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Research article

Individual variability in cortical representations of tonic pain

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A B S T R A C T

When people experience pain in everyday situations, the experience is often long-lasting and fluctuating. However, pain research predominantly focuses on artificial brief and repeated singular painful events.

Here, we aimed to approximate clinically relevant pain in 152 sessions from 38 participants who underwent four sessions each. We applied variable levels of contact heat pain to the forearm using a thermode. Participants were asked to continuously rate their pain experience through a potentiometer device. In a whole-brain approach, we related the dynamic fluctuations of cortical activity and connectivity to the time courses of pain. We also explored the variability of cortical processing across participants. In an individual approach, we compared the cortical processing pattern of each individual with the overall group findings.

The results revealed a large discrepancy between the group results that are usually reported in publications and the 4-session individual processing patterns: the group findings corroborated previous work localising tonic pain encoding to the secondary somatosensory cortex. By contrast, this region was shadowed by a variety of activity patterns across individuals, represented by a low spatial correlation between group statistics and individual results.

The current findings challenge the usefulness and applicability of group results. They do not inform us how pain is processed in the brain as none of the participants exhibited the processing pattern of the group statistics. Therapies to relieve pain that rely on the modulation of brain regions will fail unless they are adapted to an individual's unique pain processing characteristics.

1. Introduction

Pain conditions requiring medical attention are characterized by long duration and high intensity. Functional neuroimaging research, however, has predominantly focused on brief, phasic pain stimuli [1]; clinically relevant pain experiences have thus been largely neglected. This gap is significant because cortical responses to brief painful stimuli are considered as nonspecific to the pain itself and instead reflect the salience of the stimulus [2].

Neuroimaging findings on long-lasting pain are consistent. Existing neuroimaging studies of long-lasting acute pain in healthy individuals are consistent in identifying key regions involved in pain processing, such as the anterior and posterior insula, thalamus, parietal operculum, and mid-cingulate cortex [3–7]. These findings are further supported by PET studies [8]. The dorsal posterior insula has been implicated in encoding long-lasting pain intensity [9], whilst EEG studies link tonic pain to gamma oscillations in the

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mid-prefrontal cortex [10]. To date, there is only one study linking long-lasting pain intensity to ongoing fluctuations in cortical connectivity [11]. In this and other studies [12,13] investigating longer-lasting pain, higher pain intensities appear to be associated with disrupted connectivity. This contrasts with findings from brief experimental pain [14], underscoring the unique characteristics of long-lasting pain.

Interindividual differences in the perception of pain. An equally important but understudied aspect is the interindividual variability in pain perception. Pain perception is inherently subjective, with individuals reporting dramatically different responses to the same physical stimuli [15,16]. Despite this variability, a "pain network" involving core regions such as the anterior and posterior insula, anterior cingulate cortex, and somatosensory cortices has been consistently reported [17]. The implicit assumption, at least for the core regions, is that every subject will show a measurable effect in these regions and that there may be moderate differences in pain processing due to, for example, gender [18], cognitive interventions [19], or psychological factors [20]. However, this is not necessarily the case for all cortical processes, which may only occur in a subset of individuals [21]. In a similar vein, further research from our group has revealed the substantial inter-individual variability that challenges the utility of group-level statistics, especially when studying a multifaceted phenomenon such as persistent pain [6,11].

To address these gaps, our study examines individual variability in cortical processing of long-lasting pain using a robust experimental design with 38 healthy participants tested in four sessions. Given the novelty of examining individual variability in the cortical processing of long-lasting pain, our study is inherently exploratory. Rather than formulating specific hypotheses, we aim to uncover patterns and mechanisms that have not been previously identified. With implications for both basic neuroscience and clinical applications, the primary goal is to investigate the neural correlates of long-lasting pain and how they vary across individuals, thereby laying the groundwork for future hypothesis-driven research in this area.

2. Materials and methods

To maintain a clear and concise description of the methods in the main document, additional details are provided in the Supplementary Material.

Participants. This study included a group of 38 healthy subjects. All 38 subjects have been previously reported [7]. This prior article dealt with the analysis of intrinsic networks, whereas in this manuscript we report on voxel-wise effects and whole-brain connectivity findings with a specific focus on the individual. The participants (18 female/20 male; aged 28 ± 5 years) provided written informed consent. The study was approved by the Ethics Committee of the Medical Department of the Ludwig-Maximilians-Universität München (project number 19–756) and conducted following the Declaration of Helsinki.

Experimental procedure. During four fMRI recordings, participants rated their ongoing pain intensity for 20 min using an MRI-compatible potentiometer slider [7,19] on a scale from zero to 100 in steps of five, with zero representing no pain and 100 representing the highest pain the participants were willing to tolerate during the experiment. A closed-loop controller ensured that the subjective pain perception followed the predefined pain time course, which prevented unwanted drift in perception, causing sensitisation [22] or habituation phenomena [3].

