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Psychobiological Predictors and Neuromodulators of Chronic Back Pain

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ACC	anterior cingulate cortex
CBP	chronic back pain
CI	confidence interval
DMN	default mode network
DLPFC	dorsolateral prefrontal cortex
DTI	diffusion tensor imaging
EEG	electroencephalography
FA	fractional anisotropy
(f)MRI	(functional) magnetic resonance imaging
LME	linear mixed-effects model
M1	primary motor cortex
mPFC	medial prefrontal cortex
NIBS	noninvasive brain stimulation
NMDA	N-methyl-D-aspartate
PAG	periaqueductal gray
S1	primary somatosensory cortex
SBP	subacute back pain
SD	standard deviation
SE	standard error
SLF	superior longitudinal fasciculus
TBS	transcranial theta-burst stimulation
(r)TMS	repetitive transcranial magnetic stimulation

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1 INTRODUCTION

Living with chronic pain is a multifaceted experience that often greatly impacts multiple domains of an individual's functioning and may lead to social isolation and a state of suffering. The constant presence of pain can interfere with interpersonal relationships, occupational productivity, and the ability to concentrate or participate in meaningful activities, lowering overall quality of life (Furnes et al., 2015; Scholich et al., 2012). From the perspective of neurobiology, chronic pain relates to altered neural architecture and reorganization of brain networks in a persistent state of dysregulation. This sustained dysregulation within the central nervous system is characterized by altered brain plasticity, sensitization of neural pathways, and disruptions in descending pain modulation (Kuner & Flor, 2016). Importantly, it extends beyond nociceptive processing, affecting higher-order cognitive and affective functions, and influencing mood, cognition, and behavior (Apkarian et al., 2011; Kuner & Flor, 2016). Yet our knowledge about chronic pain mechanisms, especially in cases without apparent injury or disease, is greatly limited. Lack of comprehensive understanding of chronicity mechanisms further restricts effective pain prevention and management (Barroso et al., 2021). Despite the debilitating nature of chronic pain, individuals often demonstrate adaptive strategies and remarkable resilience to mitigate its effects (Sturgeon & Zautra, 2010). As accompanying neural changes in the course of chronicity are well documented, resilience may also depend on a set of neural factors whose mechanisms are not yet fully understood.

Among chronic pain conditions, chronic back pain (CBP) is highly prevalent and represents the leading cause of disability worldwide (GBD 2021 Other Musculoskeletal Disorders Collaborators, 2023; Hoy et al., 2018). Thus, identifying factors that predict the development of CBP can inform strategies to prevent its onset. Equally important is understanding the brain mechanisms involved once CBP has developed, as this knowledge can guide efforts to modulate and treat it. Notably, the psychobiological factors associated with the transition to chronic pain may differ from those involved in its amplification and maintenance. Discerning these factors can aid clinical practice in preventing and treating CBP.

The aim of this dissertation was to examine and discuss psychobiological predictors of the development of chronic back pain related to the brain structural integrity, and modulation of ongoing persistent chronic back pain by targeting the activity of brain regions implicated in the maintenance of chronic back pain. For this purpose, an introduction to CBP is laid out, starting with a brief description of nociceptive pathways and proceeding to the psychobiological mechanisms, after which brain reorganization across the course of CBP is further elaborated. Following the section on interventions for CBP with a focus on neuromodulation, the aims and hypotheses of the dissertation are introduced. Original experimental contributions are presented in the form of a study on white matter pathways predictors of CBP, and one study on the modulation of relevant regions for the maintenance of CBP using noninvasive stimulation. In the last section, the overall discussion is presented with concluding remarks and implications for clinical practice.

1.1 Chronic back pain

Chronic back pain contributes to years lived with disability more than any other pain condition (Wu et al., 2020). Therefore, it is essential to develop effective prevention and treatment strategies aimed at mechanisms and not only symptoms, for which it is important to understand how it arises, as well as how it alters neural circuits.

1.1.1 From nociception to (chronic) pain

The innate ability to detect stimuli capable of harming our bodily tissue is termed nociception. Nociception occurs when specialized somatosensory receptors with free nerve endings known as nociceptors are stimulated and an immediate reaction to protect from insult is initiated (Bourne et al., 2014). Nociceptors vary in myelination, diameter, and conduction velocity, and are located throughout the skin, muscles, joints, and viscera. While some nociceptors respond selectively to specific stimuli like mechanical pressure, cold, or heat, the most prevalent are polymodal nociceptors, which react to a range of stimuli (Dubin & Patapoutian, 2010). When nociceptors are activated, a rapid sequence of events takes place to ultimately give rise to a perception we call pain. First, information about the quality, intensity, duration, and location of noxious stimuli is transmitted to the dorsal horn in the spinal cord. Subsequently, second-order neurons primarily convey signals to the thalamus, which acts as a relay to higher-order neurons in the brain (Lee & Neumeister, 2020). These ascending pathways include both direct and indirect projections. The direct spinothalamic tract ascends from the lateral part of the thalamus mainly to the somatosensory cortices (Willis, 1985) and carries information about the magnitude, duration, and localization of pain (Lee & Neumeister, 2020). Another major nociceptive pathway ascends to the reticular formation of the brainstem and the medial thalamus. The medial spinothalamic tract projects to brain areas involved in motivational-affective regulation such as the middle and anterior cingulate cortex, limbic areas, and prefrontal cortex. Finally, the perception of pain can be modulated by descending pathways, whose main constituents are the midbrain periaqueductal gray (PAG) and the rostroventromedial medulla (RVM). The activation of descending modulatory control can terminate or limit the painful sensation/area (Bourne et al., 2014), but depending on the contextual factors and types of cells activated, it can also facilitate it (Neubert et al., 2004). Perception of acute pain is vital to avoid harm to our body and maintain its normal physiological functioning. However, sometimes pain can last long after the healing process has finished, in which case its protective function may be lost. Such pain, commonly defined by its duration or reoccurrence of more than 3 months, is termed chronic (Treede et al., 2015; Treede et al., 2019).

1.1.2 Psychobiological mechanisms of chronic pain

A great deal of research has concluded that maladaptive neuroplastic changes contribute to the pathophysiology of chronic pain conditions. Peripheral and central sensitization, dysfunctional endogenous inhibitory mechanisms, and accompanying plastic changes within brain circuits are commonly regarded as persistent pain generators (for a review, see Kuner & Flor, 2016). In addition, psychological factors such as emotion and cognition, subserved by brain regions, interact with these neurobiological processes and contribute to the development and maintenance of chronic pain, reflecting its psychobiological nature.

Following injury or inflammation, nerves in the periphery may lower their activation threshold and increase sensitivity to noxious stimuli, resulting in heightened pain perception thought to restrict further injury to the affected area. This phenomenon is regarded as peripheral sensitization (Perl et al., 1976) and involves the release of chemical mediators on a synaptic and cellular level (Voscopoulos & Lema, 2010). Typically, as the tissue heals and normal functioning is restored, afferent inputs cease, and pain is no longer perceived (Voscopoulos & Lema, 2010). However, ongoing increased transmission of peripheral inputs to the central nervous system can, in turn, lead to central sensitization. Central sensitization involves altered pain processing within the spinal cord and brain, characterized by amplified pain processing and increased sensitivity to painful stimuli and non-painful stimuli (Woolf & King, 1989; Woolf, 2011).

Already in 1965, Melzack and Wall introduced the gate control theory, which proposed that pain is shaped by central processes and modulated by inputs from the brain (Melzack & Wall, 1965). This paved the way for a recognition of the influence of cognitive, emotional, and motivational factors in pain modulation (Melzack & Casey, 1968). While the specific physiological mechanisms of the gate control theory have since been disproven, the concept that pain is not simply a direct response to tissue damage was a seminal contribution to pain research and represented an important shift from peripheral to central mechanisms (Mendell, 2014).

Today, several types of chronic pain are described and used to classify pain conditions based on pathophysiological mechanisms that are believed to generate them. When pain arises as a response to tissue damage, it is termed nociceptive, while when pain arises due to a lesion or disease of the nervous system, it is termed neuropathic. In an attempt to recognize pain resulting from altered nociceptive processing, but without evident injury, disease, or dysfunction, the International Association for the Study of Pain (IASP) task force coined the term *nociplastic pain* (Kosek et al., 2016).

Recognition that pain can be felt without obvious and measurable injury is likewise reflected in today's most accepted model of pain, the biopsychosocial model. At present, this model serves as a guiding framework among clinicians, researchers, and practitioners, as it accounts for the interplay between psychological and social factors with the biological factors in the experience of pain (Engel, 1977; Gatchel et al., 2007). Consequently, these factors are incorporated into the study of pain mechanisms and holistic pain treatment strategies (Cohen et al., 2021). The research guided by the biopsychosocial model of pain has shown that pain persistence seems to reflect central plasticity driven by dysfunctional emotional and memory processes, such as fast acquisition of fear response and impaired ability to extinguish pain-related memories, along with altered perception of body image (Flor, 2012). Nevertheless, the question remains whether the brain alterations precede chronic pain as a cause or predisposing factor to chronicity, or are they emerging as a consequence of processes such as prolonged maladaptive learning.

1.1.3 Definition

A Task Force for the Classification of Chronic Pain proposed a systematic classification of chronic pain, and the International Classification of Diseases, 11th revision (ICD-11) coding categorization has formally recognized pain as “a disease in its own right” (Treede et al., 2019, p. 20). In comparison to the former ICD-10 classification, where the codes did not focus on underlying mechanisms, a new framework prioritized pain etiology when classifying conditions. By making a clear distinction between primary and secondary chronic pain conditions, this classification defines pain with no clear etiology as primary chronic pain, while pain conditions resulting as a consequence of other diseases are defined as secondary pain syndromes (Treede et al., 2019). This practice can better guide treatment, has shown that previously “unspecified” cases of chronic pain can be assigned to appropriate groupings, and ultimately lead to chronic pain gaining better visibility (Zinboonyahgoon et al., 2021). Importantly, patients endorsed the changes in diagnostic approaches as shown by the recent survey in a large cohort (Korwisi et al., 2024). In acknowledgment of the biopsychosocial model, the new revision of the pain classification coding system also offers additional features to describe pain severity, temporal characteristics, and the presence of psychosocial factors (Treede et al., 2019).

Primary pain accounts for the majority of diagnoses in patients with chronic back pain (Finucane et al., 2020). Chronic primary pain is defined as “pain in one or more anatomic regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or significant functional disability … and that it cannot be better explained by another chronic pain condition” (Treede et al., 2015, p. 1003). In such cases, spinal imaging fails to demonstrate somatic origin, and spinal injections and/or surgery, if prescribed, fail to alleviate painful symptoms. Consistent with these findings, individuals without any painful symptoms often have structural abnormalities seen on imaging (Magora et al., 1994).

1.1.4 Aspects

Besides duration, chronic back pain encompasses various aspects that include pain intensity, temporal and spatial patterns, accompanying comorbidities, and psychological aspects. Following the distinction between the sensory and affective aspects of pain, many scales in research and clinical settings assess both the intensity and unpleasantness of pain. Individuals can report a number or a point corresponding to a certain pain level on a numerical or visual analogue scale (Turk & Melzack, 2011). Scales sometimes include additional features such as characterization of pain fluctuation patterns, where patients can indicate if they are experiencing constant pain or, for example, have pain-free periods with pain attacks in between (Freynhagen et al., 2006). Sometimes pain intensity is assessed as part of the perceived pain severity combined with reports on pain interference (how much pain is limiting daily activities) (Kerns et al., 1985). Concerning the spatial characteristics, among patients with chronic back pain, the most frequent is lower back pain (Markman et al., 2020). However, not all patients with back pain have strictly localized pain, but report the spread of the pain or other regions of the body as additional painful areas (Larsson et al., 2012). Co-occurrence of other musculoskeletal pain conditions is not rare and is associated with a worse prognosis (Øverås et al., 2021). Furthermore, it is well established that chronic pain is associated with comorbid mental disorders, primarily but not limited to depression, anxiety disorders, and addictions (Gore et al., 2012; Polatin et al., 1993). For instance, it was shown that patients diagnosed with major depressive disorder are more prone to develop chronic back pain, and vice versa, chronic back pain can precede the development of depression (Currie & Wang, 2005).

1.2 Brain reorganization across the course of chronic back pain

A large number of studies showed that the structure of the brain is changed in chronic pain conditions, together with its functioning at rest and when processing different stimuli or acute pain (Kuner & Flor, 2016). These changes are either investigated when chronic pain has already developed and compared to the brain of pain-free individuals and thus regarded as "brain signatures" (Baliki et al., 2011a; Mayr et al., 2022), or they are investigated longitudinally contrasting baseline neural parameters with the follow-up findings, in an attempt to elucidate which alterations precede and which follow the development of CBP.

1.2.1 Neural Signatures of CBP

Structural changes in the brain relate to whole brain or regional volume, cortical thickness, microstructural properties, and alterations in connectivity. Volumetric properties relate to grey matter (GM) and white matter (WM) volume, representing the size of the entire GM/WM or a specific region, and are commonly assessed using voxel-based morphometry (Ashburner & Friston, 2000). They are typically interpreted as reflecting loss or atrophy of brain tissue (e.g., Apkarian et al., 2004 in CBP). Cortical thickness of grey matter, measured via surface-based morphometry, refers to the distance between the grey and white matter boundary and the pial surface (Fischl & Dale, 2000), and is thought to reflect a complex composite of various components, including neuronal size, dendritic and synaptic density (Jernigan et al., 2011). White matter properties are commonly assessed using diffusion tensor imaging (DTI), which allows for a close look into the diffusion properties of water molecules within white matter tissue. Tractography allows for the in vivo reconstruction of major white matter pathways in humans (Conturo et al., 1999), providing the foundation for structural connectivity analysis, in which fiber connections between brain regions can be quantified (Hagmann et al., 2007). Investigation of the microstructural properties of white matter also relies on DTI, resulting in indices such as fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD). They are thought to reflect levels of general white matter integrity, axonal integrity, and myelination, respectively (Beaulieu, 2002; Song et al., 2002).

Findings on grey matter alterations in chronic pain over the past decades have been difficult to integrate, as samples differed in terms of clinical phenotypes, age, and additional factors such as medication intake or the presence of affective comorbidities. Even though the direction of change was not always uniform, in addition to a global reduction in grey matter (Baliki et al., 2011a), alterations in regions such as the somatosensory cortex, insula (Baliki et al., 2011a), hippocampus, thalamus (Apkarian et al., 2004), PAG, brainstem, and dorsolateral prefrontal and medial frontal cortices were most consistently found across studies. For example, one of the first studies investigating brain morphology in patients with back pain reported GM reduction in the DLPFC and right thalamus, which were associated with pain duration and thus interpreted as a consequence of chronicity (Apkarian et al., 2004). Another study found a decrease of GM in the somatosensory area and brainstem but an increase in GM volume/density in the left thalamus and basal ganglia (Schmidt-Wilcke et al., 2006). The latter study also found a decrease in brainstem grey matter associated with pain intensity and pain unpleasantness rather than duration, which the authors thus interpreted as a cause rather than a consequence of pain persistence (Schmidt-Wilcke et al., 2006). On the other hand, one study using a machine-learning approach found that an increase in GM matter in the somatosensory cortices and DLPFC could correctly classify CBP from healthy controls (HC) (Ung et al., 2014). This is in line with studies that found widespread cortical thickening including the somatosensory cortices (Lamichhane et al., 2021; Yang et al., 2017), which in one study were even clearly somatotopically matched with the lower back in patients with chronic low back pain (cLBP) (Kong et al., 2013).

While changes seen in areas typically involved in nociceptive processing were interpreted as a consequence of abundant and constant pain processing, alterations observed in areas not typically engaged in nociception have been explained by accompanying cognitive and emotional disturbances. For instance, lower grey matter volume in the hippocampus may be mediated by experienced stress and associated with maladaptive learning mechanisms in chronic pain (Neumann et al., 2023). Importantly, evidence from other types of chronic pain showed that typical grey matter decreases can be reversible with interventions, supporting the notion that some of the observed changes can diminish once pain is treated (Obermann et al., 2009; Rodriguez-Raecke et al., 2009).

White matter changes are also associated with chronic pain, although those are underinvestigated compared to grey matter and task-based functional studies in chronic back pain and chronic pain in general (Lieberman et al., 2014). Apart from the observation that older patients with low back pain had lower white matter volume in the left cingulate cortex compared to healthy controls (Buckalew et al., 2008), most studies have focused on white matter microstructure. Studies employing DTI showed reduced FA values in the primary somatosensory areas in patients with chronic back pain compared to pain-free individuals (Kim et al., 2020), and across different musculoskeletal conditions in the splenium of the corpus callosum (Buckalew et al., 2008; Lieberman et al., 2014) and left cingulum adjacent to the hippocampus (Lieberman et al., 2014). Moreover, higher axial diffusivity and radial diffusivity were found in the anterior limb of the internal capsule, a tract implicated in the projection from the medial thalamus to the prefrontal cortex. The FA in the splenium of the corpus callosum correlated negatively with pain duration in patients with disabling chronic low back pain (Buckalew et al., 2010), and FA in the left uncinate fasciculus, involved in emotion and memory processes, was associated with pain severity. Similar to findings in grey matter alterations, changes in white matter tracts are interpreted as involved in ascending projections coding sensory qualities of pain related to disrupted nociceptive processing, and/or tracts carrying fibers of the projections between the regions implicated in the affective and cognitive aspect of pain (Lieberman et al., 2014).

Chronic pain is commonly defined by its duration, yet what makes it distinctly different from acute pain processing is not only activation of circuits not normally active in nociception (Apkarian et al., 2011) and the augmented processing of acute painful stimuli (Giesecke et al., 2004), but also altered processing of non-painful stimuli and reorganization of cortical representations. Motor and sensorimotor cortical representations related to the painful region have long been known to shift and expand with pain persistence (Flor et al., 1997; Tsao et al., 2008). In patients with CBP, this is shown by the shift of their cortical representation of the back together with increased cortical responsivity of both painful and non-painful stimuli in this area (Flor et al., 1997). Neuroplastic changes in S1 may be related to altered tactile acuity and seem associated with pain duration (Flor et al., 1997). Since they can be reversed with treatment such as acupuncture (Kim et al., 2020), it is conceivable that they represent the consequence of chronicity.

Functional neuroimaging has provided key insights into functional reorganization in chronic pain that complements structural findings. Main approaches include resting-state functional magnetic resonance imaging (rs-fMRI), which examines spontaneous, intrinsic connectivity between brain regions in absence of any task, and task-based functional magnetic resonance imaging (fMRI), which measures brain responses to stimulus-evoked pain or during various tasks (for a review, see Lee & Tracey, 2013). Together, these methods have revealed what seems to be a robust and generalized “pain imprint” on the brain in a chronic state. Observed across several chronic pain conditions (Mansour et al., 2016), this imprint is characterized by a disruption of brain large-network organization (Barroso et al., 2021), with prefrontal connections to striatal and limbic regions having the prominent role (Vachon-Presseau et al., 2016b). For example, brain regions involved in emotion and motivation-related circuitry were most prominently activated as patients with chronic back pain reported fluctuations of their ongoing pain, with increased medial prefrontal cortex activity overlapping with high sustained pain (Baliki et al., 2006). Similarly, there is a shift from somatosensory to the prefrontal modules of the default mode network (DMN), circuitry active when there is no engagement in a specific task, and the magnitude of this change is related to the magnitude of reported pain (Mansour et al., 2016). In particular, the medial prefrontal cortex, representing the main hub of DMN, has shown decreased connectivity to other regions of DMN and increased oscillations in higher frequency ranges (Baliki et al., 2014). In a recent study, the nucleus accumbens showed reduced amplitude of spontaneous fluctuations in the low-frequency range with the persistence of pain, suggesting this may be a signature of CBP (Makary et al., 2020). Overall, these findings are suggestive of the important role of regions implicated in emotional, motivational, and reward processing.

1.2.2 Neural Predictors of CBP

Comparison of the brain of patients with chronic pain to the brain of healthy controls cannot identify whether the detected changes are a consequence of chronic pain or themselves drive the development of chronic pain. In other words, risk and resilience factors cannot be deciphered if a critical time window is not targeted for investigation. To address this question, many studies targeted the transition phase termed *subacute pain*, which is usually defined as pain lasting between 7 to 12 weeks (Dionne et al., 2008; Löffler et al., 2022; Nees et al., 2019), although other time ranges, such as 4 to 16 weeks, have also been defined as subacute (Baliki et al., 2012). During this phase, patients are at risk of developing chronic pain but are not yet considered chronic, as per the definition confined to pain duration (Treede et al., 2015).

The previously identified changes in corticolimbic and corticostriatal circuits also seem to play an important role in the development of chronic back pain (Hashmi et al., 2013). In a longitudinally followed sample of patients with subacute back pain, decreased hippocampal and amygdala grey matter volumes were found to be predictive of the transition to the chronic pain state (Vachon-Presseau et al., 2016a). Corticostriatal circuitry with greater connectivity between prefrontal cortex and striatum was previously regarded as the key factor in predicting transition to the chronic state, reflected in greater pain severity in a one-year follow-up (Baliki et al., 2012) and could recently be related to encoding of reward-related stimuli (Löffler et al., 2022). The importance of corticostriatal connectivity in chronic pain is further fostered by research into dopamine dysfunction dependent on the reward mesocorticolimbic circuitry identified in conditions such as fibromyalgia (Wood et al., 2007) and lower dopamine receptor activity in the striatum of patients with back pain was associated with greater pain sensitivity (Martikainen et al., 2015). In line with this, the smaller nucleus accumbens volume predicted persistent back pain (Makary et al., 2020). Taken together, the evident role of corticolimbic and corticostriatal circuits in the development of chronic pain points to the potential predisposing role of processes that it regulates, such as motivation, reward, and learning. In addition, as changes within these circuits seem to precede the onset of chronic pain, early interventions targeting these regions may help prevent the transition to chronic pain and consolidation of maladaptive processes (Flor, 2012).

Concerning changes in brain structural integrity and connectivity in back pain, a study by Mansour et al. found that lower fractional anisotropy of the temporal part of the left superior longitudinal fasciculus, external capsule, parts of the corpus callosum, and parts of the internal capsule could predict patients who developed chronic back pain at 1-year follow-up (Mansour et al., 2013). Furthermore, differential structural connectivity to the medial prefrontal cortex supported previous evidence on functional predictors within this region (Mansour et al., 2013). White matter contribution to chronicity has been underinvestigated (Lieberman et al., 2014) and its role in the development of chronic back pain needs to be further investigated.

1.3 Interventions for chronic back pain

Today, pain management is dominated by a combination of pharmacological and non-pharmacological approaches integrated in a multimodal approach, which utilizes neuroscientific progress in research and follows the biopsychosocial model (Flor et al., 2023).

Spinal surgery is generally ineffective in treating CBP without evident peripheral etiology (Evans et al., 2023), but as weakness of the trunk muscles has been associated with the chronicity of back pain (Maher et al., 2017), non-surgical interventions such as exercises, strength training programs, or electrical muscle stimulation have been conducted to improve postural stability and showed some level of effectiveness (Konrad et al., 2020; Lee & Kang, 2016; Searle et al., 2015). Alternative somatic methods such as acupuncture seem to be superior to no treatment but show a small to moderate magnitude of the effect, and no substantial benefit over placebo (Hutchinson et al., 2012; Sherman et al., 2009). A broad array of pharmacological treatments recommended for patients with chronic back pain range from muscle relaxants and nonsteroidal anti-inflammatory drugs (NSAIDs) to opioid medication. However, non-opioids often offer short-term relief and have limited efficacy (van der Gaag et al., 2020), while usage of opioids is restricted to the most severe cases not responsive to NSAIDs, as they have numerous adverse effects (Martell et al., 2007). In addition, the administration of the placebo opioids linked to patients' expectations and endogenous inhibition of pain had beneficial effects on a range of clinical back pain aspects (Colloca, 2019; Klinger et al., 2017).

Psychotherapeutic approaches have long been proposed to treat pain experience and its manifestations (Turk & Flor, 1984). In line with the biopsychosocial model and cognitive-behavioral approach to the development and maintenance of chronic pain (Turk, 2003), cognitive-behavioral and behavioral therapy have shown efficacy across randomized controlled trials for chronic low back pain (Henschke et al., 2010). A recent study concluded that exposure therapy and cognitive-behavioral therapy can reduce fear of movement, enhance self-efficacy, and lower disability associated with CBP (Schemer et al., 2019). Likewise, pain reprocessing therapy, aimed at changing the patient's beliefs about the threat value of pain signal was effective in treating primary CBP more than usual care or placebo (Ashar et al., 2022). Importantly, maladaptive cognition and behavior seen in CBP relate to the plasticity of higher-order brain centers (Moseley & Flor, 2012). Cortical reorganization seen in chronic states thus can be targeted with interventions such as sensory stimulation and motor training (Moseley & Flor, 2012), as well as approaches such as virtual reality that can help in combating the fear of movement and catastrophizing, but also reduce pain intensity and affect neural networks associated with chronic pain (Čeko et al., 2024).

Targeting brain regions implicated in the development of CBP, amplification, and maintenance could be achieved with interventions such as biofeedback (Sielski et al., 2017), sensory training (Kälin et al., 2016), previously mentioned psychological interventions, and virtual reality training, or by directly interfering with brain activity with methods such as neuromodulation (Knotkova et al., 2021). Apart from clinical studies that utilize different protocols to investigate which parameters would be optimal to yield a reduction in pain and pain-affected behaviors, neuromodulation can be employed in a mechanistic approach to investigate which brain regions are causally implicated in the up and downregulation of pain (Kandić et al., 2021) and could prospectively also function as novel treatment approaches.

