Klinikum der Ludwig-Maximilians-Universität München
Neurologische Klinik und Poliklinik
Direktorin: Univ. Prof. Dr. med. Marianne Dieterich, FANA, FEAN

Cortical Mechanisms of the Variable Perception and Modulation of Pain

Kumulative Habilitationsschrift
zur Erlangung der Venia Legendi im Fach
Experimentelle Neurologie

vorgelegt von
Dr. Enrico Schulz
2023

Table of Contents

Table of Contents 1

1. Introduction 3

1.1. Inter-individual differences in the perception of pain 3

1.2. Context-dependent within-subject differences in the perception of pain: modulation of brain activity by cognitive strategies 4

1.3. Inter-individual differences in pain modulation 5

1.4. Within-subject variability of the perception of tonic pain in healthy subjects 7

1.5. Within-subject variability of the perception of chronic pain 8

1.6. Studies on stability and reliability of EEG and MRI recording on pain perception. 9

2. Own Work 11

2.1. Strategy-dependent modulation of cortical pain circuits for the attenuation of pain 11

2.2. Ultra-high-field imaging reveals increased whole brain connectivity underpins cognitive strategies that attenuate pain 14

2.3. Intrinsic Network Activity Reflects the Ongoing Experience of Chronic Pain 17

2.4. Intrinsic Network Activity Reflects the Fluctuating Experience of Tonic Pain 21

2.5. Patients With Chronic Pain Exhibit Individually Unique Cortical Signatures of Pain 25

2.6. Individually Unique Dynamics of Cortical Connectivity Reflect the Ongoing Intensity of Chronic Pain 29

3. General Discussion 34

3.1. Pain Attenuation 35

3.2. Fluctuating Intrinsic Network activity Encodes Long-lasting Pain 37

3.3. Dissociating the coding of pain intensity from the encoding of rising and falling pain 39

3.4. The need for shifting vectors in experiments with continuously assessed behaviour 40

3.5. Assessment of sensitisation in tonic pain experiments using fMRI 42

3.6. Individually unique and stable cortical patterns of pain processing 43

3.7. Outlook - impact of studies testing the uniqueness of subject-specific patterns 45

3.8. Outlook - applying the concept of an individual signature of pain 46

4. References 48

5. Figure references 54

6. Abbreviations 54

7. Affidavit 55

8. References of included Manuscripts 56

9. Own Publications 56

1. Introduction

Pain has a prominent role among the human senses due to its function to warn of harm as well as for its affective-emotional component [101,114]. Painful events are therefore particularly dominant in the stream of incoming sensory information and are believed to attract more attention than other sensory modalities [34,122].

1.1. Inter-individual differences in the perception of pain

One man's pain is another man's pleasure. We have long known that perceived pain severity depends very much on the individual [68,96]. The experience of pain does not simply reflect sensory information, but can be substantially influenced by the individual's sensitivity to pain [110]. The neural response to pain changes more to these individual perceptions than to the absolute value of the external stimulus [107]. As a consequence, some individuals perceive a nociceptive stimulus as strongly painful whereas others perceive the very same event as less painful [22,68,95]. Indeed, our research has shown that 44 degrees of long-lasting heat pain may register as almost unbearable to one participant, yet hardly painful at all to another [27,107].

Depending on the specific circumstances, the perception of pain is also influenced by social factors [113], as well as by emotions and attention [129]. As these factors are thought to develop differently between individuals, they will likely contribute to an individual's "steady-state" pain experience when all other factors that we know influence pain are controlled [124]. Relatedly, when a subject is exposed to a painful event it can cause an activation of brain regions unique for that subject in a given situation, but which can change in a flexible way. This individual but flexibly-accessible pattern of activated brain regions comprises the well-known grey matter structures, which until recently had been called the pain matrix, i.e. the insular cortex, the somatosensory cortices, and the cingulate cortex. The activity pattern can also include other structures such as the amygdala and frontal cortex regions depending upon the context, cognitive state and mood [124]. Many studies are showing how these regions concertedly represent the perception and modulation of pain in the human brain. In contrast, the influence of the individual pattern of the hard-wired structural connections between regions of the pain matrix and other pain-modulating regions on the subjective experience of pain has only recently started being considered [72,108].

1.2. Context-dependent within-subject differences in the perception of pain: modulation of brain activity by cognitive strategies

Modulation of brain activity by cognitive strategies: behavioural findings. Previous research has shown that various cognitive strategies are effective to attenuate pain [4,30]. As studies were aiming to find the best strategy to attenuate pain, they have shown that healthy subjects and pain patients can successfully utilise cognitive approaches to control pain intensity and distress [40,60,62,89], as well as to increase pain tolerance [4,73]. However, by neglecting interindividual differences and individual preferences, these studies merely compared the general efficiency of various strategies. The results of these studies revealed enormous performance variability among participants: some subjects performed well on pain reduction, whereas others did not achieve a reduction of pain intensity at all. To explain the variability, the authors suggested that some of the less successful participants would have performed better with a different strategy [3,30,51]. Indeed, Lawrence et al. [69] recently found some variability for a pain patient's ability to utilise one of two predetermined cognitive strategies. For example, for some patients, the shift of attention to a non-painful body site was more effective than a reappraisal of the painful stimulus at reducing pain. For other patients the opposite was true.

In agreement with some behavioural studies [33,80], we found a superiority of two distraction strategies (counting backwards, imagining a safe place) compared to a cognitive reappraisal strategy [109]. The suggested individual preference for certain attenuation strategies between subjects [30] could not be confirmed; our results on healthy subjects have shown that most of the behavioural variance in the data is explained by a common performance factor across all strategies: our sample of healthy participants included subjects that achieved substantial pain attenuation in all three strategies and subjects that were less successful in all three strategies [109].

Modulation of brain activity by cognitive strategies: neuroimaging findings. More recently, neuroimaging has been utilised to investigate the influence of cognitive factors (i.e. attentional shift, meditation, cognitive demand) on the processing of pain perception in healthy subjects [18,42,136]. Due to the application of various techniques (EEG, PET, fMRI), sometimes low sample sizes, different tasks (attention modulation, task-related distraction, imaginal strategies, placebo application, or meditation), and varying methods

of stimulation (cold pressor test, brief laser stimulation, tonic heat pain), the results diverge substantially across studies - particularly with respect to the involvement of frontal cortical areas. Besides the amount of variability, commonly decreased cortical activity was found in regions that are known to be involved in the processing and encoding of pain, i.e. the insular cortex, the anterior and posterior cingulate cortices, as well as the primary and secondary somatosensory cortices [99,125,132]. Other studies revealed increased activity in the endogenous top-down control circuit, which includes the perigenual anterior cingulate cortex and the periaqueductal grey [13,128,134].

1.3. Inter-individual differences in pain modulation

Individually specific signature of pain. It had been suggested that an individual but flexibly-accessible pattern of activated brain regions - the individually specific signature of pain - determines the processing of pain. It may also affect the capacity to cope with painful events. However, with the advent of modern neuroimaging techniques, it is now possible to investigate whether the individual signature for pain determines a subject's performance in utilising a specific strategy to control pain. In addition, the assessment of the individual's specific signature appears to be even more important for patients who need to control the intensity of chronic pain states. Similarly, authors promoting individualised drug therapy for the treatment of pain [22,32,140] also take inter-individual differences into account. Differences in the processing of pain are suggested by incomplete response rates to medication. Causal and universal mechanisms of migraine-related cortical processes can be excluded by clinical data showing that Calcitonin gene-related peptide (CGRP) based medication works for many patients but not for all [31]. This is supported by functional imaging data showing a lack of activity for non-responders of CGRP medication in the spinal trigeminal nucleus and a reduced coupling between the spinal trigeminal nucleus and the hypothalamus [8]. Therefore, the assessment of the individual's cortical signature has the potential to contribute to the selection of an appropriate behavioural therapy. Hence, the selection of an individually tailored drug and behavioural treatment based on the subject's specific characteristics may help to cure chronic pain.

Neuroimaging of axonal connectivity in pain research. Plenty of studies revealed brain regions contributing to the processing of pain [123]. Imaging methods are perfectly suited to characterise the neuronal underpinnings of the preferred down-regulating of pain by means of cognitive approaches. One specific method, Diffusion Tensor Imaging (DTI) is

capable of characterising axonal connections within and between brain regions by utilising quantitative measures of diffusibility of water molecules along white matter tracts. To specifically explore pain-related connections, predefined anatomical regions - that are involved in the processing of pain - serve as seed points. Tracking algorithms detect white matter pathways between these regions and distant cortical areas. However, only a few studies have investigated the contribution of axonal connections to pain processing in healthy subjects. In a seminal work by Hadjipavlou et al. [50], the authors described connections originating from two subcortical regions transmitting nociceptive information from the periphery to the cortex. Pereira et al. [98] specifically investigated a region that is involved in top-down pain regulatory mechanisms – the ventral periaqueductal grey (PAG). The authors revealed fibre projections to the PAG from cortical pain processing regions such as the amygdala, the nucleus accumbens, the anterior cingulate cortex (ACC), and the prefrontal cortex (PFC). A further study [87] investigating visceral pain revealed direct connections from the insular cortex to ACC, thalamus, S1, S2, as well as to PFC. Other data [72] confirm that variances in white matter connections, as reflected by a change in fractional anisotropy between the dorsolateral prefrontal cortex (DLPFC) and thalamus, are correlated to how successful transcranial direct current stimulation of the DLPFC is in producing analgesia to a tonic pain experience. Further, these structural variances correlated not only with behavioural analgesia scores, but also with concomitant changes in cerebral blood flow between these regions as determined by arterial spin labelling. These data, and others from the same laboratory, support the concept that structural variation exquisitely relates to and influences how pain experiences are modulated. However, it remains unclear whether white matter connections between pain processing and pain-modulating regions transmit pain similarly for all subjects or whether inter-individual differences in white matter connections can influence the individual's ability to control pain.

Studies examining patients suffering from various pain syndromes provide some evidence that affected axonal connections are related to altered pain perception. Studies on various patients suffering from chronic pain found an abnormal diffusibility in cortical grey and white matter regions [25,43,76,120]. Goto et al. [48] provided further evidence by showing that the assessment of the cortico-spinal tract in central post-stroke patients (CPSP) predicts the efficiency of the antinociceptive treatment by means of rTMS (repetitive transcranial magnetic stimulation). These studies raise the possibility that the strength of white matter tracts may affect the perception of pain due to top-down modulatory mechanisms in health and disease. Again, yet to be determined is whether the individual pattern of the strength of white matter connections (the individual white matter

signature) between regions of the pain matrix and pain-modulating regions may affect the control of pain under specific conditions.

The individual signature of axonal connections may affect the perception of pain. Up to now previous pain research about conditional influences on pain perception predominantly pursued a population-based approach by averaging and, hence, eliminating the individual variability within groups. Fewer studies addressed the cortical and behavioural variability between single subjects and related individualised variations of brain activity to the subject's pain reports and individual characteristics as assessed by questionnaires [22,102,125]. These individual-based studies demonstrate the neuronal activity in response to painful stimuli is highly variable between subjects. It remains to be elucidated whether the strength of different neuronal pathways mediates the individual's ability to utilise a specific strategy to actively influence the perception of pain. Extending previous behavioural findings [30], I further hypothesise that due to the interaction of a given cognitive strategy with the individual cortical specifics, the participants become more or less able to control the intensity of pain. In other words, a specific cortical signature may influence the perception of pain, but may also influence the ability of that subject to control pain with different strategies. In accordance with previous findings using functional MRI, strong white matter connections originating from parietal and dorsolateral prefrontal brain regions [75,138] may contribute to an attention-related reduction of pain intensity. Relatedly, strong white matter connections from right-lateralised prefrontal regions might be related to efficient pain reduction by using reappraisal strategies [136].

1.4. Within-subject variability of the perception of tonic pain in healthy subjects

Although we know sensation is continuous, laboratory research has largely focused on the processing of short, discrete stimuli. Research on prolonged and continuously changing stimuli is vastly under-represented in the literature, in spite of the assumed higher ecological validity of this experimental approach: the experience of pain in clinical conditions usually lasts longer than brief laser pain, where the cortical response is mainly reflected by the salience rather than by the pain intensity [70]. Ongoing, continuous pain that is fluctuating in its intensity is a characteristic of many clinical conditions of prolonged acute and chronic pain and could be the standard for pain research.

Neuroimaging studies on long-lasting pain. Over the years, the neuronal processes that represent long-lasting tonic pain have been explored using various imaging techniques. Depending on the applied methods and the experimental protocol, studies exhibited very heterogeneous results by revealing the contribution of somatosensory [64], insular [112], cingulate [41,71], and prefrontal areas [65], which reflects the complexity of pain processing [2].

Coding the intensity of long-lasting pain. The experience and intensity of tonic and chronic pain can substantially fluctuate over time - within days [90], but also at a much shorter time scale [5,81]. A few studies [39,75,103] specifically addressed the subject-wise fluctuation of prolonged pain in healthy subjects. Due to the inherent limitations of the application of pain (cutaneous and intramuscular saline injection, as well as incisions), the studies could not control the intensity of perceived pain. Accordingly, these studies did not take habituation or sensitisation phenomena into account. As a result, the pain ratings gradually change over time and appear to reflect mainly habituation [39] or sensitisation [94], and experimental findings on cortical processes can report results that differ between the first and second half of the experiment [81]. Furthermore, the low-frequency aspects of perception are filtered out from the cortical data due to the required high-pass filtering of functional imaging sequences (EPI - echo-planar imaging).

1.5. Within-subject variability of the perception of chronic pain

Despite recently established innovative multidisciplinary patient care models, different sources of individual variability could explain why chronic pain treatment is incomplete [58,89]. Chronic pain often progresses into a complex disorder including emotional, social, physical and cognitive dysfunction [84]. Individualised treatment strategies not only better target pain, but also provide coping skills to address secondary psychological aspects of this pain disorder [15,53]. In order to make real progress in alleviating pain, we must first move away from old frameworks to establish new foundations in pain research and treatment.

Assessing individual patterns of chronic pain-related cortical processing. An extended network of brain regions is involved in pain processing and - even more important - in the *encoding* of pain intensity [123]. The known network consists of brain regions that show higher activity with increased pain intensity, e.g. the anterior [137] and posterior insula

[112]. Further, depending on individual social, cognitive and affective circumstances, recent opinions suggest an individually unique (connectivity) pattern of brain regions that shapes a subject's experience of pain [66,124].

This individually unique pattern of cortical pain processing is also suggested by previous EEG studies on pain processing in healthy subjects [107] and chronic pain patients [81], which explored the relationship between long-lasting pain and neuro-electric activity. Both studies found - across all subjects - that prefrontal gamma activity was significantly correlated with perceived pain intensity; but the variability between subjects was tremendous: only a minority of the participants exhibited a tight positive relationship between prefrontal gamma and pain perception. The majority of the participants had no effect and some had a negative effect. These data suggest that a treatment based on group statistics will only help the few most representative subjects. In order to maximise the outcome, future approaches must find a way to make treatments applicable to everyone.

1.6. Studies on stability and reliability of EEG and MRI recording on pain perception.

The assessment of individual signatures of pain processing requires reliable individual data. The investigation of reliability and stability of the pain encoding system involves some caveats that are mainly related to the repeated stimulation of pain. As a fundamental property of the pain system, repeated exposures to pain are considered to alter cortical processing along with plastic changes in grey matter. A VBM study found grey matter changes in pain-processing brain regions after one week of repeated painful stimulation for a group of sensitising participants [117]. Moreover, an fMRI study found the consequences of repeated painful stimulation in the prefrontal cortex in a follow-up study after one year [11].

However, all of these studies used slightly-to-moderately intense stimuli from pain-inflicting devices. In contrast, the experience of chronic pain over several months or years is presumed to involve different cortical functions from those in response to experimentally inflicted pain. As a consequence, the findings discussed previously may apply more to exogenous pain and less to endogenous tonic or chronic pain. It is widely assumed that chronic pain also changes cortical processing leading to a chronification of the pain disease [19,52]. Therefore, research needs to delineate longitudinal

within-subject designs that are targeting the stability of the encoding of endogenous pain in chronic pain patients. The assessment of individually unique cortical processes that encode the intensity of endogenous pain will provide a suitable foundation for a dedicated personalised medicine, e.g. an individually tailored neurofeedback treatment.

There is indeed convincing evidence for the stability of naturally fluctuating sensory processes in the brain. A study on sleep EEG exhibited enormous stability within subjects as opposed to the remarkable variability between subjects [16]. The signature of the spectral patterns of resting EEG was found to remain stable and specific for a period of more than one year [92]. Further studies related the specific characteristics of an individual's cortical processing to their specific genetic characteristics [37]. By investigating monozygotic twins, these studies avoid the problem of repeated stimulation and the concomitant familiarity with the stimulus material [97]. For the present investigation and based on these previous findings, high stability for consecutive measures of a single subject, but a considerable variability between subjects for the processing of endogenous pain, is hypothesised.

2. Own Work

2.1. Strategy-dependent modulation of cortical pain circuits for the attenuation of pain

Enrico Schulz[1,2], Anne Stankewitz[3], Viktor Witkovsky[4], Anderson M Winkler[1], Irene Tracey[1]

[1] Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[2] Department of Neurology, Ludwig-Maximilians-Universität München, 81377 Munich, Germany
[3] Department of Neurology, Technische Universität München, 81675 Munich, Germany
[4] Department of Theoretical Methods, Institute of Measurement Science, Slovak Academy of Sciences, 841 04 Bratislava, Slovak Republic

Published in Cortex (2019, 113:255-266)
https://doi.org/10.1016/j.cortex.2018.12.014

Publication Summary

Introduction. An important aspect of the study on pain is the conditions under which subjects experience pain relief [42,129,131]. Cognitive strategies to attenuate pain have been shown to be effective in various behavioural studies [4,73]. The neuronal processes that reflect these mechanisms are not yet fully understood. In a first step, we aimed to elucidate the cortical networks that contribute to three different cognitive approaches to attenuate pain.