Imaging data acquisition and processing. The data from 152 sessions (38 subjects x 4 sessions each) were recorded on a 3T MRI scanner (Siemens Magnetom Skyra, Germany). The functional MRI data were preprocessed using FSL (Version 6.0.3, [23]. For the connectivity analysis, we pursued a whole-brain parcellation approach, which divided the brain into 360 regions [24]. Additional 22 subcortical areas and 26 cerebellar regions were added. The time course of cortical activity for each of the 408 regions was computed using a principal component analysis (PCA). The first principal component was taken for further analysis. The ongoing connectivity between two brain regions was determined by Pearson's correlation coefficient over sliding windows of 15 data points (t = TR*15 = 11.4s).

Behavioural data acquisition and processing. The behavioural data were continuously recorded with a variable sampling rate but down-sampled offline to 5 Hz. We distinguished pain intensity (AMP - amplitude) from cortical processes related to the sensing of rising and falling pain (SLP - slope). A vector of the absolute slope of pain ratings (aSLP - absolute slope) represents periods of motor activity, visual input, and decision-making. We also recorded the current thermode temperatures (TEMP). To account for the unknown delay of the BOLD response and the unknown timing of cortical processing relative to the rating, we systematically shifted the rating vector between −15 s and 20 s in steps of 1 s (36 steps).

Statistical analysis. Using Linear Mixed Effects (LME) models, we aimed to determine the relationship between fluctuating pain intensity and the fluctuating cortical activity separately for each voxel or connection [25]. The fluctuating brain activity of a particular voxel is modelled through the time course of the four variables (AMP, SLP, aSLP, TEMP).

(1) brain_activity ~ AMP + SLP + aSLP + TEMP + (AMP - 1 | session) + (SLP - 1 | session) + (aSLP - 1 | session) + (TEMP - 1 | session)

The statistical model is expressed in Wilkinson notation. The first part of the model with the fixed effects (brain_activity ~ AMP + SLP + aSLP + TEMP) represents the common population effect of the distinct aspects of pain intensity on the measured outcome. All statistical tests were corrected for multiple testings using Monte-Carlo simulations; the statistical thresholds were determined using the "palm_datapval.m" function publicly available in PALM [26,27].

Topographical similarities. We tested whether the topography of the amplitude encoding (AMP) and the temperature encoding map (TEMP) resemble the topography of the neurological signature of applied physical pain (Neurologic Pain Signature (NPS; [17]). Spatial correlations using Kendall's τ (tau) coefficients were computed for the common superthreshold voxels of the NPS map and the group

activity map.

Variability measures. We aimed to quantify the variability of cortical pain processing across participants.

(2) brain_acivity ~ AMP + SLP + aSLP + TEMP + Subj + AMP:Subj + SLP:Subj + aSLP:Subj + TEMP:Subj + (1 | session) + (AMP - 1 | session)+ (SLP - 1 | session) + (aSLP - 1 | session) + (TEMP - 1 | session)

The term "AMP:Subj" addresses the variability of the amplitude of tonic pain encoding across subjects. The same was computed for the three other behavioural descriptors (SLP, aSLP, TEMP).