1.3.1 Neuromodulation in CBP

Neuromodulation is defined as any intervention that can interfere with spontaneous neural activity or induce plasticity changes in the periphery, spine, or brain (Moisset et al., 2016). In the present work, the focus is only on brain modulation and the significance of noninvasive approaches to target central psychobiological mechanisms of CBP. Noninvasive brain stimulation (NIBS) can be achieved through electrical current (transcranial electric stimulation; TES) that can alter membrane potentials (Paulus, 2011) or magnetic external stimuli (transcranial magnetic stimulation; TMS) delivered through the coil, which induce electrical field of sufficient strength to interfere with brain activity in the stimulated region and evoke action potential (Stewart & Walsh, 2006).

NIBS studies can be conducted in a therapeutic or mechanistic context. In the therapeutic context, the effects of brain stimulation are usually assessed after several sessions, and the overall goal is to relieve certain clinical symptoms. In the mechanistic context, stimulation effects are assessed during or immediately after stimulation, so that involvement of the stimulated brain region can be examined in its relevance for the task or behavior in question (Stewart & Walsh, 2006). In pain research, NIBS has helped elucidate brain circuits involved in the maintenance and development of chronic pain and has shown that both the sensory and affective expression of clinical pain can be modulated (for a review, see Kandić et al., 2021).

The success rate for therapeutic neuromodulation in chronic pain varies considerably across studies, as different targets, stimulation parameters, dosages, and underlying pain etiologies were examined, and the overall number of studies is still limited. Most studies to date targeted the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) with conflicting results in clinical improvement, and most of the evidence is confined to neuropathic pain (Lefaucheur et al., 2020; O'Connell et al., 2018). Current evidence regards high-frequency rTMS of the primary motor cortex (M1) contralateral to the painful side as efficient for the reduction of neuropathic pain and provides moderate evidence of the efficacy of high-frequency rTMS of the DLPFC for patients with fibromyalgia (Lefaucheur et al., 2020; O'Connell et al., 2018). The current body of research, however, provides limited knowledge regarding its efficacy for other types of chronic pain.

NIBS studies in primary chronic back pain remain sparse (for reviews, see O'Connell et al., 2018; Olechowski et al., 2023). One of the first studies that used transcranial direct current stimulation (tDCS) failed to show any effect of M1 stimulation on experimental and ongoing pain in patients with low back pain (Luedtke et al., 2012), while different stimulation protocols, including higher intensity and more focal electrodes, provided evidence that targeting M1 can reduce experimental pain (Jiang et al., 2020) and rTMS over M1 compared to sham resulted in reduced clinical pain scores in patients with back pain (Ambriz-Tututi et al., 2016). One of the proposed mechanisms of action of M1 on pain is through activation of the descending inhibitory pathway, due to its direct thalamic connection (Pagano et al., 2012). Motor cortex stimulation has indeed been demonstrated to activate the thalamus, which in turn activates regions involved in top-down inhibition of pain, such as the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and periaqueductal gray (PAG) matter (Garcia-Larrea & Peyron, 2007). In further support of this, positron emission tomography (PET) studies have shown that surgical motor cortex stimulation increases cerebral blood flow in regions such as the anterior and posterior cingulate cortex, prefrontal cortex, thalamus, and brainstem structures, with these changes correlating positively with long-term pain relief in patients with neuropathic pain (Peyron et al., 2007). The fact that motor cortex stimulation can affect prefrontal regions, the ACC, and the insula (Dasilva et al., 2012), regions implicated in emotional processing, is in line with evidence that rTMS over M1 can impact not only sensory but also affective dimension of ongoing chronic pain (Passard et al., 2007; Picarelli et al., 2010). Another possible mechanism of action on the pain affective component is via activation of striatal regions, as a recent study in a rodent model of neuropathic pain showed that M1 stimulation via chemo and optogenetics can reach reward circuitry through a pathway involving the nucleus accumbens and the thalamus (Gan et al., 2022).

Given its established role in emotional and cognitive modulation (Ong et al., 2019) and its influence on descending inhibitory pathways (Ossipov et al., 2014), noninvasive stimulation of the DLPFC has been likewise explored to address chronic pain and pain-related symptoms. Although rTMS targeting the DLPFC has generally been considered less effective than M1 stimulation for neuropathic pain (Attia et al., 2021), some studies have shown pain relief in conditions like fibromyalgia (Cheng et al., 2019; Forogh et al., 2021; Sampson et al., 2006). Importantly, reductions in pain preceded improvements in depressive symptoms (Short et al., 2011). Similarly, research on neuropathic pain following spinal cord injury indicated that rTMS over the left DLPFC reduced both pain and depressive scores, with pain reduction occurring before the improvement in depression scores. For chronic migraine, high-frequency rTMS has been shown to reduce pain outcomes (Brighina et al., 2004), although some studies did not replicate these positive findings (Conforto et al., 2014). Studies focusing on the

DLPFC in patients with primary chronic back pain with clinical pain outcomes as the primary measure are particularly rare (Olechowski et al., 2023).

Similar to M1 stimulation, no definitive answers can be drawn about the efficacy of DLPFC stimulation in chronic pain, owing to the heterogeneous parameters and samples explored (Ciampi de Andrade & García-Larrea, 2023). Both M1 and DLPFC are thought to influence the sensory aspect of pain in part through the thalamus and descending inhibitory pathways. M1 stimulation is known to induce thalamic changes (Garcia-Larrea & Peyron, 2007), while DLPFC stimulation in healthy individuals has been shown to reduce pain via thalamic connectivity, independent of motor cortex involvement (Lin et al., 2017). Nevertheless, the mechanisms by which DLPFC and M1 modulate pain appear to differ to some extent. For instance, both anodal M1 and DLPFC tDCS can alter functional connectivity in sensorimotor regions, but only anodal DLPFC affected both sensory and affective pain pathways, indicating that M1 mainly acts on the sensory networks (Sankarasubramanian et al., 2017). Additionally, naloxone can reverse the analgesic effects of M1 stimulation but does not alter those of right DLPFC rTMS (de Andrade et al., 2011). A study directly compared the effects of rTMS over M1 and DLPFC in the same group of patients and found that DLPFC was able to reduce pain ratings, while M1 was ineffective (Freigang et al., 2021). More research is needed to determine whether underlying etiology or other factors may influence the effectiveness of neuromodulation, by tailoring stimulation parameters to specific pain mechanisms (Ciampi de Andrade & García-Larrea, 2023).

The vast majority of NIBS studies in chronic pain obtained results after several sessions of treatment, exploring the cumulative therapeutic effects of the various stimulation protocols. To better inform treatment, mechanistic studies are needed, in which noninvasive techniques would be used to investigate immediate effects on pain and thus explore the direct involvement of different regions in chronic pain. Moreover, combining NIBS with imaging is needed to understand neural mechanisms and connectivity patterns behind the modulation of pain. In addition, regions such as the medial prefrontal cortex (mPFC) deserve exploration as targets in chronic pain (Kandić et al., 2021). Medial prefrontal cortex stimulation has been shown to modulate emotional memory (Bovy et al., 2020) and conditioned fear (Guhn et al., 2014), processes implicated in the chronicity of pain (Flor, 2012). Furthermore, mPFC activity decoded spontaneous pain in the chronic back pain state (Baliki et al., 2006), its functional connectivity to striatal regions predicted the development of chronic back pain (Baliki et al., 2012), and its abnormal functional connectivity with other brain networks is associated with chronic low back pain symptoms (Tu et al., 2019). Consistent evidence points to the mPFC as a „hub“ connecting higher and downstream regions in pain processing (Ong et al., 2019) with the anterior cingulate cortex considered a key component of this system, integrating sensory, attentional, and motivational dimensions of pain (Apkarian et al., 2011).

1.4 Aims and Hypotheses

Abundant evidence points to the relevance of corticolimbic and corticostriatal circuitry in the development of chronic back pain (Baliki et al., 2012; Hashmi et al., 2013; Vachon-Presseau et al., 2016a) and that changes in chronicity within these circuits are related to learning processes that they support (Löffler et al., 2022). While there is a growing number of studies into activity at rest and task-based activity in chronic back pain (CBP) chronicity, only one study so far has pointed to brain structural integrity as a potential biomarker for the development of CBP, identifying lower fractional anisotropy across several white matter tracts in patients who developed persistent pain (Mansour et al., 2013). It remains to demonstrate whether white matter tracts implicated in memory and learning processes can robustly predict the development of chronic back pain in both the classical classification approach and the dimensional, multiple linear regression approach to predict the severity of chronicity.

The first study therefore investigated brain white matter properties in patients with back pain longitudinally (at baseline and six-month follow-up) across three independent samples and had the following hypotheses:

H1a) *White matter tracts previously found predictive of CBP will have higher fractional anisotropy values (FA; greater structural integrity) in patients who recovered compared to those whose pain persisted (i.e., FA within these tracts will predict the persistent state).*

H1b) *Patients who recovered should also exhibit greater structural integrity within the prefrontal-limbic tract related to learning and memory, the uncinate fasciculus (i.e., FA within these tracts will predict the persistent state).*

H1c) *Lower FA at baseline will predict greater pain severity at follow-up.*

As noted earlier, imaging studies provided evidence that prefrontal-limbic and prefrontal-striatal circuitry are also implicated in the maintenance of ongoing CBP. For instance, it has been shown that activity in the mPFC during spontaneous pain is increased in patients with CBP (Baliki et al., 2006). However, no study so far has explored the causal involvement of this cortical region in CBP during ongoing pain. We, therefore, performed neuromodulation employing TMS in an active form that should inhibit the prefrontal activity over the mPFC target and as a placebo (sham), and hypothesized that:

H2a) *Active TMS condition over the mPFC, compared to sham TMS, will result in decreased pain following stimulation.*

This study further investigated how TMS over the mPFC affects brain resting-state network during continuous CBP, examining functional connectivity pre and post-stimulation, with the aim to elucidate the direct involvement of changed prefrontal connectivity on ongoing back pain perception and relief.

2 MATERIALS AND METHODS

2.1 Study 1[1]

2.1.1 Data pool

2.1.1.1 Mannheim data set[2]

This study was conducted as part of project SFB1158/B03 within the Heidelberg Pain Consortium, supported by the German Research Foundation (DFG, Deutsche Forschungsgemeinschaft).

2.1.1.1.1.1 Participants

Participants were recruited through advertisements in local newspapers and the website of the Central Institute of Mental Health in Mannheim, and patients were recruited additionally through the outpatient pain clinic of the Institute of Cognitive and Clinical Neuroscience at the Central Institute of Mental Health, general practitioners, and physiotherapy practices. We determined subjects' eligibility via a telephone screening form, which comprised questions about MRI contraindications, medication intake, current and previous drug/alcohol use, co-morbid medical and psychological conditions, and pain frequency and severity. All participants had to be between 18 and 70 years old to be eligible for study entry. Healthy controls had to be pain-free; patients with pain (subacute back pain (SBP) and chronic back pain (CBP)) had either low

[1] This study has already been published: Mišić*, M., Lee*, N., Zidda, F., Sohn, K., Usai, K., Löffler, M., Uddin, M. N., Farooqi, A., Schifitto, G., Zhang, Z., Nees, F., Geha, P., & Flor, H. (2024). A multisite validation of brain white matter pathways of resilience to chronic back pain. *Elife*, *13*. https://doi.org/10.7554/eLife.96312. Asterisks indicate shared first authorship by Mišić and Lee.

[2] This study includes three data sets: Mannheim, New Haven, and an openly available data set analyzed by collaborators (Chicago: https://www.openpain.org/). The same analysis pipeline was independently applied at Mannheim and New Haven, enabling comparison and replication. The author of this dissertation independently conducted all analyses on the Mannheim data set and additionally validated the New Haven findings on this data set. While the core contribution lies in the analysis of the Mannheim data, the inclusion of multisite validation enhances the robustness and generalizability of the findings. Further details on the external data sets and analyses are available in Mišić et al. (2024). In this dissertation, an adapted version of Study 1 methods, results, and discussion is presented.

and/or upper back pain. To be included in the study, SBP participants had to have a current back pain episode of 7–12 weeks duration. Patients with a current back pain episode and additional back pain episodes in their history were included as well if the episodes never exceeded 12 weeks per year. The inclusion criteria for the CBP group were a history of back pain longer than 6 months and a current back pain episode of more than 100 days. Participants were excluded if they reported any neurological disorder, psychotic episodes, current substance abuse, a major illness, contraindication for MRI, or another painful condition as the main pain problem.

Brain diffusion data were collected at baseline from 64 patients with SBP, 24 patients with CBP, and 24 healthy controls (HC). HC and patients with CBP were matched for age and gender. Two HC, three patients with CBP, and nine patients with SBP were excluded from the analysis due to excessive head motion defined as >3SD from the mean Euclidian distance of either translational or rotational displacement during the MRI scanning session. Additionally, two SBP patients' diffusion images failed manual quality control checks due to obvious artifacts. Six patients with SBP were excluded from the analysis because they did not have interim data at follow-up. One patient with SBP was also excluded from the analysis as an outlier due to an extreme increase in pain severity from baseline to follow-up (466 percent change, M= -15,06; hence the subject was > 6 standard deviations from the sample mean). The final sample in the analysis comprised 22 HC, 21 patients with CBP, and 46 patients with SBP.

Medication use is provided in Table 5. Supplement Study 1 (see Appendix). All participants gave written informed consent to be involved in the study. The study was approved by the Ethics Committee of the Medical Faculty of Mannheim, Heidelberg University, and was conducted in accordance with the declaration of Helsinki in its most recent form.

2.1.1.1.1.2 Clinical assessments

Patients with SBP were included in the study at baseline as one group, and their pain severity was assessed at two time points (baseline, 6-month follow-up). Change in pain severity (PS) was assessed using the percentage change in the Pain Severity scale of the German version of the West Haven-Yale Multidimensional Pain Inventory (Flor et al., 1990) from baseline assessment to the follow-up screening after 6 months using the following formula: $\Delta PS = \frac{PSfollow-up-PSbaseline}{PSbaseline} \times 100.$ Based on the pain severity percentage change, the SBP sample was divided into recovered SBP (SBPr, *N*=28), whose pain dropped by more than 20% at follow-up and persisting SBP (SBPp, *N*=18) ($\Delta PS > -20$) following criteria already published in the literature (Hashmi et al., 2012). A trained psychologist interviewed all participants to assess comorbid mental disorders using the German version of the Structured Clinical Interviews for the Diagnostic and Statistical Manual of Mental Disorders IV (SCID I)(Wittchen et al., 1997). Comorbid mental disorders are presented in Table 6. Supplement Study 1 (see Appendix). In addition, all subjects completed the German versions of the Chronic Pain Grade (CPG)(Klasen et al., 2004), the Örebro Musculoskeletal Pain Questionnaire (OMPQ yellow flag)(Langenfeld et al., 2018), the Hospital Anxiety and Depression Scale (HADS)(Herrmann et al., 1995), and the Perceived Stress Scale (PSS)(Reis et al., 2019).

2.1.1.1.1.3 MRI data acquisition

A 3 Tesla Tim TRIO whole body scanner (SIEMENS Healthineers, Erlangen, Germany), equipped with a 12-channel head coil was used to acquire the images. Shimming of the scanner was done to account for maximum magnetic field homogeneity. Participants underwent an anatomical T1-weighted the magnetization prepared rapid acquisition gradient echo (MPRAGE) imaging scan with the following sequence: TR/TE (repetition time/echo time) = 2300/ 2.98 ms, flip angle = 9°, matrix size = 240 $\times$ 256, number of slices = 192, image resolution = 1 $\times$ 1 $\times$ 1 mm^3. The diffusion weighted images were acquired using spin-echo echo planar Imaging (SE-EPI) sequence with the scan parameters as follows: TR/TE = 7400/85 ms, matrix size = 220 $\times$ 256 $\times$ 30, GRAPPA = 2, image resolution = 2 $\times$ 2 $\times$ 2 mm^3. Diffusion gradients were applied along 30 directions using a b-value of 1000 s/mm^2. One volume with no diffusion weighing was acquired at the beginning of the scan.

2.1.1.2 New Haven data set[3]

2.1.1.2.1.1 Participants

Subjects were recruited in the New Haven, Connecticut area, through flyers and internet advertisements. All participants gave written informed consent to participate in the study. The study was approved by the Yale University Institutional Review Board. Brain diffusion data were collected at baseline from 27 (12 females) patients with subacute low back pain (SBP, pain duration between 6-12 weeks), 29 (16 females) patients with chronic low back pain (CBP), and 28 (12 females) healthy controls (HC). One patient was excluded because of excessive head motion defined as >3SD from the mean Euclidian distance of either translational or rotational displacement during the MRI scanning session and one HC subject was excluded because parts of the brain were outside the field of view.
Subjects were briefly screened at first to check (1) the location of the low back pain, (2) if they were otherwise healthy, (3) non-smokers, and (4) pain duration (between 6 and 12 weeks for SBP and more than one year for CBP). If they passed this initial brief screen a more detailed screen was conducted where we assessed complete medical and psychiatric history. To be included in the study, SBP subjects needed to meet the criteria of having a new-onset 6 to12 weeks low back pain at an intensity more than 20/100 on the visual analogue scale (VAS) and report being pain-free in the year prior to the onset of back pain. Patients with CBP had to have a pain duration of at least 1 year and a pain intensity of more than 30/100. Both SBP and CBP participants had to (1) fulfill the International Association for the Study of Pain criteria for back pain (Treede et al., 2019), (2) not be currently, or during the month prior to the study, on any opioid analgesics. Patients were included if their back pain was below the 12th thoracic vertebra with or without radiculopathy and was present on more days than not. SBP and CBP diagnoses were confirmed based on history collected by an experienced clinician. Healthy control subjects were screened likewise with, besides, the absence of any history of any pain of more than 6 weeks in duration. Participants had no history of mental disorders, chronic medical conditions (e.g., diabetes, coronary artery disease), or loss of consciousness.

[3] This data was collected and analyzed by our collaborators. Details on the data and acquisition procedures are included to provide a comprehensive understanding of its characteristics and relevance to the integrated cross-validated results.

The study consisted of two time points separated by approximately one year (baseline, 1-year follow-up). At each time point participants completed one testing session in the laboratory and one scanning session. Patients whose pain dropped by more than 30% at follow-up were considered recovered, otherwise persistent. Of the SBP group, 12 patients were confirmed at follow-up as recovered subacute back pain patients (SBPr) and 16 as persistent subacute back pain patients (SBPp) and had diffusion tensor data collected.

2.1.1.2.1.2 MRI data acquisition

Participants underwent an anatomical T1-weighted scan and two consecutive 2.5-minute-long diffusion tensor imaging (DTI) scans in the same session. A Siemens 3 Tesla Trio B magnet (SIEMENS Healthineers, Erlangen, Germany) equipped with a 32-channel head coil was used to acquire the images. The 3D magnetization prepared rapid gradient echo (MPRAGE) T1-weighted acquisition sequence was as follows: TR/TE = 1900/2.52 ms, flip angle = 9°, matrix size = 256 x 256, number of slices = 176, image resolution = = $1 \times 1 \times 1$ $mm^{3.}$ The diffusion-weighted images were acquired using SE-EPI sequence using the following scan parameters: TR/TE = 2200/84.0 ms, flip angle = 90°, matrix size = $110 \times 110 \times 64$, multi-band acceleration factor = 4, image resolution = $2 \times 2 \times 2$ mm^3. Diffusion gradients were applied along 64 directions with a b-value of 1000 s/mm^2. For each set of DTI data, one volume with no diffusion weighing (i.e., b=0 s/mm^2) was acquired at the beginning of the scan.

2.1.1.3 Chicago data set (Open Pain)

The data set obtained through the OpenPain.org online database (collected in Chicago, from now on, we refer to this data set as “Chicago data set”) had 58 patients with SBP (28 females) with a baseline visit (visit 1 on OpenPain, pain duration 6-12 weeks) and 60 SBP patients (29 females) with a one-year follow-up visit (visit 4 on OpenPain) on whom diffusion images were collected. Patients were deemed recovered at one-year follow-up based on the same criterion used in the New Haven data (> 30% drop in low back pain intensity reported on the visual analogue scale). As such, we studied 35 SBPp and 23 SBPr at baseline, and 33 SBPp and 27 SBPr at follow-up. As part of this data set has been previously published in Mansour et al. (2013), details regarding the MRI acquisition can be found in that publication.

2.1.2 Data analysis

2.1.2.1 Preprocessing of DTI Data

Preprocessing of all data sets was performed employing the same procedures and the FMRIB diffusion toolbox (FDT) running on FSL version 6.0 (Smith et al., 2004). First, diffusion-weighted data were visually inspected for obvious artifacts or missing parts of the brain. Next, the data were corrected for eddy currents and head motion by employing affine registration to the no diffusion volume using eddy_openmp from the FSL toolbox. Eddy current corrects for image distortions due to susceptibility-induced distortions and eddy currents in the gradient coils (Andersson & Sotiropoulos, 2016). Brain images were then skull stripped and a diffusion tensor model was fit, using FMRIB Diffusion Toolbox (FDT) part of FSL (Behrens et al., 2003), at each voxel to calculate the fractional anisotropy (Basser et al., 1994; Smith, 2002). FA reflects the degree of water diffusion within a voxel with values ranging between 0 and 1 where large values indicate directional dependence of Brownian motion due to white matter tracts and small values indicate more isotropic diffusion and less directionality (Beaulieu, 2002).

2.1.2.2 Tract-Based Spatial Statistics

Voxel-wise statistical analysis of FA was carried out using Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) part of the FSL (Smith et al., 2004). All subjects' FA data were then aligned into a common space (MNI standard 1-mm brain) using the nonlinear registration tool FNIRT (Andersson & Sotiropoulos, 2016), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the groups. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxel-wise cross-subject statistics. Groups (i.e., SBPr and SBPp) were compared using unpaired t-test corrected for age, gender, and motion parameters. Head displacement was estimated by eddy current correction to extract the magnitude of translations and rotations. Overall head motion was then calculated as the Euclidian distance from head translations and rotations for each subject, and these measures were Z-transformed before they were entered into the design matrix as nuisance variables. The statistical significance of TBSS-based testing was determined using a permutation-based inference (Winkler et al., 2014) where the null distribution is built using 10,000 random permutations of the groups. Significance was set at $p < 0.05$, and significant clusters were identified using threshold-free cluster enhancement (Smith & Nichols, 2009).

2.1.2.3 Statistical analysis

A mask formed from the significant cluster for the SBPr>SBPp contrast in the New Haven data was used to extract FA values from the Mannheim and the OpenPain data. The FA values were first corrected for confounders and then used to build a receiver operating curve (ROC) to assess classification accuracy (recovered and persistent pain patients as binary classes) based on the brain white matter data. The statistical significance of the area under the ROC (AUC) was tested against 10,000 random permutations of the group labels to generate a random distribution of the AUC values. Additionally, we tested if FA values predict pain percentage change in a dimensional approach using multiple linear regression with the FA data entered as a predictor, and pain percentage change as an outcome. In both, classification and linear regression analysis, age, gender, and motion parameters (translation and rotation) were entered as covariates of no interest.

2.2 Study 2

This study was conducted as part of project SFB1158/B03 within the Heidelberg Pain Consortium, supported by the German Research Foundation (DFG, Deutsche Forschungsgemeinschaft).

2.2.1 Participants

2.2.1.1 Recruitment and inclusion criteria

Participants were recruited through online advertisement on the institute's website and social media, as well as using contact lists of individuals who previously participated in other studies at the institute and consented to be contacted again. All participants who applied for participation in the study were screened via telephone for eligibility. Screening involved reports on demographical and clinical data (see also Table 1), painful sites beyond the primary area of focus, average pain intensity, suffering, pain interference (based on the West Haven-Yale Multidimensional Pain Inventory), and pain duration. Inclusion criteria were age between 18 and 70 years, continuous, non-stopping episodes of back pain or back pain occurring on most days of the week (at least 4/7), of no less than 4/10 average pain intensity, and having pain duration exceeding 6 months in total.

Exclusion criteria were based on the standard contraindications for MRI and TMS procedures: any irremovable metal inside the body, pregnancy, claustrophobia, tattoos covering large portions of the body or those on the face and/or head, stroke history, neurological disorders with cognitive or physical impairments, psychotic episodes, personality disorders, current substance abuse, history of head injury, history of epilepsy in the participant or close relative. Additional study-specific exclusion criteria were non-continuous back pain, report of other chronic pain conditions, inflammatory or mechanical injury causes for back pain, sensory impairments, a major illness, left-handedness (to control for potential variability in hemispheric dominance/brain lateralization), and previous experience with TMS assessment. The study flow diagram, based on CONSORT guidelines, is depicted in Figure 1.