Methods. We investigated pain attenuation strategies using cold pain in 20 healthy participants (18 female/4 male) with a mean age of 27±5 years (21 - 37 years). The following cognitive strategies [30] have been used: (a) non-imaginal distraction by counting backwards in steps of seven; (b) imaginal distraction by imagining a safe place; and (c) reinterpretation of the pain valence (reappraisal). The participants were asked to concentrate on the cool and tingling sensations and to reinterpret these sensations as not painful. In a non-modulated condition, the participants were asked to concentrate only on the pain. During the execution of the tasks, cortical activity was measured using a 7 T MRI scanner. The participants were prompted after each trial to rate the intensity of pain.

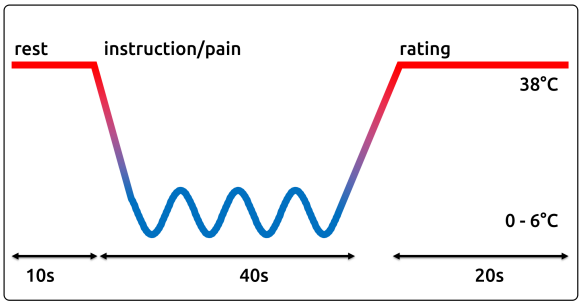

Figure 1 | Schematic time course of a single trial. After 10 s of rest painful stimulation was applied for 40 s. The pain was rated regarding intensity (10s) and unpleasantness (10s).

Data were preprocessed with FSL [57]. Linear mixed effect models were computed [139] to relate the variable pain intensities due the the application of the strategies to the variable activity of the brain.

Results. All strategies exhibited a significant relief of pain compared to an unmodulated pain condition. However, the results showed a considerable variability in performance across subjects and conditions. Among individuals, we did not find a predisposition for a certain attenuation approach: some participants performed well on all tasks and others performed low on all tasks. We further investigated the variability of performance (a) between and (b) within-subjects. We did not find a correlation of the averaged performance of the participants and the related cortical activity across trials (a). We also explored within-subjects the fluctuation of the activity of cortical regions at single trial level. Each of the three attenuation strategies (b) exhibited a different pattern of

performance-related brain activity. For example, the more successful trials showed reduced activity along the insular cortex.

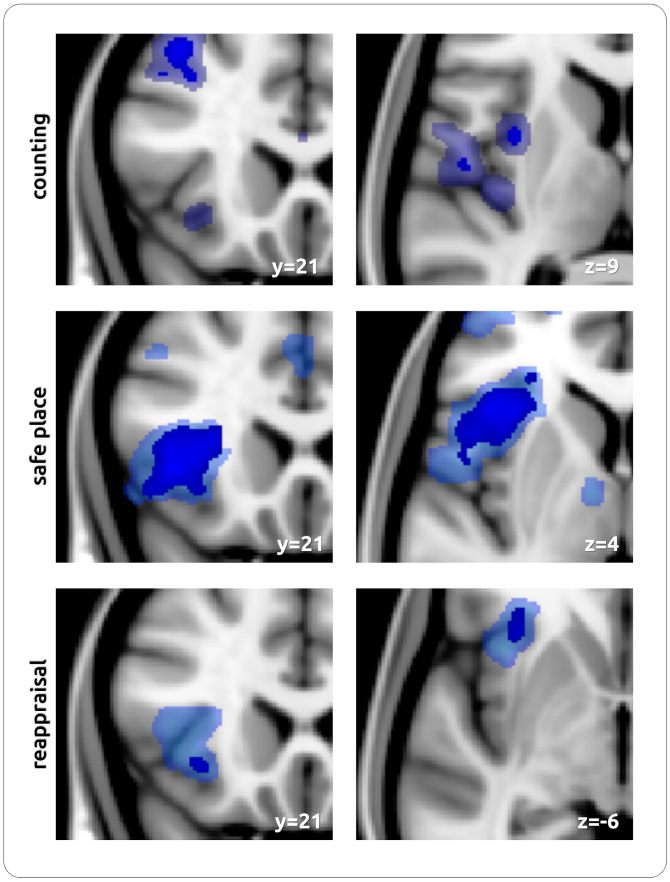

Figure 2 | The figure shows the extension of cortical modulation in the insular cortex for all three conditions. Besides PALM-corrected results (deep blue), the pale blue areas indicate a lowered statistical threshold ($p<0.001$). The "safe place" and "reappraisal" conditions exhibit a more anterior insular decrease while "counting" has a more middle and posterior insular, as well as central opercular extension.

Discussion. Among the three strategies to modulate pain, the data suggest that distraction is preferable. We revealed distinct patterns of brain regions that are suggested to reflect the modulation of the perception of pain. The results of the study may provide novel insights in the cerebral mechanisms of pain processing and pain modulation, and thus open a rich field of questions for further research, as well as new therapeutic applications. The findings could be instrumental for targeting brain regions in future attempts into the treatment of pain.

In order to do so, it needs to be elucidated whether the cortical mechanisms revealed here also apply to the processing and modulation of long-lasting pain conditions. Therefore, a follow-up study is necessary to investigate whether the present results also apply to pain patients. As an essential part of the multimodal therapy for chronic pain, patients may also benefit from additional neurofeedback techniques by using one of the cognitive strategies to directly modulate pain-related brain activity.

2.2. Ultra-high-field imaging reveals increased whole brain connectivity underpins cognitive strategies that attenuate pain

Enrico Schulz[1,2], Anne Stankewitz[2], Anderson M Winkler[1,3], Stephanie Irving[2], Viktor Witkovsky[4], Irene Tracey[1]

[1] Wellcome Centre for Integrative Neuroimaging, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[2] Department of Neurology, Ludwig-Maximilians-Universität München, 81377 Munich, Germany
[3] Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, USA
[4] Department of Theoretical Methods, Institute of Measurement Science, Slovak Academy of Sciences, 841 04 Bratislava, Slovak Republic

Published in Elife (2020, 9:e55028)
https://doi.org/10.7554/eLife.55028

Publication Summary

Introduction. The project aimed to identify neuronal structures that facilitate cognitive mechanisms to actively control pain. There are some lines of evidence that the strength of connections in the central nervous system influences the perception of pain [116,130]. Recent research in humans and animals has shown that the transmission of pain signals from the periphery to the brain is already modulated at spinal level [115]. Top-down connections that originate from prefrontal and limbic regions synapse with neurons in the spinal cord to inhibit the transmission of pain [12,36]. There is further evidence that the strength of functional and structural connectivity between regions within the cerebral cortex determines the intensity of perceived pain [72,102].

Methods. We investigated pain attenuation strategies using cold pain in 20 healthy participants (18 female/4 male) with a mean age of 27±5 years (21 - 37 years). The following cognitive strategies have been used: (a) non-imaginal distraction by counting backwards in steps of seven; (b) imaginal distraction by imagining a safe place; and (c) reinterpretation of the pain valence (reappraisal). The participants were asked to concentrate on the cool and tingling sensations and to reinterpret these sensations as not painful. In a non-modulated condition, the participants were asked to concentrate only on the pain. During the execution of the tasks, cortical activity was measured using a 7 T MRI scanner. The participants were prompted after each trial to rate the intensity of pain. Data were preprocessed with FSL [57]. The connectivity analysis was conducted as a whole-brain approach by subdividing the cortex into 360 regions [44] plus 11 subcortical regions. Functional connectivity was computed between all regions and trials. Linear mixed effect models [139] were computed to relate variable cortical connectivity to variable pain ratings at single trial level. The variability can be attributed to the fluctuating success of the application of the strategies. A diffusion weighted sequence was recorded to explore the strength of structural connectivity between the 371 brain regions.

Results. Our whole-brain approach showed across all conditions that a higher performance of pain attenuation was predominantly associated with higher functional connectivity. Consequently, we also observed an association between low pain and high connectivity for regions that belong to the core areas of pain processing, i.e. the insular and cingulate cortices. The results also showed an increased connectivity of *task-processing* brain regions is related to particularly effective attempts to attenuate pain (see [109].

All strategies showed a distinct pattern of pain-attenuation related cortical connectivity. For the counting condition, we found that some regions showed a particularly strong

connectivity: various subregions along the right insula, the left and right temporal cortices, the left parietal cortex, as well as higher order visual regions in occipito-temporal areas.

For one of the cognitive strategies (imaginal distraction), the performance of pain attenuation for some connections could be explained by measures of structural connectivity. This applies especially to connections between frontal regions and the secondary somatosensory cortex. The advantage of performance of some participants could be attributed to their stronger structural connectivity. Strong structural connectivity may enable these participants to better modulate the attenuation-related use of functional connections.

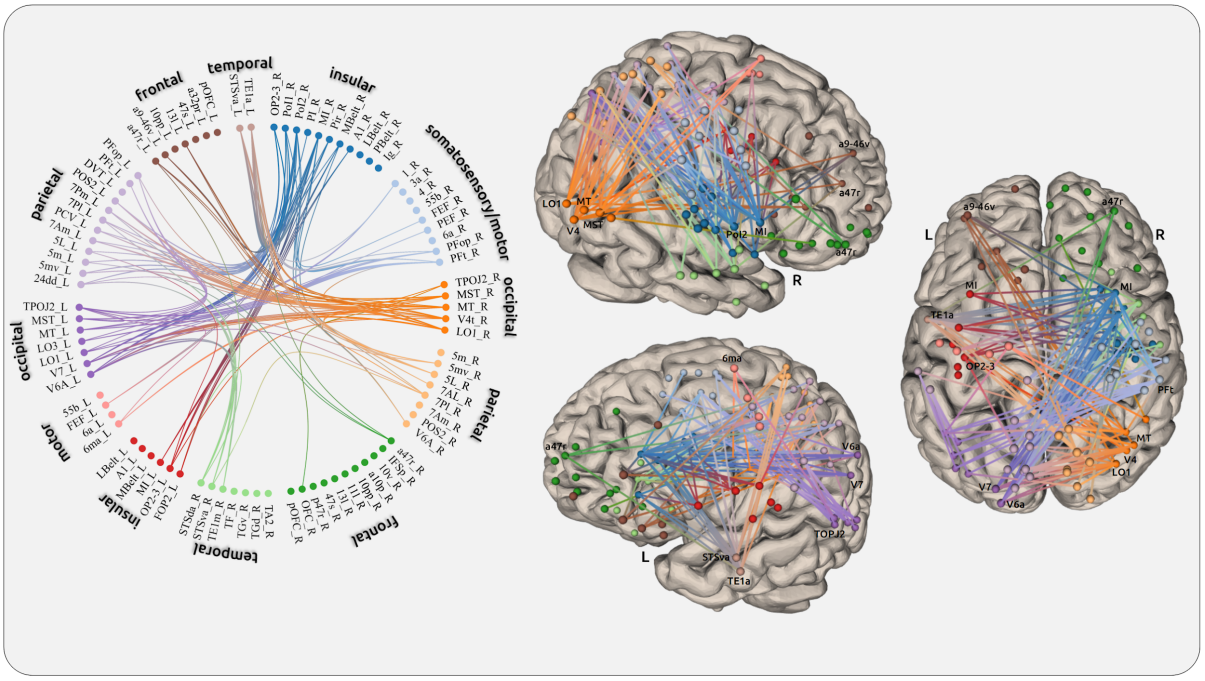

Figure 3| The connectivity plots show the statistical results of the counting condition. We selected 89 regions that showed at least 3 significant connections in any of the 3 conditions.

Discussion. The project aimed to explore whether the capability to reduce the intensity of perceived pain depends on functional as well as hard-wired connections in the brain. The whole-brain approach enables a complete and precise determination of the contributing brain regions. Therefore, the results of the study have provided novel insights in the cerebral mechanisms of pain processing and pain modulation. The findings open a rich field of questions for further research, as well as new therapeutic applications. A next step would be the adaptation of the design for further research on pain modulation and pain attenuation in chronic pain conditions. An increasingly refined assessment of a patient's unique cortical fibre connections and functional connections could help in the design of individually-tailored strategies to maximise therapeutic outcomes in the treatment of pain.

2.3. Intrinsic Network Activity Reflects the Ongoing Experience of Chronic Pain

Pauline Jahn[1]*, Bettina Deak[1]*, Astrid Mayr[1,4], Anne Stankewitz[1], Daniel Keeser [3,4], Ludovica Griffanti [5], Viktor Witkovsky [6], Stephanie Irving [1], Enrico Schulz[1,2]

[1] Department of Neurology, University Hospital LMU, Ludwig-Maximilians-Universität München, Munich, Germany

[2] Department of Medical Psychology, Ludwig-Maximilians-Universität München, Munich, Germany

[3] Department of Psychiatry, University Hospital LMU, Ludwig-Maximilians-Universität München, Munich, Germany

[4] Department of Radiology, University Hospital LMU, Ludwig-Maximilians-Universität München, Munich, Germany

[5] Wellcome Centre for Integrative Neuroimaging, Department of Psychiatry and Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

[6] Department of Theoretical Methods, Institute of Measurement Science, Slovak Academy of Sciences, Bratislava, Slovak Republic

Published in Scientific Reports (2021; 11(1):21870)
https://doi.org/10.1038/s41598-021-01340

Publication Summary

Introduction. There are a number of studies investigating intrinsic network activity which reveal altered cortical connectivity in chronic pain patients. These studies predominantly analysed the spatial distribution and the strength of the individual cortical network [1,7]. Altered cortical processing in chronic pain conditions has been reported for a number of networks. These studies compared patients with a healthy control group. In one study, chronic back pain patients showed decreased connectivity within brain regions of the DMN, i.e. the medial prefrontal cortex, and increased connectivity of the precuneus and the right lateral parietal region [7]. Another study revealed a stronger DMN-insula connectivity for chronic back pain [74]. Other studies investigated the salience network (SN). Kim et al. found a significant cluster of increased functional connectivity in the SN of patients with a chronic regional pain syndrome [63]. Chronic migraineurs also showed the opposite result, which is a decreased intrinsic connectivity of the SN [1]. In a novel approach, we analysed the progressively evolving time course of such chronic pain related intrinsic functional networks.

Methods. The study included 20 chronic back pain patients and 20 chronic migraine patients in repeated sessions (156 fMRI sessions in total). During the recording of cortical activity, the patients were asked to continuously rate the intensity of their endogenous pain. Data were preprocessed with FSL [57]. In the first step, intrinsic networks were defined by computing an independent component analysis within each patient group. A dual-regression approach extracted the time courses of the components for each chronic back pain and chronic migraine patient. Using linear mixed-effects models [139] we related the fluctuating strength of the intrinsic network to the time course of subjective pain ratings.

Results. For CBP and CM we found an average rating of 39 (±14) and 40 (±15), respectively. The pain ratings within each session were substantially fluctuating, as reflected by a high variance over the 25 min of recording: σ^2=109.3 (±126.6) for CBP and σ^2=93.3 (±62.8) for CM. For CBP, pain intensity was encoded in the salience network (the frontal operculum, the ACC, the paracingulate cortex) and in a local pontine network through a positive relationship. A negative relationship with pain intensity was found for the anterior and posterior default mode network (angular cortex, lateral occipital cortex, precuneus, PCC, nucleus accumbens, nucleus caudatus, subcallosal cortex, orbitofrontal cortex, frontal

pole, and the temporal pole). There was no effect for the change of the direction of pain intensity for CBP. The results for the pain-related activity of intrinsic functional networks for CM showed a negative relationship with pain intensity with a wide-spread network that includes the frontal pole, the precuneus and the PCC. There was no effect for the change of the direction of pain intensity for CM.