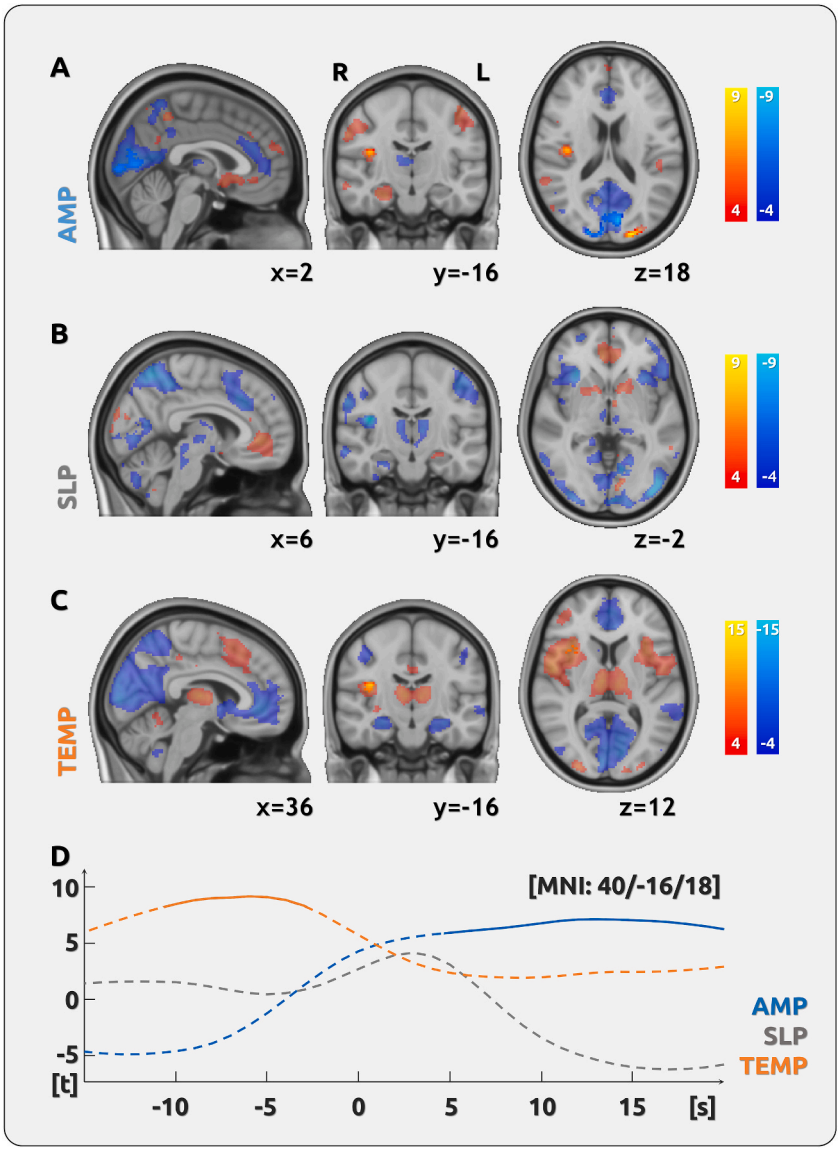

Fig. 1. Cortical processing of tonic pain. (A) The upper row of the figure displays the cortical encoding of perceived pain intensity (amplitude - AMP). We observed a positive relationship between pain intensity and cortical activity in SII. (B) Processing changes (rising and falling) in pain intensity (slope - SLP) did not yield any significant result. (C) The cortical encoding of stimulus intensity (temperature - TEMP) showed a positive relationship with cortical activity in the SII. The pale areas in A, B, and C indicate brain activity at a lowered threshold of $t > 4$, for display purposes. (D) The bottom part of the figure shows the temporal dynamics of the haemodynamic response for the significant peak in SII (MNI: 40/-16/-18) in relation to the current pain rating at time point 0 s. The period between −15s and +20s depicts the applied shifting due to the unknown cortical and haemodynamic processes. The solid line sections indicate significant effects ($p < 0.05$, PALM corrected). The maps are based on the fixed effects statistics of the voxel-wise computation of the linear mixed-effects models (t-values).

3. Results

3.1. Imaging results–tonic pain encoding of group data

The cortical activity in response to tonic pain changed during the experiment regarding a) pain rating amplitude (AMP; pain intensity), b) pain rating slope (SLP; rising and falling pain intensity), and c) applied thermode temperature (TEMP; objective stimuli intensity) and the nuisance variable absolute slope (aSLP).

AMP - pain intensity encoding. The subjective intensity of pain is encoded in the central opercular cortex, which essentially hosts the secondary somatosensory cortex (SII; Fig. 1A, Supplementary Table 1). We found an average spatial correlation between AMP and the NPS map of $\tau = -0.17$ ($p < 0.001$), indicating the fundamental differences between phasic and tonic pain processing.

SLP - direction of pain intensity changes. We did not find any significant brain region that indicates the direction of change in pain intensity (Fig. 1B).

TEMP - encoding of small temperature fluctuations. Similar to the encoding of AMP, the fluctuating time course of applied temperature is mainly encoded in the central operculum (SII; Fig. 1C–Supplementary Table 2). We found a spatial correlation between TEMP and the NPS map of $\tau = 0.15$ ($p < 0.001$).

Temporal effects. The timing of the AMP appears to occur after the TEMP maximum and also after the slider movement (Fig. 1D). However, the timing of the effects needs to be interpreted with caution due to the unknown dynamics of the haemodynamic response function (HRF).

The number of significant connections for each region of the 408 regions for pain intensity (AMP) and stimulus intensity (TEMP) is provided in Supplementary Table 3.

3.2. Imaging results–tonic pain encoding of individual subjects

We found a considerable variety of activation patterns across participants. Activation maps for all subjects are shown for AMP (Supplementary Fig. 2). The variable spatial correlation for AMP (0.22 ± 0.11) and TEMP (0.01 ± 0.20) with the group map indicates a tremendous difference in the similarity of the subject maps with the group map. This variability is also reflected by the substantial individual variation of pain-related activity of SII for AMP (Fig. 2A) and TEMP (Fig. 2B), as derived from the peak of the group AMP statistics. The participants that contributed most to the group statistics (depicted in Fig. 1) are highlighted in the individual maps (red circles in Supplementary Fig. 2). In addition, although the group statistics suggest a predominant role of the central operculum, for most of the participants other regions are of greater importance for specific individuals. In a similar vein, the central operculum appears to be of marginal importance for most individuals.

