Neurophysiological mechanisms of longer-lasting experimental pain in humans

Inaugural-Dissertation

zur Erlangung des Doktorgrades der Philosophie

an der Ludwig-Maximilians-Universität München

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Coburg

2020

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Tag der mündlichen Prüfung: 16. Juli 2019

ABSTRACT

Pain serves the protection of the body. Consequently, noxious stimuli or, more precisely, the thereby induced neurophysiological processes commonly lead to pain perception. Identical noxious stimuli, however, do not always translate into the same pain experience depending on multiple factors. To acknowledge this variability, the distinction between nociception as the neural process elicited by noxious stimuli and pain as subjective multifactorial experience is essential. During longer-lasting experimental pain and chronic pain, nociception and pain can substantially dissociate. Moreover, longer-lasting experimental pain resembles chronic pain regarding certain perceptual features such as prolonged pain duration and intensity fluctuations. Thus, longer-lasting experimental pain offers the opportunity to gain new insights into both the differential neural representation of noxious stimuli and pain and the neuronal mechanisms associated with the state of longer-lasting pain. We applied 10 minutes of painful heat stimulation to the left and right hand of 39 healthy participants while we recorded continuous pain ratings, electroencephalography (EEG), and autonomic responses. Data were analyzed in three distinct projects aiming at different aspects of neuronal mechanisms underlying longer-lasting pain.

Project 1 assessed whether stimulus intensity as proxy of nociception and pain intensity relate to distinct patterns of oscillatory brain activity. EEG recordings revealed that increases in stimulus intensity were reflected by suppressions of alpha and beta oscillations in sensorimotor areas contralateral to the stimulated hand. In contrast, increases in pain intensity were associated with enhanced gamma oscillations in the medial prefrontal cortex. More importantly, the encoding of stimulus intensity by alpha and beta oscillations in the sensorimotor areas was spatially specific, i.e. depended on the stimulus location, whereas the encoding of pain intensity by gamma oscillations in the medial prefrontal cortex was independent of stimulus location. Thus, prefrontal gamma oscillations might reflect higher-order aspects of noxious stimuli, such as salience, valence, and motivational aspects rather than precise sensory features. Project 2 investigated the relationship between stimulus intensity, pain intensity, autonomic responses, and brain activity. Skin conductance measures, as markers of sympathetic activity, co-varied more closely with stimulus intensity than with pain intensity. Correspondingly, skin conductance measures were related to suppressions of alpha and beta oscillations in the sensorimotor area contralateral to the stimulated hand. These finding suggest that skin conductance measures are in part directly elicited by nociceptive processes and, thus, at least partially independent of perceptual

processes during longer-lasting pain. Hence, these observations corroborate concepts of pain in which sensory, motivational, and autonomic processes partially independently contribute to the experience of pain. Finally, project 3 incorporated the systematic and comprehensive assessment of oscillatory brain activity, functional connectivity, and graph-theory based network measures during the state of longer-lasting pain. Longer-lasting pain was associated with suppressions of oscillatory brain activity at alpha frequencies in addition to stronger connectivity at alpha and beta frequencies in sensorimotor areas. Furthermore, sensorimotor areas contralateral to stimulation showed increased connectivity to a common area in the medial prefrontal cortex at alpha frequencies and built a sensorimotor-prefrontal network during longer-lasting pain. This network might be involved in the integration of sensory, cognitive, and motivational-affective information and, consequently, in the translation of a noxious stimulus into a subjective pain experience.

All three projects contribute to a better understanding of neuronal mechanisms underlying longer-lasting experimental pain, which serves as an experimental model for chronic pain. Since the treatment of chronic pain has remained insufficient and unsatisfactory, the current results might provide EEG-based targets for urgently needed new treatment approaches, such as non-invasive brain stimulation and neurofeedback.

ZUSAMMENFASSUNG

Schmerz besitzt eine protektive Funktion für den Körper. Daher rufen nozizeptive Reize oder vielmehr die von ihnen hervorgerufenen neurophysiologischen Prozesse meistens eine Schmerzwahrnehmung hervor. Die Transformation von einem nozizeptiven Reiz in eine Schmerzwahrnehmung kann jedoch erheblich variieren und ist neben dem Reiz abhängig von kognitiven, emotionalen und motivationalen Faktoren. Die Unterscheidung von Nozizeption und Schmerz ist daher essentiell und von grundlegender Bedeutung für die Erforschung der neuronalen Schmerzverarbeitung im Gehirn. Nozizeption bezeichnet den neuronalen Prozess der Enkodierung von nozizeptiven Reizen. Schmerz hingegen ist definiert als eine unangenehme sensorische und emotionale Erfahrung, die mit einer realen oder potentiellen Gewebeschädigung einhergeht oder mit Worten einer solchen beschrieben wird. Nozizeption betont folglich die objektive physiologische Verarbeitung und Schmerz den subjektiven Charakter der Schmerzerfahrung. Besonders bei länger anhaltendem experimentellen Schmerz und chronischem Schmerz können Nozizeption und Schmerz beträchtlich dissoziieren. Bei chronischem Schmerz, der spontan und zum Teil ohne ersichtliche physiologische Ursache auftritt, ist der Zusammenhang zwischen Nozizeption und Schmerz schwach bis hin zu nicht vorhanden. Chronischer Schmerz ist mit großem Leid und Einschränkungen für Betroffene sowie gesellschaftlich mit massiven ökonomischen Kosten verbunden. Deshalb ist es wesentlich neuronale Mechanismen der Dissoziation von Nozizeption und Schmerz besser zu verstehen.

Im Gegensatz zu kurzen phasischen nozizeptiven Reizen, die weit verbreitet zur Untersuchung der neuronalen Schmerzverarbeitung Anwendung finden, teilen länger anhaltender experimenteller Schmerz und chronischer Schmerz neben der Dissoziation auch perzeptuelle Eigenschaften wie spontane Fluktuationen. Daher kann länger anhaltender experimenteller Schmerz als Modell für chronischen Schmerz fungieren. Er ermöglicht neue Einsichten in die differentielle neuronale Verarbeitung von nozizeptiven Reizen einerseits und Schmerz andererseits. Weiterhin bietet er die Möglichkeit neuronale Mechanismen zu untersuchen, die mit dem Zustand länger anhaltenden Schmerzes über mehrere Minuten assoziiert sind. Wir applizierten schmerzhafte Hitzereize mit einer Dauer von 10 Minuten auf die linke und rechte Hand von gesunden Probanden und zeichneten simultan kontinuierliche Schmerzintensitätsbewertungen, Elektroenzephalographie (EEG) und autonome Maße auf. Die Daten wurden in drei unterschiedlichen Projekten analysiert, die auf verschiedene Aspekte der neuronalen Verarbeitung länger anhaltenden Schmerzes ausgerichtet waren.

Projekt 1 untersuchte, ob Reizintensität, stellvertretend für Nozizeption, und Schmerzintensität mit unterschiedlichen Mustern neuronaler Oszillationen zusammenhängen und ob diese Muster spezifisch für den Applikationsort des Reizes sind. Die EEG-Analysen zeigten, dass erhöhte Reizintensität mit supprimierter kortikaler oszillatorischer Aktivität im Alpha- und Beta-Frequenzband in sensomotorischen Arealen einherging. Schmerzintensität hingegen hing positive mit Gamma-Oszillationen im medialen präfrontalen Cortex zusammen. Zudem war die kortikale Verarbeitung von Reizintensität durch Alpha- und Beta-Oszillationen räumlich spezifisch, d.h. abhängig von dem Ort, an dem der Reiz appliziert wurde, wohingegen die Enkodierung von Schmerzintensität durch präfrontale Gamma-Oszillationen unabhängig von der Reizlokation stattfand. Somit ging länger anhaltender Schmerz mit einer Übersetzung von einer räumlich spezifischen Repräsentation des nozizeptiven Reizes durch Alpha-/Beta-Oszillationen im sensomotorischen Cortex hin zu einer räumlich unspezifischen Repräsentation des Schmerzes durch Gamma-Oszillationen im medialen präfrontalen Cortex einher. Letzterer umfasst Hirnareale, die in kognitive und motivational-affektive Prozesse involviert sind. Folglich scheinen präfrontale Gamma-Oszillationen weniger sensorische Eigenschaften des nozizeptiven Reizes widerzuspiegeln, sondern übergeordnete Prozesse wie Salienz, Valenz oder motivationale Aspekte.

Projekt 2 befasste sich mit dem Zusammenhang zwischen Reizintensität und Schmerzintensität mit autonomen Maßen sowie von autonomen Maßen mit Hirnaktivität. Die Frage, ob Aktivität des autonomen Nervensystems stärker mit Nozizeption oder mit Schmerz zusammenhängt ist wesentlich für das Verständnis der Entstehung von Schmerz. Ein engerer Zusammenhang zwischen Reizintensität und autonomen Maßen würde implizieren, dass Aktivität des autonomen Nervensystems (autonome Aktivität) zum Teil direkt durch nozizeptive Prozesse hervorgerufen wird und zumindest teilweise von perzeptuellen Prozessen unabhängig ist. Andererseits würde ein engerer Zusammenhang zwischen Schmerzintensität und autonomen Maßen darauf hinweisen, dass autonome Aktivität eher durch perzeptuelle Prozesse als durch nozizeptive hervorgerufen wird. Unsere Ergebnisse haben gezeigt, dass Hautleitfähigkeitsmaße als Index für die Aktivität des sympathischen Nervensystems stärker mit Reizintensität als mit Schmerzintensität zusammenhingen. Sie kovariierten zudem mit supprimierten Alpha- und Beta-Oszillationen in sensomotorischen Arealen kontralateral zur stimulierten Hand. Diese Ergebnisse legen nahe, dass bei länger anhaltendem Schmerz die Hautleitfähigkeit zum Teil direkt durch nozizeptive Prozesse moduliert wird, die unabhängig von der Schmerzwahrnehmung sind. Sie bekräftigen Schmerzkonzepte, die das Zusammenspiel von sensorischen,

motivationalen und autonomen Prozessen hervorheben, die teilweise voneinander unabhängig zu einer kohärenten Schmerzwahrnehmung beitragen.