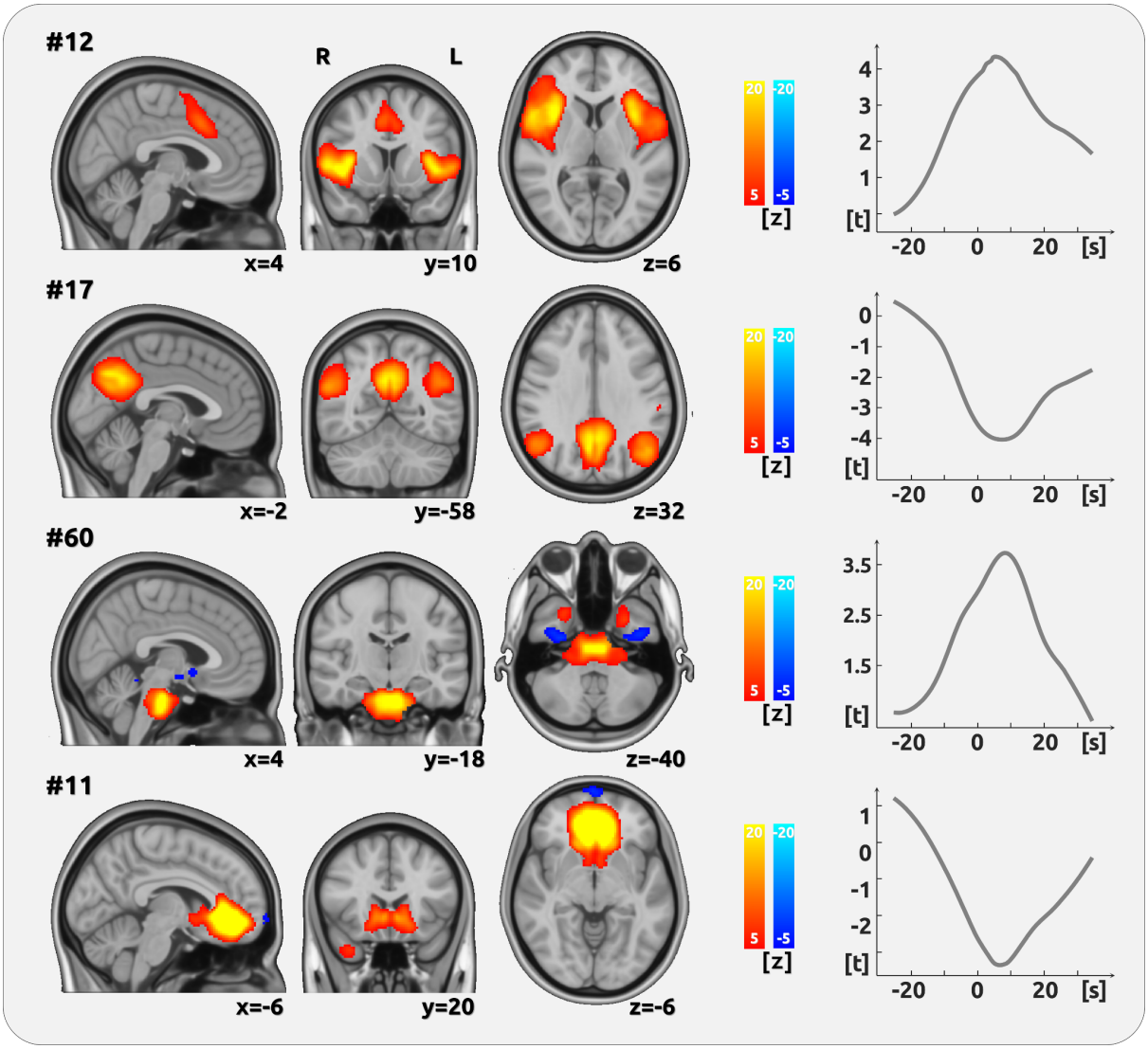

Figure 4 | Encoding of pain amplitude for CBP. The figure shows a prefrontal network whose time course exhibited a negative relationship with the time course of pain. The right side exhibits the timing of the relationship. The graph shows the results of the shifts between – 25 and 35 s in relation to the current rating (0 s).

Discussion. Here, we were taking an individual perspective and focused on the variability of the subjective perception of pain. Such dynamic aspects of the pain experience, which include phases of relatively low pain and phases of relatively high pain, can be considered as the core of the patient's suffering from pain disease. The novelty of the approach may spark future investigations into the impact of cognitive (e.g. attention) and physiological variations (e.g. autonomic responses) on pain-related activity in intrinsic networks.

Furthermore, the assessment of ongoing endogenous pain can be a promising tool to follow the success of pain-treatments: therapies that gradually lower the patient's suffering from pain should also cause a gradual decrease of pain-related intrinsic network activity.

2.4. Intrinsic Network Activity Reflects the Fluctuating Experience of Tonic Pain

Bettina Deak[1], Thomas Eggert[1], Astrid Mayr[1,3], Anne Stankewitz[1], Filipp Filippopulos[1], Pauline Jahn[1], Viktor Witkovsky [4], Andreas Straube[1], Enrico Schulz[1,2]

[1] Department of Neurology, LMU University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany

[2] Department of Medical Psychology, Ludwig-Maximilians-Universität München, Munich, Germany

[3] Department of Radiology, LMU University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany

[4] Department of Theoretical Methods, Institute of Measurement Science, Slovak Academy of Sciences, Bratislava, Slovak Republic

Published in Cerebral Cortex (2022; 32(18):4098-4109)
https://doi.org/10.1093/cercor/bhab468

Publication Summary

Introduction. Research on pain has largely focused on the processing of short, discrete pain using laser stimuli. The cortical response is suggested to reflect the salience aspects rather than the pain experience [70]. Studies on more natural pain, which is long-lasting and continuously changing, are scarce. The studies [26,39,75,94,103,112] on prolonged pain in healthy subjects exhibit inherent limitations due to the uncontrolled application of pain (cutaneous and intramuscular saline injection, as well as incisions). As a result, these studies could not take habituation or sensitisation phenomena into account.

Methods. Using fMRI, we recorded the tonic pain processing in 38 participants in a longitudinal study across 4 sessions. The participants were asked to continuously rate the intensity of applied tonic heat pain for 20 minutes. The time course of stimulation followed four different predefined and balanced trajectories of pain intensity. In order to do so, the applied stimulus temperature needed to be adapted quickly and continuously. We have developed a Matlab-based software controller that kept the pain at a predefined level. The software algorithm implicitly controlled for cortical and peripheral habituation/sensitisation, variable thermodynamics of the underlying tissue, and peripheral (adaptation of peripheral nerves) processes. For most participants, non-adapted stimulation at a constant level would lead to unbearable pain (at the end of the experiment) or no pain at all (at the beginning of the experiment).

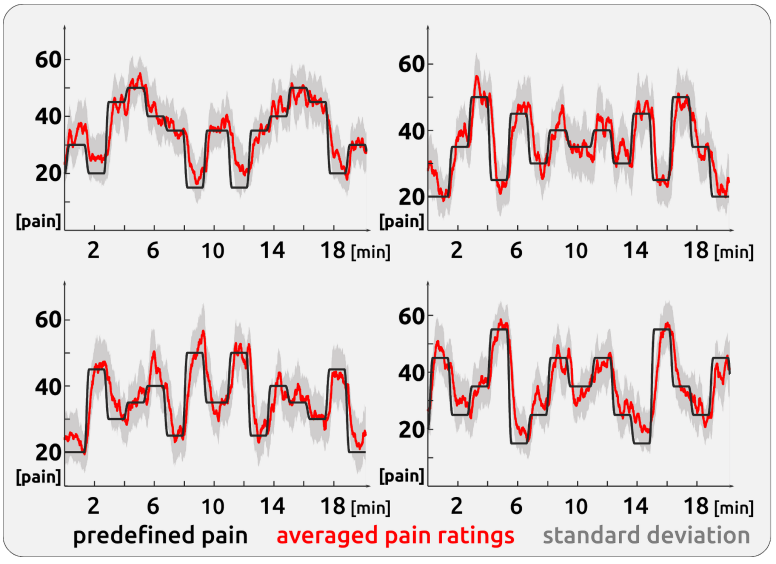

Figure 5 | Time course of painful stimulation. The figure depicts the pain time courses of the 4 sessions that were to be experienced by the participants. The controlled application of heat confirmed the success of the software algorithm; the participants largely experienced and rated the inflicted pain according to the predefined time course. The standard deviation reflects the often unpredictable dynamics of subjective pain perception.

During the recording of cortical activity, the patients were asked to continuously rate the intensity of their endogenous pain. Data were preprocessed with FSL [57]. In the first step, intrinsic networks were defined by computing a group-wise independent component

analysis. A dual-regression approach extracted the time courses of the components for each participant. Using linear mixed-effects models [139] we related the fluctuating strength of the intrinsic network to the time course of subjective pain ratings.

Results. The applied heat was continuously controlled in order to follow the predefined time course of subjective pain.

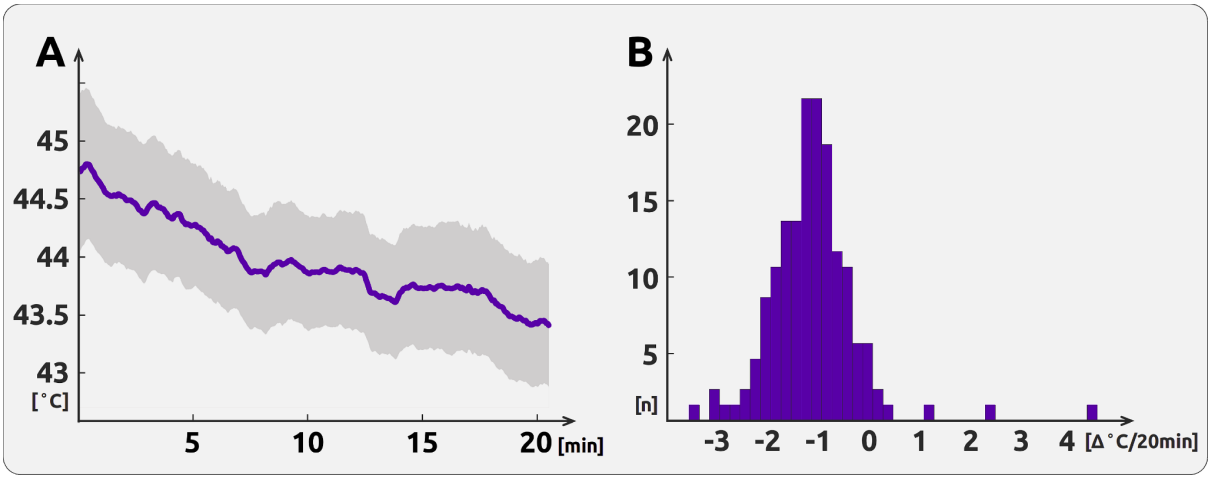

Figure 6 | Time course of the pain ratings. The left figure (A) shows the averaged time course of thermode temperature across the 20 min of painful heat pain stimulation. The blue line represents the mean for each time point; the grey area is the standard deviation. The histogram on the right (B) confirms a habituation for only 7 out of 152 sessions. For most of the sessions (n) the participants sensitise. The averaged thermode temperature was 44 °C (±0.5 °C, mean and standard deviation across the 152 sessions' 20 min average). Sensitisation to pain stimulation caused an average drop of temperature by 1.13 °C (±0.88 °C) across the 20 min of stimulation.

The analysis of the imaging data showed a dissociation of the cortical patterns of objective (temperature) and subjective (pain intensity/changes of pain intensity) processes in the human brain. Two somatosensory networks with distinct functions were revealed. One network (in bilateral SI) encodes the small fluctuations in temperature, whilst a second right-lateralised network (SI, SII, the PCC, and the thalamus) encodes the intensity of the subjective experience of pain. Consequently, the results show cortical dynamics in the somatosensory cortices that build up towards a current subjective percept of pain. We could disentangle a cascade of subsequent processing steps from the cortical registration of temperature change, the encoding of perceived change in pain perception, to the encoding of the current magnitude of pain. A posterior DMN (see below) encoded the change of temperature before the participants were consciously noticing a change in pain.

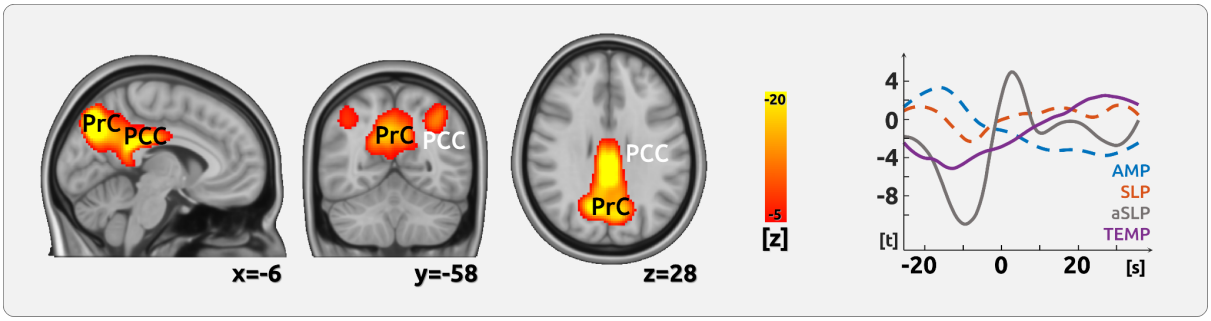

Figure 7 | Encoding of pain processing. The figure shows an intrinsic functional network that encodes the applied temperature (TEMP). The left side depicts the spatial characteristics of the networks; they were defined by the ICA. The graph on the right shows the timing of the network activity in reference to the current pain rating at time point 0s.

Discussion. In a novel paradigm we aimed to approximate the cortical processing of a more natural processing of long-lasting pain. We have disentangled the objective (temperature) and subjective (pain rating) aspects of the cortical processing of tonic pain. The analysis of intrinsic networks revealed distinct processes that contribute to the encoding of subjective and objective experimental entities. The data show a cascade of preceding and succeeding processes that flank the current moment of the evolving stream of conscious pain perception. Future studies are needed to explore how cognitive factors specifically influence certain networks in order to modulate the experience of pain.

2.5. Patients With Chronic Pain Exhibit Individually Unique Cortical Signatures of Pain

Astrid Mayr[1]*, Pauline Jahn[2]*, Anne Stankewitz[2], Bettina Deak[2], Anderson Winkler[3], Viktor Witkovsky[4], Ozan Eren[2], Andreas Straube[2], Enrico Schulz[2,5]

[1] Department of Radiology, University Hospital LMU, Ludwig-Maximilians-Universität München, Munich, Germany

[2] Department of Neurology, University Hospital LMU, Ludwig-Maximilians-Universität München, Munich, Germany

[3] Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, USA

[4] Department of Theoretical Methods, Institute of Measurement Science, Slovak Academy of Sciences, Bratislava, Slovak Republic

[5] Department of Medical Psychology, Ludwig-Maximilians-Universität München, Munich, Germany

Published in Human Brain Mapping (2022; 43(5):1676-1693):
https://doi.org/10.1002/hbm.25750

Publication Summary

Introduction. Chronic pain can be characterised as a multidimensional experience that has a profound impact on the physiological and psychological state of an individual [5,88]. Cortical data show a hypersensitisation of nociceptive neurons [45] and a reduced endogenous inhibition of the nociceptive system [35,54,118]. The current view considers the transition from acute to chronic pain as a maladapted cortical process [100,104]. However, the neural mechanisms that underlie the process of chronification are poorly understood. Previous studies have attributed the amygdala, the medial prefrontal cortex, and the nucleus accumbens as important key regions [52,77]. The cortical regions that are involved in the processing of chronic pain have primarily been investigated with experimentally-applied exogenous pain [6,46,111,127]. However, the application of experimental pain to patients and investigating pain-unspecific cortical networks at rest may reveal cortical processes that are not necessarily at the core of the pain disease.

Methods. The study included 20 chronic back pain patients and 20 chronic migraine patients in repeated sessions. During the recording of cortical activity, the patients were asked to continuously rate the intensity of their endogenous pain. Data were preprocessed with FSL [57]. Using linear mixed-effects models [139], we related the fluctuating strength of voxel-wise activity to the time course of subjective pain ratings. From the time courses of pain ratings, we disentangled the cortical encoding of the pain amplitude (AMP) from the cortical processing of changes in pain intensity (SLP). We analysed the data at group level (156 fMRI sessions in total) and at the individual level (4 fMRI sessions per patient).

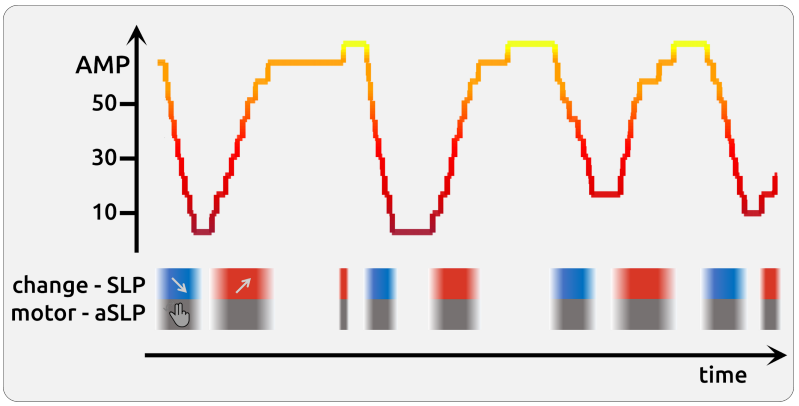

Figure 8 | Schematic illustration of a 5 min fluctuating time course of pain rating.

Results. In the first step, we were analysing the data in a classical fashion at group level. The results for chronic back pain patients show that the intensity of pain is encoded in the anterior insular cortex, the frontal operculum, and the pons (AMP). In addition, the change

of pain in chronic back pain and chronic migraine patients is mainly encoded in the anterior insular cortex.

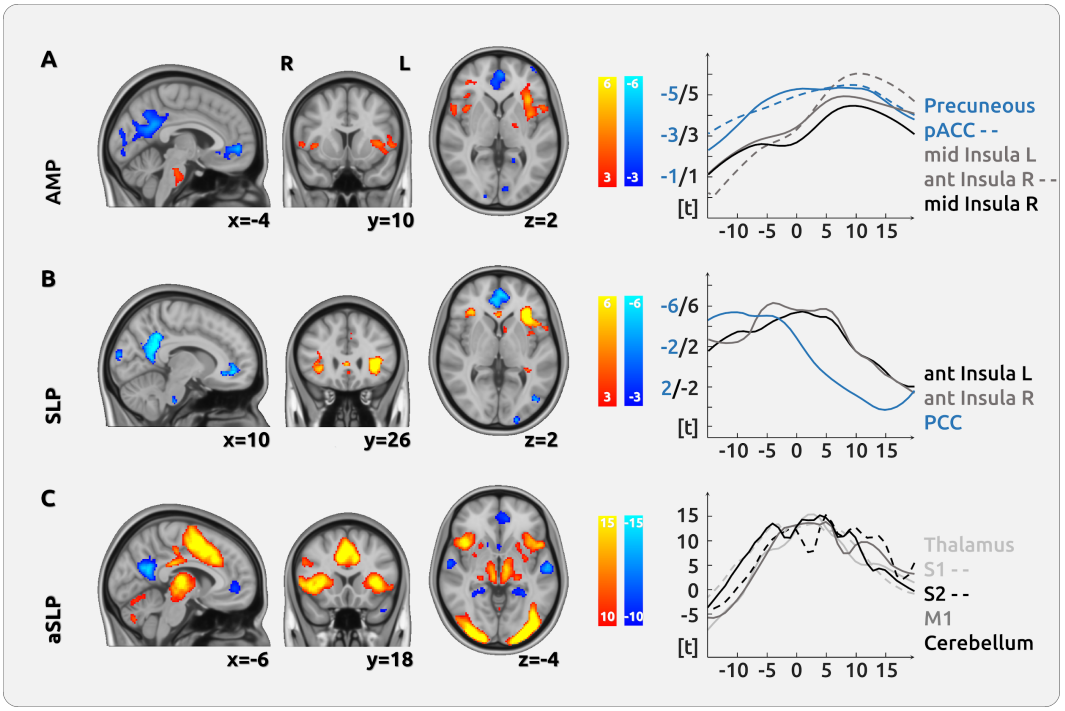

Figure 9 | Cortical processing of ongoing chronic pain in CBP. (A) The upper row shows the cortical encoding of the endogenous pain intensity (amplitude - AMP). (B) The middle row shows the processing of changes of pain intensity (slope - SLP). (C) The movement process, which prerequisites motor activity and decision making (absolute slope - aSLP), is shown in the bottom row. The graphs on the right show the temporal dynamics of the haemodynamic delay for several regions in relation to the current pain rating (at time point 0 s).