3.3. Imaging results–analysis of variability across participants

The analysis of variability in encoding tonic pain within the human brain reveals that the brain region exhibiting the greatest variability among participants is the cingulate cortex (Fig. 3A–C). This observation applies to AMP (Fig. 3A–Supplementary Table 4), SLP (Fig. 3B–Supplementary Table 5), and TEMP encoding (Fig. 3C–Supplementary Table 6). The voxel-wise analysis illustrates a continuous spectrum, ranging from regions with minimal variability to those demonstrating more pronounced variability. This continuum should be interpreted in the context of both group statistics (Fig. 1) and individual subject maps (Supplementary Fig. 2 for AMP). It is important to note that a high degree of variability does not necessarily imply the significance of a particular region for either the group or an individual nor does it indicate its insignificance.

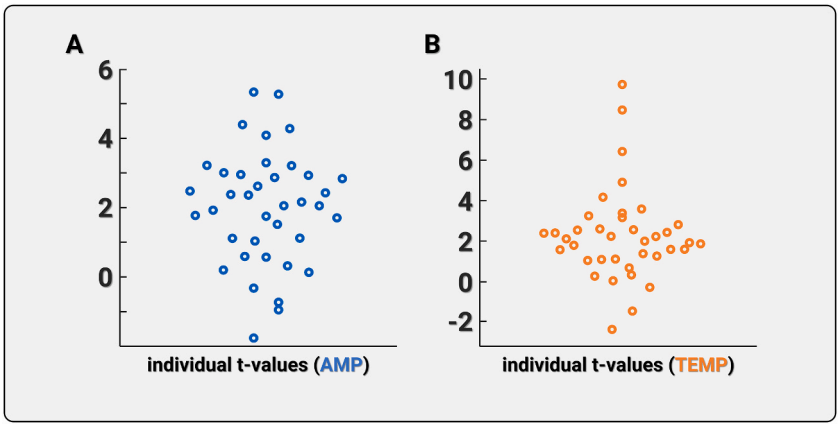

Fig. 2. Individual variability in SII. The bee plot figure shows the individual variation of amplitude (AMP) and temperature (TEMP) encoding in SII (MNI: 40/-16/-18).

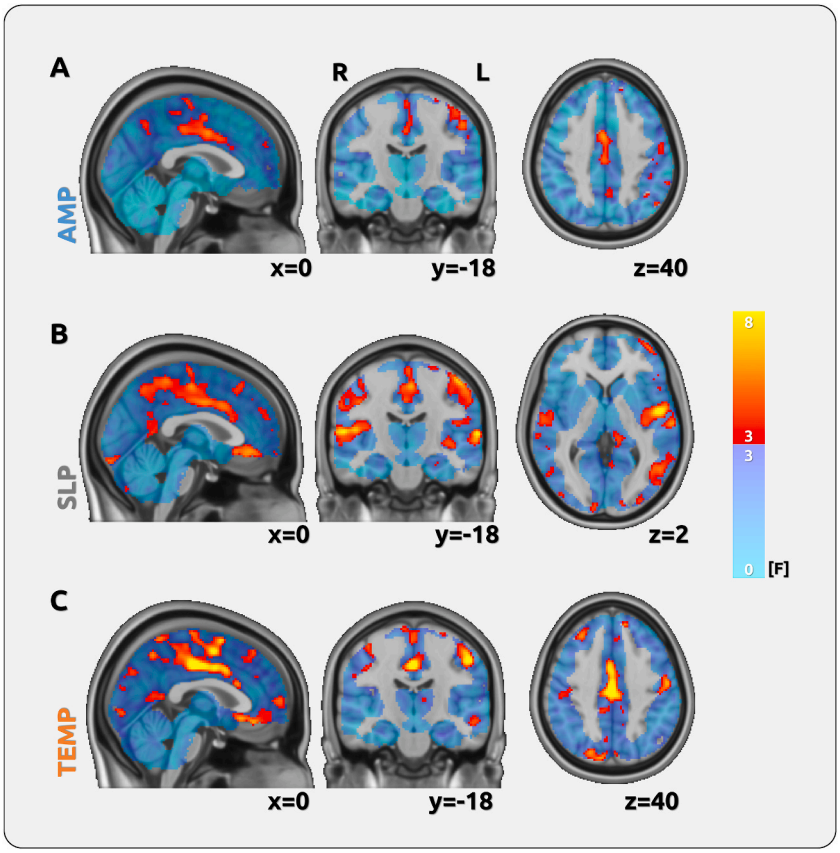

Fig. 3. Variability across participants of the cortical processing of tonic pain. The figure displays the individual variability of the cortical encoding of (A; upper row) perceived pain intensity (amplitude - AMP) along the cingulate gyrus and the primary somatosensory cortex located in the postcentral gyrus, (B; middle row) processing changes (rising and falling) in pain intensity (slope - SLP) in the cingulate cortex, and (C; lower row) cortical encoding of stimulus intensity (temperature - TEMP) along the cingulate cortex. Warm colours, representing areas with high variability; cold colours highlight areas of the lowest variability across participants. The F-values are based on the voxel-wise statistics of the linear mixed-effects model. The chosen cut-off, dividing low (blue - light blue) and high variability (red - yellow), is arbitrary (at $p < 0.001$).