Projekt 3 beinhaltet die systematische und umfassende Untersuchung von oszillatorischer Hirnaktivität, funktioneller Konnektivität und graphentheoretischen Maßen, die mit dem Zustand länger anhaltenden Schmerzes per se assoziiert sind. Bislang untersuchten Studien zu länger anhaltendem Schmerz entweder oszillatorische Hirnaktivität oder funktionelle Konnektivität auf entweder lokaler oder globaler das gesamte Gehirn betreffender Ebene. Ziel in diesem Projekt war es Hirnaktivität und Konnektivität umfassend bis hin zur Netzwerkebene zu analysieren. Die Analysen legten offen, dass länger anhaltender Schmerz mit supprimierter oszillatorischer Aktivität im Alpha-Frequenzband und erhöhter Konnektivität im Alpha- und Beta-Frequenzband im sensomotorischen Cortex einherging. Zudem wiesen kontralaterale sensomotorische Areale eine erhöhte Konnektivität hin zu einem Areal im medialen präfrontalen Cortex auf, das für beide Stimulationsseiten identisch war. Diese Konnektivität im Alpha-Frequenzband bildete ein sensomotorisches präfrontales Netzwerk, das mit dem Zustand länger anhaltenden Schmerzes zusammenhängt. Dieses Netzwerk könnte wesentlich in die Transformation von einem objektiven nozizeptiven Reiz in eine subjektive Schmerzwahrnehmung involviert sein.

Zusammenfassend erweitern die Ergebnisse aus allen drei Projekten unser Verständnis neuronaler Mechanismen, die zum einen mit der Dissoziation von Nozizeption und Schmerzwahrnehmung und zum anderen mit dem Zustand länger anhaltenden Schmerzes assoziiert sind. Die kortikale Repräsentation der Schmerzintensität durch Gamma-Aktivität im medialen präfrontalen Cortex stimmt mit Befunden überein, die zeigen, dass der Übergang von akutem zu chronischem Schmerz mit einer Verschiebung der Schmerzverarbeitung von sensorischen Hirnregionen hin zu Emotion verarbeitenden Hirnregionen einhergeht. Weiterhin hat die differentielle Repräsentation von Nozizeption und Schmerz relevante Implikationen für den klinischen Kontext, da eine ausschließliche Fokussierung auf nozizeptive Prozesse zu inadäquater Diagnostik und unzureichender Schmerztherapie bei chronischem Schmerz führen könnte. Mit der Identifikation eines sensomotorischen präfrontalen Netzwerks und schmerzrelevanter oszillatorischer Aktivität wurden potentielle Zielstrukturen und Mechanismen für die Behandlung von chronischem Schmerz offengelegt. Nicht-invasive Hirnstimulation und Neurofeedback könnten Wege darstellen, um diese neuronalen Mechanismen zu modulieren.

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1 General introduction

Pain serves to protect the integrity of the body. Therefore, noxious stimuli induce neurophysiological processes, which commonly translate into pain (Adair, Stevens, & Marks, 1968; Price, 1999; Stevens, 1957). However, the translation of noxious stimuli into pain can vary substantially (Baliki & Apkarian, 2015) and depends on cognitive (Wiech, 2016), emotional (Bushnell, Ceko, & Low, 2013), and motivational factors (Wiech & Tracey, 2013). To acknowledge this variability and to understand brain mechanisms of pain, the distinction between nociception and pain is essential. The International Association for the Study of Pain defines nociception as “the neural process of encoding noxious stimuli” and refers to pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Loeser & Treede, 2008). Nociception, thus, conceptualizes objective physiological processes elicited by noxious stimuli whereas pain refers to the subjective pain experience. Although there is a close correspondence between the two for short-lasting phasic pain (Hu & Iannetti, 2019), both can substantially dissociate with increasing pain duration. Particularly in chronic pain, the subjective pain experience often only weakly relates to noxious stimuli (Baliki & Apkarian, 2015). Interestingly, such dissociations not only occur in chronic pain but can also be observed in healthy human participants during several minutes of painful heat stimulation (Schulz et al., 2015). This indicates a stronger role of factors beyond the noxious stimulus during longer-lasting experimental pain (tonic pain), rendering it suitable as an experimental model for processes in chronic pain. Thus, tonic pain offers the opportunity to disentangle the representation of stimulus intensity as proxy of nociception and pain intensity in the human brain. Moreover, it provides insights into the state of longer-lasting pain resembling chronic pain and its concomitant shift from predominantly sensory to motivational-affective processes.

The general introduction of the current thesis is divided into four parts. The first part introduces brain regions and brain networks involved in the neuronal processing of pain. The second part points out the important role of brain oscillations for brain functions in general and for pain processing in particular. The third part summarizes the current state of research on autonomic responses to painful stimulation. Finally, the fourth part outlines the aims of the current thesis.

1.1 The brain and processing of pain

Pain is associated with activations in an extended network of brain areas including primary and secondary somatosensory, insular, cingulate, and prefrontal cortices along with subcortical structures and the brainstem (Apkarian, Bushnell, Treede, & Zubieta, 2005; Garcia-Larrea & Peyron, 2013; Tracey & Mantyh, 2007). These brain areas do not constitute a pain-specific network but belong to different functional systems of the brain and coordinate transiently for the processing of pain. Nevertheless, the possibility of a single brain area that is exclusively and solely responsible for pain perception remains under discussion (Davis, Bushnell, Iannetti, St Lawrence, & Coghill, 2015; Lieberman & Eisenberger, 2015; Segerdahl, Mezue, Okell, Farrar, & Tracey, 2015; Wager et al., 2016). A scenario in which the transient integration of neuronal activity across brain areas gives rise to pain seems more likely. Cognitive, emotional, and motivational factors influence the perceived pain, thus, requiring the integration of neuronal activity in a brain network that can dynamically adapt to these factors and adjust pain perception. Hence, pain requires effective neuronal communication (Apkarian & Chialvo, 2006; Kucyi & Davis, 2015; H. Mano & Seymour, 2015; Tracey, 2005). Fundamental to this integration are structural connections in the brain. However, flexible demands of psychological factors change on shorter timescales than provided by changes of structural connections in the brain, requiring functional connections, which dynamically and flexibly link brain areas of different functional systems of the brain (Baliki & Apkarian, 2015; Ploner, Sorg, & Gross, 2017). This conceptualization emphasizing the role of a flexible communication between brain networks and areas has recently been summarized under the term dynamic pain connectome (Kucyi & Davis, 2015).

Consequently, a growing amount of pain research has considered pain as a brain network phenomenon. Different brain networks have been shown to contribute to phasic pain. One example is the Neurologic Pain Signature (NPS), a multivariate pattern based on functional magnetic resonance imaging (fMRI) data, whose weights are optimized to predict pain intensity based on fMRI signal (Wager et al., 2013). The NPS comprises secondary somatosensory cortex, insula, anterior cingulate cortex, thalamus, periaqueductal gray matter, and other regions. Another system, termed Stimulus Intensity Independent Pain Signature-1 (SIIPS-1), describes a multivariate pattern, which is predictive of pain beyond nociception. The SIIPS-1 comprises patterns of activity in nucleus accumbens, dorsomedial prefrontal, lateral prefrontal and parahippocampal cortices (Woo et al., 2017). Moreover, the ventromedial prefrontal cortex has been implicated in pain perception via valuation

processes and emotional appraisal (H. Mano & Seymour, 2015; Woo, Roy, Buhle, & Wager, 2015).

Regarding clinical pain, there has been growing evidence demonstrating that functional and structural changes of brain networks accompany the transition from acute to chronic pain (Baliki & Apkarian, 2015; Baliki et al., 2012; Hashmi et al., 2013; Kuner & Flor, 2017; Hiroaki Mano et al., 2018; Mansour et al., 2016; Vachon-Presseau et al., 2016). Brain activity related to back pain has been shown to shift from insula, anterior cingulate cortex, thalamus, and basal ganglia to medial prefrontal cortex (mPFC), amygdala, and basal ganglia in chronic back pain (Hashmi et al., 2013). Increased white matter and functional connections within a network comprising the mPFC, amygdala, and nucleus accumbens represented risk factors for the development of chronic back pain (Baliki et al., 2012; Vachon-Presseau et al., 2016). Recent studies investigated brain network changes by applying graph-theory based approaches, which discriminated between chronic pain patients and healthy controls (Hiroaki Mano et al., 2018; Mansour et al., 2016). Graph theory is a valuable framework to better understand the characteristics of complex systems including brain networks, as it allows to describe and quantify key features of such systems with a few measures (Rubinov & Sporns, 2010). A graph characterizes networks by nodes that are connected by edges. In general, graph measures can describe either complete networks or network features of single nodes. As pain likely results from the interplay of neural activity in brain networks, graph theory-based measures may provide a proper tool to capture pain-induced alterations on a brain network level.

