& Fierro, B. (2011). Modulation of pain perception by transcranial magnetic stimulation of left prefrontal cortex. *The Journal of Headache and Pain*, 12(2), 185–191.

Brighina, F., Piazza, A., Vitello, G., Aloisio, A., Palermo, A., Daniele, O., & Fierro, B. (2004). rTMS of the prefrontal cortex in the treatment of chronic migraine: A pilot study. *Journal of the Neurological Sciences*, 227(1), 67–71.

Bräscher, A. K., Becker, S., Hoeppli, M. E., & Schweinhardt, P. (2016). Different brain circuitries mediating controllable and uncontrollable pain. *Journal of Neuroscience*, 36(18), 5013–5025.

Buhle, J., & Wager, T. D. (2010). Performance-dependent inhibition of pain by an executive working memory task. *Pain*, 149(1), 19–26.

Bunk, S., Emch, M., Koch, K., Lautenbacher, S., Zuidema, S., & Kunz, M. (2020). Pain processing in older adults and its association with prefrontal characteristics. *Brain Sciences*, 10(8), Article 477. https://doi.org/10.3390/brainsci10080477

Bunk, S., Preis, L., Zuidema, S., Lautenbacher, S., & Kunz, M. (2019). Executive functions and pain: A systematic review. *Zeitschrift fur Neuropsychologie*, 30(3), 169–196.

Caes, L., Dick, B., Duncan, C., & Allan, J. (2020). The cyclical relation between chronic pain, executive functioning, emotional regulation, and self-management. *Journal of Pediatric Psychology*, 46(3), 286–292.

Čeko, M., Shir, Y., Ouellet, J. A., Ware, M. A., Stone, L. S., & Seminowicz, D. A. (2015). Partial recovery of abnormal insula and dorsolateral prefrontal

connectivity to cognitive networks in chronic low back pain after treatment. *Human Brain Mapping*, 36(6), 2075–2092.

Chen, G., Li, Y., Dong, Z., Wang, R., Zhao, D., Obeso, I., & Yu, S. (2020). Response inhibition alterations in migraine: Evidence from event-related potentials and evoked oscillations. *The Journal of Headache and Pain*, 21(1), 1–12.

Crombez, G., Eccleston, C., Van Damme, S., Vlaeyen, J. W., & Karoly, P. (2012). Fear-avoidance model of chronic pain: The next generation. *The Clinical Journal of Pain*, 28(6), 475–483.

Crombez, G., Van Ryckeghem, D., Eccleston, C., & Van Damme, S. (2013). Attentional bias to pain-related information: A meta-analysis. *Pain*, 154(4), 497–510.

Damasio, A., & Carvalho, G. B. (2013). The nature of feelings: Evolutionary and neurobiological origins. *Nature Reviews. Neuroscience*, 14(2), 143–152.

Deldar, Z., Rustamov, N., Bois, S., Blanchette, I., & Piché, M. (2018). Enhancement of pain inhibition by working memory with anodal transcranial direct current stimulation of the left dorsolateral prefrontal cortex. *The Journal of Physiological Sciences*, 68(6), 825–836.

Eccleston, C., & Crombez, G. (1999). Pain demands attention: A cognitive-affective model of the interruptive function of pain. *Psychological Bulletin*, 125(3), 356–366.

Elkana, O., Conti, Y., Heyman, O., Hamdan, S., Franko, M., & Vatine, J. J. (2020). The associations between executive functions and different aspects of perceived pain, beyond the influence of depression, in rehabilitation setting. *Neuropsychological Rehabilitation*, 30(7), 1303–1317.

Friedman, N. P., & Miyake, A. (2017). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex*, 86, 186–204.