3.4. Connectivity results–tonic pain encoding of group data

We identified the following cortical connections, in which the strength of cortical connectivity in response to tonic pain changed during the experiment - analogous to the above-described results for brain activity - for a) pain rating amplitude (AMP; pain intensity), b) pain rating slope (SLP; rising and falling pain intensity), and c) applied thermode temperature (TEMP; objective stimuli intensity). Again, changes in pain rating are accompanied by decision-making processes, motor activity, and the perception of visual changes on the feedback monitor. These processes were modelled through the variable absolute slope (aSLP). They can not be disentangled and; therefore, will not be reported here.

AMP - pain intensity encoding. We found the subjective intensity of pain is mainly encoded through connections that involve (a) left cingulate projections to the temporal cortex, (b) bilateral opercular-insular connections, and frontoparietal connections (Fig. 4, Supplementary Spreadsheet)

SLP - direction of pain intensity changes. We did not find any significant cortical connection that indicates the direction of change in pain intensity.

TEMP - encoding of small temperature fluctuations. Similar to the encoding of AMP, the fluctuating time course of applied temperature is mainly encoded through connections from medial temporal areas, e.g. hippocampal areas to parietal and frontal regions (Fig. 5, Supplementary Spreadsheet).

Methodological remarks on the disrupted connectivity during high pain/temperature. For all significant effects, the results can be interpreted as a disruption of connectivity. This is because, for the majority of periods, the connectivity between two brain regions exhibits positive correlations (84 % ± 8 %). Since the majority of relationships between connectivity and behavioural data are negative, this means that low pain amplitudes or low temperatures are associated with periods of high positive connectivity values. Therefore, increased pain amplitudes and higher temperatures are linked to decreased, but still positive connectivity values (disruption).