Until now, the majority of studies investigating brain networks of pain in health and disease used fMRI with high spatial but rather low temporal resolution. In contrast, comparatively few studies recorded neurophysiological measures, i.e. electroencephalography (EEG), magnetoencephalography (MEG), or intracranial recordings to investigate modulations of functional connectivity and brain networks induced by pain (Gram et al., 2017; Huishi Zhang, Sohrabpour, Lu, & He, 2016; Levitt, Choo, Smith, LeBlanc, & Saab, 2017; Martel et al., 2017). The results still remain inconclusive. Neurophysiological recordings, however, combine the advantages of a high temporal resolution able to capture dynamical changes in functional brain connectivity on short timescales (Kucyi & Davis, 2015; Ploner et al., 2017) and the existence of a theoretical neurophysiological framework of neuronal communication based on brain oscillations (Fries, 2015).

Taken together, experimental pain and chronic pain emerges as a consequence of a complex interplay between several brain regions and brain networks. Accordingly,

functional connectivity and network measures have been shown to adequately reflect pain perception and the reorganization of brain networks associated with pain chronification. Since neuronal communication between brain regions plays a crucial role in pain processing, brain oscillations, which serve neuronal communication, may be fundamentally involved.

1.2 Brain oscillations and their functional significance

Brain oscillations, i.e. rhythmical fluctuations of excitability of populations of neurons, could be an effective mechanism to transiently establish synchrony within local neuronal assemblies or, on a larger scale, between distant populations of neurons. By synchronizing excitatory and inhibitory phases within a neuronal assembly, time windows of increased and decreased excitability are established. Hence, various coherently oscillating neuronal assemblies show effective properties for communication, as windows for input and output are open at the same time (Buzsaki & Draguhn, 2004; Fries, 2005, 2015; Siegel, Donner, & Engel, 2012). Brain oscillations can be recorded as mass signals by EEG, MEG, and local field potentials. Commonly, they are investigated in the frequency range of 1 to 100 Hz. Perceptual, cognitive, and behavioral functions have been ascribed to different frequency bands ranging from delta (1-3 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (14-29 Hz) to gamma (30-100 Hz) (Ploner et al., 2017; Wang, 2010). The following examples do not aim at completeness but rather illustrate the functional diversity of brain oscillations at different frequencies. Cerebral theta oscillations are shown to be prominent in working memory tasks (O. Jensen & Tesche, 2002; Meltzer et al., 2008). Alpha oscillations are associated with (spatial) attention (Haegens, Handel, & Jensen, 2011; Thut, Miniussi, & Gross, 2012) and may play an important role in inhibitory control (O. Jensen, Gips, Bergmann, & Bonnefond, 2014; Klimesch, Sauseng, & Hanslmayr, 2007). Beta oscillations are implied in movement preparation and, more generally, in large-scale top-down communication (Fries, 2015; Siegel et al., 2012; Wang, 2010). Gamma oscillations are implicated in the integration of sensory information (Singer, 1999) and described as physiological fingerprint of attention (Bauer, Oostenveld, Peeters, & Fries, 2006; Fries, 2009). However, depending on tasks and contexts, the interpretation of the functional significance varies substantially (Ploner et al., 2017).

More recently, an overarching physiological framework of brain oscillations and their potential mechanistic role in flexibly routing information flow in the brain was introduced (Bastos, Vezoli, Bosman, et al., 2015; Bastos, Vezoli, & Fries, 2015; Fries, 2015). This

framework is based on findings in the primate visual system showing an anatomical differentiation between feedforward and feedback projections. Feedforward projections predominantly originate in supragranular layers and terminate in layer IV of the cortex. In contrast, feedback projections typically originate in infragranular layers and terminate in layers other than layer IV (Felleman & Van Essen, 1991; Markov et al., 2014). This anatomical differentiation is mirrored functionally by brain oscillations of different frequencies that more strongly occur in supragranular and infragranular layers of the cortex. As recent evidence suggests, alpha and beta oscillations are stronger in infragranular layers comprising feedback connections, whereas gamma oscillations are stronger in supragranular layers comprising feedforward connections (Bastos et al., 2012; Scheeringa, Koopmans, van Mourik, Jensen, & Norris, 2016; Wang, 2010). A more recent study tested the functional link between alpha/beta and gamma oscillations on the one hand and feedback and feedforward signaling in the human visual system on the other hand (Michalareas et al., 2016). MEG data and directed functional connectivity analysis revealed that information flow from brain areas higher up in the hierarchy to brain areas lower in the hierarchy is implemented by alpha and beta oscillations. On the contrary, gamma oscillations showed increased directed connectivity in the reverse direction (Michalareas et al., 2016), providing strong evidence for the proposed framework in humans.

In summary, brain oscillations represent an effective way of neuronal communication and exhibit a variety of functional properties that are well compatible with the functional demands to the brain of flexibly adapting to perceptual, cognitive, and affective-motivational factors. An overarching physiological framework of brain oscillations was introduced postulating a role of alpha/beta and gamma oscillations for cortical feedback and feedforward information flow, respectively. In the past decade, the interest in the role of brain oscillations for pain processing and pain perception has been increasingly progressing.

1.2.1 Brain oscillations and phasic pain

Most studies on the role of brain oscillations in the processing of pain investigated brain responses to phasic noxious stimuli in the range of milliseconds. These stimuli reflect acute pain which indicates threat to the integrity of the body and normally results in protective behavior and avoidance of the noxious stimulus. These studies revealed that pain is associated with a complex spectral-temporal-spatial pattern of neuronal activity. This pattern consists of three main components. First, at latencies between 150 and 400 ms,

phasic noxious stimuli evoke a neuronal phase-locked response, i.e. a pain-related evoked potential, which is represented as a power increase in theta frequencies in the time-frequency representation. Previous studies have demonstrated that neuronal generators of this response are located in the sensorimotor cortex, in the frontoparietal operculum including the insula and the secondary somatosensory cortex as well as in the mid- and anterior cingulate cortex (Garcia-Larrea, Frot, & Valeriani, 2003; Liberati et al., 2016; Lorenz & Garcia-Larrea, 2003). Second, between 300 and 1000 ms, phasic noxious stimuli elicit a suppression of non-phase-locked activity at alpha and beta frequencies in sensorimotor and occipital areas (Hu, Peng, Valentini, Zhang, & Hu, 2013; May et al., 2012; Mouraux, Guerit, & Plaghki, 2003; Ploner, Gross, Timmermann, Pollok, & Schnitzler, 2006). Finally, phasic noxious stimuli induce an increase in oscillatory gamma activity in the sensorimotor cortex (Gross, Schnitzler, Timmermann, & Ploner, 2007; Hauck, Lorenz, & Engel, 2007; Zhang, Hu, Hung, Mouraux, & Iannetti, 2012) and in the insula (Liberati et al., 2017) 150 to 350 ms after the onset of the phasic stimulus (Ploner et al., 2017).

The amplitudes of these responses often reflect both stimulus intensity and pain intensity. Yet, how these brain areas and brain responses differentially relate to stimulus intensity and pain intensity is not fully clear. Comparatively few studies explicitly distinguished between brain responses related to stimulus intensity and pain intensity. Although the results are not fully consistent, fMRI studies provide evidence that activations in somatosensory cortices are more closely related to stimulus intensity whereas insular, cingulate and prefrontal cortices with their subdivisions were related to both stimulus intensity and pain intensity (Atlas, Lindquist, Bolger, & Wager, 2014; Baliki, Geha, & Apkarian, 2009; Bornhovd et al., 2002; Buchel et al., 2002; Kong et al., 2006; Moulton, Pendse, Becerra, & Borsook, 2012). Furthermore, EEG and MEG studies investigating oscillatory responses to phasic noxious stimuli of the same intensity demonstrated that spontaneous fluctuations of pain intensity (Gross et al., 2007), pain intensity modulated by music therapy (Hauck, Metzner, Rohlffs, Lorenz, & Engel, 2013), and pain intensity independent of the stimulus saliency (Zhang et al., 2012) are more closely related to gamma oscillations than to responses at other frequencies. Increases in pain intensity were associated with increased gamma oscillations. In contrast, manipulations of the perceived pain intensity using placebo analgesia were not accompanied by matching changes in gamma activity (Tiemann et al., 2015). Interestingly, gamma oscillations were also shown to reliably predict pain sensitivity across individuals, which further supports their crucial role for pain perception (Hu & Iannetti, 2019). Recent groundbreaking work confirmed the

relevance of gamma oscillations for pain perception using intracortical recordings in the primary somatosensory cortex of mice (Tan et al., 2019).

Overall, these results suggest that brain oscillations play an essential role in the processing of phasic noxious stimuli and reveal a complex response pattern comprising phase-locked and non-phase-locked components at various frequencies. Moreover, depending on context and pain modulation, oscillatory activity at gamma frequencies has been implicated in specifically processing pain intensity.

1.2.2 Brain oscillations and tonic pain

It remains unclear how the spectral-temporal-spatial responses to short-lasting phasic noxious stimuli as outlined above relate to longer-lasting pain persisting for months and years, which is a key feature of chronic pain (Treede et al., 2019). To fill this gap, some neurophysiological studies applied longer-lasting experimental pain, often termed tonic pain, of several minutes in healthy human participants. The goal is to elicit pain, which more closely resembles ongoing chronic pain, under controlled experimental conditions.