Gajsar, H., Meyer, M., Hasenbring, M. I., & Vaegter, H. B. (2021). Pain and executive function: No association between remote exercise-induced hypoalgesia and cognitive inhibition in pain-free participants. *Scandinavian Journal of Pain*. Advance online publication. https://doi.org/10.1515/sjpain-2021-0071

Gajsar, H., Titze, C., Konietzny, K., Meyer, M., Vaegter, H. B., & Hasenbring, M. I. (2020). Cognitive inhibition correlates with exercise-induced hypoalgesia after aerobic bicycling in pain-free participants. *Journal of Pain Research*, 13, 847–858.

Grayson, M. (2016). Pain. *Nature*, 535(7611), S1.

Greenspan, J. D., Slade, G. D., Bair, E., Dubner, R., Fillingim, R. B., Ohrbach, R., ···& Maixner, W. (2011). Pain sensitivity risk factors for chronic TMD:

Descriptive data and empirically identified domains from the OPPERA case control study. *The Journal of Pain*, 12(11), T61–T74.

Henderson, L. A., Di Pietro, F., Youssef, A. M., Lee, S., Tam, S., Akhter, R., ⋯& Macey, P. M. (2020). Effect of expectation on pain processing: A psychophysics and functional MRI analysis. *Frontiers in Neuroscience*, 14, Article 6. https://doi.org/10.3389/fnins.2020.00006

Hollins, M., Bryen, C. P., & Taylor, D. (2020). Effects of chronic pain history on perceptual and cognitive inhibition. *Experimental Brain Research*, 238(2), 321–332.

Hung, Y., Gaillard, S. L., Yarmak, P., & Arsalidou, M. (2018). Dissociations of cognitive inhibition, response inhibition, and emotional interference: Voxelwise ALE meta-analyses of fMRI studies. *Human Brain Mapping*, 39(10), 4065–4082.

Karos, K., Williams, A., Meulders, A., & Vlaeyen, J. (2018). Pain as a threat to the social self: A motivational account. *Pain*, 159(9), 1690–1695.

Karsdorp, P. A., Geenen, R., & Vlaeyen, J. W. (2014). Response inhibition predicts painful task duration and performance in healthy individuals performing a cold pressor task in a motivational context. *European Journal of Pain*, 18(1), 92–100.

Karsdorp, P. A., Schrooten, M., & Geenen, R. (2018). Attentional control and the competition between nonpain goals and the threat of pain. *European Journal of Pain*, 22(1), 181–190.

Lee, D. H., Lee, K. J., Cho, K. I., et al. (2015). Brain alterations and neurocognitive dysfunction in patients with complex regional pain syndrome. *The Journal of Pain*, 16(6), 580–586.

Lithfous, S., Després, O., Pebayle, T., & Dufour, A. (2019). Modification of descending analgesia in aging: Critical role of the prefrontal cortex. *The Clinical Journal of Pain*, 35(1), 23–30.

Lobanov, O. V., Zeidan, F., McHaffie, J. G., Kraft, R. A., & Coghill, R. C. (2014). From cue to meaning: Brain mechanisms supporting the construction of expectations of pain. *Pain*, 155(1), 129–136.

Lorenz, J., Minoshima, S., & Casey, K. L. (2003). Keeping pain out of mind: The role of the dorsolateral prefrontal cortex in pain modulation. *Brain*, 126(5), 1079–1091.

Marouf, R., Caron, S., Lussier, M., Bherer, L., Piché, M., & Rainville, P. (2014). Reduced pain inhibition is associated with reduced cognitive inhibition in healthy aging. *Pain*, 155(3), 494–502.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology*, 41(1), 49–100.

Niederstrasser, N. G., Meulders, A., Meulders, M., Struyf, D., & Vlaeyen, J. W. (2017). Executive functions deficits impair extinction of generalization of fear of movement-related pain. *European Journal of Pain*, 21(5), 886–899.

Notebaert, L., Crombez, G., Vogt, J., De Houwer, J., Van Damme, S., & Theeuwes, J. (2011). Attempts to control pain prioritize attention towards signals of pain: An experimental study. *Pain*, 152(5), 1068–1073.