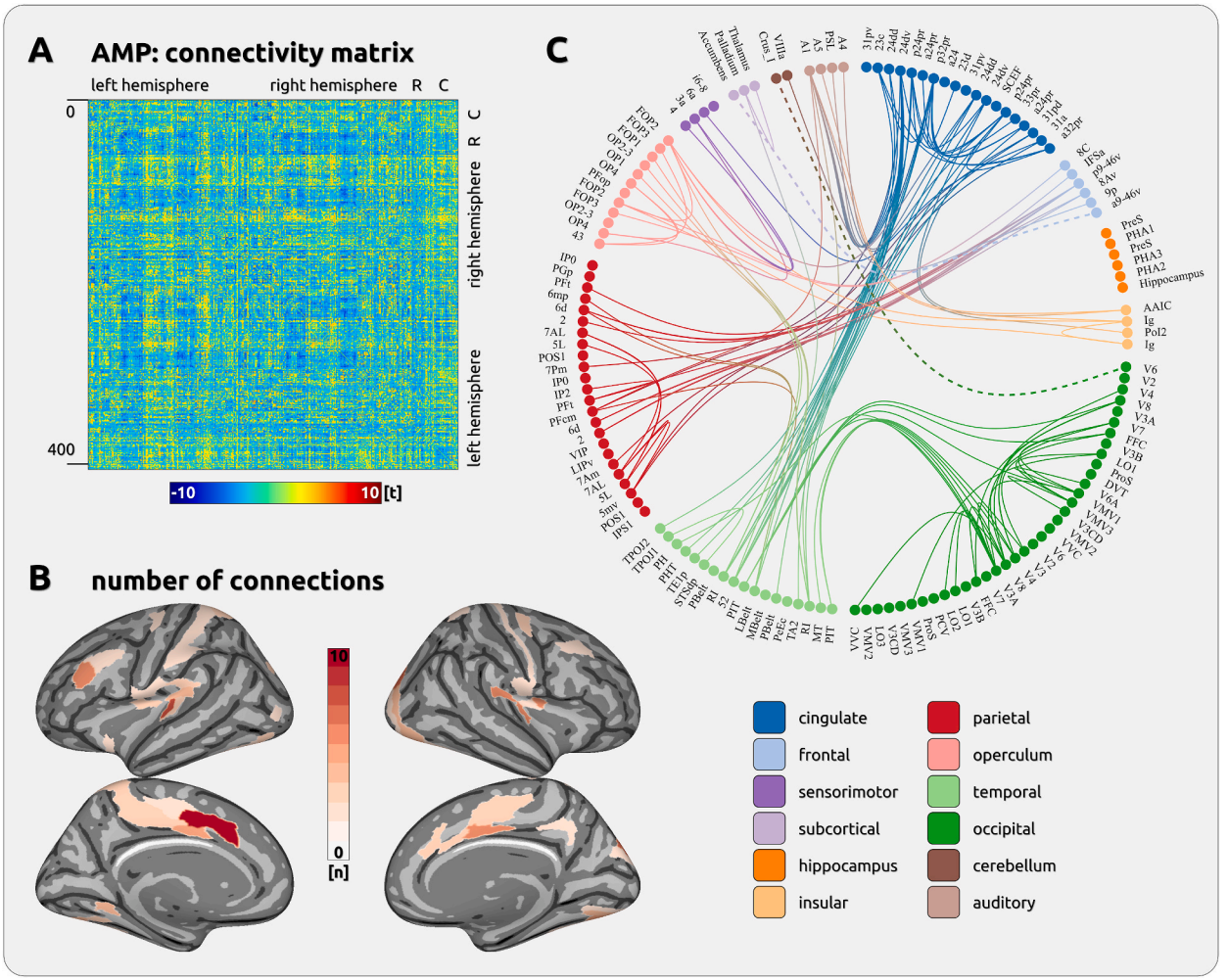

Fig. 4. Pain intensity coding through cortical connectivity. (A) The confusion matrix indicates the pain-intensity-related interconnectivity between all brain regions. Most significant connections exhibit a negative relationship between pain intensity and cortical connectivity: high pain states are associated with disrupted connectivity. (B) The cingulate cortex is the main hub for the encoding of pain intensity with up to 10 significant connections. (C). The circular plot shows all significant connections that reflect the intensity of perceived pain (Link to the NeuroMArVL Brain Data Viewer). There are only two positive relationships between cortical connectivity and pain intensity (dashed lines).

3.5. Connectivity results–tonic pain encoding of individual subjects

Similarly to the findings from the BOLD-based analyses, we identified substantial variation within the group, as evidenced by the weak correlation between the individual confusion matrices and the group confusion matrix. For AMP, we found an average correlation between the individual findings (Supplementary Fig. 2) and the group findings (Fig. 1A) of $\tau = -0.05$ (± 0.02). The same correlation for the group statistical map and the individual statistical maps for TEMP was $\tau = 0.05$ (± 0.03).

4. Discussion

Here, we aimed to approximate the commonly encountered occurrence of long-lasting pain and investigated cortical activity and connectivity. We distinguished four entities of the experiment: (a) pain intensity (amplitude), (b) changes of pain intensity (rising and falling; slope), the cortical implications of moving the slider (nuisance variable, absolute slope), and (d) objective stimulus intensity (applied thermode temperature). The main findings of the present study are that pain intensity and applied temperature were processed in the secondary somatosensory cortex and that pain perception is closely related to functional connections of the cingulate cortex. Although our group-statistical findings align reasonably well with existing literature [7,9], the substantial inter-individual variability poses a challenge to the utility of group-level statistics, particularly when studying a multifaceted phenomenon such as enduring pain [6,11].