Similar to phasic pain, studies have demonstrated that tonic pain induces suppressions of neuronal oscillations at alpha frequencies (Colon, Liberati, & Mouraux, 2017; Dowman, Rissacher, & Schuckers, 2008; Giehl, Meyer-Brandis, Kunz, & Lautenbacher, 2014; Gram, Graversen, Olesen, & Drewes, 2015; Huishi Zhang et al., 2016; Liberati et al., 2018; Nir, Sinai, Moont, Harari, & Yarnitsky, 2012; Peng, Hu, Zhang, & Hu, 2014; Shao, Shen, Yu, Wilder-Smith, & Li, 2012). As stated above, alpha oscillations have generally been implicated in cognitive functions like attention. However, correlations between alpha suppressions and pain intensity ratings have also been reported during tonic pain (Nir et al., 2012; Shao et al., 2012). Besides alpha suppressions, several studies revealed an increase of gamma oscillations during tonic pain (Li et al., 2016; Peng et al., 2014; Schulz et al., 2015). However, only a single previous EEG study (Schulz et al., 2015) exploited the substantial dissociation of stimulus intensity and pain intensity, which spontaneously occurs already during 10 minutes of painful heat stimulation, and distinguished between brain processes related to stimulus intensity and pain intensity. In this study, increases in stimulus intensity were related to suppressions of brain oscillations at beta frequencies whereas pain intensity was shown to relate to brain oscillations at gamma frequencies. Intriguingly, the differential frequency pattern encoding stimulus intensity and pain intensity also dissociated spatially by beta activity being located in the sensorimotor area and gamma activity in the mPFC. Activations in both brain areas have

been associated with sensory-discriminative and motivational-affective aspects of pain (Bushnell et al., 2013), respectively. Accordingly, during a tonic painful stimulation of 10 minutes, the representation of pain intensity by gamma activity shifted from sensorimotor areas after phasic stimulation (Gross et al., 2007) to the mPFC and, thus, to more affective brain circuitries, which also have been implicated in the development and maintenance of chronic pain (Fig. 1; Baliki et al., 2006; Hashmi et al., 2013; Vachon-Presseau et al., 2016).

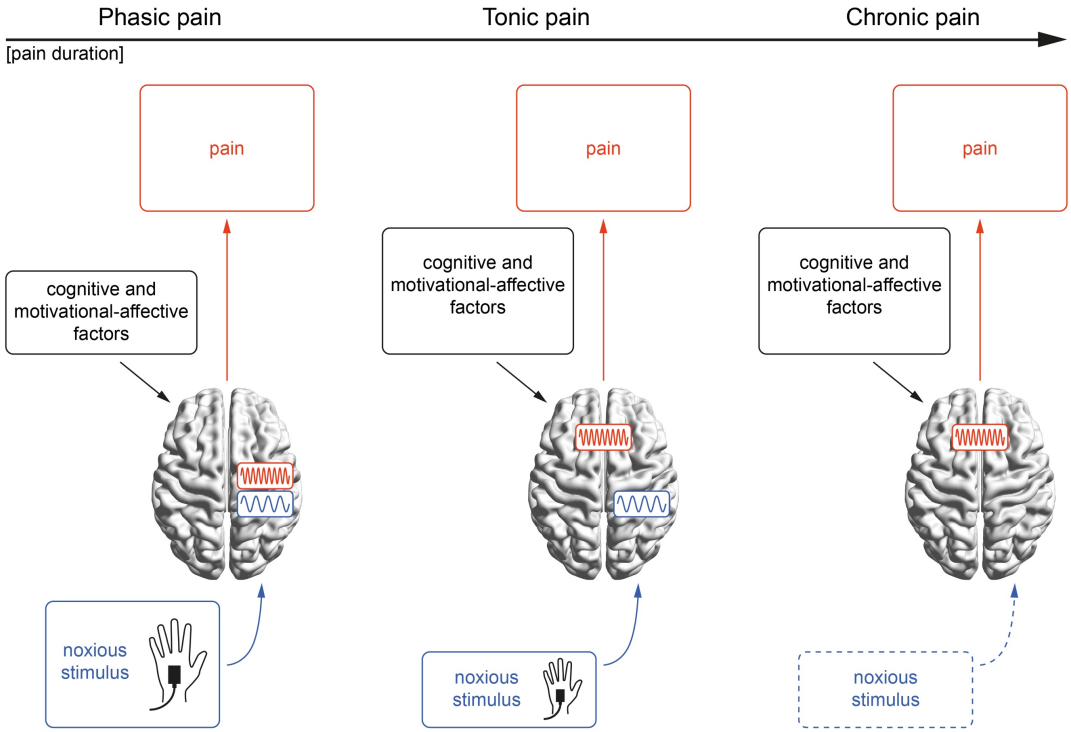

Figure 1. Translation of a noxious stimulus into pain perception depending on pain duration. During phasic pain as depicted in the left column, noxious stimulus and pain commonly well correspond with regard to their intensity. However, the translation from noxious stimuli to pain can vary substantially depending on cognitive and motivational-affective factors. In particular, during tonic pain and chronic pain, noxious stimuli and pain considerably dissociate as indicated by different box sizes in the middle and right column. On the one hand, the relationship between noxious stimuli and pain becomes weaker. On the other hand, cognitive and motivational-affective factors likely play a more important role during longer-lasting pain than during phasic pain. Finally, in chronic pain, the relationship between noxious stimuli and pain is often loose and activity in brain networks underlying motivational-affective processes becomes more prevalent. The dissociation between stimulus intensity and pain intensity is reflected by brain oscillations, schematically depicted by sine waves. Both are related to suppressions of alpha oscillations and increases in gamma oscillations in the contralateral sensorimotor cortex as response to phasic noxious stimuli (Gross et al., 2007; May et al., 2012; Ploner et al., 2006). In contrast, oscillatory gamma activity, which reflects pain intensity, shifts from sensorimotor areas to the medial prefrontal cortex during tonic pain (Schulz et al., 2015) and chronic pain (May et al., 2018), whereas alpha and beta oscillations remain to reflect stimulus intensity in the contralateral sensorimotor cortex during tonic pain (Schulz et al., 2015).

To conclude, tonic pain is related to modulations of brain oscillations in the alpha/beta and the gamma frequency bands, which differentially reflect objective stimulus intensity and subjective pain intensity, respectively. During longer-lasting pain, oscillatory gamma activity

reflecting pain intensity shifts from sensorimotor areas to the mPFC, i.e. to brain regions serving affective-motivational aspects of pain.

1.3 Autonomic responses and pain

Noxious stimuli not only induce changes in brain activity but also responses of the autonomic nervous system (Kyle & McNeil, 2014). These responses are part of the protective function of pain comprising overt motor responses and autonomic responses to avoid or escape actual or impending harm to the body. Autonomic responses provide energy and resources for protective behavior to maintain the integrity and homeostasis of the organism through physiological changes, such as changes in heart rate and skin conductance (Levenson, 2014; McEwen & Wingfield, 2003; Norman, Berntson, & Cacioppo, 2014). Thus, autonomic responses are an integral component of pain (Jänig & Levine, 2013). By recording different autonomic measures, one can derive the activity of two subdivisions of the autonomic nervous system, i.e. the sympathetic and the parasympathetic branches. Increased activity in the sympathetic nervous system leads to a rise in skin conductance and pupil dilation. The cardiovascular system exhibits a more complex pattern of sympathetic and parasympathetic influences and, hence, heart rate and heart rate variability, i.e. the variability of intervals between heart beats, can be used to investigate effects of noxious stimulation on both the sympathetic and the parasympathetic nervous system (Berntson, Quigley, Norman, & Lozano, 2017; Kyle & McNeil, 2014).

Several studies have shown that noxious stimulation elicits autonomic responses in a variety of measures including skin conductance (Chapman, Bradshaw, Donaldson, Jacobson, & Nakamura, 2014; Donaldson et al., 2003; Geuter, Gamer, Onat, & Buchel, 2014; Loggia, Juneau, & Bushnell, 2011; Mischkowski, Palacios-Barrios, Banker, Dildine, & Atlas, 2018; Treister, Kliger, Zuckerman, Goor Aryeh, & Eisenberg, 2012), pupil dilation (Chapman et al., 2014; Donaldson et al., 2003; Geuter et al., 2014; Mischkowski et al., 2018), and heart rate (Donaldson et al., 2003; Loggia et al., 2011; Moltner, Holzl, & Strian, 1990; Treister et al., 2012). These responses were related to stimulus intensity (Chapman et al., 2014; Donaldson et al., 2003; Geuter et al., 2014; Loggia et al., 2011; Mischkowski et al., 2018; Treister et al., 2012) or pain intensity or both (Chapman et al., 2014; Donaldson et al., 2003; Geuter et al., 2014; Loggia et al., 2011; Mischkowski et al., 2018; Moltner et al., 1990; Treister et al., 2012). Moreover, previous studies demonstrated that skin conductance and heart rate changes to noxious stimuli are related to brain activity in the sensorimotor, insular, cingulate, and prefrontal cortices, amygdala, hypothalamus, and brain stem (Dube et al.,

2009; Maihofner, Seifert, & Decol, 2011; Mobascher et al., 2009; Piche, Arsenault, & Rainville, 2010; Seifert et al., 2013).

Fewer studies tried to disentangle the relationships between stimulus intensity/pain intensity and autonomic responses (Geuter et al., 2014; Moltner et al., 1990). A recent study showed that pain perception mediates the relationship between noxious stimuli and autonomic responses as represented by skin conductance responses and pupil dilation (Mischkowski et al., 2018). These results suggest that autonomic responses partially depend on perceptual processes. Yet, these findings were based on rather short stimulation intervals of up to 20 s not involving a clear dissociation between nociception and pain. How autonomic responses differentially relate to stimulus intensity and pain intensity, however, has conceptual implications for the understanding of pain. A closer relationship between stimulus intensity and autonomic responses would imply that autonomic responses result directly from nociceptive rather than from perceptual processes. Consequently, the allocation of energy resources by autonomic responses to initiate protective behavior would be partially independent of pain perception. In contrast, a closer relationship between pain intensity and autonomic responses would suggest that autonomic responses more strongly depend on perceptual processes and, thus, could be more strongly influenced by cognitive and emotional-affective factors.

In summary, nociception and pain are intimately linked to activity in the autonomic nervous system, which provides energy resources for protective behavior. In addition, brain activity in several brain areas co-varies with autonomic responses. Yet, if autonomic responses are more closely related to nociceptive or pain processes remains inconclusive.