The core of the study is the analysis at the individual level. Here, we identified a more complex picture. Most of the patients exhibited a pattern of pain encoding that does not match the findings at group level. In order to increase the reliability of the individual findings, we tested the patients four times. This means that the group results appear to be driven by a few participants. We propose that each patient exhibited their own signature of endogenous pain encoding.

Discussion. Initially, we had expected that the individual results would show gradual changes from commonly activated brain regions, as revealed by the group statistics, as well as a greater similarity of pain processing within a group than between both pain groups. The results show that this is not the case and the individual findings show a broad range of cortical activity patterns. The diversity of the individual cortical signatures adds to the understanding of chronic pain as a complex and multifaceted disease. The neuroimaging results reflect the complexity of clinical observations. We deliberately decided against including the behavioural variables into the statistical analysis as any potential finding would likely join the myriad of publications with unreliable results.

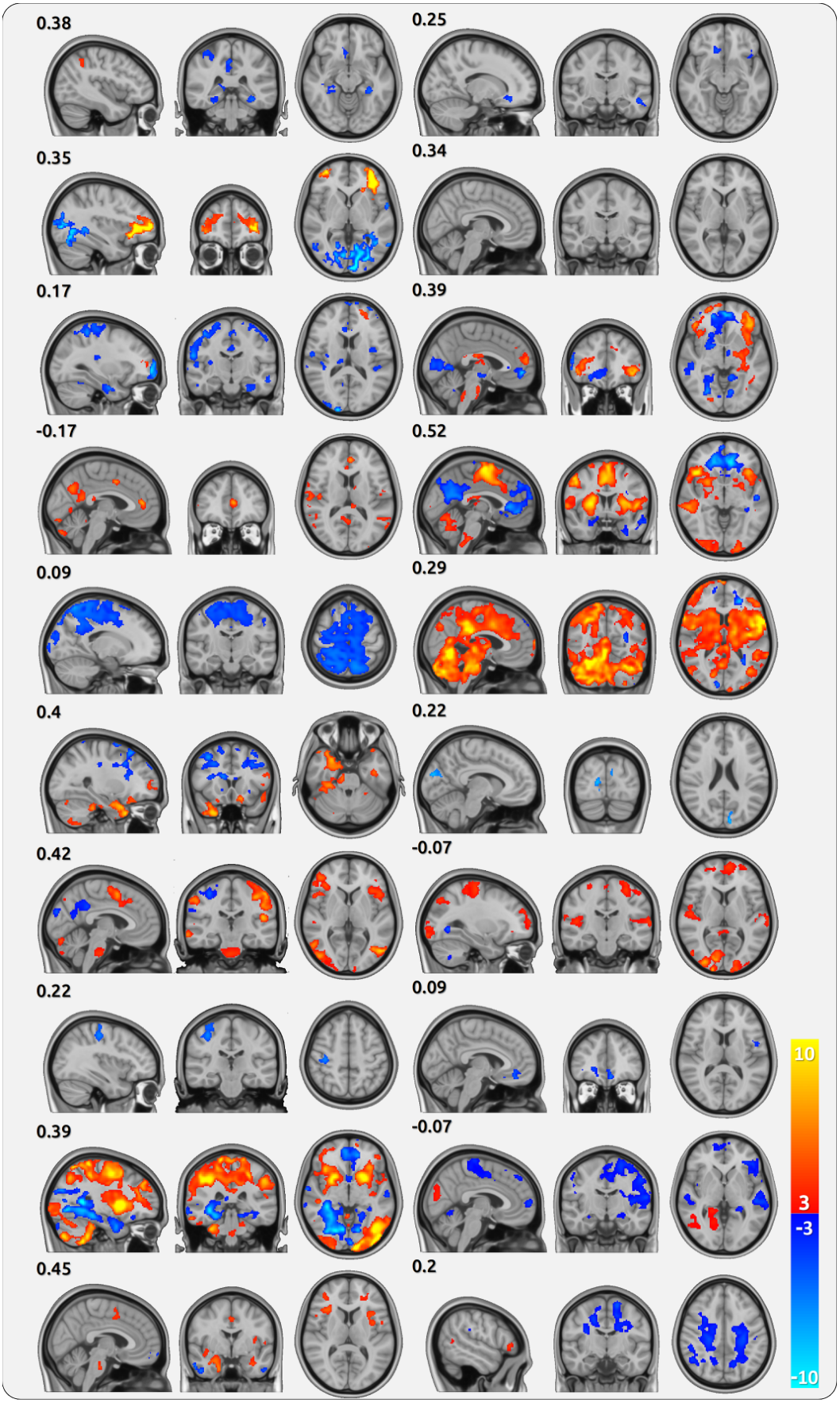

Figure 10 | Cortical processing of single CBP patients. Each triplet of maps belongs to one patient (20 in total) and shows the cortical encoding of pain (AMP) across all sessions of the patient. The numbers indicate the spatial correlation of the individual map with the group map.

2.6. Individually Unique Dynamics of Cortical Connectivity Reflect the Ongoing Intensity of Chronic Pain

Astrid Mayr[1,2], Pauline Jahn[2], Bettina Deak[2], Anne Stankewitz[2], Vasudev Devulapally[2], Viktor Witkovsky[3], Olaf Dietrich[1], Enrico Schulz[2,4]

[1] Department of Radiology, LMU University Hospital, Ludwig-Maximilians-Universität München, 81377 Munich, Germany

[2] Department of Neurology, LMU University Hospital, Ludwig-Maximilians-Universität München, 81377 Munich, Germany

[3] Department of Theoretical Methods, Institute of Measurement Science, Slovak Academy of Sciences, 841 04 Bratislava, Slovak Republic

[4] Department of Medical Psychology, Ludwig-Maximilians-Universität München, 80336 Munich, Germany

Published in PAiN (2022; 163(10): 1987-1998)
https://doi.org/10.1097/j.pain.0000000000002594

Publication Summary

Introduction. Imaging studies on chronic pain conditions have revealed altered cortical processes in the brain, e.g. changes in functional connectivity (FC), mostly in comparison to a healthy control group [86]. Deviant processes were investigated often at rest using seed-based connections of predefined brain regions [21], intrinsic cortical networks [24], and combinations of both approaches [20,91]. Although the analysis procedure in resting-state studies is relying on variable fluctuations of cortical activity, the effects are usually interpreted as stationary. By contrast, chronic pain diseases are essentially characterised by an ongoing and fluctuating endogenous pain, but the fluctuating endogenous pain has seldom been directly assessed. Specifically, it remains to be elucidated how the fluctuating endogenous pain relates to the dynamics of ongoing functional cortical connections.

Methods. The study included 20 chronic back pain patients and 20 chronic migraine patients in repeated sessions. During the recording of cortical activity, the patients were asked to continuously rate the intensity of their endogenous pain. Data were preprocessed with FSL [57]. A brain parcellation approach [44] subdivided the whole brain into 408 regions. A sliding-window whole-brain connectivity analysis for all combinations of the 408 brain regions was performed to determine the fluctuating time course of cortical connectivity for the entire brain. Using linear mixed-effects models [139], we related the fluctuating strength of cortical connectivity to the time course of subjective pain ratings. From the time courses of pain ratings, we disentangled the cortical encoding of the pain amplitude (AMP) from the cortical processing of changes in pain intensity (SLP). We analysed the data at group level (156 fMRI sessions in total) and at the individual level (4 fMRI sessions per patient).

Results. In the first step, we were analysing the data in a classical fashion at group level. The results for chronic back patients show that the intensity of pain is encoded through various cortical connections. Interestingly, most of the significant connections (41/43) were negatively related to the intensity of the endogenous pain: lower connectivity was associated with higher levels of experienced pain. We found an overall disconnection within the occipital lobe for higher pain states. Furthermore, we observed disruptions of connectivity in limbic, cingulate, and somatosensory areas. Of note, all of these 43 connections were relying on changes in positively correlated brain regions. This means that lower pain increases connectivity. We did not find any significant effect for

connections that relied on anti-correlated brain regions, i.e higher pain intensity was not associated with stronger anticorrelations between brain regions.

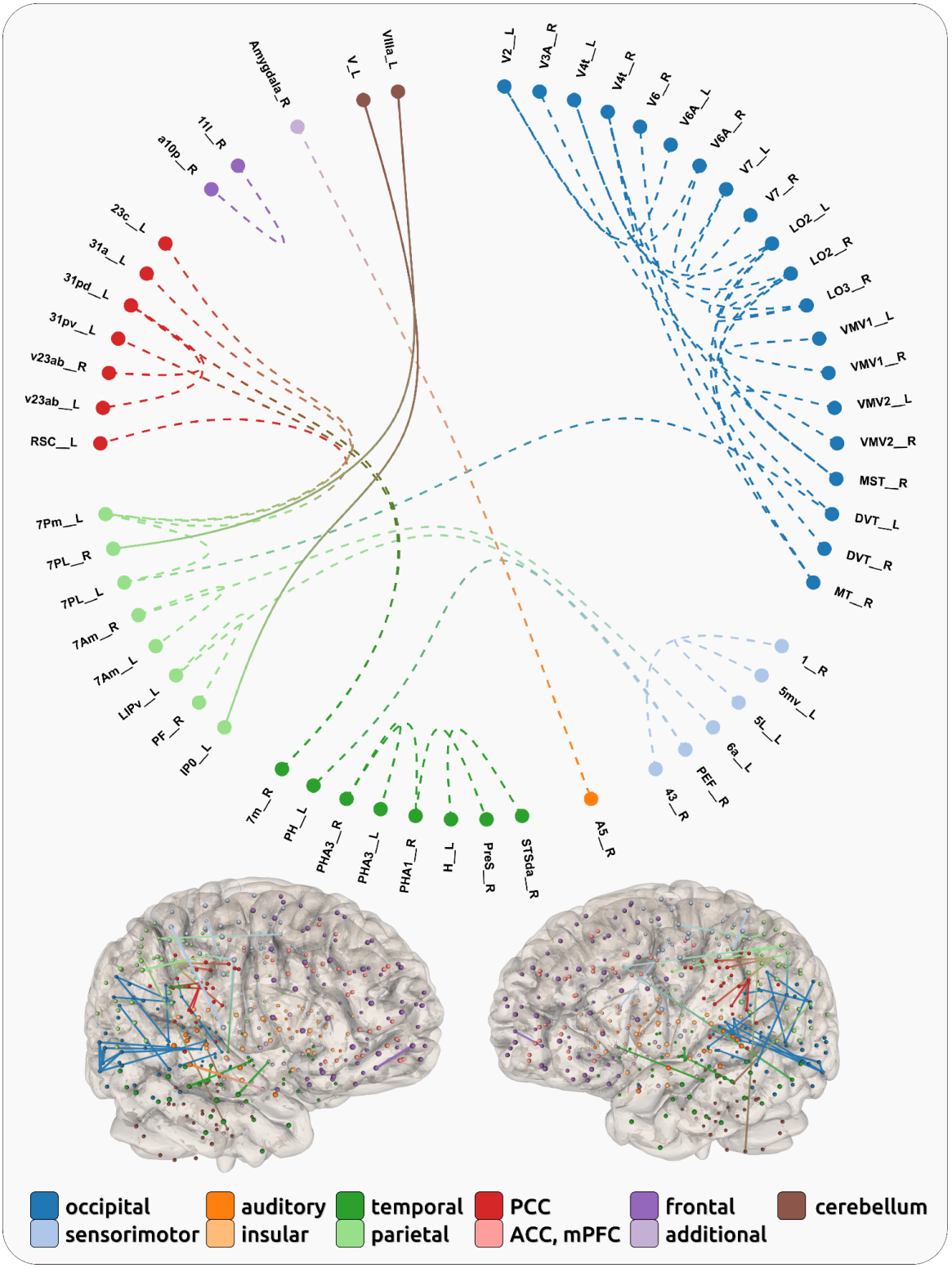

Figure 11 | Connectivity pattern for the encoding of pain intensity (AMP) across all CBP patients. Dashed lines indicate negative relationships with pain intensity; solid lines indicate positive relationships with pain intensity (link).

In a second step, we addressed the core scope of the study, which is the analysis at the individual level. Here, we identified a more complex picture. Most of the patients exhibited a pattern of pain encoding that does not match the findings at group level. In order to increase the reliability of the individual findings, we tested the patients four times. This means that the group results appear to be driven by a few participants. We propose that each patient exhibited their own connectivity signature of endogenous pain encoding.

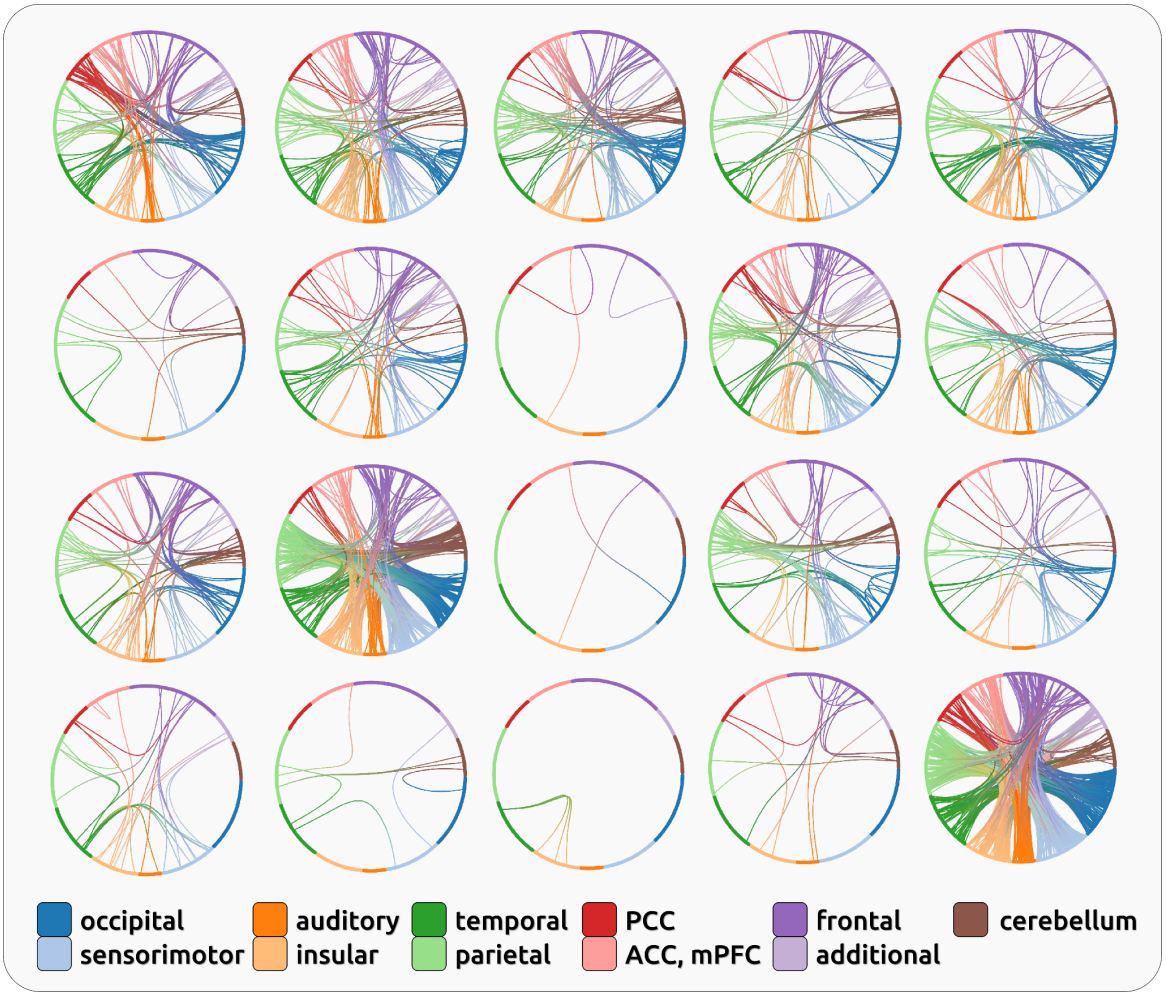

Figure 12 | Individual connectivity patterns. Circle plots for the individually-specific encoding of pain intensity (AMP) for each of the 20 CBP patients.

Discussion. Here, we found a similar result to our previous study on cortical encoding of chronic pain that was based on the BOLD effect [109]. The group results deviated substantially from the individual patterns of pain-related connectivity. Indeed, the single-subject connectivity analysis also suggests rather qualitative than gradual and quantitative differences between pain patients. The findings oppose the idea of a common neuronal core problem for chronic pain diseases [30]. The variability of the individual cortical signatures of chronic pain encoding results supports clinical observations of chronic pain as a complex and multifaceted disease.