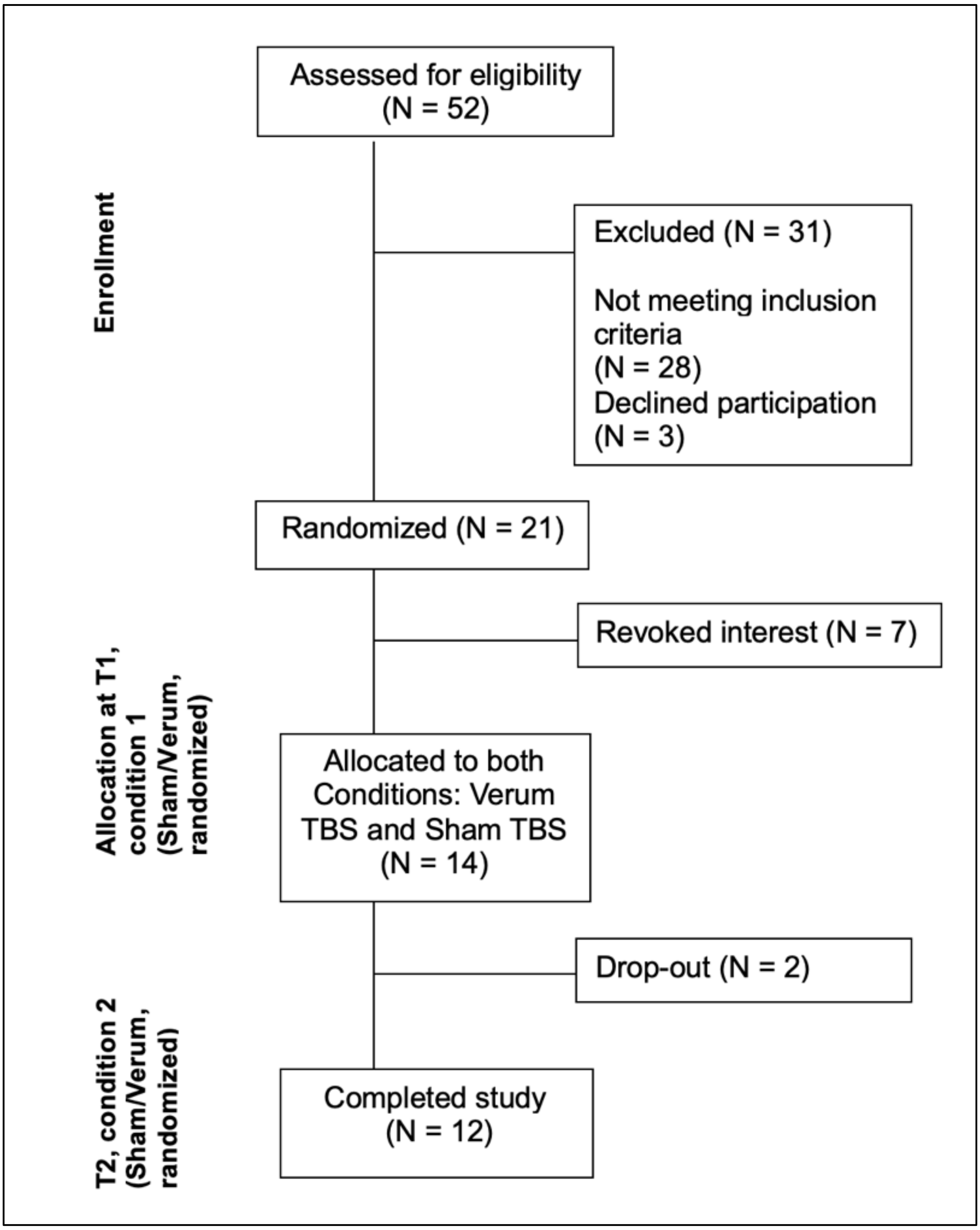

Figure 1. Study 2: Flow diagram.

Table 1. Study 2: Demographical and clinical sample description.

Variable (*N* = 12; 8f, 4m)	Mean	SD	Median	Min	Max	CI_Lower	CI_Upper	Missing
Age (years)	44.00	13.67	42.50	26.00	68.00	35.31	52.69	0
Pain duration (days)	4234.58	2700.51	4537.50	450.00	10950.00	2518.76	5950.41	0
Average pain intensity (screening)	4.25	1.22	4.00	3.00	7.00	3.48	5.02	0
Average pain suffering (screening)	5.50	2.28	4.50	3.00	10.00	4.05	6.95	0
Pain interference (screening)	5.67	2.81	5.00	2.00	10.00	3.88	7.45	0
Medical Pain (FPQ-III)	19.18	8.16	16.00	0.00	34.00	13.70	24.66	1
Minor Pain (FPQ-III)	16.27	6.99	15.00	0.00	35.00	11.58	20.97	1
Severe Pain (FPQ-III)	28.90	11.46	30.00	1.00	49.00	21.21	36.61	1
FPQ-III total score	64.36	23.80	65.00	30.00	117.00	48.38	80.35	1
Active Coping (PRSS)	3.47	0.55	3.44	2.44	4.33	3.10	3.85	0
Catastrophizing (PRSS)	1.76	0.88	1.78	0.78	3.22	1.17	2.35	0
Anxiety (HADS)	6.58	3.78	5.50	2.00	15.00	4.18	8.98	0
Depression (HADS)	6.00	3.33	5.00	2.00	10.00	3.88	8.12	0
Pain Severity (MPI)	2.94	0.83	3.00	2.00	4.33	2.42	3.47	0
Interference (MPI)	2.26	1.10	1.90	0.90	4.00	1.52	3.01	0
Negative Mood (MPI)	2.64	1.44	3.00	0.33	5.00	1.72	3.55	0
Support (MPI)	2.78	1.74	2.50	0.67	6.00	1.67	3.89	0
Life Control (MPI)	4.06	1.04	4.17	2.67	5.67	3.39	4.72	0
Negative Responses (MPI)	0.86	1.25	0.17	0.00	3.33	0.07	1.66	0
Solicitous Responses (MPI)	3.23	1.85	3.70	0.00	5.80	2.06	4.41	0
Distracting Responses (MPI)	3.03	1.55	3.17	0.00	5.33	2.04	4.01	0
Social Activity (MPI)	3.00	1.23	2.75	1.50	5.75	2.22	3.78	0
Household Activity (MPI)	3.97	0.93	3.70	2.80	6.00	3.38	4.56	0
Outside Activity (MPI)	1.49	0.92	1.10	0.33	3.33	0.90	2.08	0
Sensory Pain Dimension (SES)	26.75	6.09	24.50	18.00	38.00	22.88	30.62	0
Affective Pain Dimension (SES)	18.17	5.67	17.00	12.00	31.00	14.56	21.77	0

N, sample size; f, female, m, male; M, mean; SD, standard deviation; CI, confidence interval. Min and Max, minimum and maximum value of the respective scale in the sample. FPQ-III, Fear of Pain Questionnaire; PRSS, Pain-Related Self-Statements Scale; HADS, Hospital Anxiety and Depression Scale; MPI, West Haven-Yale Multidimensional Pain Inventory; SES, Pain Experience Scale; Average pain intensity on the screening was given on the scale 0-10. MPI on the scale 0-6.

2.2.2 Experimental procedure

2.2.2.1 Pre-intervention MRI session

Assessments were conducted over two sessions, spaced one week apart. The first session lasted approximately three hours, including preparation, breaks, and the experimental tasks. The second session, which did not include a break, took around 1.5 hours. Upon arrival on the first day, participants signed a written informed consent form. Subsequently, they took part in the (f)MRI assessments. After a 4-minute anatomical brain scan, participants completed a 10-minute resting-state task. During this task, they were instructed to remain still, keep their eyes closed, allow their thoughts to flow freely without focusing on anything specific, and avoid falling asleep. Following the resting-state scan, participants performed a simple motor task to allow for precise functional localization of the motor cortex for a subsequent TMS procedure. Explanation for this task was given prior to the MRI session and repeated with on-screen instructions just before the task began. The finger-tapping task required participants to touch each finger of their dominant right hand with the thumb of the same hand in response to visual cues. The cues were regularly paced blinking squares of different colors (blue, yellow) displayed on a screen for 10 seconds, which participants viewed via a mirror mounted on the head coil. The yellow square served as the cue to initiate movement (ON trial), prompting participants to tap their fingers. In contrast, a blue square with a different orientation indicated a no-movement period (OFF trial). The fixation cross was presented between trials. Participants were asked to move their fingers only when a yellow square was presented and to stay still the rest of the time. The finger-tapping task, structured in a block design, lasted 10 minutes. After this, participants took a one-hour break. During this time, the lab was prepared for the TMS procedure, and the fMRI data from the motor localization task were analyzed to produce a subject-specific functional motor target. The anatomical data were also used to create a medial prefrontal (mPFC) target specific to each participant for precise stimulation.

2.2.2.2 TMS intervention session

The participant's anatomical scan, motor, and mPFC targets were loaded into the Brainsight TMS neuronavigation system (Brainsight Neuronavigation System, Rogue Research Inc., Montreal, Canada), placed in the experimental room together with the TMS machine. When the participant arrived, a short interview about coffee and alcohol intake, sleep quality the day before, and familiarity with the procedure was conducted in the control room. Exclusion-specific criteria for the TMS were once more briefly checked. After this, the TMS procedure was explained in more detail. All participants were naive to the method. Participants filled out pain and mood-related questionnaires and then proceeded to the experimental room. They were asked to sit comfortably in the chair in front of the neuronavigation computer and relax their arms on the armrests. The neck was supported with a cushion to achieve the most comfortable position, and earplugs were handed for sound protection. A neuronavigation head tracker was placed around the participant's head. In the following step, skin and full 3D brain reconstruction (at 2mm peel depth) were computed, and the mPFC and motor targets were overlayed over the anatomical scan. Then, the participant's head was registered to its respective anatomical scan. After this preparation, the motor threshold (MT) procedure began, conducted by two experimenters.

The MT procedure served to account for individual differences in cortical excitability and followed the traditional definition as the lowest stimulator intensity sufficient to elicit a motor-evoked potential (MEP) of at least 50 µV peak-to-peak amplitude in a target muscle in ≥50% of trials (Rossini et al., 1994). For the reliable estimate of MT, muscle activity was recorded using electromyography (EMG) surface electrodes (Ag/AgCl) placed in a bipolar belly-tendon montage on the right abductor pollicis brevis muscle (thumb abductor). First, the skin over the target muscle was prepared with abrasive gel and alcohol, and the electrodes were filled with electrolyte conductivity gel. A ground electrode was placed on the wrist bone, and impedances were checked using Brain Vision Recorder software (Brain Products, Munich, Germany) to ensure they remained below 5 kΩ. The raw EMG signal was amplified (BrainAmp, ExG MR, Brain Products, Munich, Germany) and filtered online (bandpass 10 Hz - 500 Hz, 50 Hz notch filter), using a 100 µV scale for visual inspection of MEP amplitude.

The guidelines for the theta burst stimulation (TBS) protocols recommend 80% of the active motor threshold (aMT) as a safe but effective dosage of magnetic stimulation (Huang, 2005). To estimate their aMT, participants were instructed to lift their right arm parallel to the armrest, with the elbow positioned at an approximate 90° angle. The motor „hotspot“ was placed in the center of the individual’s functional motor mask in the left primary motor cortex, and the coil trajectory was chosen so that the handle of the coil was approximately 45° from the midline, tangential to the scalp and perpendicular to the target. Single TMS pulses were delivered with a 70 mm figure-of-eight coil operated via the MagPro X100 TMS device (MagVenture, Inc., Denmark). The initial intensity was set at 30% of a maximal stimulator for all participants, and it increased in steps by 5% in case of no observable MEP. After each delivered TMS pulse, one of the two experimenters who continuously observed the EMG signal on the screen in the adjacent control room evaluated MEP peak-to-peak amplitude. When 5 out of 10 trials resulted in MEP of at least 50 μV, the motor threshold was established, and 80% of the aMT was calculated for subsequent mPFC stimulation.

Following the motor threshold procedure, rTMS in the form of continuous theta burst stimulation (cTBS) was carried out with the same stimulator device connected to the figure-of-eight coil (BC-70 Active or BC-70 Sham coil). In a well-established cTBS protocol, patterns of a burst of three stimuli at 50 Hz repeated at 200 ms (thus, at 5 Hz theta frequency) are delivered for a 40-second-long train without interruption (Huang et al., 2005). In the verum (active) condition, a total of 600 pulses with a biphasic waveform were delivered to the center of the mPFC target. The sham coil was visually indistinguishable from the active coil, with in-built shielding that mimics sensory and auditory sensations of active stimulation while preventing neuronal stimulation. The handle of the TMS coil was oriented posteriorly, with the current flow directed anterior to posterior. Immediately preceding and immediately following mPFC stimulation, participants rated their current back pain intensity based on the Pain Severity Scale of the German version of the West Haven-Yale Multidimensional Pain Inventory (Flor et al., 1990). Pain unpleasantness was assessed additionally. The affective dimensions of valence, arousal, and dominance were likewise assessed pre- and post-stimulation using the Self-Assessment Manikin (SAM) (Bradley & Lang, 1994). One week later, the whole procedure was repeated. After both conditions (verum, sham), participants were asked to report any side effect (headache, neck pain, scalp pain, tingling sensation, itching, burning, skin redness, tiredness, concentration difficulties, and/or mood swings) on a scale 1-4 (none, mild, moderate, strong) and if they thought this was related to the stimulation (no, unlikely, likely, definitely).

To avoid order effects in a within-subjects design, participants were randomly assigned in a 1:1 ratio to receive either verum or sham as the initial condition. Since the investigator (author of this thesis) also performed experiments using two different coils (verum, sham), the study was single-blinded, while the participants were unaware of the random allocation procedure or the existence of a sham (placebo) condition. They were told that different stimulation protocols were being investigated. On day 2, upon completion of all the tasks, a debriefing session concluded the study. Participants were asked to guess which condition (verum or placebo) corresponded to each session. The study was approved by the Ethics Committee of the Medical Faculty Mannheim, University of Heidelberg (approval number: 2014-584N-MA, Amendment 8), and was conducted following the Declaration of Helsinki for good scientific practice. The study design is depicted in Figure 2.

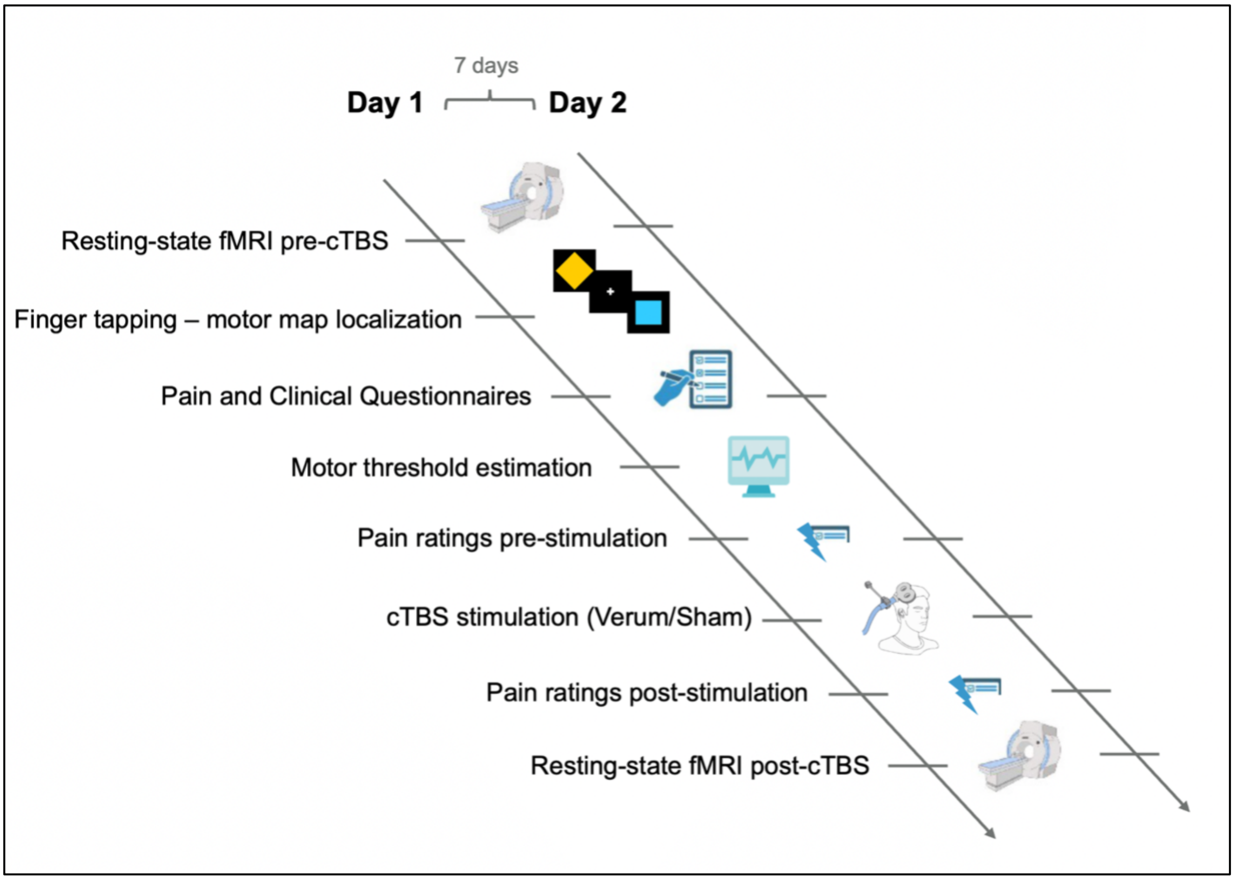

Figure 2. Study 2: Design.

fMRI, functional magnetic resonance imaging; cTBS, continuous theta-burst stimulation. The electromyography (EMG) icon representing motor threshold estimation was designed by kerismaker from Flaticon.com.

2.2.2.3 Pain, clinical, and additional variables

Participants completed the German versions of the West Haven-Yale Multidimensional Pain Inventory (MPI) (Flor et al., 1990), the Hospital Anxiety and Depression Scale (HADS) (Herrmann et al., 1995), Pain-Related Self-Statements (PRSS) (Flor et al., 1993), Fear of Pain Questionnaire (FPQ-III) (Flack et al., 2017), and Pain Perception Scale (SES) (Geissner, 1996). Past and current medication intake was also self-reported. In addition to questionnaires, participants were asked in a brief interview about their caffeine and alcohol intake on the day preceding the measurement and on the day of the measurement, as well as about how many hours of sleep they had on the evening before and whether that was less, more, or their usual average.

2.2.2.4 Acquisition of MRI data

An anatomical high-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was acquired on a 3T MAGNETOM Prisma whole body scanner (Siemens Healthineers, Erlangen, Germany), equipped with a 64-channel head coil. The parameters were as follows: voxel size of 1 mm^3 isotropic, a field of view (FOV) of 263 x 350 x 350 mm, TR/TE of 2000/3.03 ms, a flip angle of 9°, and a GRAPPA (GeneRalized Autocalibrating Partial Parallel Acquisition) acceleration factor of 2, with 192 sagittal slices and a total acquisition time of approximately 4 minutes. Shimming of the scanner was done to achieve maximum magnetic field homogeneity and a standard gradient field map was acquired at the beginning of each measurement using a dual-echo gradient echo sequence with $3mm^3$ isotropic voxel size, FoV = 240x240x143 mm, TR = 400 ms, TE1 = 4.92 ms, and TE2 = 7.38 ms. Resting-state fMRI data and functional localizer of the primary motor cortex were acquired using a T2*-weighted gradient-echo echo-planar imaging (EPI) sequence with the following parameters: 2.3 mm isotropic voxel size, TR/TE = 800/41 ms, FOV = 220x220x97 mm, a multiband acceleration factor of 6.

2.2.3 Data analysis

2.2.3.1 Functional localizer analysis and preparation of masks

Basic preprocessing and analysis of the motor localizer fMRI data were done using FSL's FEAT. Briefly, following the brain extraction of both structural and functional images, each fMRI volume was realigned to a reference volume using FSL FEAT's motion correction algorithm to correct head motion. A 5mm Full Width at Half Maximum (FWHM) Gaussian kernel was applied for spatial smoothing, and a high-pass filter with a 100-second cutoff was used to remove low-frequency noise. The functional data were registered to each subject’s anatomical image and subsequently to the standard MNI (Montreal Neurological Institute) space. Finally, prewhitening was conducted to correct for temporal autocorrelation. A custom MATLAB script (The MathWorks, Inc., Natick, MA, United States, 2022) was used to extract "motorON" (tapping) and "motorOFF" (rest) event timings from the finger-tapping task to create task-specific regressors for fMRI analysis. The six estimated motion parameters were included as nuisance regressors in the first-level analysis to account for motion-related artifacts. For each participant, the contrast of interest ('ON' versus 'OFF' events) was convolved with a gamma hemodynamic response function, and a cluster-forming Z-threshold of 2.3 and a cluster-level p-threshold of 0.05 was applied to identify areas of significant functional motor-related activity.

Next, the left motor cortex regions 4a and 4p from the Juelich atlas were thresholded, binarized, and combined to create a single left motor cortex mask (lM1) in standard MNI space. This mask was then transformed into each subject’s native functional space and applied to the ON versus OFF contrast activation map, isolating motor task-related activation in the functional space. Following the masking of motor activations, a 7mm spherical region of interest (ROI) was created around the activation peak within the left motor cortex mask, centering the ROI on the highest Z-statistic value in native functional space. This ROI was then transformed into the subject’s high-resolution anatomical space, providing a precise motor target.

To obtain a mask of the mPFC region, an automated meta-analytic search on Neurosynth (Neurosynth.org) was conducted for the term “medial prefrontal.” An mPFC mask was then created by generating an 8 mm radius sphere centered on the coordinates with the maximum z-score within the association maps (MNI -2, 54, 18; z-score = 16.2). This mask was binarized and transformed from standard space to the subject’s high-resolution anatomical native space. Visualization confirmed that the mask was accurately positioned within the medial prefrontal cortex, providing a precise target for subsequent stimulation. During the stimulation session, real-time neuronavigation was used to identify the cortical point nearest to the chosen coordinates by following the trajectory that displayed the optimal coil positioning relative to the target. This method ensured that the stimulation point was as close as possible to the intended mPFC target, thereby improving the anatomical accuracy of the stimulation.

2.2.3.2 Pre- and post-intervention (f)MRI data (pre)processing

For each participant, data were converted to BIDS (brain imaging data structure) format using dcm2bids version 3.1.1 with two runs corresponding to the pre- and post-measurements, and two sessions corresponding to the active (verum) and placebo (sham) stimulation conditions. Subsequently, data were preprocessed using fMRIPrep version 23.1.0. Details of the conducted preprocessing steps are presented in the form of a report provided by fMRIPrep below.[4]

A total of 4 fieldmaps were found available within the input BIDS structure. A B_0 nonuniformity map (or *fieldmap*) was estimated from the phase-drift map(s) measure with two consecutive GRE (gradient-recalled echo) acquisitions. The corresponding phase-map(s) were phase-unwrapped with prelude (FSL 6.0.5).

A total of 4 T1-weighted (T1w) images were found within the input BIDS dataset. All of them were corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al., 2010), distributed with ANTs 2.3.3 (Avants et al., 2008). The T1w-reference was then skull-stripped with a *Nipype* implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 6.0.5) (Zhang et al., 2001). A T1w-reference map was computed after registration of 4 T1w images (after INU-correction) using mri_robust_template (FreeSurfer 6.0.1) (Reuter et al., 2010). Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with antsRegistration (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* (Fonov et

[4] The above boilerplate text (ends with section 2.2.3.3) reproduces the standard fMRIPrep preprocessing report, which is intended to ensure transparent methodological reporting and is explicitly provided for users to copy and paste into their manuscripts *unchanged*. This type of standardized preprocessing report is considered best practice in the field. It is released under the CC0 license. The original boilerplate text was adapted solely to match the citation formatting used in this thesis.

al., 2009), TemplateFlow ID: MNI152NLin2009cAsym, *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model* (Evans et al., 2012), TemplateFlow ID: MNI152NLin6Asym).

For each of the 4 BOLD runs found per subject (across all runs and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 6.0.5) (Jenkinson et al., 2002). BOLD runs were slice-time corrected to 0.334s (0.5 of slice acquisition range 0s-0.667s) using 3dTshift from AFNI (Cox & Hyde, 1997). The BOLD time-series (including slice-timing correction) were resampled onto their original, native space by applying the transforms to correct for head-motion. These resampled BOLD time-series will be referred to as *preprocessed BOLD in original space*, or just *preprocessed BOLD*. The BOLD reference was then co-registered to the T1w reference using mri_coreg (FreeSurfer) followed by flirt (FSL 6.0.5) (Jenkinson & Smith, 2001) with the boundary-based registration (Greve & Fischl, 2009) cost-function. Co-registration was configured with six degrees of freedom. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), D temporal VARiance of the time series (DVARS), and three region-wise global signals. FD was computed using two formulations following Power et al. (2014) (absolute sum of relative motions) and Jenkinson et al. (2002) (relative root mean square displacement between affines). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al. (2014)). The three global signals are extracted within the CSF, the white matter (WM), and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*) (Behzadi et al., 2007). Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. (2017) in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by thresholding the corresponding partial volume map at 0.05, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the *k* components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al., 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. The BOLD time-series were resampled into several standard spaces, correspondingly generating the following *spatially-normalized, preprocessed BOLD runs*: MNI152NLin2009cAsym, MNI152NLin6Asym. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Automatic removal of motion artifacts using independent component analysis (ICA-AROMA, Pruim et al. (2015)) was performed on the *preprocessed BOLD on MNI space* time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM (full-width half-maximum). Corresponding "non-aggresively" denoised runs were produced after such smoothing. Additionally, the "aggressive" noise-regressors were collected and placed in the corresponding confounds file. All resamplings can be performed with *a single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964). Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer). Many internal operations of *fMRIPrep* use *Nilearn* 0.8.1 (Abraham et al., 2014), mostly within the functional processing workflow.