Ong, W. Y., Stohler, C. S., & Herr, D. R. (2019). Role of the prefrontal cortex in pain processing. *Molecular Neurobiology*, 56(2), 1137–1166.

Oosterman, J. M., Dijkerman, H. C., Kessels, R. P., & Scherder, E. J. (2010). A unique association between cognitive inhibition and pain sensitivity in healthy participants. *European Journal of Pain*, 14(10), 1046–1050.

Ponomarenko, A., & Korotkova, T. (2018). Hunger is a gatekeeper of pain in the brain. *Nature*, 556(7702), 445–447.

Rischer, K. M., González-Roldán, A. M., Montoya, P., Gigl, S., Anton, F., & van der Meulen, M. (2020). Distraction from pain: The role of selective attention and pain catastrophizing. *European Journal of Pain*, 24(10), 1880–1891.

Rouch, I., Dorey, J. M., Strippoli, M. P. F., Gholam, M., Marques-Vidal, P., Laurent, B., ···& Preisig, M. (2021). Does cognitive functioning predict chronic pain in older adult? Results from the CoLaus|PsyCoLaus longitudinal study. *The Journal of Pain*, 22(8), 905–913.

Saldanha, J. S., Zortea, M., Deliberali, C. B., Nitsche, M. A., Kuo, M. F., Torres, I. L. D. S., ···& Caumo, W. (2020). Impact of age on tDCS effects on pain threshold and working memory: Results of a proof of concept cross-over randomized controlled study. *Frontiers in Aging Neuroscience*, 12, Article 189. https://doi.org/10.3389/fnagi.2020.00189

Schroeter, M. L., Zysset, S., Wahl, M., & von Cramon, D. Y. (2004). Prefrontal activation due to Stroop interference increases during development—An event-related fNIRS study. *Neuroimage*, 23(4), 1317–1325.

Seminowicz, D. A., & Moayedi, M. (2017). The dorsolateral prefrontal cortex in acute and chronic pain. *The Journal of Pain*, 18(9), 1027–1035.

Seminowicz, D. A., Wideman, T. H., Naso, L., Hatami-Khoroushahi, Z., Fallatah, S., Ware, M. A., ···& Stone, L. S. (2011). Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *Journal of Neuroscience*, 31(20), 7540–7550.

Short, E. B., Borckardt, J. J., Anderson, B. S., Frohman, H., Beam, W., Reeves, S. T., & George, M. S. (2011). Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: A randomized, controlled pilot study. *Pain*, 152(11), 2477–2484.

Silvestrini, N., Chen, J. I., Piché, M., Roy, M., Vachon-Presseau, E., Woo, C. W., ···& Rainville, P. (2020). Distinct fMRI patterns colocalized in the cingulate

cortex underlie the after-effects of cognitive control on pain. *Neuroimage*, 217, Article 116898. https://doi.org/10.1016/j.neuroimage.2020.116898

Stern, P., & Roberts, L. (2016). The future of pain research. *Science*, 354(6312), 564–565.

Tabor, A., Keogh, E., & Eccleston, C. (2017). Embodied pain—negotiating the boundaries of possible action. *Pain*, 158(6), 1007–1011.

Tabry, V., Vogel, T. A., Lussier, M., Brouillard, P., Buhle, J., Rainville, P., ··· & Roy, M. (2020). Inter-individual predictors of pain inhibition during performance of a competing cognitive task. *Scientific Reports*, 10(1), 1–11.

Todd, J., van Ryckeghem, D., Sharpe, L., & Crombez, G. (2018). Attentional bias to pain-related information: A meta-analysis of dot-probe studies. *Health Psychology Review*, 12(4), 419–436.