3. General Discussion

The general discussion summarises and condenses the findings of 6 publications that are related to the encoding of pain intensity in the human brain. The studies cover a wide spectrum of mechanisms that reflect different levels of pain intensity: in healthy controls (studies 1,2,4) and patients (studies 3,5,6), during short-lasting (studies 1,2) and long-lasting pain (studies 3,4,5,6), in regard to applied (studies 1,2,4) and naturally fluctuating pain (studies 3,5,6), as well as by measuring fMRI BOLD activity (studies 1,5), functional connectivity (studies 2,6), and intrinsic network connectivity (studies 2,4). The common aspect of all manuscripts is the use of similar statistical models whose essential core is the relationship between the magnitude of fMRI-based measures and the corresponding magnitudes of pain intensity (model = fmri ~ pain_intens).

(1) The first two studies utilised cognitive strategies in order to attenuate pain in a group of healthy subjects (discussed in 8.1.). The strategies are built upon previous behavioural research indicating they are effective to attenuate pain [4,30]. These previous studies were mostly aiming at finding the best strategy to attenuate pain. The overall group statistics on the imaging data for both studies exhibited statistically significant results. The design included only a single recording per participant and did not follow the individual approach of the final two included studies. In light of these more recent studies, the group-level approach of the earlier studies can not be relied upon. For this reason, the discussion is being kept shallow and refrains from an in-depth evaluation of the outdated findings. Nevertheless, they contribute to the methodological foundation for future more reliable and meaningful research.

(2) Studies 3 and 4 were investigating the progress of pain-related intrinsic network activity in healthy controls and chronic pain patients (discussed in 8.2. to 8.5.). For these studies, many of the utilised methodological approaches on prolonged pain, as well as the combination of the methods, were relatively new in neuroimaging research. This applies, for example, to the event-free design, the shifting procedures, and the windowed connectivity analysis. The statistical model using LMEs combined the widely used so-called first-level (at individual level) and second-level (at group level) steps. For these reasons, the general discussion focuses on methodological aspects.

(3) The final two studies were utilising a dedicated subject-focussed approach (discussed in 8.6. and 8.7.). We recorded chronic pain patients across 4 fMRI sessions. The studies rely on the methodological advances of the previous studies and aimed to explore whether individuals exhibit their own cortical patterns of pain processing. We have quantified whether the cortical processing patterns of the individuals are reflected by the group statistics. The repeated recordings across several weeks provide confidence in the reliability of the single-subject findings. These studies have clinical implications as they provide methodological considerations on the selection of cortical targets for neuromodulatory techniques (e.g. neurofeedback or brain stimulation techniques).

3.1. Pain Attenuation

The rationale for studies 1 and 2 was driven by the need to find the cortical underpinnings of strategies to attenuate pain. Ideally, the best cognitive strategies could be used to support cognitive-behavioural therapies or neurofeedback interventions. As a first step, this has been investigated in healthy participants. The major advantage in comparison to previous behavioural research on pain attenuation [30,126] is that each participant applied all three cognitive strategies, which prevents potential sampling effects as a consequence of the assignment to experimental groups. Beyond the discussion of how to embed the studies in the current literature, I am giving an outlook on future studies on pain-attenuation strategies used by patients with a similar design in order to elucidate the mechanisms of psychological interventions to remedy pain.

No individual preference for a certain strategy. As shown in the two publications [108,109], we observed a superiority for two distraction strategies (counting backwards and imagining a safe place) over the cognitive reappraisal strategy. We rejected the idea of an individual preference for certain attenuation strategies between subjects, where one participant shows a clear advantage for the use of one strategy, whereas another participant may show a clear gain in performance when using a different strategy [30]. The high percentage of explained variance for a common performance factor across all strategies and subjects suggests the opposite: there is a gradient from high-performers that master all strategies, to underperformers that fail for all strategies [109]. Overall, the

performance of the strategies exceeds published effects from placebo studies, which often exclude non-responders [133,134]. This renders cognitive interventions a very promising tool to support pain treatment. It remains to be elucidated in future research whether these behavioural findings hold in a larger clinical sample.

Cognitive factors modulate pain-related brain activity. There is a large number of neuroimaging studies investigating the influence of cognitive factors on pain using different strategies (i.e. attentional shift, meditation, cognitive demand) in healthy samples [18,42,136] and pain patients [17] with various imaging techniques, different tasks, with and without specific types of pain stimulation. Although the findings diverge across studies, there's a general agreement on the involvement of parts of the insular cortex, of the perigenual ACC, and of the PAG for pain management [124], which had made these regions the first choice for neurofeedback interventions [28,105,106]. In our study, the more successful trials are related to reduced activity of different parts of the insular cortex. Pain attenuation with means of distraction by counting backwards reduced the activity of the posterior insula, whereas cognitive reappraisal reduced pain-related activity in the anterior insula [109]. However, for each of the three tasks, we found a different pattern of brain activity that reflects the performance of pain attenuation.

The study on connectivity also found different patterns of cortical connectivity for each of the three conditions [108]. The reflection of the connectivity findings in the second study, in light of the current literature, is hampered by the low number of studies on functional connectivity [101,130], as well as their methodological shortcomings. This is essentially attributed to the low amount of data points (sometimes only a single time point per trial) to provide a reliable measure of connectivity. The most surprising finding of our study is that a higher performance of pain attenuation (resulting in low pain) was predominantly associated with higher functional connectivity. This implies an association of low pain and high connectivity also for the classical pain-processing regions, i.e. the insular and cingulate cortices, which is unprecedented in the current literature. This can be attributed to the much longer analysis window (~30 s) on which the single trial connectivity estimates are relying on. The analysis is also unaffected by misleading connectivity scores driven by rising and falling pain and commonly rising and falling brain activity across brain regions. To prevent this phenomenon we were only analysing the plateau phase of the painful stimulation.

Group results may not represent single-subject cortical processes. Follow-up studies from our lab suggest a more complex picture: group results on pain encoding did not reflect most individual data, but were instead driven by a few individuals. Therefore, it is highly doubtful that the brain regions and functional connections that have been found significant in the first two studies at group level (using a single recording per participant) would be reliably detectable at subject level. Conversely, NFB studies that have used group statistics to determine target regions did not obtain an effect in the first place [105,106] or could not replicate the findings [28,119]. Nevertheless, these previous intervention studies were well-designed and were resting on the most recent and commonly accepted findings. To overcome shortcomings from intervention studies that ground their target processes on group statistics, follow-up studies require repeated recordings to reliably assess cortical processes to attenuate pain at subject level. Based on a large number of individual recordings, machine learning algorithms can determine the individual pain attenuation-related processes that are reliably present across all recordings.

3.2. Fluctuating Intrinsic Network activity Encodes Long-lasting Pain

Intrinsic networks. In recent years there is a general interest in the study of the contribution of intrinsic networks to the processing of pain. Therefore, in two publications (studies 3 and 4) we used a blind source separation approach (ICA) to determine intrinsic networks in our large dataset from healthy participants (152 recordings; [27] and chronic pain patients (2 x 78 recordings; [56]. However, unlike most studies on intrinsic network activity, we were following the temporal dynamics of each network by analysing the fluctuating time courses of the independent components. Consequently, we determined several intrinsic networks, whose amplitudes were covarying with the intensity of perceived pain (AMP variable) and the direction of changes in pain intensities (rising and falling pain: SLP variable). For a more detailed description of these variables and their differences see publications 3, 4, 5, or 6 or the general discussion in 8.3.). For chronic back pain patients, we found a positive relationship between the intrinsic network time courses and AMP, e.g. for the salience network, and a negative relationship with both subnetworks of the DNM. For chronic migraine patients, we found a positive relationship with AMP for a prefrontal network. We did not find any effect for the change-indicating variable SLP. For the encoding of tonic pain in healthy participants, the results show a more complex

picture. Here, we have an additional variable included, which is a vector of the small fluctuations of temperature (TEMP) from the thermode that delivered the heat pain. Some intrinsic networks are related to only one aspect, AMP or TEMP, e.g. a right-lateralised somatosensory network which exclusively encodes pain intensity. In contrast, a bilateral network consisting of the paracingulate cortex and the nucleus accumbens selectively encodes the fluctuations of TEMP. This means that the later network is processing different levels of neuronal input without the contribution of consciousness. In addition, we can reasonably consider the cascade-like processing for networks related to both AMP and SLP (#29, #78, #70). For example, for a network consisting of the inferior frontal, the superior temporal, and the marginal gyri, the cortical processing of the changes (SLP) always precedes the processing of intensity (AMP).

Previous research has mostly focused on analysing 3D maps of the independent component analysis. This single map for each participant does not contain any information about temporal dynamics over the recording time - such as done by Zhou et al. [141]. These maps have often been correlated with various external variables (e.g. behavioural or questionnaire scores). However, the interpretability of these 3D maps associated with questionnaire data is often not reliable and replicable [79]. Furthermore, findings on 3D maps are generally interpreted as differences in connectivity, which can not be argued against, but the data can not enlighten us on the functional relevance of such joint ongoing fluctuations of cortical activity. In contrast, network time courses - as detected by our studies - reflect the varying map strengths and indicate periods of high and low cortical activity during the scanning period; they can be meaningfully interpreted through the experimental design (tasks as well as simultaneously recorded parameters such as pain ratings of skin conductance). Moreover, studies on 3D maps ignore these fluctuations and can not reveal the functional implications of the troughs and peaks of the oscillations. This is very important because the troughs and peaks represent distinct cortical states during the recording.

Novel aspects of the analysis of intrinsic networks. In our studies [27,56], we decided to focus on the pain-related fluctuation of the components' time courses in order to explore the functional relevance of intrinsic networks. Naturally, these functional time series can not be related to single questionnaire scores, but can only be analysed in relation to other ongoing data. In our analyses, we have a clear hint of what happens during the peaks and troughs of the joint oscillations between voxels because we can relate the components' time courses to the time courses of subjective pain perception. For most networks in both studies, high intensities of pain are related to high amplitudes of intrinsic network activity. Currently, there is no other study on fluctuating intrinsic network activity related to any

ongoing behavioural measure. Consequently, the fundamental differences of our new approach do not allow any comparison with findings from 3D map-based statistics [67], which often investigate such 3D network effects between pain patients and healthy controls [91].

3.3. Dissociating the coding of pain intensity from the encoding of rising and falling pain

Independent entities encode the perception of pain. There is a common rationale in our analysis strategies for the investigation of long-lasting pain that requires a more in-depth discussion. This applies to the study of endogenous pain in chronic pain patients (studies 3, 5, and 6) and the study of tonic pain in healthy subjects (study 4). The analysis of ongoing pain can be described with three (AMP, SLP, aSLP for the study on pain patients) or four (AMP, SLP, aSLP, TEMP for the study on healthy subjects) independent entities that explain the time course of network activity [56,83]. AMP can be considered as the principal aspect and reflects the different levels of perceived pain, encoded with numbers between 0 (no pain) and 100 (highest experienced pain) in steps of 5.

Phases of increasing, decreasing, and stable pain were coded as [1 -1 0], respectively. In statistics, such contrasts are commonly used in different imaging studies to compare conditions with fMRI software packages (e.g. SPM12). When using such coding, it implies a categorical comparison and not a linear relationship. For the analysis, we were essentially contrasting rinsing [1] and falling pain [-1]. Both phases include motor activity due to the moving slider as well as decision-making processes immediately before each movement. However, these aspects apply to either phase and can be considered cancelled out for the contrast [-1 1]. The contrast between rising pain and stable pain [1 0] does not make much sense as the perception of change vs. no change is contaminated with motor activity and decision processes. In other words, the SLP variable contrasts phases of increasing pain with phases of decreasing pain. We implicitly assume that both phases have a similar underlying process regarding motor activity, decision-making, and visual processing. We further assumed that both phases differ regarding cognitive, sensory, and emotional aspects. For example, if pain relief would have a similar emotional component as increasing pain and similar activity in the amygdala, we would not detect anything. However, if pain relief has a stronger emotional component than pain increase, we would detect the cortical effect.

Introduction of a nuisance variable. For the coding of aSLP - a nuisance/junk vector, which includes motor, decision making, vision, and attention - we kept the same absolute numbers [0 1]. Here, we can not disentangle the different processes that were caught up by the aSLP vector, and thus can not interpret these results. However, this vector is of the utmost value for (a) disentangling motor/decision/vision/attention aspects from AMP and SLP, and (b) providing a quality/plausibility check: the results show a strong effect with high t-values.

One important aspect of modelling the additional aspects (SLP, aSLP, TEMP) of the pain rating process is that they explain variance in the data that is different from the principal aspect: the encoding of pain amplitude (AMP). Due to the deliberate experimental stimulation design and the advanced statistical modelling, we can assume that the AMP variable does reflect the magnitude of the subjects' perception of pain, irrespective of whether the pain is rising, falling, or stable.

3.4. The need for shifting vectors in experiments with continuously assessed behaviour

The pain rating is embedded in a number of cortical processes with variable timings. A further methodological aspect that needs a more in-depth discussion is the continuous movement of the potentiometer slider. This was required in the event-free studies 3, 4, 5, and 6. Each movement indicated a change in pain. However, each moment of change is embedded in a cascade of interwoven steps. Preceding processes can influence the current rating and the current rating can have an impact on subsequent cortical activity and connectivity. In contrast to previous work [5,52], we included the shifting because we did not know the exact timing of the processes that determine pain ratings or how they are determined by the change in pain intensity. The shifting also takes the unknown delay of the haemodynamic response into account. For example, there is a hypothetical rating with an amplitude of 45 after 3 min 25 s. The cascade of processes that led to the rating of 45 could have started at 3 min 15 s and the rating at 3 min 25 s could have influenced further functional connections after 3 min 30 s. An analysis without shifts would only analyse pain ratings and cortical connectivity from the same time point: the rating at 3 min 25 s would have been related to the cortical connectivity at 3 min 25 s, which would neglect much of what is processed in the brain.

The temporal cascade of cortical activity is disentangled through shifting. The continuous design required a shifting of the behavioural vectors in order to optimise the timing. The large lag of the shifting time range provides a good plausibility test; e.g. we shifted the behavioural vectors between -15 s and +20 s in the experiment on patients. Computing such a broad window may appear of no value but the -ideally- bell-shaped curve for some processes provides certainty for our novel approach as the relevant processes are expected within the limits of the shifts and not at the margins. During the recording of the tonic pain data from healthy subjects, it was noticeable that there is a substantial delay between the change in temperature and the change in pain ratings. This has been confirmed in the statistical analysis and can be seen on the right side of the imaging results figures 3, 4, and 5 in Deak et al. [27]; most of the significant TEMP effects occur before the time point "0" (~20 s). For this reason, we extended the shift for this study on tonic pain [27] between -25 s and +35 s.

Interpreting the time lag between vectors. Each vector (AMP, SLP, and aSLP; additionally TEMP for the studies on tonic pain) has its own statistical parameter. This is visible on the right side of the results figures, e.g. in [56]: sometimes there is a cascade of processes, where the peak of SLP is occurring before the peak of AMP. In addition, the different temporal and topographical results for AMP and TEMP in the study on healthy participants [27] show that there is no linear translation between the temperature change and the change in pain intensity: otherwise, the findings would be more or less identical. The shifted model separates the 4 vectors in time, however, this can only be interpreted within a component, which is noticeable for components #5, #7 and #55 [27]. These components show a very early effect of temperature long before the rating of the participant; it took some time before the participants realised a modification of the temperature. A further interesting component is #70: we see a negative relationship with SLP, then AMP, and finally a positive relationship with TEMP. This can be interpreted as a drop of cortical activity with high and increasing pain (negative t-value), which might indicate a slight "oversteering" of the temperature regulation (the lag makes it difficult to exactly adjust the right temperature), and requires an immediate reduction of the temperature (positive lag and positive t-value).

Double shifting for the connectivity analysis. A whole-brain exploratory approach on pain-related functional connectivity (study 6) was applied; the ongoing and windowed connectivity allows for assessing the variable dynamics of cortical connectivity during the scanning sessions. We were computing windowed correlations between the time courses from all pairs of 408 brain regions, that were based on the parcellation atlas by Glasser

[44]. The total number of analysed connections was 82824 ((408*407-408)/2 - half of the confusion matrix without the diagonal).

The shifts were permitted to vary for different connections. We applied two types of shifts. *First*, for the computation of the ongoing connectivity, we assumed a variable delay of information transfer for the *functional connectivity between two brain regions*. We systematically shifted the time course of cortical activity from -4 to 4 data points with an offset of one data point. This resulted in nine systematically shifted connectivity time courses. The fifth of the 9 shifts represents the time course of connectivity with no delay in information transfer from one brain region to the other. *Second, s*imilar to the analysis on ongoing cortical activity, we also included a *variable delay between functional connectivity and pain*. Similar to studies 3, 4, and 5, the second procedure shifts the time course of ongoing pain against the time course of ongoing connectivity. This procedure accounts for the unknown timing of cortical processing in reference to the current rating; some preceding ongoing functional connections may influence later changes in pain ratings, and other connections are immediately related to the rating behaviour, or are influenced by the rating process and are occurring afterwards.