1.4 Aims of the thesis

The current thesis pursued the overall goal to investigate oscillatory brain activity and autonomic responses associated with longer-lasting pain in healthy human participants using EEG. Up to now, brain oscillations and autonomic activity have mostly been assessed in the context of phasic pain whereas reported relationships between stimulus intensity, pain intensity, brain activity, and autonomic responses in longer-lasting pain remain inconclusive. Similar to chronic pain, a spontaneous dissociation of stimulus intensity and pain intensity can be observed during several minutes of painful heat stimulation (Schulz et al., 2015). Thus, tonic pain provides an experimental model for some characteristics of chronic pain. Chronic pain is associated with enormous individual suffering (Rice, Smith, & Blyth, 2016) and economic costs for the society (Breivik, Eisenberg, O'Brien, & Openminds,

2013; Gaskin & Richard, 2012) but its treatment still remains unsatisfactory (Global Burden of Disease Study, 2017). The current thesis investigated tonic pain with the ultimate goal to advance the understanding of neurophysiological processes underlying longer-lasting pain and, finally, to foster the development of new treatment approaches for chronic pain.

In the experimental paradigm of the current thesis, painful heat stimuli of 10 min duration were applied to the left and right hand of healthy human participants while continuous pain ratings, EEG, skin conductance, and electrocardiography (ECG) were recorded. The analysis of the data set was divided into three projects dedicated to three distinct aspects of the neural representation of longer-lasting pain.

The aim of project 1 was to confirm and extend the results of a previous study (Schulz et al., 2015), which investigated the differential encoding of stimulus intensity and pain intensity by brain oscillations at beta and gamma frequencies, respectively. More importantly, our goal was to determine whether the representation of stimulus intensity and pain intensity in the brain reflects sensory features such as stimulus location or spatially independent processes potentially underlying salience, valence, or motivational aspects.

In project 2, we pursued the goal to assess whether autonomic responses are more closely related to stimulus intensity or pain intensity to reveal whether nociceptive processes induce autonomic responses partially independently of perceptual processes. This would indicate an early allocation of energy resources by autonomic responses depending on nociceptive processes.

Project 3 aimed to comprehensively characterize the state of longer-lasting pain during tonic heat stimulation by investigating oscillatory brain activity and functional connectivity on a global, i.e. whole-brain, and local level. To assess the state of longer-lasting pain, we analyzed brain activity across the entire stimulation interval independent of instantaneous stimulus intensity or pain intensity. The analysis spanned from rather basic measures of oscillatory brain activity to functional brain connectivity up to the whole-brain network level.

2 Project 1 – Brain oscillations differentially encode noxious stimulus intensity and pain intensity

The current chapter consists of a research manuscript entitled "Brain oscillations differentially encode noxious stimulus intensity and pain intensity". The manuscript provides first evidence about the spatially specific representation of stimulus intensity at alpha and beta frequencies in the sensorimotor area and a spatially independent representation of pain intensity at gamma frequencies in the medial prefrontal cortex during painful heat stimulation. The manuscript was published in NeuroImage in 2017.

Contributions:

Authors: *Moritz Maximilian Nickel, Elisabeth Susanne May, Laura Tiemann, Paul Schmidt, Martina Postorino, Son Ta Dinh, Joachim Gross, Markus Ploner*

The author of this thesis is the first author of the manuscript. **M.M.N.** and M. Ploner conceived the experiment. **M.M.N.**, E.S.M., L.T., and M. Postorino conducted the data acquisition. **M.M.N.** performed the analysis, with consultation of E.S.M., P.S., and J.G., under the supervision of M. Ploner. **M.M.N.** and M. Ploner wrote the manuscript. All authors discussed the results and revised the final manuscript.

Research manuscript:

Nickel, M. M., May, E. S., Tiemann, L., Schmidt, P., Postorino, M., Ta Dinh, S., . . . Ploner, M. (2017). Brain oscillations differentially encode noxious stimulus intensity and pain intensity. *Neuroimage, 148*, 141-147. doi:10.1016/j.neuroimage.2017.01.011

3 Project 2 – Autonomic responses to tonic pain are more closely related to stimulus intensity than to pain intensity

The current chapter consists of a research manuscript entitled “Autonomic responses to tonic pain are more closely related to stimulus intensity than to pain intensity”. Using the dissociation of stimulus intensity and pain intensity during painful heat stimulation, for the first time, the manuscript shows that skin conductance measures are more closely related to stimulus intensity than to pain intensity and negatively co-vary with alpha and beta oscillations in the contralateral sensorimotor cortex. The manuscript was published in PAIN in 2017.

Contributions:

Authors: *Moritz Maximilian Nickel, Elisabeth Susanne May, Laura Tiemann, Paul Schmidt, Martina Postorino, Son Ta Dinh, Markus Ploner*

The author of this thesis is the first author of the manuscript. **M.M.N.** and M. Ploner conceived the experiment. **M.M.N.**, E.S.M., L.T., and M. Postorino conducted the data acquisition. **M.M.N.** performed the analysis, with consultation of P.S., under the supervision of M. Ploner. **M.M.N.** and M. Ploner wrote the manuscript. **M.M.N.**, E.S.M., L.T., P.S., S.T.D., and M. Ploner discussed the results and revised the final manuscript.

Research manuscript:

Nickel, M. M., May, E. S., Tiemann, L., Postorino, M., Ta Dinh, S., & Ploner, M. (2017). Autonomic responses to tonic pain are more closely related to stimulus intensity than to pain intensity. *Pain, 158*(11), 2129-2136. doi:10.1097/j.pain.0000000000001010

4 Project 3 – Neural oscillations and connectivity characterizing the state of tonic experimental pain in humans

The current chapter consists of a research manuscript entitled “Neural oscillations and connectivity characterizing the state of tonic experimental pain in humans”. The manuscript presents a comprehensive analysis of brain oscillations, functional connectivity, and brain network measures characterizing the longer-lasting experimental pain state. The manuscript was published in Human Brain Mapping in 2020.

Contributions:

Authors: *Moritz Maximilian Nickel, Son Ta Dinh, Elisabeth Susanne May, Laura Tiemann, Vanessa Desirée Hohn, Joachim Gross, Markus Ploner*

The author of this thesis is the first author of the manuscript. **M.M.N.** and M. Ploner conceived the experiment. **M.M.N.**, E.S.M., L.T., and M. Postorino conducted the data acquisition. **M.M.N.**, S.T.D. performed the analysis and provided analytical tools, with consultation of J.G. and under the supervision of M. Ploner. **M.M.N.** and M. Ploner wrote the manuscript. All authors discussed the results and revised the final manuscript.

Research manuscript:

Nickel, M. M., Ta Dinh, S., May, E. S., Tiemann, L., Hohn, V. D., Gross, J., & Ploner, M. (2020). Neural oscillations and connectivity characterizing the state of tonic experimental pain in humans. *Hum Brain Mapp, 41*(1), 17-29. doi:10.1002/hbm.24784

5 General discussion

The current thesis focused on the neurophysiological processes of tonic pain in humans as measured by EEG and autonomic recordings. In particular, brain oscillations, functional connectivity, and skin conductance revealed systematic activity and connectivity patterns reflecting tonic pain. As tonic pain shares important characteristics with chronic pain, the presented findings might also provide new insights into neuronal mechanisms underlying chronic pain. The general discussion is organized in four sections and provides an overview of the main findings of the current thesis. In the first section, main findings of all three projects will be discussed and related to each other. In the second section, methodological considerations and limitations across all three studies will be outlined. The third section comprises suggestions and ideas for future research leading to the final section of conclusions.

5.1 Main findings and their implications across projects

To advance the understanding of the differential representation of stimulus intensity and pain intensity in the human brain and to gain new insights into neuronal patterns associated with the longer-lasting pain state, the three projects represent three different approaches to analyze EEG and autonomic data recorded in the same experiment. In the current paradigm, we applied tonic painful heat stimuli to the left and right hand of healthy participants while they were asked to continuously rate the instantaneous pain intensity. Subsequently, we contrasted pain conditions with respective control condition which consisted of a visual tracking task. During the whole procedure, EEG, skin conductance, and ECG were recorded. Project 1 aimed to find distinct patterns of oscillations encoding stimulus intensity and pain intensity and to investigate their spatial specificity. In project 2, we aimed to determine whether autonomic responses are more closely related to stimulus intensity or pain intensity. Finally, project 3 consisted of a comprehensive EEG analysis of brain oscillations, functional connectivity, and brain networks in longer-lasting pain states.

5.1.1 Project 1 – Oscillatory encoding of stimulus and pain intensity

Previous studies rarely disentangled brain responses related to noxious stimuli and pain. Up to now, only a single study applied tonic heat stimuli and revealed distinct patterns of brain oscillations related to stimulus intensity and pain intensity (Schulz et al., 2015). In

particular, stimulus intensity was reflected by decreases in beta activity in the sensorimotor area whereas pain intensity was associated with increased gamma activity in the mPFC.

To extend this observation and to assess the spatial specificity of the encoding of stimulus intensity and pain intensity, i.e. whether the encoding depends on the laterality of the stimulated hand, we contrasted pain left and pain right conditions (Nickel, May, Tiemann, Schmidt, et al., 2017). Our results show that stimulus intensity is negatively related to alpha and beta oscillations in sensorimotor areas contralateral to the stimulated hand. In contrast, as shown by the conjunction analysis, pain intensity is encoded by gamma oscillations in the mPFC independent of stimulus location.