2.2.3.3 Functional connectivity analysis

Connectivity analysis was done in Nilearn version 0.10.3 running on Python version 3.11. The first four volumes were disregarded from the analysis to account for saturation effects. Detrend, demean, and denoising were applied to preprocessed functional data. Nuisance regressors in the design matrix for first-level analysis for each run and subject comprised of the six base motion parameters and their six temporal derivatives, the first five white matter and first five CSF components (extracted from anatomical CompCor regressors), global signal intensity, and calculated cosine parameters that served as a high-pass filter. In the same regression step, the signal from the volumes regarded as motion outliers (based on a threshold of 0.5 mm FD or 1.5 standardized DVARS) was regressed out. A low-pass filter was applied at 0.1 cut-off frequency. Mean time series were extracted from the seed defined as an 8mm radius mask positioned on the same coordinates as the target mask during stimulation. Following the same approach, time series were also extracted from a whole-brain mask. Additionally, a smoothing kernel of 5mm full-width at half maximum Gaussian kernel was applied. Seed-to-voxel Pearson's correlation maps were calculated and Fisher-z transformed for further statistical analysis and correlations with pain measures.

Further analysis aimed to identify brain regions where functional connectivity changes differed between the verum and sham conditions. After fitting the first-level model for each subject, run, and session using the mPFC seed time series as a regressor of interest, difference maps were computed by subtracting pre-run contrast maps from post-run within each condition. These difference maps were then fed into the second-level model. The second-level design matrix included subject-specific intercepts to account for the repeated measures design, as well as covariates for age and gender. A paired t-test was conducted at the group level to compare the difference maps between the sham and verum conditions.

The resulting z-maps were thresholded to identify regions showing significant changes in functional connectivity between conditions. Inferences were performed at the cluster level. Clusters were identified using a voxel-level threshold of $p < 0.001$ (uncorrected), forming clusters of contiguous suprathreshold voxels. A minimum cluster size of 10 contiguous voxels was applied to exclude small, potentially spurious clusters. A cluster-level family-wise error (FWE) correction using non-parametric permutation testing was applied on the remaining clusters to account for multiple comparisons. The FWE rate was controlled at $\alpha = 0.05$ through 5000 permutations.

To investigate how the intervention influenced connectivity between the large-scale brain networks, exploratory analysis was done with computation of ROI-to-ROI functional connectivity (FC) measures using the Yeo 7-network atlas (Yeo et al., 2011). This atlas uses parcellation based on seven networks. The average time series were extracted from the default mode network (DMN), salience network, somatomotor network, dorsal attention network, ventral attention network, limbic network, and frontoparietal control network. For each subject and condition, FC matrices were computed using Pearson's correlation coefficients between the extracted time series, separately for the pre- and post-stimulation sessions. Then, for each network pair, a paired, two-tailed t-test on the pre- and post-intervention connectivity values was performed to assess whether connectivity changed significantly.

The results were evaluated both uncorrected ($p < 0.05$) and after controlling for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) correction. In addition, effect sizes (Cohen's d) were calculated for the significant network pairs by dividing the t-statistic by the square root of the number of subjects.

2.2.3.4 Statistical analysis

After testing the assumptions for the linear mixed-effects model (linearity, normality of residuals, and homoscedasticity), the effects of condition (Verum vs. Sham) and time (Pre vs. Post) on pain intensity and pain unpleasantness while controlling for age and gender were tested in two separate linear mixed-effects models (LME). An interaction term between Condition and Time was included to test whether changes from Pre to Post differed between conditions. Independence of random effects was assumed based on the study design (as the study design included a random selection of subjects and random assignment to conditions). Given potential limitations in sample size and to ensure robust interval estimates, bootstrapped confidence intervals were computed using 1000 simulations. Bootstrapping was done to address the instability of traditional confidence intervals, providing a more reliable estimate of uncertainty around fixed-effect estimates. Where appropriate, post hoc comparisons were performed with a Bonferroni adjustment to control for multiple comparisons. Correlations between functional connectivity estimates, pain changes, and other clinical variables were likewise corrected for age and gender. All statistical analyses were done in R (version 4.3.2; R Core Team, 2023).

3 RESULTS

3.1 Study 1

3.1.1 Sample characteristics

For demographic and clinical characteristics of the different groups of the New Haven and Chicago data set see Appendix, Table 7. Supplement Study 1 and Table 8. Supplement Study 1.

Demographic and clinical characteristics of the Mannheim data set are presented in Table 2. Of the 46 patients with SBP at baseline, 28 were classified as recovered (SBPr) at six-month follow-up, based on a definition for recovery as a reduction of more than 20% in back pain severity relative to baseline. For the remaining 18 patients with SBP, pain persisted at follow-up, classifiying them as having persistent back pain (SBPp). The SBPr and SBPp groups did not significantlly differ in age, back pain duration (t(df) = 0.2(41.5,2), p = 0.84) or gender distribution ($\chi2$= 0.0002, df = 1, p = 0.99). They did not significantly differ in average reported pain severity at baseline (t(df) = 0.06(34.5), p = 0.95) (see Table 2).

Table 2. Study 1: Mannheim sample characteristics.

	HC (*N*=22)	**CBP** (*N*=21)	**SBPr** (*N*=28)	**SBPp** (*N*=18)	**t(df)‡, p-value**	**Missing**
Age in years	36.9 (14.4)	40.0 (16.0)	32.8 (12.0)	32.1 (11.2)	+0.19(38.2), 0.85	0/0/0/0
Gender (m/f)	12/10	11/10	8/20	6/12	+0.0002(1),0.99‡	0/0/0/0
Number of days with pain during last year	NA	247 (84.0)	74.8 (43.2)	72.4 (34.9)	+0.2(41.5,2), 0.84	NA/1/0/0
Delta pain severity (FU-BL): absolute	NA	NA	-1.90 (1.18)	0.19 (0.71)	-7.47(43.8), $<10^{-9}$*	NA/NA/0/0
Delta pain severity (FU-BL): percentage	NA	NA	-50.9 (27.3)	8.73 (26.0)	-7.45(37.7), $<10^{-9}$*	NA/NA/0/0
Pain severity (MPI)	NA	4.92 (1.38)	3.80 (1.43)	3.78 (1.54)	+0.06(34.5), 0.95	NA/1/0/0
Interference (MPI)	NA	2.43 (1.23)	1.48 (1.01)	1.49 (1.00)	-0.03(32), 0.97	3/0/2/2
Negative mood (MPI)	NA	2.83 (1.07)	2.40 (1.08)	2.71 (1.15)	-0.87(30.5), 0.39	3/0/2/2
Life control (MPI)	NA	3.97 (0.971)	4.05 (1.24)	3.54 (1.23)	+1.3(32), 0.2	3/0/2/2
Support (MPI)	NA	2.60 (1.85)	1.85 (1.28)	1.56 (1.41)	+0.66(29.4), 0.52	3/0/2/2
ÖMPQ	NA	78.1 (19.5)	63.6 (21.1)	69.7 (16.1)	-1.06(37.9), 0.3)	12/1/2/2
CPG[a]	NA	1.00 [0, 6.00]	0 [0, 4.00]	0 [0, 6.00]	-0.65(25.9), 0.52	9/0/0/2
Active coping (PRSS)	NA	3.30 (0.74)	2.94 (0.96)	3.14 (0.66)	-0.76(36.6), 0.45	NA/6/4/3
Catastrophizing (PRSS)	NA	1.35 (0.87)	1.09 (0.73)	1.10 (0.76)	-0.02(28.9), 0.98	NA/6/4/3
Anxiety (HADS)	4.37 (2.39)	8.24 (4.47)	7.27 (4.63)	7.47 (3.60)	-0.15(35.3), 0.88	3/0/2/3
Depression (HADS)	6.21 (6.12)	6.00 (4.40)	4.42 (4.23)	4.60 (2.85)	-0.15(37.9), 0.87	3/0/2/3
Perceived stress (PSS)	4.74 (5.00)	11.0 (5.23)	12.0 (5.25)	11.4 (5.07)	+0.34(32.7), 0.73	3/0/2/2

‡, t-score (degrees of freedom); †, Chi-square test; *, p < 0.05; MPI, West Haven-Yale Multidimensional Pain Inventory; CPG, Chronic Pain Grade; ÖMPQ, Örebro Musculoskeletal Pain Questionnaire; PRSS, Pain-Related Self-Statements Scale; HADS, Hospital Anxiety and Depression Scale; HC, healthy control; CBP, chronic back pain; SBP, patients with subacute back pain; SBPp/r, patients with SBP with persistent pain or recovered pain after 6 months; FU, follow-up after 6 months; BL, baseline assessment; SD, standard deviation; NA, not applicable. Values show the group mean and standard deviation in parenthesis. [a]For the Chronic Pain Grade the median and interquartile range are shown.

3.1.2 Whole-brain Tract-Based Spatial Statistics

A whole-brain comparison of FA over the white matter skeleton using permutation testing (unpaired t-test, $p < 0.05$, threshold-free cluster enhancement (TFCE) corrected for age, gender, and two motion parameters (translation and rotation) revealed two clusters, one in the right superior longitudinal fasciculus (SLF) tract (cluster size = 409 voxels, MNI-coordinates of peak voxel: x = 26, y = -33, z = 45, *p*(TFCE) = 0.041, t(max) = 3.57) and one in the right corticospinal tract/superior corona radiata (cluster size = 381 voxels, MNI-coordinates of peak voxel: x = 29, y = -16, z = 21, *p*(TFCE) = 0.041, t(max) = 3.63) that were significantly greater in SBPr (*N* = 28) compared to SBPp (*N* = 18) (see Figure 3). In addition, two smaller clusters were also identified in the same tract of the right SLF (cluster size = 39 voxels, MNI-coordinates of peak voxel: x = 36, y = -13, z = 34, *p*(TFCE) = 0.048, t(max) = 3.19) and right corticospinal tract (cluster size = 13 voxels, MNI-coordinates of peak voxel: x = 21, y = -27, z = 42, *p*(TFCE) = 0.049, t(max) = 2.41) as significantly different between SBPr and SBPp patients. In the next step, the FA values from the significant clusters of the Mannheim data were extracted and compared across all groups at that site. Recovered patients also had the largest FA values across groups, even greater than HC, although this difference did not reach significance level ($p = 0.12$) (Figure 3).

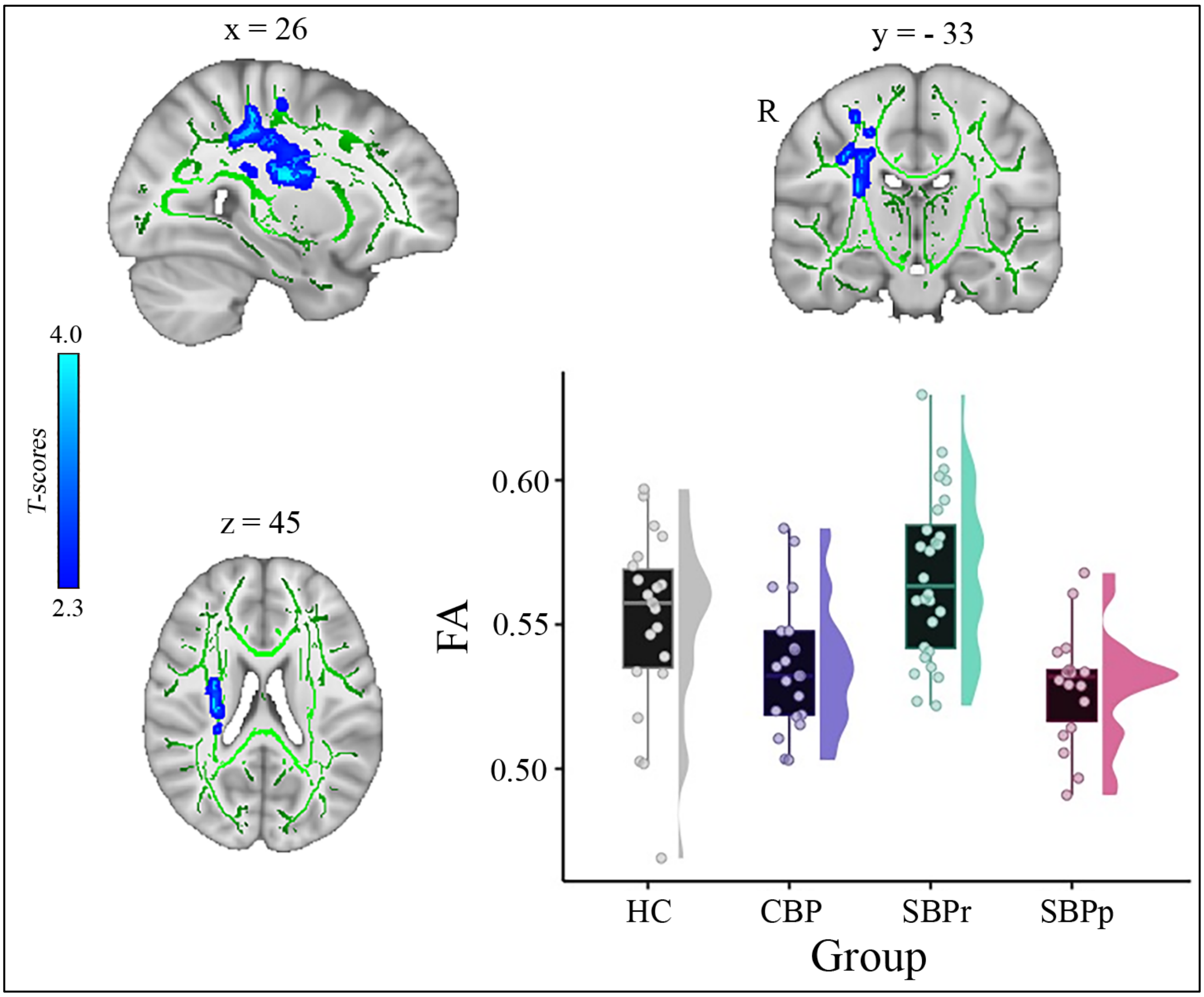

Figure. 3. Study 1: A whole brain comparison over the white matter skeleton between patients who recovered and patients whose pain persisted and distribution of fractional anisotropy values for each group at baseline (Mannheim data set).

Results of unpaired t-test ($p < 0.05$, 10,000 permutations) show significantly increased fractional anisotropy (FA) within the right superior longitudinal fasciculus (SLF, in blue) in patients who recovered (SBPr) compared to patients whose pain persisted (SBPp) at six-months follow-up. Rain clouds include boxplots and the FA data distribution for each group (including HC, healthy controls; CBP, patients with chronic back pain) depicted on the right side of each boxplot. Jittered circles represent single data points, the middle line represents the median, the hinges of the boxplot the first and third quartiles, and the upper and lower whiskers 1.5*IQR (the interquartile range).

To test whether FA baseline values from the significantly different clusters could predict the change in pain severity from baseline to follow-up, we did multiple regression analysis with FA values as predictor and the change in pain severity percentage as outcome. In this model, FA values were predictive of pain severity at the 6-month follow-up (adjusted R^2 = 0.120, *p* = 0.011). To confirm that this result was not driven by age, gender, or head motion, we entered these parameters in a new model adjusting the prediction for covariates. FA values were still predictive of chronicity, with added variables improving the model fit (new model: adjusted R^2 = 0.236, *p* = 0.007; difference between models: *F*(2,67) = 3.67, *p* = 0.046). Figure 4 depicts the correlation between FA values and pain severity with higher FA values (greater structural integrity) associated with greater reduction in pain (percentage change).

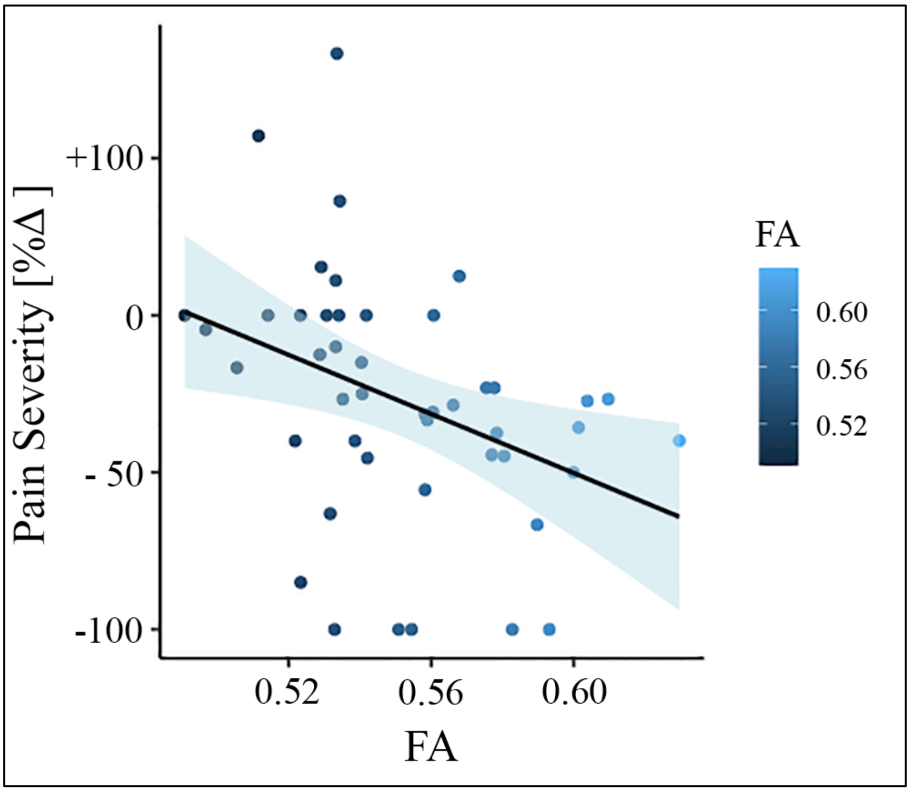

Figure 4. Study 1: Association between white matter fractional anisotropy (FA) values and percent change in pain severity (Mannheim data set).

Higher FA values in the right superior longitudinal fasciculus (SLF) are associated with greater pain reduction (from baseline to follow-up) in the Mannheim data set.

In the other independent data set (New Haven), SBPr also showed larger FA within the cluster of fibers part of the right superior longitudinal fasciculus (SLF) (MNI-coordinates of peak voxel: x = 35; y = - 13; z = 26 mm; t(max) = 4.61). Figure 5 shows FA values and their distributions for each group within the SLF cluster. As in Mannheim data set, SBPr patients had the largest FA values in the right SLF cluster, even larger than in HC, although this difference did not reach statistical significance (*p* = 0.11).

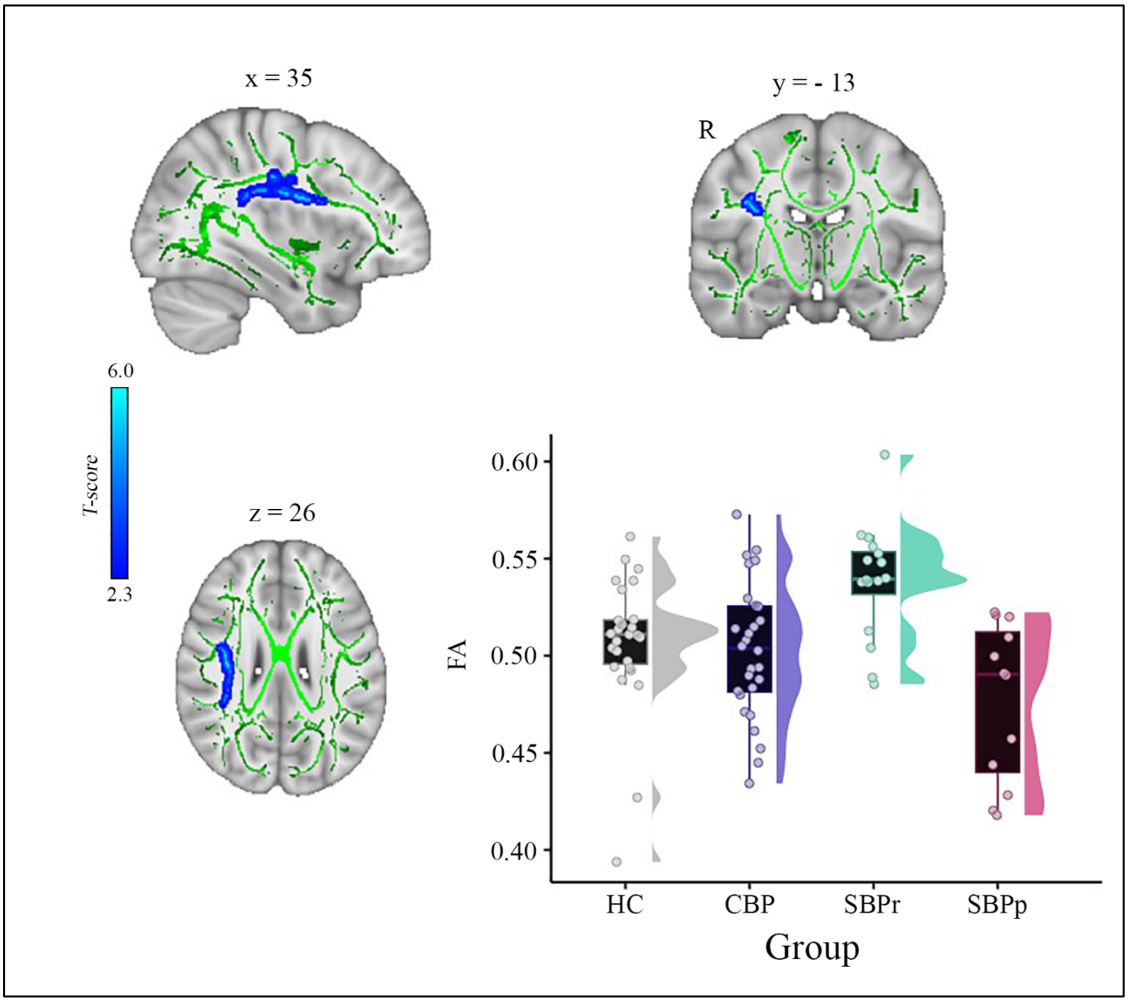

Figure 5. Study 1: A whole brain comparison over the white matter skeleton between patients who recovered and patients whose pain persisted and distribution of fractional anisotropy values for each group at baseline (New Haven data set).

Results of unpaired t-test ($p < 0.05$, 10,000 permutations) show significantly increased FA (fractional anisotropy) within the right superior longitudinal fasciculus (SLF, in blue) in patients who recovered (SBPr) compared to patients whose pain persisted (SBPp) at one-year follow-up. Rain clouds include boxplots and the FA data distribution for each group (including HC, healthy controls; CBP, patients with chronic back pain) depicted on the right side of each boxplot. Jittered circles represent single data points, the middle line represents the median, the hinges of the boxplot the first and third quartiles, and the upper and lower whiskers 1.5*IQR (the interquartile range).

To test whether baseline FA values predict the change in pain severity from baseline to follow-up in the New Haven data set, we did multiple regression analysis[5] with FA values as predictor and the percentage change in pain severity as outcome. In this model, FA values were predictive of pain severity at the one-year follow-up (adjusted R^2 = 0.202, p = 0.009). To confirm that this result was not driven by age, gender, or head motion, we entered these parameters in a new model adjusting the prediction for these covariates. FA values were still predictive of the change in pain intensity, with added variables improving the model fit (new model: adjusted R^2 = 0.259, p = 0.037; difference between models: $F(2,67)$ = 1.50, p = 0.237). Figure 6 depicts the correlation between FA values in the right SLF and pain severity with higher FA values (greater structural integrity) associated with greater reduction in pain (percentage change).

[5] Statistical analysis of this and Chicago data set after FA extraction (multiple regression, correlations) and all graphical representations (all Study 2 Figures 3-8) were done by the author of this dissertation. The whole-brain tbss analysis of New Haven and Chicago data set was done by the collaborators.

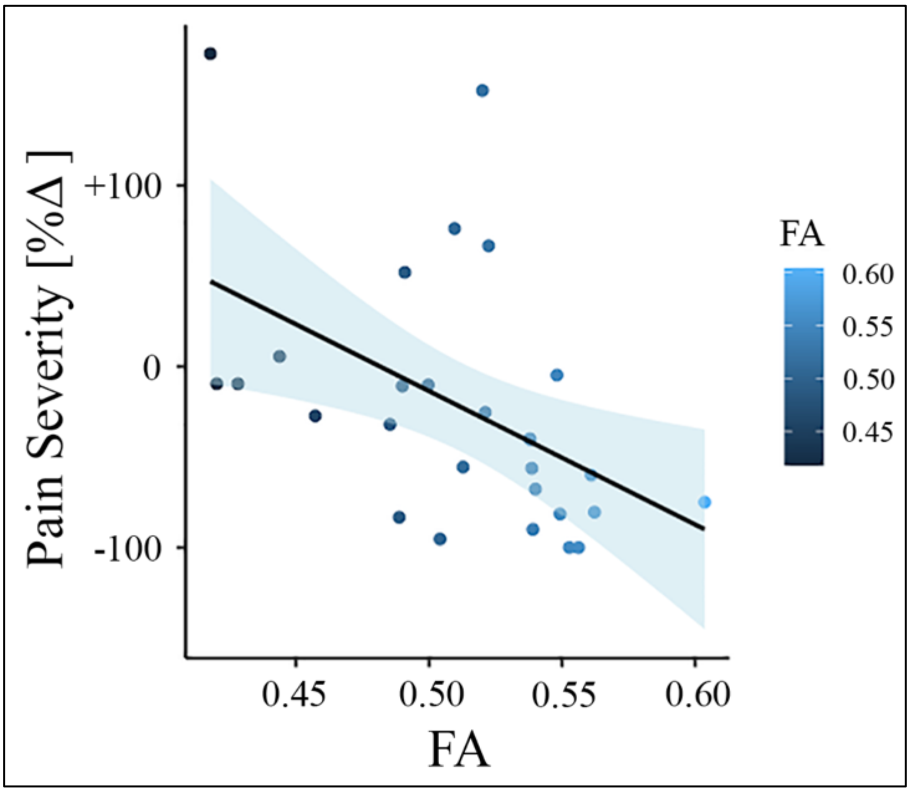

Figure 6. Study 1: Association between white matter fractional anisotropy (FA) values and percent change in pain severity (New Haven data set).