3.5. Assessment of sensitisation in tonic pain experiments using fMRI

Assessment of cortical processes related to sensitisation or habituation is not possible. All studies investigating long-lasting cortical processes (Studies 3, 4, 5, and 6) require a balanced design with a similar amount of pain experience throughout the time course of the experiment. This means that pain ratings can not systematically increase or decrease over the time course of the recording and participants with an excessive slope of ratings had to be excluded from the study. For studies on tonic pain, the stimulation had to be adapted in a way that prevents any slope in pain ratings, i.e. in cases where the end of the experiment consists of higher pain ratings than the beginning. There are two examples from EEG studies that illustrate this issue: unlike previous work from this group [107], EEG studies by Nickel & Ploner [93,94] did not adapt the temperature, which resulted in an effect of order throughout the 10 min experiment. The pain ratings at the end were higher than the pain ratings at the beginning. The findings of the authors may have - at least partly - reflected the sensitisation of the participant instead of the encoding of pain. A further study from the same group [81] on chronic pain patients included participants with steadily increasing chronic pain. As a result, the reported effect was valid only for the first

5 minutes but was not found for the analysis of the last 5 minutes. These issues would have been more pronounced in our extended (20 and 25 min) paradigm and are even more severe for fMRI data. Sensitisation processes occur as very low-frequency drifts; the lower pain at the beginning of the experiment will induce lower pain-related cortical activity in the beginning compared to the end, where we can expect higher pain-related activity due to the higher pain. However, such effects in the data will be inevitably removed due to the mandatory filtering requirements of the fMRI sequence. Consequently, sensitisation can only be assessed indirectly as a behavioural measure in a tonic pain paradigm as the slope of the temperature time course. However, the underlying cortical mechanisms can not be investigated for the following two reasons: scanner drift and effect of order. Sensitisation is part of the stimulation (see temperature time course) but this needs to be statistically and experimentally controlled. Intermingling the encoding of pain intensity with sensitisation would have flawed the results.

Although we can not assess the cortical processes related to sensitisation, the paradigm required to take sensitisation into account. For this reason, a low number of chronic pain patients (studies 3, 5, and 6) had to be excluded from the study. In the study on tonic pain (study 4), most participants would have sensitised over the time course of one session if we had always applied the same level of temperature. In order to keep the subjective pain at a predefined level, we developed a closed-loop stimulation; the control for sensitisation in this loop resulted in a steadily decreasing temperature with small fluctuations. Due to the mandatory high-pass filtering of the MRI sequence, we were only able to investigate the small high-frequent fluctuations in the temperature time course and not the slow decline of the adapted temperature.

3.6. Individually unique and stable cortical patterns of pain processing

To date, previous pain research about conditional influences on pain perception predominantly pursued a population-based approach by averaging and, hence, eliminating the between-subject variability within groups. Fewer studies addressed the cortical and behavioural variability between single subjects and related subjects' pain reports and individual characteristics [22,23] to individual variations of brain activity. *However, the implicit interpretation of variability remains untouched: we assume a common core of cortical processing of pain with recurring contributions e.g. of the insula cortex, the ACC, and the primary somatosensory cortex.* Individual variations are considered noisy or factor-driven

variations of the group findings with more or less pronounced contributions from the core regions. Unfortunately, this is barely the case and individual maps often deviate from the common core. We have therefore investigated individual patterns of pain-related cortical processing (studies 5 and 6).

To increase confidence in the single-subject findings, we recorded each patient 4 times. Consequently, the individual cortical patterns of chronic pain-related cortical activity are not reflected by the group statistics for most participants. This is corroborated by previous EEG studies, where data from individuals do not match the overall group statistics [82,107]. For example, we explored the relationship between long-lasting heat pain and neuro-electric activity [107] and found - across all subjects - that prefrontal gamma activity was significantly correlated with perceived pain intensity; however, the variability between subjects was vast (see supplementary material of this publication): a quarter of the participants exhibited a very tight relationship between prefrontal gamma amplitude and pain perception. A further third of the participants did not show any relationship or had a negative relationship between gamma activity and pain. In further studies on the processing of brief laser stimuli, the results were driven by a subgroup of participants who exhibited a gamma response [110,122].

Individually unique and stable cortical patterns of pain processing. The individually unique processing of pain in the human brain was addressed in two studies (5 and 6). We found substantial differences regarding the patterns of activated brain regions and connections between subjects. Many chronic lower back pain patients were using the perigenual ACC to encode pain, other patients were utilising different subregions of the insular cortex, and further patients were processing pain in the posterior cingulate cortex. However, in all participants, we found a substantial contribution of a number of brain areas that are not necessarily known to be related to the processing of pain. Moreover, many of the chronic pain patients did not show any activity in the insular cortex or the cingulate cortex. The computed spatial correlations indicate that individual maps are not slight variations of the group statistics. None of the patients exhibited such a group pattern of cortical activity. These findings challenge current attempts to suggest gamma oscillations as a cortical biomarker for chronic pain [14].

An individual's unique signature of pain could support therapeutic decisions. Authors have promoted individualised pharmacological therapy for the treatment of pain [22,32,140], which entails taking into account markers of inter-individual differences. The selection of an individually tailored drug and cognitive/behavioural treatment based on the subject's specific characteristics may help to treat chronic pain. For neuroimaging research,

individually unique cortical patterns need to be found that reflect the individual modulation of pain and are stable enough to monitor the treatment progress. These unique patterns of stable processes are considered to serve as modifiable targets for therapies, e.g. individually tailored neurofeedback training, cognitive-behavioural intervention or pharmacological treatment. Therefore, the assessment of the individual's cortical signature may serve as a tool for an appropriately tailored therapy for each and every patient.

Individual stable patterns. The question that has not been answered so far is, which of the individual processes are stable and reliable across repeated sessions. Only recurring processes can be reliably targeted in neuromodulatory interventions. Machine learning tools would be able to specifically address this question. In case there is sufficient stability of a potentially suited cortical process, it allows the algorithm to predict the intensity of pain from unknown cortical data of a patient with the highest accuracy. According to the theory of individually specific maps, the learned parameters would only be applicable to the same subject.

3.7. Outlook - impact of studies testing the uniqueness of subject-specific patterns

An individual perspective on cortical processing. It has been known for a long time that factors linked to genes and development can shape the features of the brain [38,55,121]. However, how these features relate to the way individuals are processing tasks has not caught much attention so far. The first work on individually unique cortical processes in neuroimaging dates back to as early as 2009. A study on a series of memory retrieval tasks found unique cortical activity patterns across individuals that were not reflected by the group statistics [85]. Interestingly, these patterns were stable over several months. A similar approach to obtain individual profiles with several recordings from the same individuals has also been pursued by the Midnight Scan Club initiative (MSC - twitter.com/club_scan) for research on resting-state data on the basal ganglia [49], the cerebellum [78] and the neocortex [47]. The work by this group is considered as an important contribution to the understanding of human cortical processing [29]. Doubts on neuroimaging findings of group results arose, but many of these doubts have been addressed in the context of statistics and data processing [9,10].

As mentioned above, findings on individual variations of cortical processing are explained by associated factors. The goal to explain individual cortical variations with external factors such as questionnaires has two implications. *First,* it drives neuroimaging studies to large samples, because only large sample sizes provide enough statistical power and reliability [79]. *Second*, such approaches to explain interindividual variability implicitly consider individual variations as either noise or explainable by other dimensional factors. As discussed above, the latter implies a "common mode" of cortical processing for a certain task that is being gradually modulated by an army of external factors. For the research on pain, there are a number of studies using behavioural or epidemiological variables to explain individual differences and implicitly assume that variations are gradually different, e.g. differences in the cortical processing of chronic pain are thought to be explained by pain intensity, catastrophising scores, or disease years. However, this might not be the case and the currently neglected "gestalt" of the individual cortical activity patterns may deviate substantially from the pattern of the group statistics. On the one hand, this is questioning whether it is meaningful to assume a common mode of cortical processing across individuals. On the other hand, approaches on qualitative differences with distinct individual cortical processing patterns have rarely been pursued so far [9,83].

3.8. Outlook - applying the concept of an individual signature of pain

Future projects should be aimed at combining two lines of pain research and connect seamlessly to previous studies on individually unique cortical processes: The mandatory next step would be to investigate the applicability as well as the cortical underpinnings of pain attenuation strategies in pain patients. A longitudinal within-subject design across multiple recordings should be investigating the stability of the underlying individually unique cortical processes to attenuate endogenous pain in chronic pain patients.

Neurofeedback. Neurofeedback training is a particularly promising and innovative approach to self-management in order to attenuate the suffering from pain. Using NFB, one learns from their own brain activity how to modulate future brain activity [59,135]. Due to the high temporal resolution, the almost negligible delay, and the feasibility of the method, EEG has been widely employed for NFB on pain [59]. However, the number of studies aimed to alleviate pain is limited and the theoretical foundation for the chosen approach to target alpha activity is tenuous at best [58,61]. Other studies have explored

the possibility to influence pain perception with means of real-time functional Magnetic Resonance Imaging (fMRI). DeCharms and colleagues [28] targeted the anterior cingulate cortex (ACC) to feedback the activity of this region to healthy controls and patients. After initial success, the authors could not replicate their results in a follow-up study [119]. In two other recent NFB studies, the authors were also not able to attenuate the intensity of perceived pain [105,106]. Taken together, NFB studies have not yet been successful to alleviate pain.

In line with the concept of an individually specific "signature of pain", an innovative NFB approach should explicitly target those pain-related processes that are relevant to an individual subject. However, the low signal-to-noise ratio and potential fluctuations of cortical processing make the assessment of a single subject's cortical pain signature tremendously challenging. A reliable assessment of cortical processing with repeated recordings is mandatory in order to disentangle a subject's stable signature from random fluctuations of brain activity that are valid only for a single measure. These patterns of stable processes are considered to be unique for each subject and can be utilised to serve as a basis for a more successful, patient-centred, and individualised treatment of chronic pain with methods that are developed for the modulation of cortical processes (e.g. NFB training, electrical, or magnetic brain stimulation).

4. References

[1] Androulakis XM, Krebs K, Peterlin BL, Zhang T, Maleki N, Sen S, Rorden C, Herath P. Modulation of intrinsic resting-state fMRI networks in women with chronic migraine. Neurology 2017;89:163–169.

[2] Apkarian AV, Bushnell MC, Treede R-D, Zubieta J-K. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9:463–484.

[3] Asghari A, Nicholas MK. Personality and pain-related beliefs/coping strategies: a prospective study. Clin J Pain 2006;22:10–18.

[4] Baker SL, Kirsch I. Cognitive mediators of pain perception and tolerance. J Pers Soc Psychol 1991;61:504–510.

[5] Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, Apkarian AV. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci 2006;26:12165–12173.

[6] Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. Neuron 2010;66:149–160.

[7] Baliki MN, Mansour AR, Baria AT, Apkarian AV. Functional reorganization of the default mode network across chronic pain conditions. PLoS One 2014;9:e106133.

[8] Basedau H, Sturm L-M, Mehnert J, Peng K-P, Schellong M, May A. Migraine monoclonal antibodies against CGRP change brain activity depending on ligand or receptor target – an fMRI study. eLife 2022;11. doi:10.7554/elife.77146.

[9] Bennett CM, Miller MB. How reliable are the results from functional magnetic resonance imaging? Ann N Y Acad Sci 2010;1191:133–155.

[10] Bennett CM, Wolford GL, Miller MB. The principled control of false positives in neuroimaging. Soc Cogn Affect Neurosci 2009;4:417–422.

[11] Bingel U, Herken W, Teutsch S, May A. Habituation to painful stimulation involves the antinociceptive system--a 1-year follow-up of 10 participants. Pain 2008;140:393–394.

[12] Bingel U, Lorenz J, Schoell E, Weiller C, Büchel C. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 2006;120:8–15.

[13] Bingel U, Schoell E, Herken W, Büchel C, May A. Habituation to painful stimulation involves the antinociceptive system. Pain 2007;131:21–30.

[14] Black CJ. Intracortical Localization of a Promising Pain Biomarker. J Neurosci 2020;40:9549–9551.

[15] Blyth FM, March LM, Nicholas MK, Cousins MJ. Self-management of chronic pain: a population-based study. Pain 2005;113:285–292.

[16] Buckelmüller J, Landolt H-P, Stassen HH, Achermann P. Trait-like individual differences in the human sleep electroencephalogram. Neuroscience 2006;138:351–356.

[17] Buffington ALH, Hanlon CA, McKeown MJ. Acute and persistent pain modulation of attention-related anterior cingulate fMRI activations. Pain 2005;113:172–184.

[18] Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. Nat Rev Neurosci 2013;14:502–511.

[19] Cauda F, Palermo S, Costa T, Torta R, Duca S, Vercelli U, Geminiani G, Torta DME. Gray matter alterations in chronic pain: A network-oriented meta-analytic approach. NeuroImage : Clinical 2014;4:676–686.

[20] Cauda F, Sacco K, Duca S, Cocito D, D'Agata F, Geminiani GC, Canavero S. Altered resting state in diabetic neuropathic pain. PLoS One 2009;4:e4542.

[21] Chen Z, Chen X, Liu M, Dong Z, Ma L, Yu S. Altered functional connectivity of amygdala underlying the neuromechanism of migraine pathogenesis. J Headache Pain 2017;18:7.

[22] Coghill RC, Eisenach J. Individual differences in pain sensitivity: implications for treatment decisions. Anesthesiology 2003;98:1312–1314.

[23] Coghill RC, McHaffie JG, Yen Y-F. Neural correlates of interindividual differences in the subjective experience of pain. Proc Natl Acad Sci U S A 2003;100:8538–8542.

[24] Coppola G, Di Renzo A, Petolicchio B, Tinelli E, Di Lorenzo C, Parisi V, Serrao M, Calistri V, Tardioli S, Cartocci G, Schoenen J, Caramia F, Di Piero V, Pierelli F. Aberrant interactions of cortical networks in chronic migraine: A resting-state fMRI study. Neurology 2019;92:e2550–e2558.

[25] DaSilva AFM, Granziera C, Tuch DS, Snyder J, Vincent M, Hadjikhani N. Interictal alterations of

the trigeminal somatosensory pathway and periaqueductal gray matter in migraine. Neuroreport 2007;18:301–305.
[26] Davis KD, Aghaeepour N, Ahn AH, Angst MS, Borsook D, Brenton A, Burczynski ME, Crean C, Edwards R, Gaudilliere B, Hergenroeder GW, Iadarola MJ, Iyengar S, Jiang Y, Kong J-T, Mackey S, Saab CY, Sang CN, Scholz J, Segerdahl M, Tracey I, Veasley C, Wang J, Wager TD, Wasan AD, Pelleymounter MA. Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities. Nat Rev Neurol 2020;16:381–400.
[27] Deak B, Eggert T, Mayr A, Stankewitz A, Filippopulos F, Jahn P, Witkovsky V, Straube A, Schulz E. Intrinsic Network Activity Reflects the Fluctuating Experience of Tonic Pain. Cereb Cortex 2022; 32(18):4098-4109.
[28] deCharms RC, Maeda F, Glover GH, Ludlow D, Pauly JM, Soneji D, Gabrieli JDE, Mackey SC. Control over brain activation and pain learned by using real-time functional MRI. Proc Natl Acad Sci U S A 2005;102:18626–18631.
[29] D'Esposito M. Are individual differences in human brain organization measured with functional MRI meaningful? Proc Natl Acad Sci U S A 2019;116:22432–22434.
[30] Devine DP, Spanos NP. Effectiveness of maximally different cognitive strategies and expectancy in attenuation of reported pain. J Pers Soc Psychol 1990;58:672–678.
[31] Diener H-C, Förderreuther S, Gaul C, Giese F, Hamann T, Holle-Lee D, Jürgens TP, Kamm K, Kraya T, Lampl C, May A, Reuter U, Scheffler A, Tfelt-Hansen P. Prevention of migraine with monoclonal antibodies against CGRP or the CGRP receptor. Neurological Research and Practice 2020;2. doi:10.1186/s42466-020-00057-1.
[32] Dionne RA, Bartoshuk L, Mogil J, Witter J. Individual responder analyses for pain: does one pain scale fit all? Trends Pharmacol Sci 2005;26:125–130.
[33] Dubreuil DL, Endler NS, Spanos NP. Distraction and Redefinition in the Reduction of Low and High Intensity Experimentally-Induced Pain. Imagin Cogn Pers 1987;7:155–164.
[34] Eccleston C, Crombez G. Pain demands attention: a cognitive-affective model of the interruptive function of pain. Psychol Bull 1999;125:356–366.
[35] Edwards RR. Individual differences in endogenous pain modulation as a risk factor for chronic pain. Neurology 2005;65:437–443. doi:10.1212/01.wnl.0000171862.17301.84.
[36] Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, Büchel C. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron 2009;63:533–543.
[37] van 't Ent D, van Soelen ILC, Stam CJ, De Geus EJC, Boomsma DI. Strong resemblance in the amplitude of oscillatory brain activity in monozygotic twins is not caused by "trivial" similarities in the composition of the skull. Hum Brain Mapp 2009;30:2142–2145.
[38] Fagiolini M, Jensen CL, Champagne FA. Epigenetic influences on brain development and plasticity. Curr Opin Neurobiol 2009;19:207–212.
[39] Favilla S, Huber A, Pagnoni G, Lui F, Facchin P, Cocchi M, Baraldi P, Porro CA. Ranking brain areas encoding the perceived level of pain from fMRI data. Neuroimage 2014;90:153–162.
[40] Fernandez E, Turk DC. The utility of cognitive coping strategies for altering pain perception: a meta-analysis. Pain 1989;38:123–135.
[41] Fuchs PN, Peng YB, Boyette-Davis JA, Uhelski ML. The anterior cingulate cortex and pain processing. Front Integr Neurosci 2014;8:35.
[42] Gard T, Hölzel BK, Sack AT, Hempel H, Lazar SW, Vaitl D, Ott U. Pain attenuation through mindfulness is associated with decreased cognitive control and increased sensory processing in the brain. Cereb Cortex 2012;22:2692–2702.
[43] Geha PY, Baliki MN, Harden RN, Bauer WR, Parrish TB, Apkarian AV. The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. Neuron 2008;60:570–581.
[44] Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, Ugurbil K, Andersson J, Beckmann CF, Jenkinson M, Smith SM, Van Essen DC. A multi-modal parcellation of human cerebral cortex. Nature 2016;536:171–178.
[45] Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. Nature Medicine 2010;16:1248–1257. doi:10.1038/nm.2235.
[46] Gollub RL, Kirsch I, Maleki N, Wasan AD, Edwards RR, Tu Y, Kaptchuk TJ, Kong J. A Functional Neuroimaging Study of Expectancy Effects on Pain Response in Patients With Knee Osteoarthritis. J Pain 2018;19:515–527.
[47] Gordon EM, Laumann TO, Gilmore AW, Newbold DJ, Greene DJ, Berg JJ, Ortega M, Hoyt-Drazen C, Gratton C, Sun H, Hampton JM, Coalson RS, Nguyen AL, McDermott KB,