The findings of modulations of alpha, beta, and gamma oscillations associated with tonic pain are in accordance with previous studies which observed suppressions of oscillatory brain activity at alpha and beta frequencies (Colon et al., 2017; Giehl et al., 2014; Gram et al., 2015; Huishi Zhang et al., 2016; Liberati et al., 2018; Nir et al., 2012; Peng et al., 2014; Shao et al., 2012) and increases in gamma oscillations (Dowman et al., 2008; Peng et al., 2014; Veerasarn & Stohler, 1992) during tonic pain. Furthermore, our observations of alpha/beta and gamma oscillations encoding stimulus intensity and pain intensity, respectively, replicated the results of our previous study (Schulz et al., 2015). More importantly, our results extend the previous study by revealing that the translation from a noxious stimulus into pain is associated with a change from a spatially specific processing mode by alpha and beta oscillations to a spatially independent processing mode by gamma oscillations. The stimulus-dependent representation of noxious stimuli by contralateral alpha/beta oscillations indicates that they likely reflect sensory features such as stimulus location. In contrast, the stimulus-independent representation of pain by prefrontal gamma oscillations suggests a strong dependence on higher-order processes such as salience, valence, or motivational aspects.

Overall, the findings of project 1 support the differential processing of stimulus intensity and pain intensity by spectrally and spatially separable neuronal oscillations during painful heat stimulation. The results extend our knowledge about brain mechanisms of nociception and pain and their dissociation during longer-lasting pain.

5.1.2 Project 2 – Relationships between autonomic responses and stimulus/pain intensity

Autonomic responses have long been a target to find objective biomarkers for the prediction of perceived pain (Nahman-Averbuch & Coghill, 2017). Recently, a study (Geuter et al., 2014)

obtained skin conductance and pupil dilation measures and achieved predictive accuracies for pain, which are comparable to accuracies resulting from brain activation patterns predictive for pain (Wager et al., 2013). However, only few studies disentangled the relationships of autonomic responses to stimulus intensity and pain intensity (Geuter et al., 2014; Moltner et al., 1990). The precise relationships between stimulus intensity, pain intensity, brain activity, and autonomic responses are not yet clear.

To separate these relationships, we analyzed the recorded autonomic measures and again exploited the dissociation of stimulus intensity and pain intensity during tonic heat stimulation (Nickel, May, Tiemann, Postorino, et al., 2017). The results show that skin conductance measures, more precisely the skin conductance level and the number of spontaneous skin conductance fluctuations, are more closely related to stimulus intensity than to pain intensity. In line with our findings of project 1, skin conductance measures were related to alpha and beta oscillations in contralateral sensorimotor areas, i.e. related to brain activity associated with stimulus intensity, but not to gamma oscillations in the mPFC associated with pain intensity. No significant relationships were found between heart rate and stimulus intensity or pain intensity. These observations indicate that sympathetic autonomic responses to noxious stimuli do not fully depend on pain perception but that noxious stimuli induce autonomic responses at least partially independent from perceptual processes during tonic pain.

Ample evidence shows significant relationships between stimulus intensity, pain intensity, and autonomic responses. There are studies indicating a link between autonomic responses and noxious stimulus intensity on the one hand (Chapman et al., 2014; Donaldson et al., 2003; Geuter et al., 2014; Loggia et al., 2011; Treister et al., 2012) and between autonomic responses and pain perception on the other hand (Chapman et al., 2014; Donaldson et al., 2003; Geuter et al., 2014; Loggia et al., 2011; Moltner et al., 1990; Treister et al., 2012). Yet, previous work rarely differentiated stimulus from pain intensity. Two studies observed that skin conductance, pupil diameter (Geuter et al., 2014), and heart rate changes (Moltner et al., 1990) were more closely related to pain intensity than to stimulus intensity. However, these studies applied brief heat stimuli with a duration of at most 20 seconds in contrast to tonic heat stimuli of 10 minutes duration that were employed in the current paradigm. As indicated by psychophysiological (Chen & Treede, 1985; Price, Harkins, & Baker, 1987; Rainville, Feine, Bushnell, & Duncan, 1992) and neurophysiological (Schulz et al., 2015) evidence, the duration of pain critically influences its perceptual features

and the underlying neural processes. Thus, the deviating results could be explained by different durations of noxious stimulation.

Project 2 integrated skin conductance measures and measures of cardiac psychophysiology. Both measures are driven by partially different parts of the autonomic nervous system. Skin conductance closely depends on the state of sweat glands which are predominantly sympathetically innervated and, thus, is mainly driven by the sympathetic branch of the autonomic nervous system (Dawson, Schell, & Filion, 2017). This part of the nervous system is centrally involved in the response to threat, which is often assessed in stress-related frameworks (Murison, 2016). On the contrary, heart rate responses are driven by both the sympathetic and parasympathetic branches of the autonomic nervous system (Berntson et al., 2017). Consequently, our findings of a significant relationship between skin conductance responses and stimulus intensity but not between heart rate and stimulus intensity might indicate that the sympathetic and parasympathetic nervous system, including their distinct functions and cerebral representations (Beissner, Meissner, Bar, & Napadow, 2013), are differently involved. Alternatively, the lack of a significant relationship between heart rate and stimulus intensity could result from a lower sensitivity of the applied approach to detect changes in heart rate during tonic pain.

Taken together, the findings suggest that autonomic responses to pain do not exclusively emerge from perceptual but partly directly from nociceptive processes. This is congruent with the conceptualization of pain in which partially independent sensory, affective-motivational, and autonomic processes contribute to the final experience of pain.

5.1.3 Project 3 – Neural characteristics of longer-lasting pain states

Most evidence on the cerebral representation of pain is based on studies of short-lasting phasic pain whose brain mechanisms likely differ from longer-lasting pain states (Baliki & Apkarian, 2015; Kuner & Flor, 2017). Studies using EEG, MEG, and intracranial recordings to investigate the neural representation of tonic pain are comparatively scarce. They have shown modulations of amplitudes (Colon et al., 2017; Giehl et al., 2014; Huishi Zhang et al., 2016; Liberati et al., 2018; Nir et al., 2012; Peng et al., 2014; Schulz et al., 2015) and peak frequencies of brain oscillations (Furman et al., 2017; Nir, Sinai, Raz, Sprecher, & Yarnitsky, 2010) as well as changes in functional connectivity (Gram et al., 2017; Huishi Zhang et al., 2016; Levitt et al., 2017; Martel et al., 2017). However, a comprehensive analysis of oscillatory brain activity and functional connectivity on a local, i.e. spatially specific, and global, i.e. whole-brain, scale is missing so far. Project 3 therefore aimed to

comprehensively characterize the local and global patterns of neural oscillations and functional connectivity reflecting the state of longer-lasting pain in humans.

To this end, we analyzed the EEG data of the aforementioned paradigm and contrasted oscillatory and functional connectivity measures up to the whole-brain level between pain conditions and the respective non-painful control conditions (Nickel et al., 2020). Whereas project 1 investigated the instantaneous relationship of brain activity with stimulus intensity and pain intensity, project 3 focused on characterizing the state of longer-lasting pain per se, i.e. across the entire stimulation interval independent of the current stimulus intensity or pain intensity. By systematically investigating the patterns of neural oscillations and functional connectivity, the analysis revealed local suppressions of alpha activity over sensorimotor cortices during tonic pain. Concomitantly, functional connectivity in the alpha frequency band between sensorimotor cortices contralateral to the stimulated hand and the mPFC was enhanced. Directed connectivity analysis suggests bottom-up signaling of nociceptive information in alpha frequencies from somatosensory areas to the mPFC. Thus, the present results identify a potential network underlying the translation of nociceptive input into perceived pain during longer-lasting pain. Regarding global measures of brain oscillations or graph-theory based network measures, we only found a single effect of tonic pain when using the debiased weighted phase lag index (Vinck, Oostenveld, van Wingerden, Battaglia, & Pennartz, 2011) as connectivity measure. This effect of a higher global clustering coefficient in the alpha frequency band indicates increased functional segregation during tonic pain.

The lack of dominant global changes in oscillatory brain activity in project 3 deviates from previous studies reporting both increasing (Nir et al., 2010) and decreasing (Furman et al., 2017) peak alpha frequencies during tonic pain. This disagreement might be attributed to differences in control conditions. Whereas previous studies used passive control conditions, we applied an active control condition using a visual tracking task matching the cognitive load of the continuous pain rating procedure. Since cognitive load can influence the peak alpha frequency (Haegens, Cousijn, Wallis, Harrison, & Nobre, 2014; Mierau, Klimesch, & Lefebvre, 2017), a contrast of pain conditions to passive and active control conditions might yield different results. Similar to a lack of global oscillatory brain activity changes, we did not find significant global changes of functional connectivity as reflected by graph theory-based measures using the phase locking value (Lachaux, Rodriguez, Martinerie, & Varela, 1999). This is congruent with literature revealing that functional connectivity networks assessed by EEG are stable across time in healthy participants (Chu

et al., 2012; Kramer et al., 2011). However, while scrutinizing global network measures based on the debiased weighted phase lag index, which is considered to be less sensitive to volume conduction, we found an enhanced global clustering coefficient in the alpha band indicating increased functional segregation during tonic pain. Although such changes of global network measures have been shown in different neurologic and psychiatric disorders using EEG or MEG (Stam, 2014; Stam, Jones, Nolte, Breakspear, & Scheltens, 2007; Yu et al., 2017), neurophysiological evidence for similar changes in chronic pain does not exist so far.