Higher FA values in the right superior longitudinal fasciculus (SLF) are associated with greater pain reduction (from baseline to follow-up) in the New Haven data set.

3.1.3 Validation of the results

We tested the accuracy of local diffusion properties of the right SLF extracted from the mask of voxels passing threshold in the New Haven data (Figure 5) in classifying the Mannheim patients into persistent and recovered. We used a simple cut-off (Green & Swets, 1966) for the evaluation of the area under the receiver operating characteristic (ROC) curve (AUC). FA values corrected for age, gender, and head displacement, accurately classified SBPr (N = 28) and SBPp (N = 18) patients from the Mannheim data set with an AUC = 0.66 (p = 0.031, tested against 10,000 random permutations), validating the predictive value of the right SLF cluster (Figure 7).

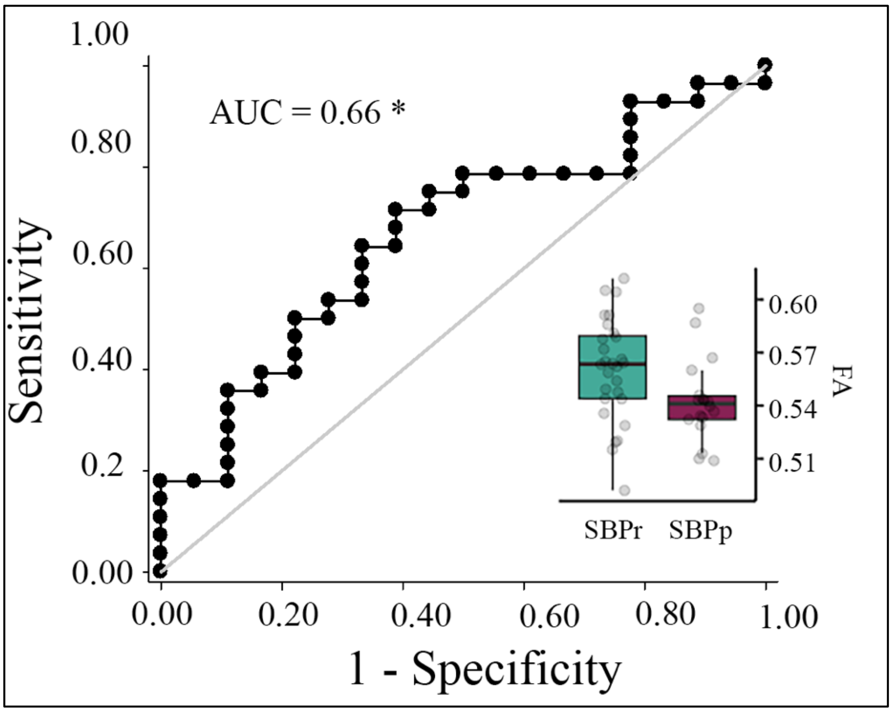

Figure 7. Study 1: Validation of the accuracy of fractional anisotropy (FA) in the right superior longitudinal fasciculus (SLF) in classifying Mannheim patients.

The SLF cluster from the New Haven set accurately classifies patients who recovered (SBPr) and those whose pain persisted (SBPp) in the Mannheim data set at a six-month follow-up. Classification accuracy is based on the receiver operating characteristic (ROC) curve. Circles on the boxplots represent single data points, the middle line represents the median, the hinges of the boxplot the first and third quartiles, and the upper and lower whiskers 1.5*IQR (the interquartile range). AUC: area under the curve; * $p < 0.05$.

To further validate the right SLF predictive power, the same mask was used to extract FA values from SBPr and SBPp groups available in the Chicago data set. FA values were calculated for two time points; one obtained at baseline (visit 1), when pain was still subacute, and at a one-year follow-up (visit 2), when pain had either remitted or persisted. FA values of the right SLF accurately classified SBPr (*N* = 23) and SBPp (*N* = 35) patients from Chicago with an AUC = 0.70 (*p* = 0.0043) at baseline (Figure 8A), and SBPr (*N* = 28) and SBPp (*N* = 34) patients with an AUC = 0.66 (*p* = 0.014) at follow-up (Figure 8B), validating the predictive cluster from the right SLF at yet another site. The correlation between FA values in the right SLF and pain severity in the Chicago data set showed marginal significance (*p* = 0.055) at visit 1 and higher FA values were significantly associated with a greater reduction in pain at visit 2 (*p* = 0.035).

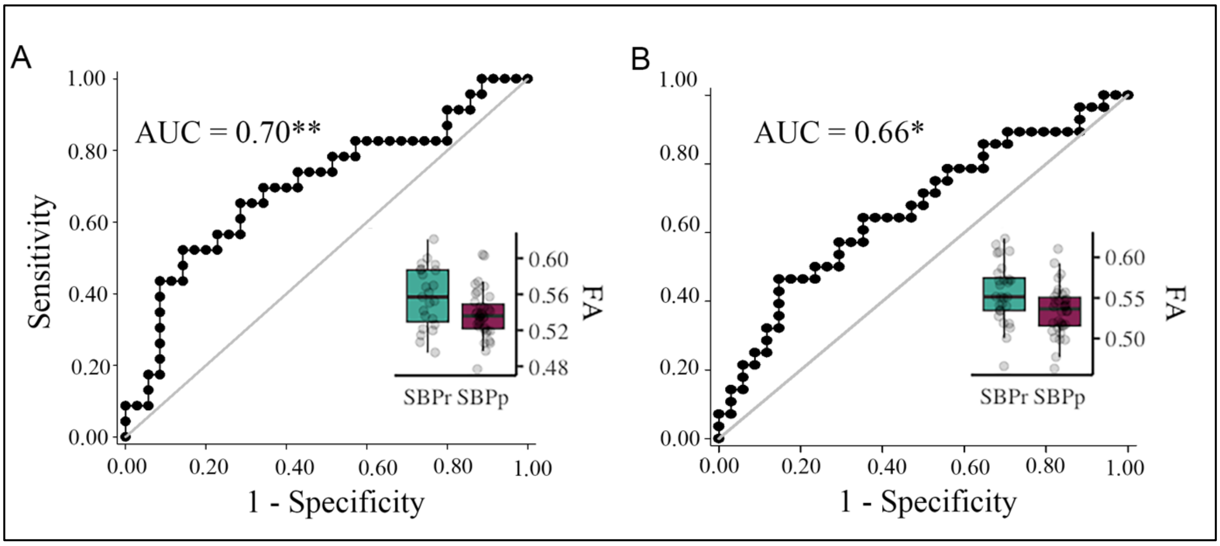

Figure 8. Study 1: Validation of the accuracy of fractional anisotropy (FA) in the right superior longitudinal fasciculus (SLF) in classifying Chicago patients.

The right SLF cluster from the New Haven data set accurately classifies patients who recovered (SBPr) and those whose pain persisted (SBPp) in the Chicago (OpenPain) data set at visit 1 (baseline) (A) and visit 2 (one-year follow-up) (B). Classification accuracy is based on the receiver operating characteristic (ROC) curve. Circles on the boxplots represent single data points, the middle line represents the median, the hinges of the boxplot the first and third quartiles, and the upper and lower whiskers 1.5*IQR (the interquartile range). AUC: area under the curve; * *p* < 0.05; ** *p* < 0.01.

3.2 Interim discussion

The white matter properties of the right SLF were significantly different between SBPr and SBPp patients across three different sites: Mannheim, New Haven, and Chicago. Furthermore, SBPr patients showed larger FA values than pain-free controls in the right SLF in both the Mannheim and New Haven data sets. This suggests that this white matter property is a biomarker of resilience to pain chronicity where pain-free controls are composed of both high and low resilience individuals. Consistent with the concept of resilience, higher baseline fractional anisotropy in the right SLF predicted a greater percentage reduction in pain intensity at follow-up. Despite the implication of the uncinate fasciculus in learning and memory (Von Der Heide et al., 2013), which are important processes in the emergence of chronic pain (Timmers et al., 2019), we did not detect any microstructural alterations in this tract. Alterations of the uncinate fasciculus were noted in the fiber complexity (Bishop et al., 2018) but not in fractional anisotropy (Lieberman et al., 2014) in patients with CBP compared to pain-free controls. This suggests that either FA is not the appropriate measure used for studying the uncinate fasciculus in relation to pain, or that this tract is not involved in chronic aversive learning.

The SLF is a large bundle of white matter association fibers connecting occipital, temporal, and lateral parietal lobes with the ipsilateral frontal lobe (Thiebaut de Schotten et al., 2011). In vivo studies in humans have anatomically subdivided the SLF into dorsal (SLF I), middle (SLF II), and ventral (SLF III) branches that run in parallel (Makris et al., 2005), while the inclusion of the fourth component, the arcuate fasciculus, has been questioned by some authors due to its distinct anatomical trajectory that runs from the frontal to the temporal lobe (Janelle et al., 2022). The SLF is an essential anatomical substrate for major cognitive functions such as language (left SLF), memory, emotions, motor planning, and visuospatial processing (Mesulam, 2000). The right SLF is particularly important in visuospatial attention to the extra-personal space and the positioning of the body in the physical space (Amemiya & Naito, 2016). It connects frontal and parietal areas critical in the top-down control of attention during tasks involving any sensory modality (Mesulam, 2000). The SLF cluster found in our and in two other independent data sets spans all three branches of the SLF white matter tract.

Studies in patients with brain lesions have supported the importance of the right SLF in top-down attention processing. For example, patients who underwent glioma resection with damages to the right medial superior and middle frontal gyrus, brain regions traversed by SLF I and II, showed persistent visuospatial cognitive dysfunction postoperatively (Nakajima et al., 2017). Similarly, patients with right prefrontal glioma with the resection cavity located in a region overlapping SLF I and SLF II had persistent spatial working memory deficits even in the absence of motor and language deficits (Kinoshita et al., 2016). Lesions within the SLF II have been linked to visuospatial neglect (Thiebaut de Schotten et al., 2014; Vallar et al., 2014), supporting the role of this subcomponent in visuospatial awareness. Together the literature on the right SLF role in higher cognitive functions suggests, therefore, that resilience to chronic pain might be related to a top-down phenomenon involving visuospatial and body awareness.

Higher FA values in the right SLF have been associated with better performance in sustained attention in children (Klarborg et al., 2013) and people suffering from attention deficits or hyperactivity disorder (Konrad et al., 2010; Makris et al., 2008; Thomas et al., 2015). After a stroke, patients who had higher baseline FA values within SLF II showed higher success rates in the visuomotor task after 4 weeks of learning compared to those with lower baseline FA values (Buch et al., 2012). Similarly, a recent study showed that SLF II underwent plastic changes after learning of tracking movement tasks requiring both top-down attentional processes and bottom-up somatosensory feedback to adjust one's own movement, and the degree of this plasticity predicted task-related success (Shiao et al., 2022). Since the constant adaptation of motor control in these tasks is dependent on spatial awareness and proprioception, the integrity of the SLF II appears important to their intact functioning.

Proprioception, which is a bottom-up somatic signal closely related to visuospatial processing, is critical for recognizing one’s own body position and hence the awareness of the physical self. Changes at the higher-order level of proprioceptive processing can also affect body perception (Goossens et al., 2019). The right SLF connects a network of brain regions involved in proprioceptive awareness and allows us to perceive ourselves as separate entities from external animate and inanimate objects (Naito et al., 2016). Lesions of this white matter bundle and/or of the right parietal lobe are associated with hemispatial neglect of the left side of extra-personal space and, in extreme cases, of one’s own body parts (Mesulam, 2000). Specifically, SLF II and SLF III subcomponents have been linked to dysfunctions in proprioception. The inferior frontoparietal network, connected by the SLF III, showed predominant right-hemispheric activation during both the visual self-face recognition and limb proprioceptive illusion task, which suggests importance of this tract in self-awareness independent of the sensory modality and body parts involved (Morita et al., 2017). Similarly, changes in limb position in relation to posture activate the same network, hence suggesting that constant awareness of our body position and corrective feedback on our body schema is indeed dependent on this tract (Amemiya & Naito, 2016).

Although the findings on the direct association between impaired proprioception and CBP are inconclusive due to the variety of methods used to measure proprioceptive performance (Ghamkhar & Kahlaee, 2019; Lin et al., 2019; Tong et al., 2017), there is evidence that the central processing of back-related proprioceptive signals is affected in chronic low back pain (Goossens et al., 2019; Tsay et al., 2015). Indeed, it has been shown that pain perception influences body representation (Schwoebel et al., 2001), and body representation is altered in patients with chronic pain as investigated by psychophysical (Gilpin et al., 2014; Tsay et al., 2015), and neuroimaging studies (Flor et al., 2006; Goossens et al., 2019; Moseley & Flor, 2012). Interestingly, in some cases disturbances in body representation occurred before the development of chronic pain (Bultitude & Rafal, 2010) and predicted decreased analgesic response to an exercise treatment (Tanaka et al., 2021), suggesting a causal role of such a distortion in chronicity. While we did not collect proprioceptive and attention measures in the patients with SBP, our results suggest that these measures could be useful to separate resilient and at-risk patients.

The asymmetry of the functions subserved by the SLF is notable as lesions to the right but not left SLF lead to hemispatial neglect on the left side, suggesting that vulnerabilities and strength in the neural substrate mediating attention and visuospatial processing contribute to the long-term risk or resilience to chronic pain. The observation that the structural properties of such a large association fiber network predict pain chronicity also suggests that risks and vulnerabilities to chronic pain may be determined by large, distributed frontoparietal networks on the right side of the brain. Interestingly, compared to pain-free controls, patients with low back pain show functional connectivity alterations in the dorsal visual stream involved in visuospatial attention and subserved by the SLF tract, but not in the ventral visual stream (Shen et al., 2019). The results motivated us to explore different diffusion-based parameters, primarily focusing on structural connectivity.

Our results along with previous studies suggest that resilience to chronicity of back pain may be related to the structural integrity (i.e., FA) of the right SLF. Like Mansour et al. (Mansour et al., 2013) we observed that SBPr patients show larger FA values than the pain-free controls while the SBPp patients show similar FA values to the patients with CBP suggesting that the pain-free population is made up of high and low-risk groups (Figure 3; Figure 5). Notably, though, the DTI-based FA results reported by Mansour et al. were on the left side of the brain. While larger data sets are required to explain this discrepancy, it does suggest that resilience to chronic pain might also be a widespread brain property involving other large-scale brain networks. CBP state has been associated with white matter changes across several tracts (Lieberman et al., 2014), but here we show that the SLF tract is particularly important in the transition phase of subacute to CBP state, predicting long-term chronicity in a lateralized, right-dominant manner. As pain turns chronic, it is likely to progressively involve other neural pathways, indicating changes within broader neural networks. In fact, neural signatures of sustained and chronic pain are predominately observed in somatomotor, frontoparietal, and dorsal attention networks (Lee et al., 2021), which corresponds to the microstructural changes in tracts found in the chronic state. The right SLF, however, shows changes already at half a year into chronicity, remains stable at one year, and could therefore serve as a potential biomarker to address the need for early detection of risk.

In task-based and resting state neuroimaging studies the brain activity in the frontoparietal area was not typically observed as a risk factor for persistent pain. Instead, functional connectivity between the medial prefrontal cortex and nucleus accumbens (Baliki et al., 2012), as well as the processing of reward signals in the same pathway (Löffler et al., 2022) were shown to be predictive of back pain chronicity. Investigations into structural properties showed that the risk for the development of CBP is related to a smaller nucleus accumbens and hippocampi (Baliki et al., 2012; Makary et al., 2020; Vachon-Presseau et al., 2016a) in the SBPp patients relative to the other groups. Conversely, larger amygdala volume seems to be a protective factor against chronicity, as it was greater in SBPr than in both the persistent pain group and the pain-free group (Vachon-Presseau et al., 2016a). In the same vein, we observed greater FA values within SLF in SBPr not only compared to SBPp but also to healthy controls. The involvement of the frontoparietal area can thus be regarded as part of structural "resilience circuitry".

Despite different time frames for the follow-up, initial (baseline) pain intensities (and accordingly different criteria for subgrouping SBP into SBPr/SBPp), population, sites, scanners, and pain questionnaires/screening used, we successfully validated results across three different sites. Moreover, we carefully addressed the potential confounding effects of head displacement, which can lead to either positive or negative bias (Ling et al., 2012) by accounting for it in the analysis. This points towards the robustness of the integrity of the SLF as a biomarker of resilience to CBP, with a potential for clinical translation.

3.2.1 Limitations and outlook

Our results are based on heterogeneous samples, heterogeneous pain measures, different criteria for recovery, and different scanners across sites. We believe that the data presented here is nevertheless robust since multisite validated but needs replication. The model performances we reported reflect the prognostic accuracy of our model. Even though our model performance is average-to-good, which currently limits its usefulness for clinical translation, we believe that future models would further improve accuracy by using larger homogenous sample sizes and uniform acquisition sequences. Future studies could validate our results with increased sample sizes and using the same criteria across sites. In addition, our studies did not evaluate functions subserved by the right SLF such as proprioception or other types of visuo-spatial tasks. We believe that the results strongly support the future assessment of such cognitive functions in the study of risk and resilience to chronic pain.

3.2.2 Conclusion

We have identified a brain white matter biomarker of resilience to CBP and validated it in multiple independent cohorts at different sites. This biomarker is easy to obtain (~10 min of scanning time) and could open the door for translation into clinical practice, as future models on diffusion data are likely to improve accuracy by obtaining the data from larger sample sizes and using the same acquisition sequences. Although chronic pain may eventually affect other neural networks, the microstructural changes in the right SLF tract are evident early in the course of the illness and remain stable as pain progresses. Future studies should investigate how this brain structural predisposition to CBP may impact brain function, information processing, and neural networks. This could lead to potential neural targets for early interventions such as neurofeedback

(Bucolo et al., 2022) or brain stimulation (Kandić et al., 2021). In addition, cognitive and behavioral processes associated with the right SLF, such as proprioception and attentional functions, should be examined in subacute stages, as targeting these processes could add to the effective prevention of chronicity. Integrating findings from studies that used questionnaire-based tools and showed remarkable predictive power (Tanguay-Sabourin et al., 2023), with neurobiological measures that can offer mechanistic insights into the development of chronic pain, could enhance predictive power in CBP prognostic modeling.

To establish the clinical usefulness of a biomarker, it should be tested in various populations, settings, and contexts, and ideally be cost-effective and simple to implement (Davis et al., 2020). In this regard, we have introduced a promising biomarker found in brain white matter, which has considerable potential for clinical application in the prevention and treatment of CBP.

3.3 Study 2

3.3.1 Sample characteristics

The collected data included 12 patients with constant back pain. Day 1 fMRI data were completed by 14 patients. However, one subject had to be excluded due to revealed brain anatomical abnormalities. Another patient completed Day 1 but missed the Day 2 appointment a week later and was subsequently unable to schedule within the timeframe necessary for meaningful follow-up data collection. The average pain intensity reported on screening was 4.25 (SD=1.22) on a 0-10 rating scale, while the average score on the MPI pain severity scale (0-6) was 2.94 (SD=0.83). On average, the sample did not exhibit high levels of anxiety (M=6.58, SD=3.78) or depression (M=6.00, SD=3.33), but the variability showed that some individuals may have been experiencing clinically significant emotional distress. Participants had been suffering from back pain for an average of 11 years. The sample had a disproportional gender distribution, with 8 females and 4 males.

The reported regular medication included nonsteroidal anti-inflammatory drugs (NSAIDs) for three participants, serotonin-norepinephrine reuptake inhibitors (SNRIs) (one participant), beta-1 selective adrenergic receptor blocker (one participant), angiotensin-converting enzyme (ACE) inhibitors (one participant), statins (one participant), dexamethasone ophthalmic solution (one participant), hormonal contraceptives (three participants). Occasional use of benzodiazepines was reported by one participant. Past use was reported for benzodiazepines (five participants), opiates (two participants), statins (one participant), and cannabinoids (one participant). Two participants were regular smokers. All participants abstained from alcohol and caffeine consumption on the evening and morning prior to the study, as they were advised via telephone screening. All participants, with the exception of two, reported having a typical amount of sleep the night before the session. After the debriefing session, of the 12 participants, 7 (58%) guessed correctly, while 5 (42%) guessed incorrectly which session involved the sham (placebo) condition. A binomial test confirmed that the proportion of correct guesses (58%) was not significantly different from the chance level (50%; p = 0.774), suggesting that blinding was maintained.

3.3.2 The effects of TBS on pain and functional connectivity

3.3.2.1 Pain intensity and unpleasantness

Results of the linear mixed-effects model (LME) revealed a nearly significant main effect of Time (*p* = 0.051), indicating an overall reduction in pain intensity levels from pre to post. Post-hoc tests of simple effects within each condition showed a marginal reduction in pain intensity in the Verum condition (*p* = 0.05) but not in the Sham condition (*p* = 0.394). Even though the overall trend of pain reduction was present within both conditions (see Figure 9), the interaction between Condition and Time was estimated at 0.33, not significant (*p* = 0.420), suggesting that the Pre-Post difference did not differ significantly between Verum and Sham. All p-values reported here and in Table 3 and Table 4 are unadjusted for the two outcome variables; Bonferroni correction for the two pain measures ($\alpha = 0.05/2 = 0.025$) yielded all effects non-significant (see Notes 1 and 2).

Table 3. Study 2: Pain intensity LME model.

	Pain Intensity Model		
Predictors	*Estimates*	*95% CI*	*p*
(Intercept) (Pre Verum)	1.52	-0.232 3.367	0.107
Condition (Sham vs Verum)	0.33	-0.250 0.951	0.256
Time (Post vs Pre)	-0.58	-1.158 -0.021	0.051
Age	0.02	-0.014 0.050	0.315
Gender	-0.06	-0.998 0.837	0.894
Condition:Time	0.33	-0.449 1.127	0.420
Random Effects			
σ^2	0.50		
$\tau_{00\ ID}$	0.46		
ICC	0.48		
N_{ID}	12		
Observations	48		
Marginal R^2 / Conditional R^2	0.152 / 0.559		

Note 1. Since pain intensity and unpleasantness were defined a priori as primary outcomes representing interrelated facets of the same construct, each was evaluated at $\alpha = 0.05$ without adjustment for multiple comparisons. When adjusting for two primary outcomes using the Bonferroni method ($\alpha = 0.05/2 = 0.025$), neither effect reached significance and adjusted $p = 0.15$ for the main effect Time.

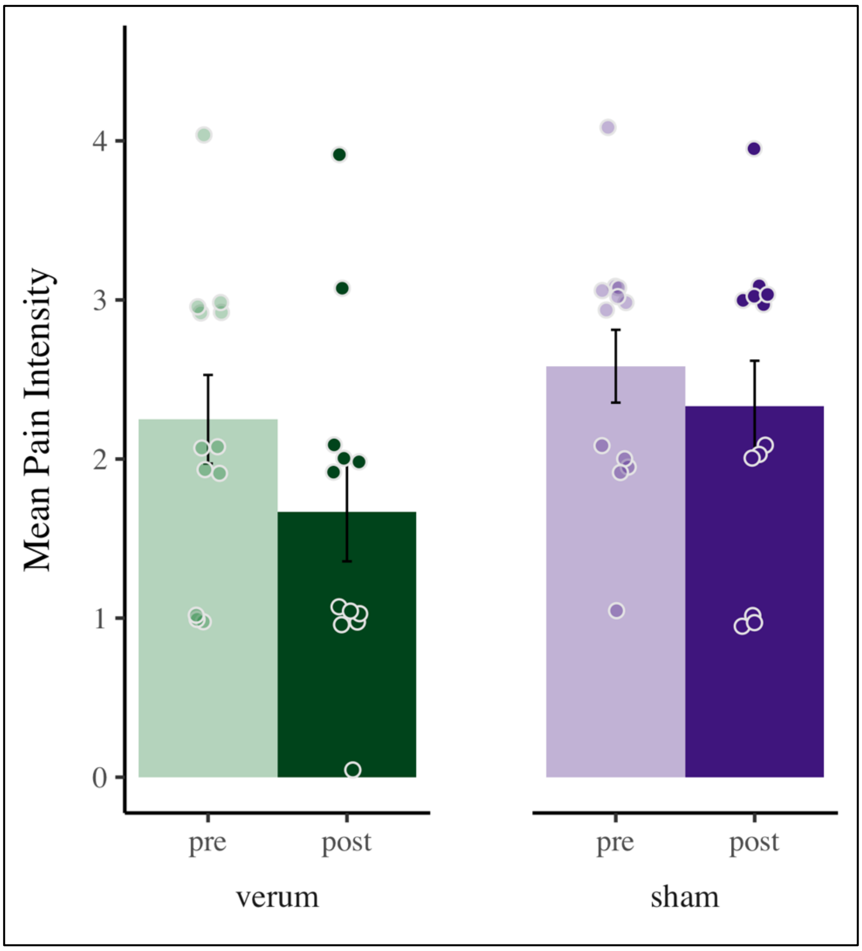

Figure 9. Study 2: Bar plots of mean pain intensity across stimulation conditions and time points.