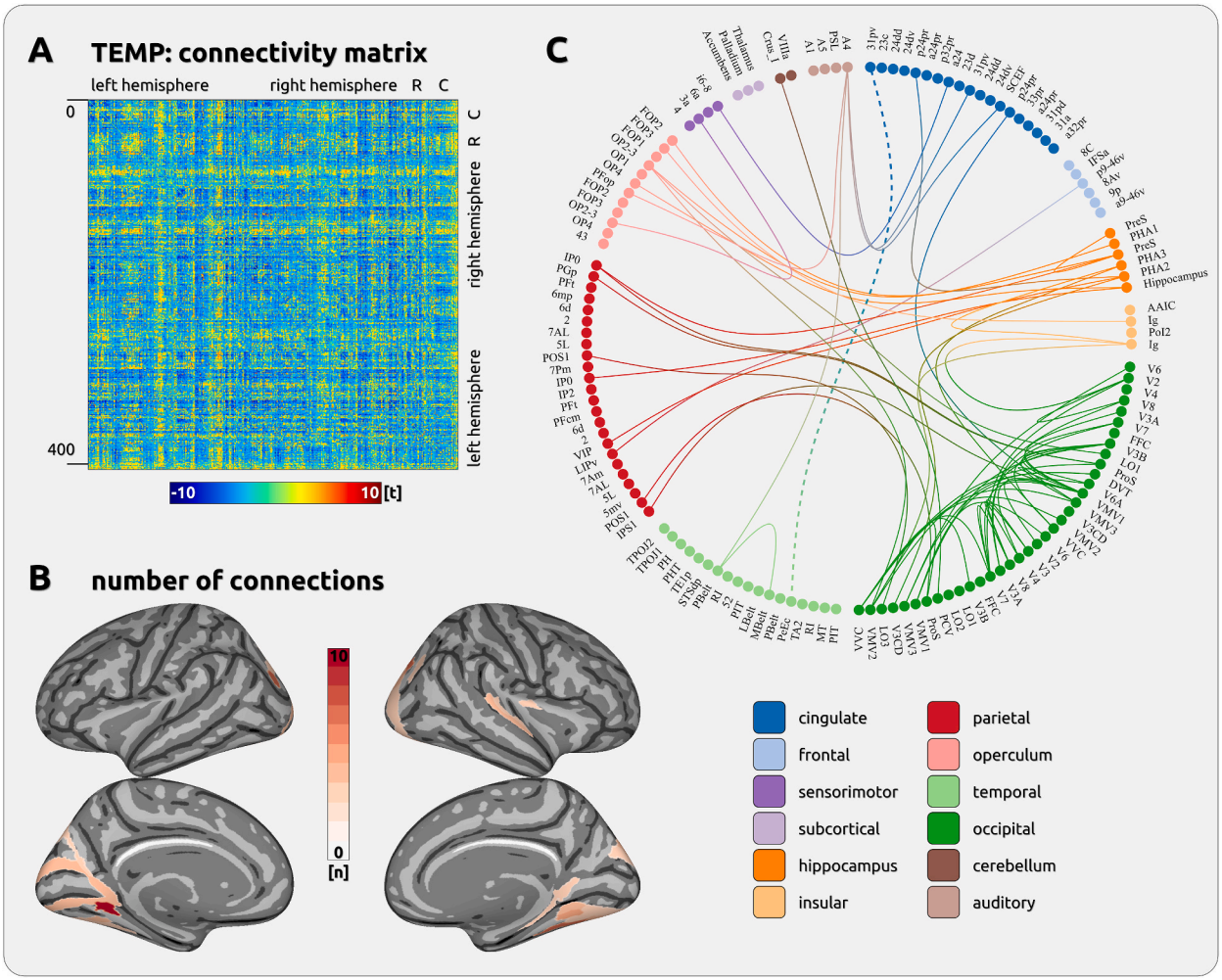

Fig. 5. Temperature coding through cortical connectivity. (A) The confusion matrix shows the temperature-related connectivity between all brain regions. Most significant connections exhibit a negative relationship between pain intensity and cortical connectivity: high temperatures are associated with disrupted connectivity. (B) Occipital brain regions presumably indicate changes on the computer screen. Moreover, we discovered the encoding of temperature for right medial temporal and insular connections (C). The circular plot displays all significant connections that reflect the temperature applied. Only one positive correlation between cortical connectivity and temperature (dashed line) was found (Link to the NeuroMArVL Brain Data Viewer).

4.1. Tonic pain intensity encoding at group level

To date, only two neuroimaging studies [7,9] and two EEG studies [10,22] have previously addressed the fluctuating dynamics of tonic pain in healthy participants. Here, across the entire sample of 38 participants and 4 repeated recordings, we found a positive relationship between cortical activity and the amplitude of pain ratings in the secondary somatosensory cortex, located at the boundary of the central and parietal operculum. Due to the prolonged and continuous stimulation, as well as our statistical design that disentangles pain-related from non-specific cortical processes, our group results on tonic pain encoding are not confounded by transient and salient stimulation schemes that are reflected by activations of regions belonging to the saliency network [2,28]. Our current finding is in line with Segerdahl and colleagues, which localised the encoding of tonic pain in the dorsal posterior insula. The authors assigned a fundamental role of SII for the experience of pain and proposed it as a likely human homologue of the nociceptive region identified from animal studies.

The group connectivity findings are in line with the current literature in two aspects. First, the posterior part of the cingulate cortex (or midcingulate cortex) has been widely described to fulfil an important role in the processing of pain [1]. Second, the previously revealed negative relationship between pain intensity and cortical connectivity for long-lasting pain stimulation [11,29] has been corroborated. The common interpretation of inferential statistics is that our group statistical results reflect a general signature of tonic pain encoding. Instead, most participants do not even remotely share the cortical processing patterns of the group statistics. Whilst only a few individuals' patterns are consistent with those shown in the group statistics, almost all participants show distinct cortical

activations and functional connections that are not captured by the group-level analyses. More surprisingly, for many participants, the SII region is not the most important brain region for encoding pain intensity. Thus, our results highlight the complexity of long-lasting pain processing; our pattern -based approach goes beyond the limitations of voxel-wise measures of variability (see Fig. 2). Whilst we acknowledge that for some domains (e.g., neurophysiological evoked potentials of sensory processes) there is a common denominator of cortical processing, we suggest rigorous testing at individual level for other complex human states such as cognitive or emotional states.