Local suppressions of alpha oscillations at electrodes covering sensorimotor areas during tonic pain are well compatible with previous studies as mentioned in the section on project 1 above. These suppressions likely indicate activation and increased excitability (Klimesch, 2012; Klimesch et al., 2007) of the sensorimotor cortex during the processing of tonic pain. Intriguingly, our results show that these local suppressions of alpha oscillations coincide with local increases of functional connectivity in the same brain areas at similar frequencies. We observed medium to large effect sizes of connectivity modulations induced by tonic pain. This further supports the crucial role of functional connectivity and brain networks in the processing of pain in the human brain (Apkarian & Chialvo, 2006; Kucyi & Davis, 2015; H. Mano & Seymour, 2015; Tracey, 2005). Moreover, present findings of increased functional and directed connectivity at alpha frequencies from sensorimotor areas contralateral to the stimulated hand to the mPFC are in line with accumulating evidence that the mPFC plays an important role in valuation and affective processes after noxious stimulation (Woo et al., 2015) and the development, maintenance, and encoding of chronic pain (Baliki et al., 2006; Hashmi et al., 2013; Vachon-Presseau et al., 2016).

In summary, the results of project 3 suggest that the state of longer-lasting pain entails changes in brain oscillations and functional connectivity predominantly on a local level. More importantly, the analysis revealed a sensorimotor-prefrontal network connected at alpha frequencies which might be a crucial neuronal network and mechanism associated with the state of longer-lasting pain.

5.1.4 Implications across projects

As pointed out in the previous sections, we assessed three different aspects of tonic pain and its underlying neuronal processes using data acquired in one experiment. First, we identified the spectrally and spatially differential encoding of stimulus intensity as proxy of nociception and pain perception. Next, our results demonstrated that sympathetic activity

as reflected by skin conductance is more closely related to nociception than to pain perception during tonic pain. Finally, we found that the state of longer-lasting pain is mainly associated with local modulations of brain activity and functional connectivity at alpha frequencies comprising stronger connectivity in a sensorimotor-prefrontal network during a longer-lasting pain state than during a non-painful state. Overall, the results of the three perspectives yield the following three key aspects for discussion.

First, alpha and beta oscillations in contralateral sensorimotor cortices reflected nociception rather than subjective pain perception in a spatially specific manner, i.e. depending on the stimulus location, during tonic pain. Furthermore, as shown in project 3, the alpha suppressions by the noxious stimulus were associated with an increase in connectivity at similar frequencies in sensorimotor areas contralateral to the stimulated hand. As proposed by Donner and Siegel (2011), alpha and beta oscillations might be linked to long-range interactions in the brain. Our findings of enhanced connectivity between contralateral sensorimotor cortices and mPFC at alpha frequencies are well compatible with this view. Moreover, the negative relationship between skin conductance measures and alpha/beta oscillations in contralateral sensorimotor areas further the interpretation of alpha/beta oscillations being more strongly involved in processing nociceptive information than pain, since skin conductance was more closely related to noxious stimulus intensity. The link between skin conductance responses and alpha/beta activity in contralateral sensorimotor cortices is particularly intriguing since current concepts of cortical autonomic control mainly focus on cingulate and insular cortices rather than sensorimotor areas (Beissner et al., 2013; Critchley & Harrison, 2013). However, these concepts refer to autonomic control in general but do not necessarily apply to the processing of tonic pain. With regard to the cerebral control of autonomic responses to noxious stimuli, most studies (Dube et al., 2009; Mobascher et al., 2009; Seifert et al., 2013) observed a significant relationship between sensorimotor cortices and autonomic responses (see also Maihofner et al., 2011; Piche et al., 2010). Recently, an anatomical study (Dum, Levinthal, & Strick, 2016) identified major pathways of the primate cerebral cortex to the adrenal medulla as major sympathetic effector. As major network, cortical motor areas and parts of the somatosensory cortex exhibited multisynaptic connections with the adrenal medulla and, thus, controlled sympathetic autonomic activity. Taken together, these findings support concepts of pain which emphasize the integration of sensory, cognitive, affective-motivational, and autonomic processes resulting in a coherent perception of pain (Fields, 1999; Garcia-Larrea & Peyron, 2013; May et al., 2017; Price, 2000).

Second, as put forward by previous studies, neural activity in the mPFC is closely related to pain perception in healthy participants (Kragel et al., 2018; Schulz et al., 2015; Woo et al., 2015) and chronic pain patients (Baliki et al., 2006; Hashmi et al., 2013; Vachon-Presseau et al., 2016). In project 1, we found a significant covariation between gamma oscillations in the mPFC and pain intensity during tonic pain. Whereas alpha and beta oscillations might implement long-range communication, gamma oscillations have been linked to a more locally confined processing of information (Donner & Siegel, 2011). Our findings extend previous observations (Schulz et al., 2015) to the point that the brain area in which pain intensity was encoded did not depend on the stimulus location, i.e. on the laterality of the stimulated hand. Consequently, the mPFC might serve as a hub region that is responsible for the integration of sensory, cognitive, and affective-motivational processes that affect pain perception. In particular, the close anatomical proximity of brain areas, whose activity patterns can be separated and ascribed to specific domains as pain, cognitive control, and negative emotions (Kragel et al., 2018), renders the mPFC suitable for the integration of sensory and contextual information into a coherent percept and an appropriate behavioral response. As shown in project 3, we identified a sensorimotor-prefrontal network with increased directed connectivity from contralateral sensorimotor areas to the mPFC, which is in accordance with its hub-like properties and the integration of sensory information transmitted via contralateral somatosensory cortices in the alpha frequency band.

Third, besides activations by tonic pain, neural activity in the mPFC has been implicated in the development, maintenance, and encoding of chronic pain (Baliki et al., 2006; Hashmi et al., 2013; Vachon-Presseau et al., 2016). During the transition from early acute pain to chronic pain, the cerebral pain processing seems to shift from brain regions commonly associated with acute experimental pain (Apkarian et al., 2005) to emotion-related brain circuits (Baliki & Apkarian, 2015; Hashmi et al., 2013). Similarly, our analysis revealed pain-related gamma oscillations in the mPFC already after 10 minutes of painful heat stimulation, in contrast to gamma responses in the primary somatosensory cortex induced by phasic noxious stimuli (Gross et al., 2007). This might indicate that pain processing shifts from sensory brain regions to emotion-related brain regions already within 10 minutes of painful heat stimulation. During both chronic pain and tonic pain, a dissociation between noxious stimuli and pain perception occurs. In everyday life, the translation of a noxious stimulus to a pain percept varies to dynamically adjust it to behavioral demands. Under most situations, this variability is highly adaptive. On the contrary, in chronic pain, when longer-lasting pain occurs without adequate noxious input,

the dissociation between nociception and pain is maladaptive (Baliki & Apkarian, 2015). Since chronic pain and tonic heat pain both yield a partial decoupling of nociceptive input and pain, the latter offers a promising way to shed light on underlying neural mechanisms of chronic pain under controlled experimental conditions.

5.2 Methodological considerations and limitations

Considering that a single tonic heat pain experiment constitutes the basis of all three projects, it is particularly important to note potential methodological issues and limitations and how they could have differently affected the results of each project. In this section, the most relevant methodological issues regarding the EEG analysis and the analysis of autonomic responses in a tonic heat pain paradigm will be outlined. EEG combines various advantageous properties. It provides a direct measure of neuronal activity with a high temporal resolution in the millisecond range and is rather a low-cost and broadly available tool to record brain activity. However, as every neuroimaging method, EEG entails some limitations and disadvantages.

First, although source localization techniques have substantially improved the spatial resolution over the past three decades (He, Sohrabpour, Brown, & Liu, 2018), the spatial resolution of EEG still remains rather limited. Correspondingly, the results of project 1 and project 3 showed quite broad clusters of significant relationships between brain oscillations and stimulus/pain intensity or of power changes and connectivity changes, which were not confined to a single brain region. Second, volume conduction and field spread effects across the scalp are inherent to EEG and can influence EEG-based connectivity analyses in general and zero-phase lag connectivity in particular, which is included in the phase locking value used in project 3. Thus, we also applied the debiased weighted phase lag index, which is less susceptible to volume conduction (Vinck et al., 2011). Importantly, experimental (Roelfsema, Engel, Konig, & Singer, 1997; Vicente, Gollo, Mirasso, Fischer, & Pipa, 2008) and modelling (Gollo, Mirasso, Sporns, & Breakspear, 2014; Viriyopase, Bojak, Zeitler, & Gielen, 2012) evidence indicates that physiological long-range connectivity can also occur with zero-phase lag rendering it difficult to separate physiological from artifactual zero-phase lag connectivity. However, several arguments indicate that the findings of project 3 reflect physiological rather than spurious connectivity (Bastos & Schoffelen, 2016; Cohen, 2014; Palva & Palva, 2012; Schoffelen & Gross, 2009). Firstly, we performed all connectivity analyses in source space which reduces volume conduction confounds. Secondly, the results of all projects are based on contrasts between pain and control conditions, which

diminishes the influence of volume conduction effects as they would similarly occur in both conditions. Finally, connectivity between the sensorimotor and prefrontal cortex significantly differed between pain and control conditions even when controlling for power changes indicating that connectivity effects cannot be fully explained by power effects. Nevertheless, we ultimately cannot completely rule out alternative explanations for the observed connectivity pattern between sensorimotor areas and mPFC, which might involve common input by one or more additional sources in combination with volume conduction effects, an inherent confound and limitation of connectivity analyses of scalp EEG recordings.

Besides EEG, autonomic responses served as key neurophysiological measures, which were assessed and related to stimulus intensity and pain intensity in project 2. Specifically, with respect to skin conductance in the context of heat stimulation, one limitation applies concerning the tonic heat paradigm. Skin conductance recordings were obtained at the same hand to which heat stimuli were applied. This was done as the contralateral hand was used for continuous pain ratings, which would have led to excessive movement artifacts in skin conductance recordings. Therefore, we cannot rule out that peripheral phenomena have contributed to our observations. However, such a contribution seems unlikely since a control experiment using a similar setup did not show any difference in skin conductance measures between the ipsilateral and contralateral hand.