Error bars represent the standard error of the mean. Individual subject means are shown as dots, overlaid on group-level bar plots. Ratings reflect the West Haven-Yale Multidimensional Pain Inventory (MPI) pain intensity item scale (0-6).

A linear mixed-effects model was likewise used to assess the effects of *Condition* and *Time* on pain unpleasantness while controlling for covariates *Age* and *Gender* (Table 6). P-values for primary outcomes were presented in the table unadjusted; a Bonferroni correction for two pain measures ($\alpha = 0.05/2 = 0.025$) yielded $p_{corr} = 0.16$ for the only marginally significant main effect of Time in pain unpleasantness model (see Note 2 below Table 4).

Table 4. Study 2: Pain unpleasantness LME model.

	Pain Unpleasantness Model		
Predictors	*Estimates*	*95% CI*	*p*
(Intercept) (Pre Verum)	2.72	0.573 4.874	**0.020**
Condition (Sham vs Verum)	0.33	-0.359 1.011	0.366
Time (Post vs Pre)	-0.67	-1.390 0.015	0.075
Age	-0.00	-0.041 0.042	0.988
Gender	-0.56	-1.744 0.598	0.337
Condition:Time	0.08	-0.902 1.060	0.873
Random Effects			
σ^2	0.80		
$\tau_{00\ ID}$	0.67		
ICC	0.45		
N_{ID}	12		
Observations	48		
Marginal R^2 / Conditional R^2	0.124 / 0.523		

Note 2. When adjusting for two primary outcomes using the Bonferroni method ($\alpha = .05/2 = .025$), neither effect reached significance and adjusted $p = 0.16$ for the main effect of Time.

There was a trend towards a significant reduction in pain unpleasantness from Pre to Post stimulation (Figure 10), and the main effect of *Time* showed a marginal decrease of pain unpleasantness ($p = 0.075$), while *Condition* or the interaction were not statistically significant ($p > 0.05$). This indicates a lack of evidence for condition-specific effects on changes in pain unpleasantness.

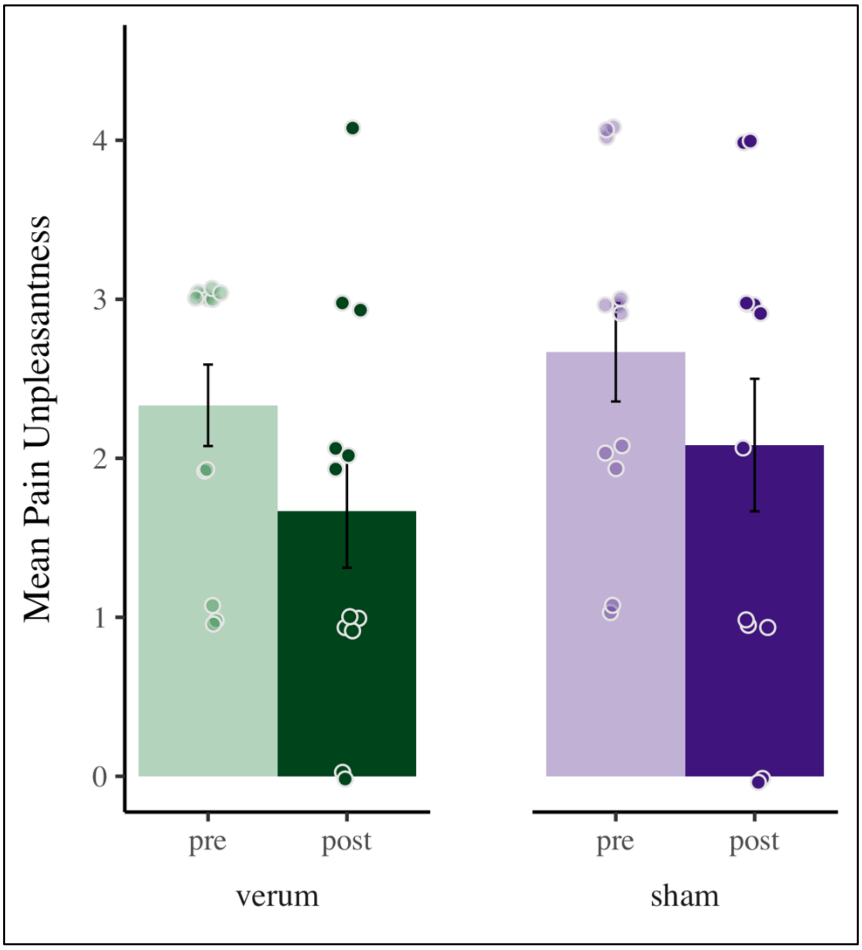

Figure 10. Study 2: Bar plots of mean pain unpleasantness across stimulation conditions and time points.

Individual subject means are shown as dots, overlaid on group-level bar plots. Ratings reflect the West Haven-Yale Multidimensional Pain Inventory (MPI) pain intensity item scale (0-6).

On an individual level, substantial within-subject variability was observed in the relative changes in pain intensity and unpleasantness from pre- to post-intervention across conditions (see Appendix, Figure 14. Supplement Study 2). In the verum condition, pain intensity decreased more from pre to post compared to the sham condition for a subset of subjects. Specifically, four out of twelve subjects showed greater pain reduction in the verum condition than in the sham condition, while two experienced similar reductions across both conditions. In contrast, five subjects showed no change in either condition, and one subject experienced an increase in pain intensity in the verum condition greater than in the sham condition. Changes in pain unpleasantness were even more variable. Six subjects exhibited an overall reduction, with four showing a greater decrease in the verum condition and two in the sham condition. Three subjects showed no change, one experienced equal reduction across conditions, one found pain more unpleasant post-verum than post-sham, and one experienced increased unpleasantness in the verum condition alongside a reduction in the sham condition. These findings underscore the high degree of individual variability in pain intensity and unpleasantness responses, even within the same intervention condition.

3.3.2.2 Secondary outcomes: Arousal, Dominance, and Valence

Secondary analyses of Arousal, Dominance, and Valence were conducted to rule out the possibility that the observed effects of stimulation were driven by changes in general affective state, as these measures were not central to the main hypotheses. Linear mixed-effects models were fitted separately for each secondary outcome (Arousal, Dominance, Valence), with the same fixed effects: Condition (Verum vs. Sham), Time (Pre vs. Post), their interaction, and the covariates Age and Gender as in the main model. No significant Time × Condition interaction was found for any of the affective dimensions before and after Bonferroni-correction ($\alpha = .05/3 = .017$) of the *p*-values for the three exploratory tests (raw *p*-values = 1.000, 0.688, 0.076; Bonferroni $p = 1.000$, 1.000, 0.230). Main effects of Time (all raw $p > 0.05$ ranged 0.094–0.771; Bonferroni-corrected $p = 0.282$–1.000), and of Condition (raw *p*-values 0.087–1.000; Bonferroni-corrected $p = 0.261$–1.000) likewise did not reach significance. Thus, neither the interaction nor any main effect was statistically significant in the uncorrected analyses, and this non-significance persisted after adjustment for three comparisons. The change over time in each secondary measure for both verum and sham conditions is presented in Appendix, Figure 15. Supplement Study 2 and Table 9. Supplement

Study 2 reports the full effect estimates and uncorrected and corrected p-values for all secondary analyses.

3.3.2.3 Changes in functional connectivity

The functional connectivity analysis revealed decreased connectivity of the mPFC (verum vs. sham) with a cluster located in the left thalamus, identified using the Harvard-Oxford atlas (z > 3.86, $p < 0.001$, k=64, MNI coordinates: [-12, -16, 6]), as presented in Figure 11.

Region	Cluster ID	X	Y	Z	Peak Stat	Cluster Size (mm3)
Left Thalamus	1	-12	-16	6	-3.8574	64

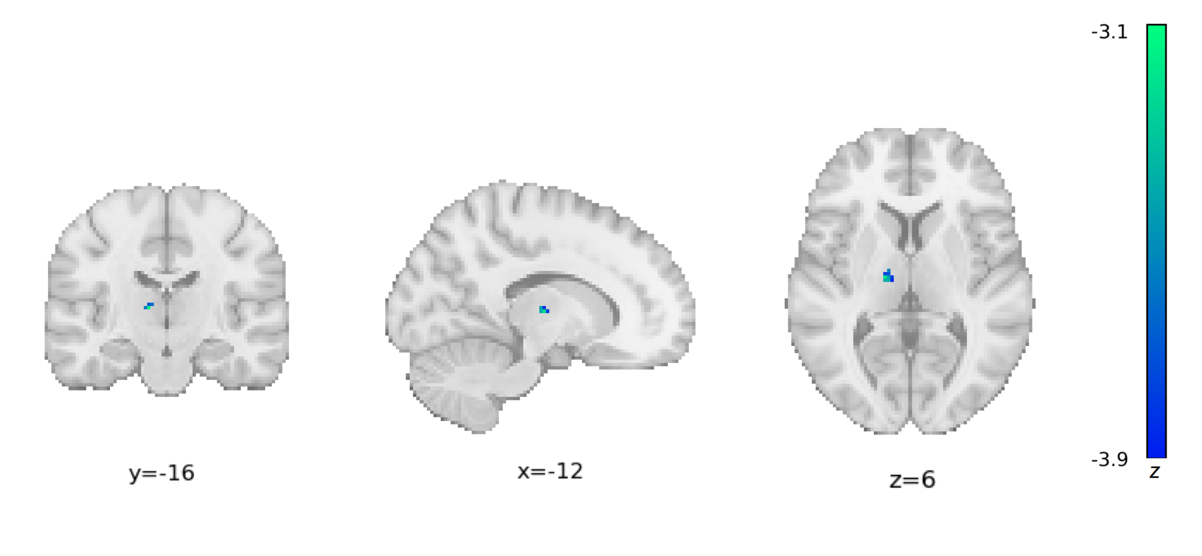

Figure 11. Study 2: Decrease in functional connectivity between the mPFC and a left thalamic cluster in the verum versus sham condition.

The statistical map was thresholded at z ≥ 3.1 ($p < 0.001$ uncorrected) at the voxel level, and significant clusters were determined using cluster-level correction (*p*FWE < 0.05). The color bar reflects z-scores for voxels in the significant cluster.

3.3.3 Association of brain connectivity with behavioral outcomes

3.3.3.1 FC and pain ratings

To investigate if changes in functional connectivity are associated with changes in pain measures, the mean Fisher z-transformed seed-to-voxel connectivity values from the mPFC–thalamus cluster were extracted for each subject, separately for each stimulation condition (verum, sham) and time point (pre-TBS, post-TBS). Subsequently, Spearman ρ correlation coefficients (corrected for age and gender) were calculated. The FC change (post-pre) was correlated with the changes in pain intensity and unpleasantness for each condition separately (verum and sham).

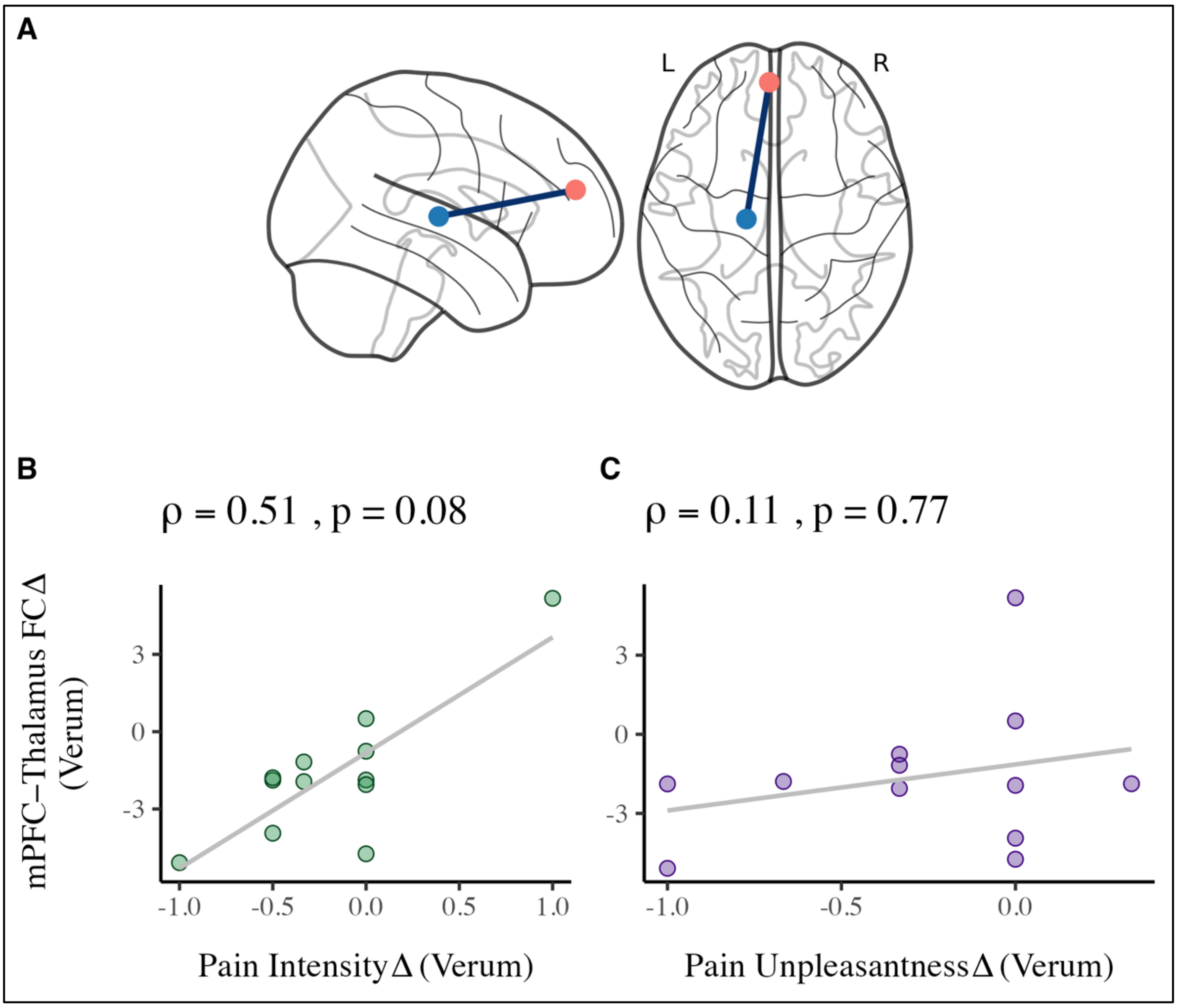

Figure 12. Study 2: Association between the functional connectivity changes (FCΔ) and pain changes in the verum condition.

(A) The nodes representing the FC between the medial prefrontal cortex (mPFC) target (orange) and the left thalamus (blue) that significantly differed between verum and sham conditions from pre- to post-theta-burst stimulation. The functional connectivity changes showed a marginally significant positive correlation with the pain intensity change (B), while the association with pain unpleasantness change was not significant (C). Negative values represent a decrease, while positive values represent an increase in both FC and pain variables.

A Spearman's rank correlation analysis revealed a moderate positive correlation (Figure 12B) between changes in connectivity and pain intensity changes in the verum condition with marginal significance (ρ=0.506, p = 0.084), while the association with pain unpleasantness change was not significant (Figure 12C) (ρ=0.105, p = 0.773). In the sham condition, neither change in pain intensity nor in pain unpleasantness was significantly associated with the connectivity change (ρ = -0.102, p = 0.779 for intensity and ρ = -0.080, p = 0.825 for unpleasantness). A leave-one-out sensitivity analysis revealed that the Spearman correlation remained in a moderate-to-strong range (ρ = 0.38–0.68) across all 12 iterations, but that omission of two particular subjects reduced the correlation to ρ = 0.38 (p = 0.19).

3.3.3.2 FC and other clinical variables

Exploratory analysis revealed that functional connectivity changes in the significant cluster (mPFC-Thalamus) in either of the condition (verum, sham) did not correlate with any of the measures reported in Table 2. Importantly, stimulation intensity (represented by active motor threshold) correlated only with gender, as expected (p = 0.049), but did not significantly correlate with changes in functional connectivity nor with the pain changes (all p > 0.05).

3.3.4 Exploratory analysis on ROI-to-ROI functional connectivity

Results of paired t-tests on the FC difference matrices showed no significant change from pre- to post-stimulation in ROI-to-ROI connectivity in the sham condition, at either the uncorrected or FDR-corrected level (all p > 0.1). Likewise, in the verum condition, no results survived FDR correction. However, uncorrected (exploratory) paired t-tests (α = 0.05) revealed significant changes over time in two network pairs in the verum condition: Limbic–DMN connectivity decreased from pre- to post-TBS (mean difference −0.020, SD = 0.027, t(11) = −2.499, p = 0.032, Cohen’s d = −0.721 Hedges’ g = –0.671, 95 % CI for d = [–1.441, –0.001]; and Limbic–SMN connectivity increased from pre- to post-TBS (mean difference 0.019, SD = 0.024, t(11) = 2.491, p = 0.033, Cohen’s d = 0.719, Hedges’ g = 0.669, 95 % CI [0.08, 1.36]). We computed Cohen’s for reported effects, but we also report Hedges’ g (bias-corrected d) and its 95% CI (using bootstrap) to account for small sample bias. See also Figure 13.

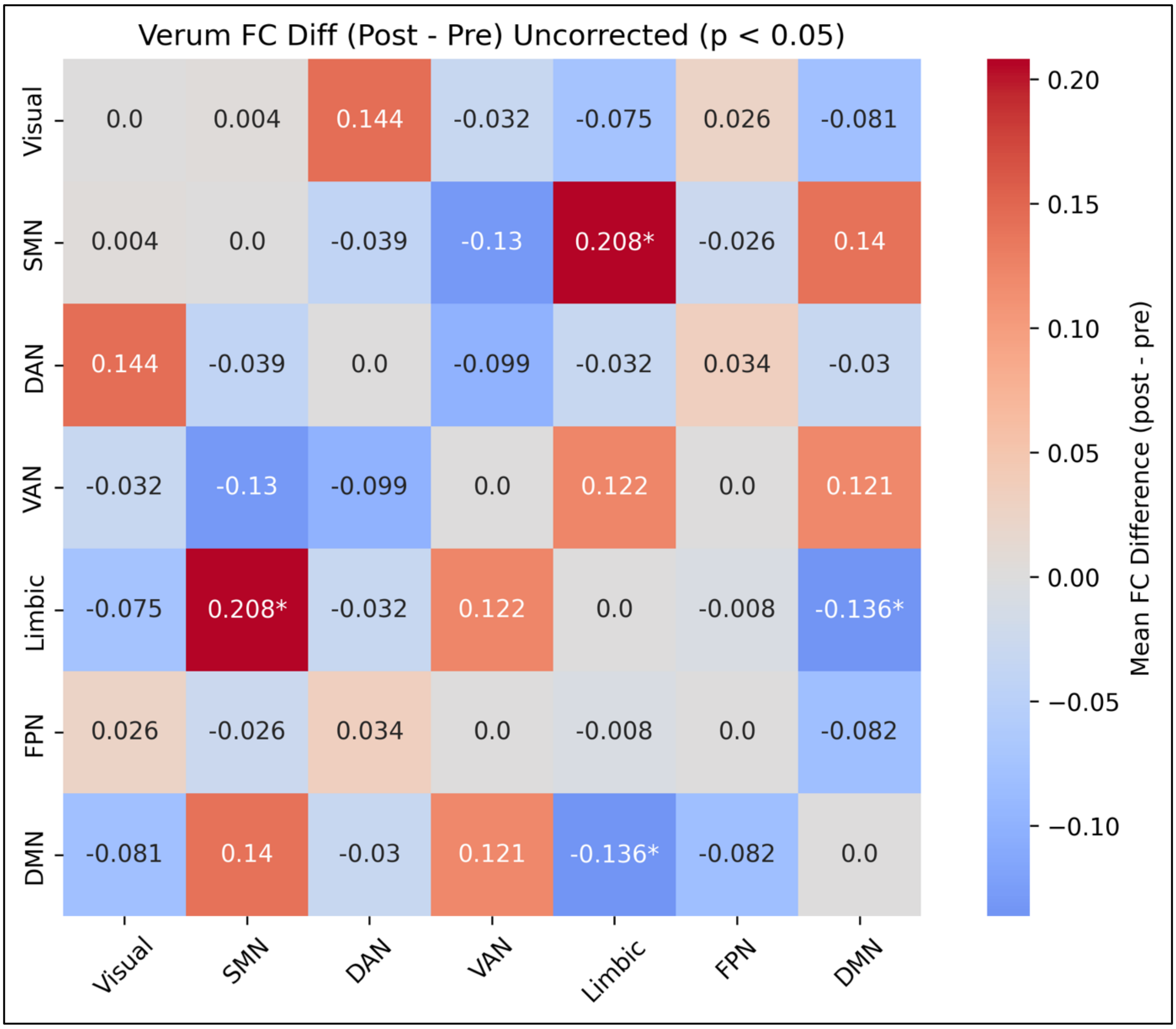

Figure 13. Study 2: Connectivity changes across seven large-scale cortical networks.

Heatmaps display the mean functional connectivity (FC) difference (Diff) values (post minus pre) for each network pair in the verum condition. The asterisks indicate statistically significant differences (uncorrected at α = 0.05). From left to right (on the x-axis): visual network; SMN, somatomotor network; DAN, dorsal attention network; VAN, ventral attention network; limbic network; FPN, frontoparietal network; DMN, default mode network.

3.3.5 Side effects of TBS

Reported side effects included mild to moderate neck pain (three participants following the sham stimulation and one following verum stimulation), mild mood swings (one participant following verum and one participant following sham stimulation), and concentration difficulties (one participant following verum stimulation), all regarded as unrelated to TBS. One participant reported mild tiredness after verum stimulation graded as slightly related to TBS, while for one participant the same level of tiredness after sham stimulation was reported as non-related to stimulation. Further reported side effects were mild to moderate headache (three participants after verum, one of which graded it as slightly related to TBS, and three after sham, all non-related to TBS), mild tingling sensation (one participant after verum rated as likely related to TMS, and two after sham, one of which rated it as non-related to TBS, the other rated as slightly related to TBS).

3.4 Interim discussion

This study explored the effects of continuous theta-burst stimulation over the medial prefrontal cortex on back pain intensity, unpleasantness, and functional connectivity in patients with persistent chronic back pain. Results indicate that a continuous TBS protocol over the mPFC produced a trend towards a statistically significant reduction of the intensity of pain post- compared to pre-stimulation for both the verum and the sham condition. Seed-based FC analysis revealed significantly decreased connectivity of the mPFC with the thalamus in the active compared to the sham cTBS. Exploratory analysis showed that changes in pain were not significantly correlated with other clinical variables.

It was hypothesized that the active cTBS over the mPFC in comparison to sham would decrease ratings of chronic pain. This assumption was based on the role of the mPFC in chronic pain and mechanisms involved in chronic pain such as emotional learning and emotion regulation (He et al., 2020; Lesting et al., 2011; Milad & Quirk, 2002). Moreover, sustained back pain was found to be related to increased activity in the mPFC (Baliki et al., 2006). Pain intensity and pain unpleasantness ratings both showed a trend towards a statistically significant reduction, but the interaction term did not reach significance, indicating no differential effect of active cTBS versus sham. This finding may be partially attributable to placebo or non-specific effects, such as expectation of improvement or attention to the intervention. Placebo mechanisms can strongly influence both brain networks and behavioral outcomes in healthy controls (Zunhammer et al., 2021) as well as in chronic pain (Chen et al., 2024). The functional connectivity of the mPFC has, moreover, been linked to placebo responses in chronic back pain (Hashmi et al., 2012). Thus, it is possible that such mechanisms also influenced responses to the TBS and sham interventions, leading to similar pain reduction trends across conditions. In healthy individuals, decreased mPFC activity has been observed when they expected experimentally decreased pain (Koyama et al., 2005). Similarly, patients with fibromyalgia compared to healthy controls showed reduced mPFC activity when they anticipated a gain in a monetary reward task (Martucci et al., 2018). This suggests that participants in our study may have anticipated pain relief in both conditions, potentially modulating their baseline neural network activity based on the extent of their expectations. The limited variability of levels of fear of pain and catastrophizing across participants, reflected by the narrow dispersion range in these variables, may have prevented differentiation of effects on sensory and affective components, contributing to their similar modulation. Catastrophizing and fear of pain are known to impact both pain dimensions (Quartana et al., 2009), but as a part of negative affectivity associated to chronic pain, they may be particularly relevant to perceived unpleasantness, as threat value prescribed to pain is shown to separate sensory and affective components of chronic pain (Talbot et al., 2019).