Shimony JS, Snyder AZ, Schlaggar BL, Petersen SE, Nelson SM, Dosenbach NUF. Precision Functional Mapping of Individual Human Brains. Neuron 2017;95:791–807.e7.
[48] Goto T, Saitoh Y, Hashimoto N, Hirata M, Kishima H, Oshino S, Tani N, Hosomi K, Kakigi R, Yoshimine T. Diffusion tensor fiber tracking in patients with central post-stroke pain; correlation with efficacy of repetitive transcranial magnetic stimulation. Pain 2008;140:509–518.
[49] Greene DJ, Marek S, Gordon EM, Siegel JS, Gratton C, Laumann TO, Gilmore AW, Berg JJ, Nguyen AL, Dierker D, Van AN, Ortega M, Newbold DJ, Hampton JM, Nielsen AN, McDermott KB, Roland JL, Norris SA, Nelson SM, Snyder AZ, Schlaggar BL, Petersen SE, Dosenbach NUF. Integrative and Network-Specific Connectivity of the Basal Ganglia and Thalamus Defined in Individuals. Neuron 2019. doi:10.1016/j.neuron.2019.11.012.
[50] Hadjipavlou G, Dunckley P, Behrens TE, Tracey I. Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: a diffusion tensor imaging study in healthy controls. Pain 2006;123:169–178.
[51] Hamilton NA, Zautra AJ, Reich JW. Affect and pain in rheumatoid arthritis: do individual differences in affective regulation and affective intensity predict emotional recovery from pain? Ann Behav Med 2005;29:216–224.
[52] Hashmi JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, Schnitzer TJ, Apkarian AV. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain 2013;136:2751–2768.
[53] Haythornthwaite JA, Menefee LA, Heinberg LJ, Clark MR. Pain coping strategies predict perceived control over pain. Pain 1998;77:33–39.
[54] Henderson LA, Peck CC, Petersen ET, Rae CD, Youssef AM, Reeves JM, Wilcox SL, Akhter R, Murray GM, Gustin SM. Chronic pain: lost inhibition? J Neurosci 2013;33:7574–7582.
[55] Jahanshad N, Lee AD, Barysheva M, McMahon KL, de Zubicaray GI, Martin NG, Wright MJ, Toga AW, Thompson PM. Genetic influences on brain asymmetry: A DTI study of 374 twins and siblings. Neuroimage 2010;52:455–469.
[56] Jahn P, Deak B, Mayr A, Stankewitz A, Keeser D, Griffanti L, Witkovsky V, Irving S, Schulz E. Intrinsic network activity reflects the ongoing experience of chronic pain. Sci Rep 2021;11:21870.
[57] Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. Neuroimage 2012;62:782–790.
[58] Jensen MP, Day MA, Miró J. Neuromodulatory treatments for chronic pain: efficacy and mechanisms. Nat Rev Neurol 2014;10:167–178.
[59] Jensen MP, Gertz KJ, Kupper AE, Braden AL, Howe JD, Hakimian S, Sherlin LH. Steps toward developing an EEG biofeedback treatment for chronic pain. Appl Psychophysiol Biofeedback 2013;38:101–108.
[60] Jones DA, Rollman GB, White KP, Hill ML, Brooke RI. The relationship between cognitive appraisal, affect, and catastrophizing in patients with chronic pain. J Pain 2003;4:267–277.
[61] Kayiran S, Dursun E, Dursun N, Ermutlu N, Karamürsel S. Neurofeedback intervention in fibromyalgia syndrome; a randomized, controlled, rater blind clinical trial. Appl Psychophysiol Biofeedback 2010;35:293–302.
[62] Keefe FJ, Kashikar-Zuck S, Robinson E, Salley A, Beaupre P, Caldwell D, Baucom D, Haythornthwaite J. Pain coping strategies that predict patients' and spouses' ratings of patients' self-efficacy. Pain 1997;73:191–199.
[63] Kim J, Kang I, Chung Y-A, Kim T-S, Namgung E, Lee S, Oh JK, Jeong HS, Cho H, Kim MJ, Kim TD, Choi SH, Lim SM, Lyoo IK, Yoon S. Altered attentional control over the salience network in complex regional pain syndrome. Sci Rep 2018;8:7466.
[64] Kim J, Loggia ML, Cahalan CM, Harris RE, Beissner F, Garcia RG, Kim H, Barbieri R, Wasan AD, Edwards RR, Napadow V. The somatosensory link in fibromyalgia: functional connectivity of the primary somatosensory cortex is altered by sustained pain and is associated with clinical/autonomic dysfunction. Arthritis & Rheumatology (Hoboken, N J) 2015;67:1395–1405.
[65] Krummenacher P, Candia V, Folkers G, Schedlowski M, Schönbächler G. Prefrontal cortex modulates placebo analgesia. Pain 2010;148:368–374.
[66] Kucyi A, Davis KD. The dynamic pain connectome. Trends Neurosci 2015;38:86–95.
[67] Kucyi A, Hodaie M, Davis KD. Lateralization in intrinsic functional connectivity of the temporoparietal junction with salience- and attention-related brain networks. J Neurophysiol 2012;108:3382–3392.
[68] Lanier LH. VARIABILITY IN THE PAIN THRESHOLD. Science 1943;97:49–50.

[69] Lawrence JM, Hoeft F, Sheau KE, Mackey SC. Strategy-dependent dissociation of the neural correlates involved in pain modulation. Anesthesiology 2011;115:844–851.
[70] Legrain V, Domenico GDIG, Plaghki L, Mouraux A. The pain matrix reloaded A salience detection system for the body. ProgNeurobiol 2011;93:111–124.
[71] Lieberman MD, Eisenberger NI. The dorsal anterior cingulate cortex is selective for pain: Results from large-scale reverse inference. Proc Natl Acad Sci U S A 2015;112:15250–15255.
[72] Lin RL, Douaud G, Filippini N, Okell TW, Stagg CJ, Tracey I. Structural Connectivity Variances Underlie Functional and Behavioral Changes During Pain Relief Induced by Neuromodulation. Sci Rep 2017;7:41603.
[73] Litt MD. Self-efficacy and perceived control: cognitive mediators of pain tolerance. J Pers Soc Psychol 1988;54:149–160.
[74] Loggia ML, Kim J, Gollub RL, Vangel MG, Kirsch I, Kong J, Wasan AD, Napadow V. Default mode network connectivity encodes clinical pain: An arterial spin labeling study. Pain 2013;154:24–33. doi:10.1016/j.pain.2012.07.029.
[75] Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain 2003;126:1079–1091.
[76] Lutz J, Jager L, de Quervain D, Krauseneck T, Padberg F, Wichnalek M, Beyer A, Stahl R, Zirngibl B, Morhard D, Reiser M, Schelling G. White and gray matter abnormalities in the brain of patients with fibromyalgia: a diffusion-tensor and volumetric imaging study. Arthritis Rheum 2008;58:3960–3969.
[77] Makary MM, Polosecki P, Cecchi GA, DeAraujo IE, Barron DS, Constable TR, Whang PG, Thomas DA, Mowafi H, Small DM, Geha P. Loss of nucleus accumbens low-frequency fluctuations is a signature of chronic pain. Proceedings of the National Academy of Sciences 2020;117:10015–10023.
[78] Marek S, Siegel JS, Gordon EM, Raut RV, Gratton C, Newbold DJ, Ortega M, Laumann TO, Adeyemo B, Miller DB, Zheng A, Lopez KC, Berg JJ, Coalson RS, Nguyen AL, Dierker D, Van AN, Hoyt CR, McDermott KB, Norris SA, Shimony JS, Snyder AZ, Nelson SM, Barch DM, Schlaggar BL, Raichle ME, Petersen SE, Greene DJ, Dosenbach NUF. Spatial and Temporal Organization of the Individual Human Cerebellum. Neuron 2018;100:977–993.e7.
[79] Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, Donohue MR, Foran W, Miller RL, Hendrickson TJ, Malone SM, Kandala S, Feczko E, Miranda-Dominguez O, Graham AM, Earl EA, Perrone AJ, Cordova M, Doyle O, Moore LA, Conan GM, Uriarte J, Snider K, Lynch BJ, Wilgenbusch JC, Pengo T, Tam A, Chen J, Newbold DJ, Zheng A, Seider NA, Van AN, Metoki A, Chauvin RJ, Laumann TO, Greene DJ, Petersen SE, Garavan H, Thompson WK, Nichols TE, Yeo BTT, Barch DM, Luna B, Fair DA, Dosenbach NUF. Reproducible brain-wide association studies require thousands of individuals. Nature 2022;603:654–660.
[80] Marino J, Gwynn MI, Spanos NP. Cognitive mediators in the reduction of pain: the role of expectancy, strategy use, and self-presentation. J Abnorm Psychol 1989;98:256–262.
[81] May ES, Nickel MM, Dinh ST, Tiemann L, Heitmann H, Voth I, Tolle TR, Gross J, Ploner M. Prefrontal gamma oscillations reflect ongoing pain intensity in chronic back pain patients. Hum Brain Mapp 2018. doi:10.1002/hbm.24373 [doi].
[82] May ES, Nickel MM, Dinh ST, Tiemann L, Heitmann H, Voth I, Tölle TR, Gross J, Ploner M. Prefrontal gamma oscillations reflect ongoing pain intensity in chronic back pain patients. Hum Brain Mapp 2019;40:293–305.
[83] Mayr A, Jahn P, Stankewitz A, Deak B, Winkler A, Witkovsky V, Eren O, Straube A, Schulz E. Patients with chronic pain exhibit individually unique cortical signatures of pain encoding. Hum Brain Mapp 2022. 43(5):1676-1693.
[84] McCracken LM, Barker E, Chilcot J. Decentering, rumination, cognitive defusion, and psychological flexibility in people with chronic pain. J Behav Med 2014;37:1215–1225.
[85] Miller MB, Donovan C-L, Van Horn JD, German E, Sokol-Hessner P, Wolford GL. Unique and persistent individual patterns of brain activity across different memory retrieval tasks. Neuroimage 2009;48:625–635.
[86] Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth 2019;123:e273–e283.
[87] Moisset X, Bouhassira D, Denis D, Dominique G, Benoit C, Sabate JM. Anatomical connections between brain areas activated during rectal distension in healthy volunteers: a visceral pain network. Eur J Pain 2011;14:142–148.
[88] Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. Prog Neurobiol 2011;93:385–404.
[89] Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized

controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain 1999;80:1–13.
[90] Mun CJ, Suk HW, Davis MC, Karoly P, Finan P, Tennen H, Jensen MP. Investigating intraindividual pain variability: methods, applications, issues, and directions. Pain 2019;160:2415–2429.
[91] Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum 2010;62:2545–2555.
[92] Näpflin M, Wildi M, Sarnthein J. Test–retest reliability of resting EEG spectra validates a statistical signature of persons. Clin Neurophysiol 2007;118:2519–2524.
[93] Nickel MM, May ES, Tiemann L, Postorino M, Dinh ST, Ploner M. Autonomic responses to tonic pain are more closely related to stimulus intensity than to pain intensity. Pain 2017;158:2129–2136.
[94] Nickel MM, May ES, Tiemann L, Schmidt P, Postorino M, Dinh ST, Gross J, Ploner M. Brain oscillations differentially encode noxious stimulus intensity and pain intensity. Neuroimage 2017;148:141–147.
[95] Nielsen CS, Price DD, Vassend O, Stubhaug A, Harris JR. Characterizing individual differences in heat-pain sensitivity. Pain 2005;119:65–74.
[96] Nielsen CS, Staud R, Price DD. Individual differences in pain sensitivity: measurement, causation, and consequences. J Pain 2009;10:231–237.
[97] van Pelt S, Boomsma DI, Fries P. Magnetoencephalography in twins reveals a strong genetic determination of the peak frequency of visually induced γ-band synchronization. J Neurosci 2012;32:3388–3392.
[98] Pereira EA, Lu G, Wang S, Schweder PM, Hyam JA, Stein JF, Paterson DJ, Aziz TZ, Green AL. Ventral periaqueductal grey stimulation alters heart rate variability in humans with chronic pain. Exp Neurol 2010;223:574–581.
[99] Peyron R, Garcia-Larrea L, Gregoire MC, Costes N, Convers P, Lavenne F, Mauguiere F, Michel D, Laurent B, García-Larrea L, Grégoire MC, Costes N, Convers P, Lavenne F, Mauguière F, Michel D, Laurent B. Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. Brain 1999;122 (Pt 9:1765–1780.
[100] Phillips CJ. The Cost and Burden of Chronic Pain. Reviews in Pain 2009;3:2–5.
[101] Ploner M, Lee MC, Wiech K, Bingel U, Tracey I. Flexible cerebral connectivity patterns subserve contextual modulations of pain. Cereb Cortex 2011;21:719–726.
[102] Ploner M, Lee MC, Wiech K, Bingel U, Tracey I. Prestimulus functional connectivity determines pain perception in humans. Proc Natl Acad Sci U S A 2010;107:355–360.
[103] Pogatzki-Zahn EM, Wagner C, Meinhardt-Renner A, Burgmer M, Beste C, Zahn PK, Pfleiderer B. Coding of incisional pain in the brain: a functional magnetic resonance imaging study in human volunteers. Anesthesiology 2010;112:406–417.
[104] Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science 2000;288:1769–1772.
[105] Rance M, Ruttorf M, Nees F, Schad LR, Flor H. Neurofeedback of the difference in activation of the anterior cingulate cortex and posterior insular cortex: two functionally connected areas in the processing of pain. Front Behav Neurosci 2014;8:357.
[106] Rance M, Ruttorf M, Nees F, Schad LR, Flor H. Real time fMRI feedback of the anterior cingulate and posterior insular cortex in the processing of pain. Hum Brain Mapp 2014;5798:5784–5798.
[107] Schulz E, May ES, Postorino M, Tiemann L, Nickel MM, Witkovsky V, Schmidt P, Gross J, Ploner M. Prefrontal Gamma Oscillations Encode Tonic Pain in Humans. Cereb Cortex 2015;25:4407–4414.
[108] Schulz E, Stankewitz A, Winkler AM, Irving S, Witkovský V, Tracey I. Ultra-high-field imaging reveals increased whole brain connectivity underpins cognitive strategies that attenuate pain. Elife 2020; Sep 2;9:e55028;.
[109] Schulz E, Stankewitz A, Witkovský V, Winkler AM, Tracey I. Strategy-dependent modulation of cortical pain circuits for the attenuation of pain. Cortex 2019;113:255–266.
[110] Schulz E, Tiemann L, Schuster T, Gross J, Ploner M. Neurophysiological coding of traits and states in the perception of pain. Cereb Cortex 2011;21:2408–2414.
[111] Schwedt TJ, Krauss MJ, Frey K, Gereau RW. Episodic and chronic migraineurs are hypersensitive to thermal stimuli between migraine attacks. Cephalalgia 2011;31:6–12.
[112] Segerdahl AR, Mezue M, Okell TW, Farrar JT, Tracey I. The dorsal posterior insula subserves a fundamental role in human pain. Nat Neurosci 2015;18:499–500.
[113] Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the

affective but not sensory components of pain. Science 2004;303:1157–1162.
[114] Sitges C, García-Herrera M, Pericás M, Collado D, Truyols M, Montoya P. Abnormal brain processing of affective and sensory pain descriptors in chronic pain patients. J Affect Disord 2007;104:73–82.
[115] Sprenger C, Eippert F, Finsterbusch J, Bingel U, Rose M, Büchel C. Attention modulates spinal cord responses to pain. Curr Biol 2012;22:1019–1022.
[116] Sprenger C, Finsterbusch J, Büchel C. Spinal cord-midbrain functional connectivity is related to perceived pain intensity: a combined spino-cortical FMRI study. J Neurosci 2015;35:4248–4257.
[117] Stankewitz A, Valet M, Schulz E, Wöller A, Sprenger T, Vogel D, Zimmer C, Mühlau M, Tölle TR. Pain sensitisers exhibit grey matter changes after repetitive pain exposure: a longitudinal voxel-based morphometry study. Pain 2013;154:1732–1737.
[118] Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. Expert Rev Neurother 2012;12:577–585.
[119] Sulzer J, Haller S, Scharnowski F, Weiskopf N, Birbaumer N, Blefari ML, Bruehl AB, Cohen LG, deCharms RC, Gassert R, Goebel R, Herwig U, LaConte S, Linden D, Luft A, Seifritz E, Sitaram R. Real-time fMRI neurofeedback: Progress and challenges. Neuroimage 2013;76:386–399.
[120] Sundgren PC, Petrou M, Harris RE, Fan X, Foerster B, Mehrotra N, Sen A, Clauw DJ, Welsh RC. Diffusion-weighted and diffusion tensor imaging in fibromyalgia patients: a prospective study of whole brain diffusivity, apparent diffusion coefficient, and fraction anisotropy in different regions of the brain and correlation with symptom severity. Acad Radiol 2007;14:839–846.
[121] Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen VP, Huttunen M, Lönnqvist J, Standertskjöld-Nordenstam CG, Kaprio J, Khaledy M, Dail R, Zoumalan CI, Toga AW. Genetic influences on brain structure. Nat Neurosci 2001;4:1253–1258.
[122] Tiemann L, Schulz E, Gross J, Ploner M. Gamma oscillations as a neuronal correlate of the attentional effects of pain. Pain 2010;150:302–308.
[123] Tracey I. Imaging pain. Br J Anaesth 2008;101:32–39.
[124] Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55:377–391.
[125] Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, Matthews PM. Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci 2002;22:2748–2752.
[126] Turk DC, Meichenbaum D, Genest M. Pain and Behavioral Medicine: A Cognitive-Behavioral Perspective. Guilford Press, 1983.
[127] Vachon-Presseau E, Roy M, Woo C-W, Kunz M, Martel M-O, Sullivan MJ, Jackson PL, Wager TD, Rainville P. Multiple faces of pain: effects of chronic pain on the brain regulation of facial expression. Pain 2016;157:1819–1830.
[128] Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, Erhard P, Tolle TR. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain--an fMRI analysis. Pain 2004;109:399–408.
[129] Villemure C, Bushnell MC. Cognitive modulation of pain: how do attention and emotion influence pain processing? Pain 2002;95:195–199.
[130] Villemure C, Bushnell MC. Mood influences supraspinal pain processing separately from attention. J Neurosci 2009;29:705–715.
[131] Wager TD, Atlas LY. How Is Pain Influenced by Cognition? Neuroimaging Weighs In. Perspect Psychol Sci 2013;8:91–97.
[132] Wager TD, Atlas LY, Lindquist MA, Roy M, Woo C-W, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med 2013;368:1388–1397.
[133] Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 2004;303:1162–1167.
[134] Wager TD, Scott DJ, Zubieta J-K. Placebo effects on human mu-opioid activity during pain. Proc Natl Acad Sci U S A 2007;104:11056–11061.
[135] Weiskopf N. Real-time fMRI and its application to neurofeedback. Neuroimage 2013;62:682–692.
[136] Wiech K, Kalisch R, Weiskopf N, Pleger B, Stephan KE, Dolan RJ. Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. J Neurosci 2006;26:11501–11509.
[137] Wiech K, Lin C-SS, Brodersen KH, Bingel U, Ploner M, Tracey I. Anterior insula integrates information about salience into perceptual decisions about pain. J Neurosci 2010;30:16324–16331.