Treede, R. D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., ···& Wang, S. J. (2019). Chronic pain as a symptom or a disease: The IASP classification of chronic pain for the International Classification of Diseases (ICD-11). *Pain*, 160(1), 19–27.

van Steenbergen, H., Eikemo, M., & Leknes, S. (2019). The role of the opioid system in decision making and cognitive control: A review. *Cognitive, Affective, & Behavioral Neuroscience*, 19(3), 435–458.

Verhoeven, K., Dick, B., Eccleston, C., Goubert, L., & Crombez, G. (2014). The role of executive functioning in children' s attentional pain control: An experimental analysis. *Pain*, 155(2), 413–421.

Verhoeven, K., Van Damme, S., Eccleston, C., Van Ryckeghem, D. M., Legrain, V., & Crombez, G. (2011). Distraction from pain and executive functioning: An experimental investigation of the role of inhibition, task switching and working memory. *European Journal of Pain*, 15(8), 866–873.

Vlaeyen, J. W., Morley, S., & Crombez, G. (2016). The experimental analysis of the interruptive, interfering, and identity-distorting effects of chronic pain. *Behaviour Research and Therapy*, 86, 23–34.

Wager, T. D., Atlas, L. Y., Lindquist, M. A., Roy, M., Woo, C. W., & Kross, E. (2013). An fMRI-based neurologic signature of physical pain. *The New England Journal of Medicine*, 368(15), 1388–1397.

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., ···& Cohen, J. D. (2004). Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science*, 303(5661), 1162–1167.

Wallwork, S. B., Grabherr, L., O' Connell, N. E., Catley, M. J., & Moseley, G. L. (2017). Defensive reflexes in people with pain–a biomarker of the need to protect? A meta-analytical systematic review. *Reviews in the Neurosciences*, 28(4), 381–396.

Wiech, K. (2016). Deconstructing the sensation of pain: The influence of cognitive processes on pain perception. *Science*, 354(6312), 584–587.

Wiech, K., Kalisch, R., Weiskopf, N., Pleger, B., Stephan, K. E., & Dolan, R. J. (2006). Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. *The Journal of Neuroscience*, 26(44), 11501–11509.

Woo, C. W., Roy, M., Buhle, J. T., & Wager, T. D. (2015). Distinct brain systems mediate the effects of nociceptive input and pain self-regulation. *PLoS Biology*, 13(1), Article e1002036. https://doi.org/10.1371/journal.pbio.1002036

Woo, C. W., Schmidt, L., Krishnan, A., Jepma, M., Roy, M., Lindquist, M. A., ···& Wager, T. D. (2017). Quantifying cerebral contributions to pain beyond nociception. *Nature Communications*, 8(1), 1–14.

Wood, J. N., & Grafman, J. (2003). Human prefrontal cortex: Processing and representational perspectives. *Nature Reviews. Neuroscience*, 4(2), 139–147.

Yarnitsky, D., Granot, M., & Granovsky, Y. (2014). Pain modulation profile and pain therapy: Between pro- and antinociception. *Pain*, 155(4), 663–665.

Zhao, J., Mo, L., Bi, R., He, Z., Chen, Y., Xu, F., ···& Zhang, D. (2021). The VLPFC versus the DLPFC in downregulating social pain using reappraisal and distraction strategies. *Journal of Neuroscience*, 41(6), 1331–1343.

Zheng, Y., Zhang, T., Yang, X., Feng, Z., Qiu, F., Xin, G., ···& Liu, Y. (2020). A survey of chronic pain in China. *The Libyan Journal of Medicine*, 15(1), 1730550.

Zhou, S., Després, O., Pebayle, T., & Dufour, A. (2015). Age-related decline in cognitive pain modulation induced by distraction: Evidence from event-related potentials. *The Journal of Pain*, 16(9), 862–872.

Zhou, S., Kemp, J., Després, O., Pebayle, T., & Dufour, A. (2015). The association between inhibition and pain tolerance in the elderly: Evidence from event-related potentials. *European Journal of Pain*, 19(5), 669–676.

Note: Figure translations are in progress. See original paper for figures.