The observed change in medial prefrontal TBS-induced functional connectivity showed decreased connectivity with the left thalamus at MNI coordinates likely within or near the mediodorsal thalamus (MD). The thalamus is a key component of the sensory-discriminative dimension of pain (Cross, 1994), but its medial part is also recognized as a higher-order relay involved in complex cognitive processes (Mitchell, 2015) and cognitive-affective integration (Metzger et al., 2010; Sherman & Guillery, 1996). The mPFC and MD have reciprocal connections (Delevich et al., 2015), where the thalamus integrates the feedback from the mPFC with other inputs to shape cortical processing and influence cortico-cortical connectivity (Collins et al., 2018; Sherman, 2016). The mPFC-thalamus pathway is part of the descending endogenous mPFC-thalamus-PAG pain-inhibitory pathway (You et al., 2022). Overactivation of the mPFC can produce excessive activation in the thalamus or alter PAG activity in a way that facilitates rather than suppresses pain, as excitatory alterations in the mPFC disrupt the balance of descending inhibition and facilitation (Ong et al., 2019). Furthermore, the evidence from animal studies suggests that chronic pain increases the coherence between the mediodorsal nucleus of the thalamus and mPFC (Cardoso-Cruz et al., 2013), and abnormal thalamocortical connectivity is linked to CBP in patients with chronic low back pain (Tu et al., 2020). By disrupting the mPFC activity, active TBS may have restored a more adaptive balance between top-down control and thalamic sensory processing. In addition, it has been demonstrated that the MD enhances the local connectivity of the prefrontal cortex, facilitating sustained and specific neural activity required for cognitive tasks (Schmitt et al., 2017). Thus, the MD is not a passive relay of signals but actively amplifies and refines prefrontal activity to effectively process information. In the context of chronic pain, this suggests that MD-mPFC connectivity may sustain maladaptive patterns of pain processing in the PFC, reinforcing persistent and dysfunctional pain-related thoughts and emotions. This is in line with findings that reported that in patients with chronic pain greater pain rumination was associated with stronger functional connectivity between the mPFC and multiple regions involved in descending pain modulation, including the medial thalamus, precuneus, retrosplenial cortex, and periaqueductal gray (Kucyi et al., 2014). These results highlight the role of mPFC-medial thalamus communication in sustaining maladaptive cognitive-emotional processing of pain, potentially as part of a broader dysfunction within the default mode and descending modulatory networks.

Repetitive TMS, including continuous theta-burst stimulation (cTBS), can induce neuroplastic changes ranging from network-level reorganization to cellular and synaptic modifications (for reviews, see Jayathilake et al., 2025; Kuner & Flor, 2016). see e.g. Jayathilake et al., 2025; Kuner & Flor, 2016). Even one session of cTBS has been shown to trigger early short-term structural and functional changes in the targeted cortical region (Jung & Lambon Ralph, 2021). The after-effects of TMS/cTBS have been linked to N-methyl-d-aspartate (NMDA) receptor-dependent long-term potentiation (LTP) and long-term depression (LTD)-like mechanisms (Huang et al., 2007). The same mechanism, specifically, LTP-like plasticity, has also been implicated in central sensitization, where persistent synaptic strengthening leads to sustained nociceptive amplification (Ji et al., 2003; Klein et al., 2004), and has been discussed as a mechanism contributing to a transition from acute to chronic pain (Rygh et al., 2005). While resting-state functional connectivity cannot reveal neurotransmitter-specific changes, the observed decrease in mPFC–thalamus connectivity may reflect a downstream consequence of altered mPFC excitability, potentially triggering early synaptic modulation and a renormalization of disrupted excitatory-inhibitory balance in neurotransmission within this brain region (Kang et al., 2021).

While there was a trend toward a significant reduction in pain measures, the changes in arousal, dominance, and valence were small and non-significant, suggesting that mPFC stimulation may have modulated affective-sensory integration without broadly altering emotional valence or arousal. The Self-Assessment Manikin, in the context of this study, was used to measure participants' general emotional response rather than pain-related affective reactions. Therefore, the absence of change in valence, arousal, and dominance ratings does not necessarily indicate stronger modulation of the sensory over the affective component of pain, as such general measures may not adequately capture the specific emotional dimensions associated with chronic pain, in line with evidence that clinical pain can be modulated via TMS without affecting mood (Borckardt et al., 2009).

Nevertheless, evidence for a stronger modulation of the sensory component of chronic back pain in this study may come from the observation that, under verum stimulation, changes in mPFC-left thalamus connectivity showed a trend toward significant correlation only with changes in pain intensity. A positive correlation between mPFC-thalamus FC and pain intensity changes indicated that increased FC was associated with the smaller pain reduction. Conversely, greater reductions in mPFC-thalamus functional connectivity were associated with greater pain intensity reduction. This relationship was absent for the pain unpleasantness. This could either indicate a methodological limitation or reflect the greater complexity of the affective component of pain compared to its sensory dimension (Price, 2000). In addition, clinical pain reduction involves mechanisms beyond functional connectivity in the mPFC-thalamus network. The observed neural change in this study may relate to the stimulation effect in the CBP stage, rather than direct circuit involvement in the ongoing processing of pain. The active TBS condition might have induced neuroplastic effects specific to the brain altered due to chronic pain, which may, however, not necessarily translate to immediate pain reduction. Immediate pain relief might require downstream or indirect networks that were outside of the TBS range of stimulation in this study. Conventional TMS cannot directly reach subcortical areas (Wagner et al., 2007), which may be directly involved in ongoing pain. Moreover, the association between neural changes and pain outcomes may emerge over longer follow-up periods (Delon-Martin et al., 2024). Longitudinal studies are needed to test whether neural changes observed immediately after TBS predict delayed or sustained pain reduction.

Exploratory analysis on ROI-to-ROI connectivity showed that active TBS over the mPFC has decreased functional connectivity between the default mode network (DMN) and the cortical limbic network, while increasing coupling between the limbic and somatomotor networks, although only at an uncorrected threshold. In the Yeo-7 parcellation, the limbic network comprises the orbitofrontal cortex (OFC) and anterior temporal pole (ATP), regions with direct anatomical connections to subcortical limbic structures, while the DMN includes the mPFC, posterior cingulate cortex (PCC), angular gyrus, and lateral temporal cortex (Yeo et al., 2011). The observed reduction in DMN-OFC/ATP connectivity may reflect a normalization of maladaptive affective processing associated with chronic pain. Previous studies in chronic back pain have reported increased connectivity between the mPFC (a key DMN node) and limbic regions such as the amygdala (Mao, Yang, Yang, et al., 2022), as well as increased coupling between the DMN and insula (Baliki et al., 2011b; Tagliazucchi et al., 2010). Enhanced connectivity between DMN regions, such as the vmPFC, and salience areas such as anterior insula has been suggested to reflect maladaptive self-referential processing, a tendency in patients with chronic pain to become overly focused on their thoughts and feelings about pain, such as worrying about its meaning, persistence, or impact, which can intensify the pain experience and emotional distress (Johansson et al., 2024). As both OFC and ATP have strong connections with the amygdala and anterior insula (Du et al., 2020; Olson et al., 2007), their reduced connectivity with the DMN could indicate a shift away from emotionally amplified pain processing, toward a more adaptive brain state characterized by decreased internal focus on pain. In addition, the mPFC and OFC are co-activated as part of an emotion-related network linked to the development of persistent back pain (Hashmi et al., 2013). Since the stimulation site was in the mPFC, it is conceivable that inhibitory cTBS may have also affected adjacent OFC regions, leading to concurrent disruption of both DMN and limbic network interactions.

In parallel, the increase in OFC/ATP–SMN connectivity may reflect a compensatory network reorganization following mPFC stimulation. The OFC has been shown to encode the relative unpleasantness of pain in context, rather than its absolute intensity, supporting its role in cognitive appraisal and value-based modulation of pain experiences (Winston et al., 2014). The increased connectivity may therefore reflect stronger interaction between the OFC and SMN, representing an enhanced integration of emotional and sensory processing. While aberrant increased connectivity within the SMN has been linked with intensity of chronic back pain (Li et al., 2018), studies have also reported decreased resting-state connectivity between the sensorimotor network and key affective areas that regulate pain (e.g. insula, thalamus, prefrontal cortex) to impaired pain modulation (Flodin et al., 2014). Our finding may thus reflect the opposite: an adaptive compensatory adaptation, in which the cortical limbic network engages with sensorimotor regions to reevaluate the emotional meaning of pain, reducing its perceived threat or distress. Although these results did not survive correction for multiple comparisons and must be interpreted with caution, they may reflect a compensatory reorganization of large-scale brain networks. Specifically, regions involved in affective valuation may decouple from maladaptive self-referential pain processing, likely due to reduced excitability and weakened interactions between the mPFC and limbic cortical areas, while instead increasing their engagement with the sensorimotor network to restore affective-sensory integration within prefrontal regulatory systems.

3.4.1 Limitations and outlook

The present study involved patients with persistent chronic back pain to examine the effects of neuromodulation on ongoing clinical pain and the role of associated neural network changes. Despite having persistent pain with all patients reporting an intensity of more than 4 out of 10 on the screening, for some participants back pain on the day of the measurement was lower particularly directly before (two prior to verum and another two prior to sham) and possibly during TMS, which could have resulted in floor effects. The mPFC is progressively recruited as ongoing pain increases and pronounced mPFC activity only occurs if pain levels remain consistently high, replacing the transient changes observed in other regions (Baliki et al., 2006). Future studies could consider inducing pain by movement to exacerbate back pain prior to stimulation. Secondly, the small sample size may have limited the ability to detect more subtle connectivity changes extending beyond the affected mPFC-thalamus connectivity. The observed reduction in mPFC-thalamus connectivity was significant in the left thalamus but not the right thalamus. It cannot be excluded that a limited sample size presented here may have reduced power to detect more subtle bilateral changes, if present. Moreover, the direction of connectivity changes under direct modulation may vary across individuals, potentially masking significant effects in other regions. For some patients, increased mPFC-thalamus connectivity may indicate heightened engagement with emotional regulation of sensory processing, while for others, decreased connectivity may reflect adaptive disengagement. This variability could account for the lack of significant findings in other key regions involved in chronic pain and emotional salience, such as the nucleus accumbens or amygdala (Kuner & Flor, 2016). Future task-based paradigms may help to reveal connectivity changes in those regions that might not be as prominently modulated in resting-state analyses. In addition to the necessity to replicate TBS-induced connectivity results in a larger sample, future studies should examine whether expectations mediate the effects of TBS on FC and its association with changes in the intensity of back pain. Collecting these measures both pre- and post-intervention would allow for a better understanding of their roles in modulating TBS effects and whether their influence is specific to pain modulation or extends to broader cognitive-affective processes. Furthermore, larger samples would allow for stratifications based on clinical characteristics to explore individual variability in connectivity changes. Given the small sample size and restricted range in pain change values (no reported change in 5 of 12 participants), the correlational results of pain ratings with FC warrant caution. Another important consideration is that this study was designed to check if the mPFC is directly involved in the ongoing chronic pain, and therefore was mechanistic and not therapeutic in nature. Considering the median pain duration in this sample of over 12 years, it is likely that maladaptation in brain networks evolved over such a long time requires multiple sessions to result in changes on the behavioral level. As NIBS studies in chronic pain suggest that long-term interventions may be needed (O'Connell et al., 2018), this inherently limits the current intervention study to produce effects on pain. Lastly, the findings of the present study provided possible parameters for affecting mPFC connectivity to downstream regions such as the thalamus. Further investigation and optimization of the parameters of this type of neuromodulation are necessary to understand their potential in affecting the neural network of patients with chronic back pain. Importantly, the present study was designed as an initial step toward characterizing the neural impact of mPFC stimulation on ongoing pain. Future studies are needed to test the network-level mechanisms more conclusively.

3.4.2 Conclusion

Together, the findings suggest that mPFC-thalamus connectivity is differentially affected by cTBS compared to sham stimulation in patients with chronic back pain. This change could represent reduced integration of sensory processing modulated by emotion-related regions or a shift towards a more balanced state by reducing maladaptive mPFC hyperconnectivity in the verum condition. In contrast, functional connectivity in the sham condition may correspond to placebo or non-specific effects that do not strongly target these maladaptive networks. Despite the trend towards pain reduction, direct effects of TBS-induced changes could not be established on a behavioral level. Whether the mPFC is causally involved in processing of ongoing back pain remains to be further investigated and it may be dependent on sample characteristics.

4 GENERAL DISCUSSION

This thesis aimed to explore psychobiological mechanisms involved in chronic back pain (CBP) and the modulation of CBP through noninvasive brain stimulation targeting the medial prefrontal cortex to elucidate its direct involvement in ongoing CBP processing. Two studies were conducted to investigate these aspects, and their findings are integrated below to advance the understanding of the neural pathways involved in the development and maintenance of chronic pain.

1.1 Summary of findings

Study 1 examined structural brain changes as predictors for the development of CBP, focusing on white matter integrity. The study involved patients with subacute back pain (SBP), divided into those who recovered (SBPr) and those whose pain persisted (SBPp) after one year. At baseline, SBPr group showed significantly higher fractional anisotropy (FA) in the right SLF compared to SBPp group, partly supporting the hypothesis that white matter tracts previously linked to the development of CBP (Mansour et al., 2013) would exhibit lower FA in those who transition to chronic pain. The structural integrity of this white matter tract, particularly involved in cognitive and attentional processing, was predictive of chronicity at follow-up. Further validation across three sites reinforced the predictive value of FA in the SLF for pain recovery. These findings emphasize the importance of brain structural integrity as a potential biomarker for resilience and risk of chronic pain. The study further hypothesized that uncinate fasciculus microstructure, a prefrontal-limbic tract associated with learning and memory, would also differentiate SBPr and SBPp groups. However, no corresponding FA differences in the uncinate fasciculus were detected, suggesting either that fractional anisotropy is not the optimal measure for capturing its involvement in CBP progression or that this tract is not central to chronic aversive learning. This partially aligns with earlier findings that found altered axonal integrity but no FA changes in the uncinate fasciculus in persons with an already developed CBP state compared to persons without CBP (Lieberman et al., 2014).

Study 2 investigated the effects of cTBS over the mPFC on intensity of pain, unpleasantness of pain, and brain connectivity in patients with CBP to demonstrate an involvement of the mPFC in ongoing chronic pain. The study found a trend towards reduced pain intensity and unpleasantness post-stimulation, but these changes were not significantly different between the verum and sham conditions. Functional connectivity analysis revealed that mPFC connectivity with the left thalamus decreased significantly after active stimulation, suggesting an involvement of this pathway in the state of persistent chronic pain. Correlational analyses indicated that these changes in mPFC-thalamus connectivity were marginally significantly associated with pain intensity but not with pain unpleasantness. These results suggest that mPFC modulation may influence the ongoing intensity of CBP. However, due to the potential placebo effects and individual variability, the findings on behavioral (pain outcomes) level were inconclusive. The lack of significant pain reduction may also be related to the chronic nature of the pain in the sample, indicating that longer or repeated interventions may be necessary to observe significant effects.

4.1 Integration of Findings

Together, these studies contribute to the growing body of evidence that brain structure and function play a central role in chronic pain. Study 1 showed that higher integrity of the right SLF predicts resilience against the transition from subacute to chronic back pain, aligning with evidence that attention, bodily awareness, emotional regulation, and sensory integration shape the development of chronic pain (Baliki et al., 2008; Kuner & Flor, 2016; Vachon-Presseau et al., 2016b). Notably, the findings also provide additional evidence that the right SLF may function as a critical resilience factor in a distinctly lateralized manner, indicating a potential role for large-scale frontoparietal networks in the transition from subacute to chronic back pain. Study 2 examined whether modulating medial prefrontal cortex (mPFC) activity through continuous theta-burst stimulation (cTBS) could reduce chronic pain. Although pain scores did not show significant improvements, the observed reduction in mPFC–thalamus connectivity following active stimulation offers insights into the neural mechanisms underlying such modulation, aligning with evidence that corticothalamic network alterations play a critical role in the pathophysiology of CBP (Tu et al., 2020). The results support the idea that, while mPFC stimulation may have effects on downstream regions, the behavioral outcomes on chronic pain may require multi-session intervention.

The results from both studies highlight the importance of examining the psychobiological underpinnings of chronic pain, particularly in relation to brain connectivity and structural integrity. The findings emphasize the value of identifying and influencing key neural pathways, including the SLF and mPFC–thalamus circuit, when refining treatments for chronic pain.

4.1.1 Brain white matter as a part of a broader "resilience network" in CBP

The findings from the first study suggest that brain white matter involvement in the development of chronic back pain may be linked to long-range association fibers within the right frontoparietal network. Moreover, the tracts that predict chronic pain onset may differ from those that contribute to its maintenance.

The frontoparietal network (FPN) plays a role in chronic back pain, as evidenced by multiple studies. Enhanced connectivity between the FPN, somatomotor network (SMN), and thalamus has been shown in patients with chronic low back pain compared to healthy controls, suggesting that persistent pain reshapes large-scale brain networks involved in attention, sensory processing, and cognitive control (Zhu et al., 2024). Additionally, patients with cLBP showed abnormal effective connectivity in the cingulo-frontal-parietal cognitive attention network, characterized by increased prefrontal-to-mid-cingulate connectivity and decreased connectivity between the mid-cingulate and superior parietal cortex (Mao et al., 2022). Furthermore, the FPN, along with the SMN and dorsal attention networks, has been identified as a key area where neural signatures of sustained and chronic pain are predominantly observed (Lee et al., 2021). The SLF, as part of the frontoparietal network, may thus serve as a crucial node in the reorganization of neural circuits associated with both pain processing and cognitive functions in chronic pain. Haggard et al. (2013) underline that the somatosensory and parietal projections are important in relating body representation and pain, providing spatial location coding of pain in interplay with other sensory modalities. In the development of chronic back pain, the salient nature of pain stimuli can lead to overt attention toward pain and how the pain is "coded" with constant self-adaptation affecting movements, posture, and ultimately the body schema. If the structural integrity of the neural system that underlies this process is compromised, the efficacy of the required adjustment is also endangered, which might represent a risk factor for the development of chronic back pain. The finding that recovered patients exhibited higher FA in the SLF than even healthy controls suggests that SLF integrity may function more as a resilience factor, actively supporting recovery rather than lower SLF integrity merely serving as a risk factor for back chronicity. An important question that remains to be investigated is whether the integrity of the SLF as a resilience factor in CBP extends to other chronic pain conditions. A recent review of diffusion MRI studies in chronic primary pain conditions suggests that the heterogeneous white matter alterations reported across subtypes, such as fibromyalgia, primary visceral pain, and primary headache, may in part reflect differences in imaging methods and derived metrics (Bautin et al., 2025). However, the review highlights a set of consistently implicated white matter tracts, most notably the corpus callosum and projection fibers such as the thalamic radiations, which are frequently reported across studies and may represent key substrates of network-level reorganization in the chronic stage of pain. In addition, the superior longitudinal fasciculus (SLF) also ranks among the more commonly reported tracts (Bautin et al., 2025). While in our Study 1 structural integrity of the predictive FA in the right SLF was validated across three different sites, validating these white matter signatures in longitudinal cohorts of other chronic pain conditions is necessary to further our understanding of the interplay between attention, cognition, and white matter integrity. In addition, longitudinal studies are needed to decipher if the SLF is more critically involved in the transition to chronicity, rather than its maintenance. Together, these findings point to the importance of interhemispheric and thalamocortical communication pathways in the pathophysiology of chronic pain, while also suggesting that different white matter tracts may play distinct roles depending on the stage of chronicity.

4.1.2 Mechanisms of disruption of maladaptive mPFC connectivity in ongoing CBP

The decreased FC between the mPFC and thalamus following TBS likely results from a combination of altered network dynamics, neurotransmitter modulation, synaptic plasticity mechanisms, and disrupted oscillatory synchrony.

The mPFC neuromodulation affecting thalamus may have disrupted broader maladaptive thalamo-cortical and thalamo-subcortical connections, producing diffuse effects rather than locally confined activation. The thalamus is a central relay station in the brain, transmitting and integrating signals between cortical and subcortical regions (Alexander et al., 1986). Thus, the mPFC-thalamus pathway can modulate pain through descending pain inhibition via the mPFC-thalamus-periaqueductal gray (PAG) pathway, where the mPFC exerts descending control by influencing thalamic activity and its projections to the PAG, and disruptions in this circuit lead to impaired top-down inhibition (Henderson et al., 2013; Ong et al., 2019). The TBS could have engaged the descending inhibitory mPFC-thalamus-PAG pathway to reduce pain perception at the spinal cord level rendering top-down inhibition more effective. However, the thalamus is also involved in sensory and affective components of pain, forming extensive connections with limbic and striatal pathways (Grodd et al., 2020; Kamali et al., 2023; Lenz et al., 1995; Peters et al., 2016) that are integral in the emotional-motivational processing of CBP (Hashmi et al., 2013). Indirectly perturbing these subcortical pathways could have led to the effects seen in the mPFC-thalamic pathway. For instance, increased thalamic activity can enhance emotional responses to pain via direct connections to the amygdala. In chronic pain the paraventricular thalamus showed hyperexcitability that enhanced excitatory input to basolateral amygdala (Tang et al., 2024), while optogenetic activation of this pathway in animal models of chronic pain induced both pain-like and anxiety-like behaviors and their inhibition reversed these effects (Liang et al., 2020; Tang et al., 2024). In addition, suppression of projections from the insula to the amygdala and thalamus has been shown to contribute to pain reduction and antidepressant-like effect (Chen et al., 2024). By disrupting FC between the mPFC and thalamus via TBS, connections between thalamus and other regions may have been perturbed, partially restoring a broader network of excitatory-inhibitory imbalance seen in CP across functional, electrophysiological and neurochemical levels (Gil Avila et al., 2025; Henderson et al., 2013; Kang et al., 2021). On a neurochemical level, observed changes in mPFC-thalamus FC may be mediated by alterations in the regulation of specific neurotransmitters. For example, in individuals suffering from chronic neuropathic pain, magnetic resonance spectroscopy revealed reduced inhibitory neurotransmitter levels in the thalamus, which correlated with increased functional connectivity between the thalamus and cortical regions, including the somatosensory cortices, anterior insula, and cerebellar cortex (Henderson et al., 2013). The TBS might downregulate glutamatergic activity in the mPFC, leading to decreased excitatory input to the thalamus. cTBS is also thought to induce long-term depression (LTD)-like plasticity, reducing excitatory glutamate transmission in targeted circuits (Huang et al., 2007). In addition, TMS-induced changes at the cellular level may underlie the observed differences in functional connectivity and their correlation with psychological factors such as anxiety and pain sensitivity. While TMS of the mPFC can modulate neural activity in a regionally focused manner, it does not allow selective targeting of specific cell types, layers, or neuronal assemblies and the mechanisms driving neuronal activation and stimulation propagation through adjacent networks are still not fully understood (Siebner et al., 2022). The variability in responses across participants may therefore reflect individual differences in baseline neurochemical states. Future studies combining TBS with magnetic resonance spectroscopy or PET imaging could provide deeper insights into how neurochemical changes mediate TBS effects on the brain in CBP.

The observed TBS effects on connectivity may also reflect modulation of neural oscillatory activity in the thalamocortical loop, particularly in the theta frequency range. Within the framework of thalamocortical dysrhythmia (TCD), reduced thalamic activity that leads to compensatory low-frequency oscillations is believed to sustain dysfunctional communication between the thalamus and cortex (Llinás et al., 1999). TCD has been proposed as a model of many abnormal states, as it was observed in patients across different disorders in comparison to healthy controls, including chronic pain conditions (Walton et al., 2010). Although results regarding chronic back pain are inconclusive (Schmidt et al., 2012), there is evidence for TDC in other chronic pain conditions (Sarnthein et al., 2006; Walton et al., 2010). While the decrease in connectivity might disrupt thalamocortical integration (which in the condition of TBS could explain the slight pain reduction), it may also amplify maladaptive oscillatory states, which could explain the lack of significant effects on a behavioral level. It is conceivable that stimulation at theta frequencies influenced intrisic theta oscillations and their cortico-thalamic coherence, as TMS tuned to a specific frequency can entrain intrinsic oscillations in that frequency range (Herrmann et al., 2016) and greater baseline activity in the theta range in the rostral anterior cingulate cortex can predict effects of prefrontal stimulation (Nishida et al., 2019). TBS may have disrupted the excitatory input from the mPFC to the thalamus, leading to desynchronization of maladaptive theta oscillations. Future electrophysiological studies may provide more direct insights into the relationship between mPFC-thalamus connectivity and oscillatory modulation in chronic back pain.

4.1.3 Common long-range networks of chronicity

Results of Study 1 suggest that structural integrity of the right SLF, long-range associative tract, is predictive of pain development, likely due to its role in integrating body schema and attentional processes with sensory input. On the other hand, results of Study 2 suggest that the mPFC-thalamus circuit is susceptible to neuromodulation in a developed state of CBP and may play a key role in the maintenance of ongoing back pain. These findings highlight that the persistence of chronic back pain cannot be attributed to isolated brain regions but rather emerges from dysfunctions within interconnected long-range neural networks. These networks facilitate cross-functional integration, neural flexibility, and communication, processes that are essential not only for the transition to chronic pain but also for its maintenance. The mediodorsal thalamus is particularly important in sustaining mPFC activity over time, helping to maintain cognitive control, behavioral flexibility, and adaptive responses based on goal-directed rules (Bruinsma et al., 2022; Parnaudeau et al., 2018; Schmitt et al., 2017). The differential susceptibility of the mPFC-thalamus network to neuromodulation in CBP suggests that dysfunction within this pathway may impair the role of thalamus in effectively regulating mPFC-related control, leading to rigid and maladaptive neural processing that reinforces persistent pain perceptions. Particularly, the role of the thalamus in amplifying and maintaining cortical representations (Schmitt et al., 2017) may contribute to the continued engagement of cognitive and emotional processes related to CBP, even in the absence of nociceptive input. Disruptions within this network can thus enable pain representations to dominate neural dynamics and sustain the chronic pain state. Further supporting the role of disrupted long-range neural communication in CBP, dysregulated corticothalamic connectivity may be linked to pathological alterations in theta oscillations, which are critical for long-range communication between neural regions (von Stein & Sarnthein, 2000). Therefore, by perturbing theta oscillations, TBS might have disrupted inefficient neural information processing in CBP.