[138] Wiech K, Seymour B, Kalisch R, Stephan KE, Koltzenburg M, Driver J, Dolan RJ. Modulation of pain processing in hyperalgesia by cognitive demand. Neuroimage 2005;27:59–69.
[139] Witkovský V. Estimation, testing, and prediction regions of the fixed and random effects by solving the Henderson's mixed model equations. Measurement science review 2012;12:234–248.
[140] Woodcock J, Witter J, Dionne RA. Stimulating the development of mechanism-based, individualized pain therapies. Nat Rev Drug Discov 2007;6:703–710.
[141] Zhou J, Greicius MD, Gennatas ED, Growdon ME, Jang JY, Rabinovici GD, Kramer JH, Weiner M, Miller BL, Seeley WW. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. Brain 2010;133:1352–1367.

5. Figure references

Figure 1 | Schematic time course of a single trial (Schulz et al., 2019)..... 12
Figure 2 | Cortical pain modulation in the insular cortex (Schulz et al., 2019)..... 13
Figure 3| Statistical results of connectivity the counting condition (Schulz et al., 2020)..... 16
Figure 4 | Encoding of pain amplitude for CBP (Jahn et al., 2021)..... 19
Figure 5 | Time course of painful stimulation (Deak et al., 2022)..... 22
Figure 6 | Time course of the tonic pain ratings (Deak et al., 2022)..... 23
Figure 7 | Encoding of tonic pain processing (Deak et al., 2022)..... 24
Figure 8 | Illustration of Fluctuating time course of pain rating (Mayr et al., 2022)..... 26
Figure 9 | Cortical processing of ongoing chronic pain in CBP (Mayr et al., 2022)..... 27
Figure 10 | Cortical processing of single CBP patients (Mayr et al., 2022)..... 28
Figure 11 | Connectivity pattern for the encoding of pain intensity in CBP (Mayr et al., 2022) 31
Figure 12 | Individual connectivity patterns of 20 CBP patients (Mayr et al., 2022)..... 32

6. Abbreviations

EEG	Electroencephalography
BOLD	Blood Oxygen Level-Dependent
fMRI	functional Magnetic Resonance Imaging
IHS	International Headache Society
PAG	periaqueductal grey
LME	Linear Mixed-Effect Models
CGRP	Calcitonin gene-related peptide
AIC	anterior insular cortex
CopC	central opercular cortex
PCC	posterior cingulate cortex
ACC	anterior cingulate cortex
LOC	lateral occipital cortex
ITG	inferior temporal gyrus
SFG	superior frontal gyrus
SMA	supplementary motor area
CopC	central opercular cortex
STG	superior temporal gyrus
PRE	Precuneous
FPo	frontal pole
PreCG	precentral gyrus

SPL superior parietal lobe

7. Affidavit

I hereby confirm that I have written this habilitation thesis independently. All parts that were taken from published and non-published work either verbally or in substance are clearly marked as such. This habilitation thesis has not been presented to any examination office in the same form.
I further declare that I have not completed a habilitation procedure in the same topic without success. No academic degree has been withdrawn from me. No prosecutions are pending against me that could result in the withdrawal of an academic degree.

Enrico Schulz
Munich, 08/09/2022

8. References of included Manuscripts

(1) Schulz E, Stankewitz A, Witkovský V, Winkler AM, Tracey I. (2019) Strategy-dependent modulation of cortical pain circuits for the attenuation of pain. *Cortex*. Apr;113:255-266.
(2) Schulz E, Stankewitz A, Winkler AM, Irving S, Witkovský V, Tracey I. (2020) Ultra-high-field imaging reveals increased whole brain connectivity underpins cognitive strategies that attenuate pain. *eLife*. Sep 2;9:e55028.
(3) Jahn P, Deak B, Mayr A, Stankewitz A, Keeser D, Griffanti L, Witkovsky V, Irving S, Schulz E (2021) Intrinsic Network Activity Reflects the Ongoing Experience of Chronic Pain. *Scientific Reports*. 11(1):21870.
(4) Deak B, Eggert T, Mayr A, Stankewitz A, Filippopulos F, Jahn P, Witkovsky V, Straube A, Schulz E (2022) Intrinsic Network Activity Reflects the Fluctuating Experience of Tonic Pain. *Cerebral Cortex*. 32(18):4098-4109.
(5) Mayr A, Jahn P, Stankewitz A, Deak B, Winkler AM, Witkovsky V, Eren O, Straube A, Schulz E (2022) - Patients With Chronic Pain Exhibit Individually Unique Cortical Signatures of Pain. *Human Brain Mapping*. 43(5):1676-1693
(6) Mayr A, Jahn P, Deak B, Stankewitz A, Devulapally V, Witkovsky V, Dietrich O, Schulz E (2022) - Individually Unique Dynamics of Cortical Connectivity Reflect the Ongoing Intensity of Chronic Pain. *PAiN*. 163(10): 1987-1998.

9. Own Publications

First or last authorships

(1) Bassez I, van de Steen F, Hackl, S, Jahn P, Mayr A, Marinazzo D, **Schulz E** (2022) Investigation on How Dynamic Effective Connectivity Patterns Encode the Fluctuating Intensity of Chronic Pain. Neurobiology of Pain; IF: 3.43

(2) Stankewitz A, **Schulz E** (2022) Intrinsic Network Connectivity Reflects the Cyclic Trajectory of Migraine Attacks. Neurobiology of Pain; IF: 3.43

(3) Mayr A, Jahn P, Deak B, Stankewitz A, Devulapally V, Witkovsky V, Dietrich O, Schulz E (2022) - Individually Unique Dynamics of Cortical Connectivity Reflect the Ongoing Intensity of Chronic Pain. PAiN; 163(10): 1987-1998. IF: 7.4

(4) Mayr A, Jahn P, Stankewitz A, Deak B, Winkler AM, Witkovsky V, Eren O, Straube A, Schulz E (2022) - Patients With Chronic Pain Exhibit Individually Unique Cortical Signatures of Pain. *Human Brain Mapping* ; IF: 4.8

(5) Deak B, Eggert T, Mayr A, Stankewitz A, Filippopulos F, Jahn P, Witkovsky V, Straube A, **Schulz E** (2022) Intrinsic Network Activity Reflects the Fluctuating Experience of Tonic Pain. *Cerebral Cortex*; 32(18):4098-4109. IF: 3.7

(6) Jahn P, Deak B, Mayr A, Stankewitz A, Keeser D, Griffanti L, Witkovsky V, Irving S, **Schulz E** (2021) Intrinsic Network Activity Reflects the Ongoing Experience of Chronic Pain. Scientific reports; Nov 8;11(1):21870; IF: 5.0

(7) Liebisch AP , Eggert T, Shindy A, Valentini E, Irving S, Stankewitz A, **Schulz E** (2021) - A Novel Tool for the Removal of Muscle Artefacts from EEG: Improving Data Quality in the Gamma Frequency Range. *Journal of Neuroscience Methods*. Jul 1;358:109217; IF: 2.99

(8) Stankewitz A, Keidel L, Rehm M, Irving S, Kaczmarz S, Preibisch C, Witkovsky V, Zimmer C, Tölle TR, **Schulz E** (2021) Migraine Attacks as a Result of Hypothalamic Loss of Control. *NeuroImage:clinical*. Aug 16;32:102784; IF: 4.88

(9) **Schulz E**, Stankewitz A, Winkler AM, Irving S, Witkovský V,, Tracey I. (2020) Ultra-high-field imaging reveals increased whole brain connectivity underpins cognitive strategies that attenuate pain. *eLife*. Sep 2;9:e55028; IF: 8.14

(10) **Schulz E**, Stankewitz A, Witkovský V, Winkler AM, Tracey I. (2019) Strategy-dependent modulation of cortical pain circuits for the attenuation of pain. *Cortex*. Apr;113:255-266.; IF: 4.01

(11) Michail G, Dresel C, Witkovský V, Stankewitz A, **Schulz E** (2016) Neuronal oscillations in various frequency bands differ between pain and touch. *Frontiers in Human Neuroscience*. Apr 29;10:182; IF: 3.21

(12) **Schulz E**, May ES, Postorino M, Tiemann L, Witkovsky V, Schmidt P, Gross J, Ploner M (2015) Prefrontal gamma oscillations encode tonic pain in humans. *Cerebral Cortex*. Nov;25(11):4407-14; IF: 8.29

(13) **Schulz E**, Zherdin A, Tiemann L, Plant C, Ploner M. (2012) Decoding an Individual's Sensitivity to Pain from the Multivariate Analysis of EEG Data. *Cerebral Cortex*. 22(5):1118-1123. IF: 6.83.

(14) **Schulz E**, Tiemann L, Witkovsky V, Schmidt P, Ploner M (2012) γ Oscillations are involved in the sensorimotor transformation of pain. *J Neurophysiol*. May;22(5):1118-23; IF: 3.31

(15) **Schulz E**, Tiemann L, Schuster T, Gross J, Ploner M (2011) Neurophysiological Coding of Traits and States in the Perception of Pain. *Cerebral Cortex*. Oct;21(10):2408-14; IF:

6.54

(16) **Schulz E**, Maurer U, van der Mark S, Bucher K, Brem S, Martin E, Brandeis D (2009) Reading for meaning in dyslexic and young children: distinct neural pathways but common endpoints. *Neuropsychologia*. Oct;47(12):2544-57; IF: 4.35.

(17) **Schulz E**, Maurer U, van der Mark S, Bucher K, Brem S, Martin E, Brandeis D (2008) Impaired semantic processing during sentence reading in children with dyslexia: combined fMRI and ERP evidence. *Neuroimage*. May 15;41(1):153-68; IF: 5.69.

Co-authorships

(18) Brem S, Maurer U, Kronbichler M, Schurz M,Richlan F, Blau V, Reithler J, van der Mark S, **Schulz E,** Bucher K, Moll K, Landerl K, Martin E, Goebel R, Schulte-Körne G, Blomert L, Wimmer H, Brandeis D (2020) Visual word form processing deficits driven by severity of reading impairments in children with developmental dyslexia. *Scientific Reports.* Oct 30;10(1):18728; IF: 4.38

(19) Stankewitz A, Sorg C, von Kalckreuth A, **Schulz E**, Valet M, Neufang S, Zimmer C, Henningsen P, Gündel H, Wohlschläger AM, Tölle TR. (2018) Fronto-Insular Connectivity during Pain Distraction Is Impaired in Patients with Somatoform Pain. *J Neuroimaging*. Nov;28(6):621-628; IF: 2.08

(20) Chehadi O, Rusu AC, Konietzny K, **Schulz E**, Köster O, Schmidt-Wilcke T, Hasenbring MI. (2018) Brain structural alterations associated with dysfunctional cognitive control of pain in patients with low back pain. *Eur J Pain*. Apr;22(4):745-755; IF: 3.19

(21) Tiemann L, May ES, Postorino M, **Schulz E**, Nickel MM, Bingel U, Ploner M (2015) Differential neurophysiological correlates of bottom-up and top-down mediated modulations of pain. *Pain*. Feb;156(2):289-296; IF: 5.56

(22) Tiemann L, Heitmann H, **Schulz E**, Baumkötter J, Ploner M (2014) Dopamine precursor depletion influences pain affect rather than pain sensation. *PloS One*. 23;9(4):e96167; IF: 3.23

(23) Moll K, **Schulz E,** et al., (2014) Cognitive mechanisms underlying reading and spelling development in five European orthographies. *Learning and Instruction*. Feb; 29(1):65:77; IF: 5.08

(24) Becker J, **Schulz E** et al. (2014) Genetic analysis of dyslexia candidate genes in the European cross-linguistic NeuroDys cohort. *European journal of human genetics*. May;22(5):675-80; IF: 4.35.

(25) Ilg R, **Schulz E** et al. (2013) Simultaneous Electroencephalographic and Functional Magnetic Resonance Imaging Indicate Impaired Cortical Top-Down Processing in Association with Anesthetic-induced Unconsciousness. *Anesthesiology*. Nov;119(5):1031-42; IF: 6.17

(26) Stankewitz A, Valet M, **Schulz E**, Wöller A, Sprenger T, Vogel D, Zimmer C, Mühlau M, Tölle TR (2013) Pain sensitisers exhibit grey matter changes after repetitive pain exposure - a longitudinal VBM study. *Pain*. 154(9):1732-1737; IF: 5.84

(27) Landerl K, **Schulz E** et al. (2013) Predictors of developmental dyslexia in European orthographies with varying complexity. *Journal of child psychology and psychiatry, and allied disciplines*. Jun;54(6):686-94; IF: 5.67.

(28) Stankewitz A, **Schulz E**, May A (2013) Neuronal correlates of impaired habituation in response to repeated trigemino-nociceptive but not to olfactory input in migraineurs: An fMRI study. *Cephalalgia*. Mar;33(4):256-65; IF: 3.48.

(29) Tiemann L, **Schulz E**, Winkelmann A, Ronel J, Henningsen P, Ploner M. (2012)

Behavioral and neuronal investigations of hypervigilance in patients with fibromyalgia syndrome. *PLoS One*. 7(4):e35068; IF: 3.73.

(30) Maurer U, **Schulz E**, Brem S, van der Mark S, Bucher K, Martin E, Brandeis D (2011) The development of print tuning in children with dyslexia: Evidence from longitudinal ERP data supported by fMRI. *Neuroimage*. Aug 1;57(3):714-22; IF: 5.9.

(31) van der Mark S, Klaver P, Bucher K, Maurer U, **Schulz E**, Brem S, Martin E, Brandeis D (2011) The left occipitotemporal system in reading: disruption of focal fMRI connectivity to left inferior frontal and inferior parietal language areas in children with dyslexia. *Neuroimage*. Feb 1;54(3):2426-36; IF: 5.9.

(32) Tiemann L, **Schulz E**, Gross J, Ploner M (2010) Gamma oscillations as a neuronal correlate of the attentional effects of pain. *Pain*. Aug;150(2):302-308; IF: 5.36.

(33) van der Mark S, Bucher K, Maurer U, **Schulz E**, Brem S, Buckelmuller J, Kronbichler M, Loenneker T, Klaver P, Martin E, Brandeis D (2009) Children with dyslexia lack multiple specializations along the visual word-form (VWF) system. *Neuroimage*. Oct 1;47(4):1940-9; IF: 5.74.

(34) Maurer U, Bucher K, Brem S, Benz R, Kranz F, **Schulz E**, van der Mark S, Steinhausen HC, Brandeis D (2009) Neurophysiology in preschool improves behavioral prediction of reading ability throughout primary school. *Biol Psychiatry*. Aug 15;66(4):341-8; IF: 8.67.

Book chapters

(35) Stankewitz A, Sprenger T, **Schulz E**, Tölle TR (2013) Positron emission tomography for assessing neuronal activity and metabolism in acute and chronic pain. In: Pain Models: Translational Relevance and Applications. IASP Press.

(36) Stankewitz A, Sprenger T, **Schulz E**, Tölle TR (2014) Contribution of positron emission tomography (PET) for understanding neuronal activation and neurotransmission in pain. In: Postoperative Pain: Science and Clinical Practice. IASP Press.

Editorials

(37) Valentini E, **Schulz E** (2020) Automatised application of pinprick-evoked potentials improves investigation of central sensitisation in humans. *Clin Neurophysiol*. Oct;131(10):2482-2483; IF: 3.71