4.2. Disentangling temperature encoding at group level

Our study confirms previous findings that demonstrate differential cortical processing between the subjective aspect, i.e. the pain percept, and the objective aspects, i.e. the applied thermode temperature [10]. Whilst the precursor study identified distinct neuronal oscillations for discriminating pain intensity (fronto-central gamma activity) and temperature fluctuations (beta activity), our current investigation temporally separated the (late) processing of subjectively experienced pain from the (earlier) processing of various levels of applied heat. Although direct statistical tests for the temporal differences in temperature and amplitude processing are not feasible, the data reasonably suggest that temperature processing precedes pain intensity processing. This temporal effect underscores the notion that the subjective experience of pain is not a mere transition from the physically measurable stimulation to the subsequent assessment of subjective perception. If the transformation from the physical (temperature) to the psychological (pain rating) domain were direct, we would not observe a decline in the TEMP effect towards the time point of the slider movement. In a similar vein, the late effect for AMP was temporally dissociated from the temperature curve, indicating that the encoding of AMP is to some extent independent of the encoding of applied temperature. The dissociation of temperature and pain encoding is also in line with our observations during the recordings. Whilst continuously monitoring temperature and pain ratings by the experimenter for safety reasons, we noticed a clear temporal gap of 10s and more between the change of temperature and the subsequent change of pain ratings.

4.3. Variability of individual cortical processes

In recent years there is growing evidence of individually-specific and distinct cortical processes across subjects. Similar to our analysis of variability, other groups have paved the way and explored cortical areas that exhibit larger or smaller differences across individuals [30]. The implicit assumption, however, is that there is an underlying commonality of brain activity across individuals that is moderately shaped by individual factors, e.g. personality traits, gender, disease severity, or disease duration [31]. Relatedly, differences in cortical processing across individuals are rather considered a nuisance than an opportunity [32] and are aimed to be "explained" by an army of factors with often little effect sizes across large-scale population data [33].

We and others have challenged the interpretation of group statistics [33] by taking a more individualistic view [6,34,35]. This requires reliable data at subject level that can only be obtained by repeated recordings of the same individual [6,11,21,34]. These studies challenge the assumption of a common cortical processing network that is universally valid for all participants and conditions (and only slightly modulated by some factors). It may not be the exception but the rule that only a minority of the participants show the patterns that have been reported in group-level statistics [6,11,21], even though the group-level effect has been replicated numerous times. We have addressed this recently for painful laser-induced gamma oscillations, which are present in a minority of the study participants [21].

The knowledge about individual cortical processing is of particular importance when cortical areas need to be selected for therapeutic intervention using brain stimulation techniques (magnetic, electric, or sound stimulation; neurofeedback). The description of group statistics or the knowledge of areas of particular variability can only be of minor importance because, as illustrated in the present findings, they do not enlighten us on the specific pain-related "fingerprint" of the individual. In other words, a personalised treatment plan on pain attenuation would target individually selected brain regions. By contrast, neuromodulation treatments using neurofeedback or electrical stimulation techniques that rely on group statistics would likely target the SII region. Given the current individual variability in the importance of SII as well as the various failures of invariant neurofeedback interventions strongly suggest taking into account the uniqueness of individual pain processing [36–38].

5. Conclusion

The representation of an individual's unique cortical connectivity patterns evolving during the experience of persistent pain exhibits substantial variability compared to group-level statistics. This observation aligns with previous findings from studies that differentiate between individual and group-level analyses in patients with chronic pain.

Considering the practical implications in everyday clinical practice, this outcome should not come as a major surprise, given the diverse therapeutic strategies and successes observed in clinical pain treatment that stem from individual experiences. The emerging paradigms of personalised medicine and its accomplishments further support the significance of our data. These findings endorse the development of individualised treatment plans tailored to meet each patient's specific needs.

Our study represents a significant step in recent neuroscientific research, aiming not only to present reliable patterns in group-level statistics but also to shed light on individual variations. As has been done previously [21], a subsequent question that needs to be addressed is whether the individually unique pain processing maps are stable across sessions. This current work highlights the challenges involved in treating patients with enduring pain, as evidenced by the notable interindividual variability observed in pain-related cortical activity.

CRediT authorship contribution statement

Bettina Deak: Writing – review & editing, Writing – original draft, Project administration, Investigation, Formal analysis, Data curation. **Anne Stankewitz:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization. **Astrid Mayr:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Viktor Witkovsky:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Pauline Jahn:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Enrico Schulz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Data availability

The data can be provided by Dr Enrico Schulz pending scientific review and a completed material transfer agreement. Requests for the data should be submitted to: es@pain.sc.

Ethics approval

The study was approved by the Ethics Committee of the Medical Department of the Ludwig-Maximilians-Universität München (project number 19–756) and conducted following the Declaration of Helsinki.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e42458.

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