Interestingly, brain organization in adolescents with pain symptoms shares fundamental similarities with neural connectivity in adult CBP, particularly in the basothalamo-cortical network (Heukamp et al., 2024). This suggests that alterations in thalamocortical connectivity may serve as an early neurobiological indicator for vulnerability to chronic pain, as the developmental disturbances in these circuits, whether due to stress, injury, or maladaptive plasticity, can shape long-term pain processing. They can also serve as a perpetuating factor in ongoing pain, as the findings on neuromodulation effects on this circuit suggest. In further support of this, studies on the maturation of thalamocortical pathways show that the MD-mPFC pathway has an extended developmental window, which makes it especially vulnerable to environmental stressors (Ferguson & Gao, 2014), known risk factors for chronic pain (Bushnell et al., 2015; Flor et al., 2011; Nees et al., 2019). The heightened plasticity of this network in early development provides an opportunity for reciprocal MD-mPFC innervation to shape the cognitive and emotional regulation of pain. It can also predispose the mPFC to stress-related dysregulation, leading to maladaptive connectivity patterns that may persist into adulthood and later impair top-down modulation, heighten the affective salience of pain, and contribute to the persistence of pain.

As chronicity develops, white matter abnormalities may also reflect a progression from localized disruptions toward large-scale network dysfunctions and impaired neural communication. One of the most consistent findings regarding WM alterations in chronic musculoskeletal pain and CBP is reduced FA in the corpus callosum (CC) (Lieberman et al., 2014). In patients with disabling CBP, FA reductions in the splenium of the CC have been associated with longer pain duration (Buckalew et al., 2010), suggesting that interhemispheric communication deficits may intensify with prolonged pain. A recent study using higher-order diffusion modeling further supports this, showing that patients with CBP exhibit lower fiber density in multiple tracts, including the corpus callosum, spinothalamic tract, and thalamic projections (Robertson et al., 2023). The identification of thalamic white matter abnormalities in CBP aligns with the findings of Study 2, where mPFC-thalamus connectivity was modulated in already developed chronic pain states and suggests that thalamocortical disruptions, whether structural or functional, could be a key mechanism linking white matter degeneration with persistent pain. Taken together, these findings align with the broader conceptualization of chronic pain as a disorder of disrupted network communication and pathological neural imbalance (Vanneste & De Ridder, 2021). Future research should investigate how early-life stress, structural vulnerabilities in the SLF, and maladaptive thalamocortical plasticity interact to shape pain persistence and the response to interventions.

4.2 Limitations

Apart from those limitations already noted in the limitation sections of the included studies, there are several other important and shared limitations regarding both studies. Both studies included small to moderate sample sizes, even though the advantage of the first study is a validation across three different sites and samples, which includes heterogeneity in the sample characteristics. However, the is no warranty that the results can be generalized to the population of patients with CBP.

Larger and more diverse samples are needed to confirm the robustness of the findings. Larger samples would enable stratifying participants by cognitive, emotional, and pain characteristics, for example, based on pain duration, anxiety levels, and attentional bias, which can reveal more nuanced associations between structural integrity, baseline functional connectivity, and clinical outcomes. In regard to TMS, subgroups of patients according to these variables may reveal responders and non-responders to the TMS intervention. Some individuals might rely on mPFC-thalamus connectivity for pain modulation, while others may depend on different neural circuits. More heterogeneous samples should in further steps be used to investigate patients with comorbid musculoskeletal pain conditions, as they often accompany CBP and share similarities (Hoy et al., 2018). Secondly, multimodal studies are needed to fully disentangle how structural predispositions or locally targeted regions interact with functional compensatory mechanisms in CBP. Although both studies provide valuable insights into brain connectivity changes associated with CBP, neither can definitively establish antecedents and consequences. Future longitudinal studies with multimodal designs, such as combining TMS with concurrent neuroimaging, could help clarify predictive relationships.

A key challenge in targeting the mPFC is its broad involvement in pain modulation, cognitive control, and emotional regulation, making it difficult to isolate its specific contribution to chronic pain (Huang et al., 2019). In acute pain, cognitive control and negative emotion seem to be distinctly represented in mPFC subregions with the ventromedial prefrontal cortex (vmPFC) linked to negative emotion (Kragel et al., 2018). In chronic pain this distinction can result in an over-reliance on emotional and evaluative pain representations and shift processing toward the vmPFC, in line with previous findings showing altered vmPFC activity and connectivity in CBP (Hashmi et al., 2013; Letzen et al., 2020; Löffler et al., 2022). However, TMS cannot directly target the ventral part of the mPFC, which may be particularly relevant for pain modulation. While dorsomedial mPFC stimulation can influence broader prefrontal-thalamic circuits, modulation of the vmPFC may require alternative approaches, such as neurofeedback (Mayeli et al., 2020).

4.3 Future directions

The presented studies have several implications for the treatment of CBP. Effective treatment for chronic pain must account for the distinct mechanisms underlying its progression and provide tailored interventions considering individual differences in cognitive and emotional characteristics. Findings regarding changes in structural integrity within the SLF could inform future neuromodulation targets in subacute phases of CBP in order to prevent its development to a chronic stage. For example, the dorsolateral parts of the prefrontal cortex, which are connected via the SLF (Thiebaut de Schotten et al., 2011), may be targeted in subacute stages with neuromodulation techniques. Moreover, individualized targets can be derived based on the most prominent prefrontal-subcortical task-specific changes in tasks probing functions dependent on SLF, such as attentional or interoceptive functions. This would further contribute toward a tailored mechanistic approach in CBP. In addition, noninvasive neuromodulation techniques have already proven promising in reducing CBP by modulating thalamocortical dysrhythmia (Ahn et al., 2019), which supports the notion that the modulation of corticothalamic circuits in the chronic stage can target maladaptive plasticity that maintains it. Future research should explore individual differences in mPFC connectivity and the potential reversibility of neuroplasticity induced by chronicity through targeted neuromodulation and cognitive interventions, as well as their combination. Targeting distinct prefrontal subregions based on individual characteristics could also potentially improve intervention responses. If more tailored targeting of mPFC connectivity proves successful in reducing ongoing CBP, treatments targeting mPFC beyond NIBS, such as neurofeedback, but also more indirect approaches such as virtual-reality-based interventions or cognitive-behavioral therapy, could help restore mPFC connectivity to regulate pain more adaptively. These interventions could aim at reverting top-down modulation and weakening the cognitive and affective contributors to persistent pain.

4.4 Conclusion

A comprehensive understanding of the mechanisms of CBP requires the integration of insights from diverse research modalities, probing both the neural and psychological profiles of patients. The findings of this dissertation point to a possible mechanistic pathway in which maladaptive structural organization of the white matter tract related to attention, the right superior longitudinal fasciculus, may increase vulnerability to CBP, while targeted mPFC stimulation could modulate this circuitry to diminish the maintenance of pain. Targeting mPFC may offer a way to disrupt maladaptive mechanisms of the maintenance of pain by altering the communication with subcortical structures, such as the thalamus, as active and sham stimulation approaches engaged this pathway distinctly. Importantly, the results highlight the need for an integrated model of chronic pain that accounts for both structural predisposing factors and neuromodulation-based network changes. This raises the question whether individuals with greater SLF integrity or specific microstructural properties are more likely to benefit from mPFC stimulation, which could inform the treatment of chronic pain. Translating these findings into clinical practice requires further exploration on how variability in structural connectivity interacts with cognitive and psychological factors, such as attention biases and pain catastrophizing, to modulate predisposition to chronic pain and shape treatment outcome. Ultimately, a multimodal strategy based on combined findings on neuroimaging, brain stimulation, and behavioral interventions may help identify subtypes of patients with chronic pain who differ in their psychobiological risk factors. Moving toward personalized interventions based on individual structural and functional brain characteristics could maximize the benefits of such treatments and reduce the affective and cognitive burden of chronic pain.

5 SUMMARY

This dissertation investigated psychobiological mechanisms underlying chronic back pain (CBP). In Study 1, longitudinal diffusion tensor imaging data were used to assess whether white matter structural integrity could predict the transition from subacute to chronic back pain. The data pool consisted of data sets originating from three different sites. Patients with subacute back pain who recovered at follow-up showed significantly greater fractional anisotropy (FA) in the right superior longitudinal fasciculus (SLF) at baseline across all sites. The FA from the right SLF predicted recovery in both classification and dimensional approach. This suggests that SLF integrity, involved in attention and proprioception, may serve as a resilience factor against the development of chronic back pain and highlights the role of frontoparietal networks in pain vulnerability. Study 2 examined the effects of continuous theta-burst stimulation over the medial prefrontal cortex (mPFC) on ongoing pain modulation and brain connectivity in patients with persistent CBP to elucidate the role of mPFC in chronic state. While behavioral pain outcomes did not significantly differ between sham and active stimulation, functional connectivity between the mPFC and the left thalamus was reduced after active compared to sham stimulation. This supports the involvement of this circuit in pain maintenance and suggests that mPFC stimulation can modulate descending pain control pathways. The findings of these two complementary studies contribute to a mechanistic understanding of how different brain regions and networks interact in the onset and maintenance of chronic back pain, providing preliminary insights for targeted interventions. Future research should investigate how longitudinal changes in functional connectivity following neuromodulation relate to intervention response in chronic back pain, while also examining structural brain characteristics as potential promising targets for preventing the transition from subacute to chronic pain and cognitive-emotional factors to optimize outcomes for patients suffering from chronic pain.

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7 APPENDIX

Table 5. Supplement Study 1: reported medication use (Mannheim sample).

	Regular use	Occasional use	Past use
NSAIDs	6 SBP,3 CBP	1 HC, 2 SBP, 3 CBP	1 HC, 22 SBP, 14 CBP
Statins	2 CBP	/	/
Angiotensin receptor blockers	2 SBP	1 CBP	/
Proton-pump inhibitors	1 SBP	/	/
Antihistamines	1 CBP	1 HC, 1 CBP	/
Benzodiazepines	/	1 CBP	1 SBP, 2 CBP
ACE inhibitors	/	/	1 CBP
Cannabinoids	/	/	1 SBP

Table 6. Supplement Study 1: Comorbid mental disorders (Mannheim sample); diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV).

	Code	Diagnosis	Acute	Remitted
SBP	296.26	Major depressive disorder, single episode		10
	296.30/296.36	Major depressive disorder, recurrent	1	1
	300.29	Specific phobia	1	
	300.30	Obsessive-compulsive disorder		1
	305.xx	Abuse: Opioids/Amphetamine/Cannabis/ Sedative-, hypnotic-, or anxiolytic-related		1
	307.10	Anorexia Nervosa		2
	307.51	Bulimia Nervosa		2
	309.81	Posttraumatic stress disorder		2
CBP	296.26	Major depressive disorder, single episode		2
	296.33	Major depressive disorder, recurrent severe without psychotic features		2
	296.36	Major depressive disorder, recurrent	2	1
	300.01	Panic disorder, without agoraphobia	2	
	300.22	Agoraphobia without history of panic disorder		1
	303.90	Dependence: Alcohol		1
	304.10	Dependence: Sedative-, hypnotic-, or anxiolytic-related		1
	304.30	Dependence: Cannabis		1
	305.xx	Abuse: Opioids/Amphetamine/Cannabis/ Sedative-, hypnotic-, or anxiolytic-related		1
	307.10	Anorexia Nervosa	1	
	307.51	Bulimia Nervosa		1

Table 7. Supplement Study 1: New Haven sample characteristics.

	HC (*N*=28)	**CLBP** (*N*=28)	**SBPr** (*N*=16)	**SBPp** (*N*=12)	**t(df)‡, p-value**	**Missing**
Age (years)	30.1(10.1)	30.7 (11.9)	30.8 (8.8)	38.0 (12.5)	+ 1.80(26), 0.08	0/0/0/0
Gender (m/f)	16/12	12/16	11/5	7/5	+ 0.32(1), 0.57†	0/0/0/0
BMI (Kg/m2)	24.1 (3.6)	24.2 (3.7)	25.5 (5.2)	26.2 (4.5)	+ 0.35(26), 0.73	0/0/0/0
Delta pain severity: absolute	NA	NA	- 25.4 (15.4)	8.0 (17.2)	**+ 5.0(26), <10^{-4}***	NA/NA/0/0
Delta pain severity: percentage	NA	NA	- 66.3 (26.9)	39.1 (68.1)	**+ 5.7(26), <10^{-5}***	NA/NA/0/0
Pain Duration	NA	5.3 (4.7)	8.6 (3.6)	10.9 (3.1)	+ 1.87(26), 0.08	0/0/0/0
Pain Intensity	NA	4.5 (2.0)	36.7 (18.8)	33.7 (15.9)	- 0.45(26), 0.66	NA/0/0/0
BDI	2.6 (3.3)	6.4 (6.0)	7.4 (4.8)	3.1 (3.8)	**- 2.65(26), 0.02***	0/0/0/0
BAI	3.4 (5.7)	7.6 (8.2)	6.4 (6.8)	4.8 (2.8)	- 0.75(26), 0.46	0/0/0/0
MPQ	NA	10.6 (4.6)	9.2 (5.2)	9.1 (4.2)	- 0.08(26), 0.93	NA/0/0/0
PCS	NA	15.2 (9.8)	12.8 (11.4)	11.3 (8.1)	- 0.40(25),0.69	NA/0/1/0

‡, t-score (degrees of freedom); †, Chi-square test; *, $p < 0.05$; BMI, body mass index; BDI, Beck's Depression Index; BAI, Beck's Anxiety Index; MPQ, McGill Pain Questionnaire; PCS, Pain Catastrophizing Scale. Values show the group mean and standard deviation in parenthesis.

Table 8. Supplement Study 1: Chicago (Open Pain) sample characteristics.

	SBPr (*N*=23)	**SBPp** (*N*=35)	**t(df) ‡, p-value**	**SBPr** (*N*=28)	**SBPp** (*N*=34)	**t(df)‡, p-value**	**Missing**
Age (years)	41.7 (12.0)	43.6 (9.3)	+0.7(56), 0.48	43.7 (11.5)	45.3 (9.6)	+ 0.61(60),0.54	0/0/0/0
Gender (m/f)	12/9	16/19	1.6(1),0.2†	15/13	17/17	0.08(1), 0.78†	0/0/0/0
Delta pain severity: absolute	- 40.6 (20.8)	-3.4 (15.6)	+ 7.8(56), $<10^{-6}$ *	- 43.1 (20.6)	- 3.2(15.6)	**+ 8.7(60), $<10^{-6}$***	0/0/0/0
Delta pain severity: percentage	- 68.9 (26.2)	-1.6 (31.9)	+ 8.4(56), $<10^{-6}$ *	- 69.7 (25.9)	0.3 (31.6)	**+ 9.3(60), $< 10^{-6}$***	0/0/0/0
Pain Duration (weeks)	9.9 (4.1)	8.4 (4.3)	- 1.3(55), 0.18	67.8 (5.6)	65.2 (5.7)	- 1.8(60), 0.07	0/1/0/0
Pain Intensity	58.0 (15.2)	67.7 (17.2)	+ 2.3(56),0.03*	18.0 (16.8)	65.7(15.8)	**+ 11.5(60), $<10^{-6}$***	0/0/0/0
BDI	5.7 (5.2)	7.3 (4.6)	+ 1.0(39), 0.31	6.3 (6.6)	16.0 (9.5)	+ 1.4(42), 0.16	7/10/10/8
MPQ	10.9 (4.5)	18.2 (17.9)	+ 1.9(54), 0.06	13.4 (26.3)	16.0 (9.5)	**+ 4.3 (56), $<10^{-4}$ ***	0/2/3/1

‡, t-score (degrees of freedom); †, Chi-square test; *, $p < 0.05$; BDI, Beck's Depression Index; MPQ, McGill Pain Questionnaire; SBPp/r, patients with SBP with persistent pain or recovered pain.

Table 9. Supplement Study 2: Results for the main effects of the three secondary measures Arousal, Dominance, and Valence, and Time-by-Condition interaction effects from linear mixed model analyses.

Measure	Term	Estimate	SE	t	p	p_{corr}	CI.lo	CI.hi
Arousal	(Intercept)	3.405	0.710	4.794	0.001	0.004	1.826	4.984
Arousal	Time	-0.083	0.284	-0.294	0.771	1.000	-0.660	0.494
Arousal	Condition	-0.500	0.284	-1.764	0.087	0.522	-1.077	0.077
Arousal	Age	-0.025	0.013	-1.885	0.092	0.552	-0.054	0.005
Arousal	Gender	0.276	0.365	0.758	0.468	1.000	-0.548	1.101
Arousal	Time:Condition	0.000	0.401	0.000	1.000	1.000	-0.816	0.816
Dominance	(Intercept)	3.358	0.899	3.735	0.005	0.027	1.330	5.386
Dominance	Time	-0.083	0.145	-0.573	0.571	1.000	-0.379	0.213
Dominance	Condition	-0.250	0.145	-1.719	0.095	0.570	-0.546	0.046
Dominance	Age	0.007	0.017	0.433	0.675	1.000	-0.031	0.046
Dominance	Gender	-0.024	0.474	-0.050	0.961	1.000	-1.095	1.047
Dominance	Time:Condition	0.083	0.206	0.405	0.688	1.000	-0.335	0.502
Valence	(Intercept)	2.239	0.696	3.218	0.010	0.062	0.669	3.810
Valence	Timepost	-0.167	0.097	-1.722	0.094	0.566	-0.364	0.030
Valence	Condition	0.000	0.097	0.000	1.000	1.000	-0.197	0.197
Valence	Age	0.026	0.013	1.942	0.084	0.504	-0.004	0.056

Table 9. Supplement Study 2 (continued).

Valence	Gender	0.697	0.367	1.900	0.090	0.539	-0.133	1.527
Valence	Time:Condition	0.250	0.137	1.827	0.077	0.461	-0.028	0.528

SE: standard error of the mean; p_{corr}: p-value corrected for multiple comparisons across three dependent variables;
CI.lo / CI.hi: lower and upper 95% confidence intervals.

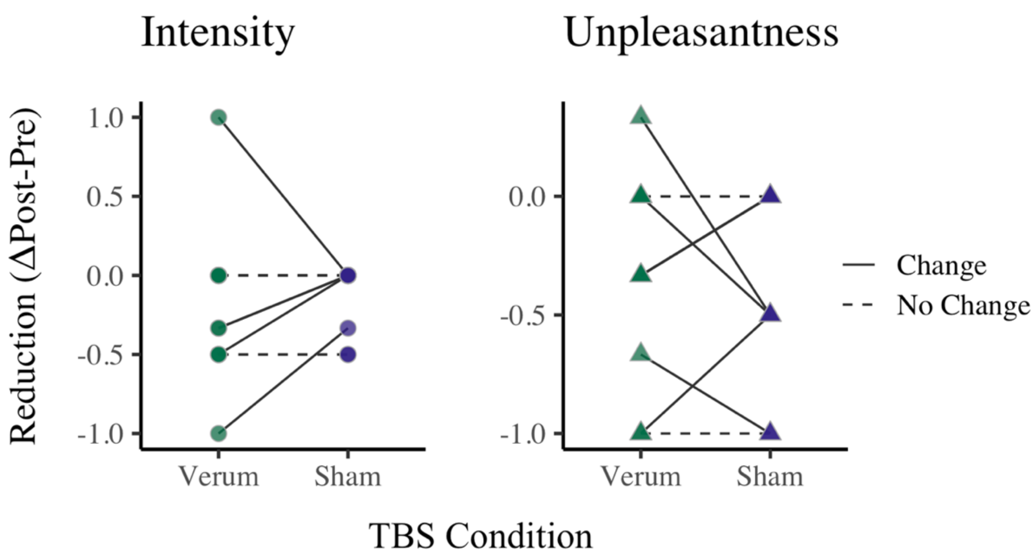

Figure 14. Supplement Study 2: Individual changes in pain intensity and unpleasantness trajectories.

Subjects (N = 12) with negative values in each respective condition ((post − pre) / pre < 0) show a decrease in pain levels from pre to post. Colored points (green verum and violet sham), mark how changes differ across conditions. Solid line indicate change, and dash line no change in pain levels. TBS: transcranial theta-burst stimulation.

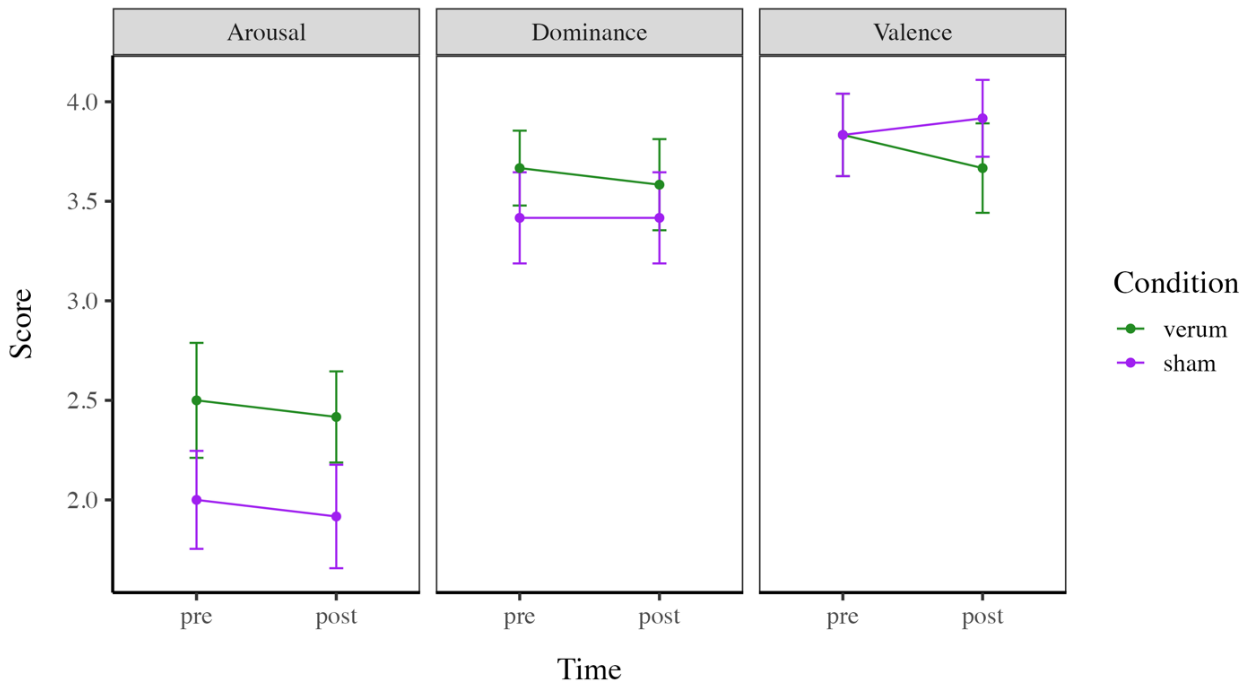

Figure 15. Supplement Study 2: Changes in arousal, dominance, and valence scores from pre- to post theta-burst stimulation under the verum and sham conditions.

Scores from Self-Assessment Manikin (SEM), 5-point scale version (*N* = 12).

8 CURRICULUM VITAE

PERSONAL INFORMATION

Name:	Mina Mišić (née Kandić)
Date of Birth:	23.06.1992
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SCHOOL EDUCATION

1999-2007	Primary School
2007-2011	Secondary School (Gymnasium)
17.06.2011	Secondary School Leaving Certificate (Abitur)

ACADEMIC EDUCATION

01.10.2011	Beginning of Psychology degree program University of Belgrade, Belgrade, Serbia
15.09.2015	Bachelor of Science in Psychology (B.Sc.) University of Belgrade, Belgrade, Serbia Grade: 8,59/10
20.01.2020	Master of Science in Neurocognitive Psychology (M.Sc.) Carl von Ossietzky University of Oldenburg Master thesis: „Exploring Frequency-Specific TMS Effects on Visual Detection – Searching for the Arnold Tongue on a Behavioural Level" Grade: 1,39
February 2021-present	Doctoral studies in Neuropsychology and Clinical Psychology, Medical Faculty Mannheim, Heidelberg University

PROFESSIONAL CAREER

01.02.2020-present	Scientific staff member at the Central Institute of Mental Health, Mannheim
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01.10.2014-01.03.2017	Assistant in Experimental Research at the Department of Clinical Neurophysiology, Military Medical Academy, Belgrade (Serbia)

AWARDS/SCHOLARSHIPS

2017-2020	Konrad Adenauer Stiftung – Scholarship for talented foreign students for master's studies in Germany (Begabtenförderung)

PUBLICATIONS IN PEER-REVIEWED JOURNALS

Zhang W., Löffler M., Usai K., **Mišić M.,** Nees F., Flor H. (2025). Hypervigilance to pain may predict the transition from subacute to chronic back pain: A longitudinal observational study. *Journal of Pain Research, 18,* 3141-3158. https://doi.org/10.2147/JPR.S512911

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