Finally, our observations apply to the present paradigm using tonic heat pain but do not necessarily generalize to all types of noxious stimuli with different durations. However, the tonic heat pain paradigm yields spontaneous dissociations of stimulus intensity and pain intensity and thereby offers the opportunity to gain insights into the differential relationship between stimulus intensity, pain intensity, brain activity, and autonomic responses. In addition, the paradigm enabled us to replicate the results within one experimental session, since both the left and the right hand were stimulated in separate conditions.

5.3 Future directions

The findings of the current thesis emphasize the importance of brain oscillations and functional connectivity for the processing of longer-lasting pain. They further underline the differential representation of nociception and pain by brain oscillations and skin conductance responses. In light of these results, important steps for future research can be deduced that can confirm the relevance of brain oscillations for chronic pain and probe the causal role of brain oscillations for nociception and pain perception in general.

Previous fMRI studies showed that prefrontal areas reflect ongoing pain in various chronic pain populations (Baliki et al., 2006; Baliki, Schnitzer, Bauer, & Apkarian, 2011; Geha et al., 2007; Hashmi et al., 2013). Therefore, instead of experimental heat pain, it is of interest how spontaneously occurring fluctuations of chronic pain are associated with oscillations in the brain. A recent study (May et al., 2018) took the first step and demonstrated that the currently experienced pain level in chronic back pain patients is encoded by prefrontal gamma oscillations, which well corresponds to the results of the current thesis. It remains unclear, however, if the correlate of prefrontal gamma activity generalizes across chronic pain populations and constitutes a common neurophysiological marker and potential biomarker of chronic pain. To this end, chronic pain with different etiologies should be investigated and overlaps in oscillatory activity patterns encoding ongoing pain should be explored.

In addition, the current thesis might inspire research on the transition from phasic pain to tonic pain. Neurophysiological activity patterns seem to substantially depend on noxious stimulus duration (Gross et al., 2007; Schulz et al., 2015), which raises the question of intermediate states. However, intermediate states and their neuronal activity patterns are unknown. They might provide integral information about underlying neural mechanisms of the diverging representation of phasic and tonic pain as well as partially mimic the transition from acute to chronic pain (Hashmi et al., 2013; Vachon-Presseau et al., 2016). A feature of this transition might be a gradual shift from pain processing in nociceptive to emotional circuits. Promising tools to assess this transition include multivariate approaches, which integrate not one but multiple features of neurophysiological data to predict pain as behavioral outcome, as well as machine learning approaches to identify predictive neuronal patterns (Haxby, Connolly, & Guntupalli, 2014; Schulz, Zherdin, Tiemann, Plant, & Ploner, 2012; Wager et al., 2013). Microstate analysis (Khanna, Pascual-Leone, Michel, & Farzan, 2015), which identifies quasi-stable, rapidly switching topographies of activations, could be another tool to capture the neuronal dynamics associated with the transition from phasic to tonic pain.

So far, studies of longer-lasting pain have investigated brain oscillations as correlates of stimulus intensity or pain intensity either in tonic heat pain paradigms (Nickel, May, Tiemann, Schmidt, et al., 2017; Schulz et al., 2015) or in chronic back pain (May et al., 2018). However, the correlative nature of these results does not enable us to infer causality. Proving the causal relationship requires methods for the controlled manipulation of brain oscillations and the observation of predicted effects on relevant outcomes such as pain perception.

Given the recent evidence, alpha oscillations in the sensorimotor area and gamma oscillations in the prefrontal cortex might serve as suitable targets for non-invasive brain stimulation (Polania, Nitsche, & Ruff, 2018; Thut et al., 2017; Vosskuhl, Struber, & Herrmann, 2018). In particular, transcranial alternating current stimulation (tACS) and repetitive transcranial magnetic stimulation (rTMS) provide the opportunity to modulate neuronal activity in a frequency-specific manner (Polania et al., 2018; Thut et al., 2017; Vosskuhl et al., 2018). Surprisingly, studies that specifically aimed at modulating brain oscillations at certain frequencies using tACS or rTMS to determine the effects on pain perception (Ahn, Prim, Alexander, McCulloch, & Frohlich, 2019; Arendsen, Hugh-Jones, & Lloyd, 2018) have been scarce. Proving a causal role of oscillatory alpha and gamma activity for nociception and pain perception could imply the entrainment of alpha and gamma activity over sensorimotor and prefrontal areas in an tonic heat pain paradigm. Effects on pain perception and changes of network dynamics could provide mechanistic insights into the neuronal processing of longer-lasting pain. More importantly, based these insights, prefrontal gamma oscillations might serve as a therapeutic target for non-invasive brain stimulation (M. P. Jensen, Day, & Miro, 2014) and neurofeedback (Sitaram et al., 2017) in the treatment of chronic pain.

5.4 Conclusions

Pain serves to protect the integrity of the body. Consequently, pain commonly results from noxious stimuli, i.e. from thereby induced neurophysiological processes (Adair et al., 1968; Price, 1999; Stevens, 1957). However, this translation process can vary substantially. Although this variability is highly adaptive under most conditions, it becomes maladaptive in chronic pain, when longer-lasting pain occurs without adequate noxious stimuli or at abnormal low stimulus intensities (Baliki & Apkarian, 2015). Importantly, such dissociations can also be observed during tonic pain, which offers the opportunity to investigate the differential neural representation of nociception and pain under controlled experimental conditions. The current thesis extends our understanding of this dissociation by showing a spatially specific oscillatory activity pattern encoding stimulus intensity at alpha/beta frequencies in contralateral sensorimotor areas and a spatially independent oscillatory activity pattern encoding pain intensity at gamma frequencies in the medial prefrontal cortex. The distinction between nociception and pain is central to understand brain mechanisms of pain as the prioritization of one or the other might have potential consequences for the clinical context. In chronic pain therapy, the assumption of a linear

translation of nociception into pain might result in an inappropriate focus on nociceptive processes leading to insufficient treatment effects, for example by pharmacological and operative therapy. To identify the brain mechanisms that underlie nociception and pain might therefore advance the understanding, diagnosis, and treatment of chronic pain. Moreover, our results show that skin conductance measures are more closely related to stimulus intensity and its cerebral representations than pain intensity. These findings corroborate concepts of pain in which sensory, motivational, and autonomic processes partially independently contribute to the final experience of pain. Finally, our results suggest a core network for the processing of longer-lasting pain, which comprises the sensorimotor and medial prefrontal cortex and synchronizes at alpha frequencies. This network might play a crucial role in the translation of nociception into the subjective experience of pain and might help to identify targets for new approaches to treat chronic pain, such as non-invasive brain stimulation and neurofeedback (M. P. Jensen et al., 2014; Polania et al., 2018).

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ABBREVIATIONS

ECG	electrocardiography
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
MEG	magnetoencephalography
mPFC	medial prefrontal cortex
NPS	Neurologic Pain Signature
rTMS	repetitive transcranial magnetic stimulation
SIIPS-1	Stimulus Intensity Independent Pain Signature-1
tACS	transcranial alternating current stimulation

ACKNOWLEDGEMENTS

First of all, I would like to thank Prof. Dr. Hermann Müller for his support and supervision as well as for providing the opportunity to write my thesis at the Faculty of Psychology and Educational Sciences of the LMU. My special thanks also go to Prof. Dr. Markus Ploner – the head of the pain research group I have been a part of – who has motivated, supported and encouraged me throughout the whole way of my PhD. His enthusiasm and genuine interest in neuroscience in general and in pain research in particular have been truly inspiring. I thank him for fruitful discussions and suggestions, which greatly improved my work, and last but not least for his patience.

Furthermore, I would like to thank Elisabeth May, Laura Bok, Son Ta Dinh, Vanessa Hohn, Martina Postorino, and Henrik Heitmann, a.k.a. the PainLab, for their always helpful input and support during the years and the exceptional atmosphere. I will remember all the joyful hours in and out of office sharing stories, wandering through the woods looking for salamanders and hiking on mountain tops after work. My thanks also go to many other people of the TUM-NIC who have created a truly special environment. I very much appreciate to have been a part of it. Moreover, I would like to thank Prof. Dr. Joachim Gross for his invaluable methodological input.

My family has always been there for me no matter my decisions or the circumstances. This is the greatest gift one can ever receive. I am profoundly grateful to have you and excited to see how much the family has grown through the recent years! Finally, I would like to thank Karo. Not only her great support but also the knowledge that there is another rolmonica playing melodies at the same tune has made the last years of my PhD very special.

DECLARATION OF AUTHOR CONTRIBUTIONS

Project 1

Authors: *Moritz Maximilian Nickel, Elisabeth Susanne May, Laura Tiemann, Paul Schmidt, Martina Postorino, Son Ta Dinh, Joachim Gross, Markus Ploner*

The author of this thesis is the first author of the manuscript. **M.M.N.** and M. Ploner conceived the experiment. **M.M.N.**, E.S.M., L.T., and M. Postorino conducted the data acquisition. **M.M.N.** performed the analysis, with consultation of E.S.M., P.S., and J.G., under the supervision of M. Ploner. **M.M.N.** and M. Ploner wrote the manuscript. All authors discussed the results and revised the final manuscript.

Project 2

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Project 3

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The author of this thesis is the first author of the manuscript. **M.M.N.** and M. Ploner conceived the experiment. **M.M.N.**, E.S.M., L.T., and M. Postorino conducted the data acquisition. **M.M.N.**, S.T.D. performed the analysis and provided analytical tools, with consultation of J.G. and under the supervision of M. Ploner. **M.M.N.** and M. Ploner wrote the manuscript. All authors discussed the results and revised the final manuscript.