Sensory-evoked perturbational complexity in human EEG: Effects of stimulus temperature and peripheral sensitisation in nociceptive processing

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Abstract

The perturbational complexity index (PCI), grounded in systems dynamic and information theory, quantifies the brain's capacity for differentiation and integration of neural activity. While it has been used to characterise consciousness states following transcranial magnetic stimulation, its responsiveness to sensory perturbations remains underexplored. Here, using two publicly available datasets, we computed state-transition PCI from thermal-evoked responses recorded over 32-64 scalp channels. Dataset 1 combined three stimulus intensities (10 °C, 42 °C, 60 °C) with topical application of thermosensitive TRP-channel agonists (menthol 20 %, capsaicin 1 %) or vehicle; Dataset 2 manipulated the block-wise transition probability of receiving cold (≈ 15 °C) or hot (≈ 58 °C) stimulation. PCI scaled non-linearly with temperature, being lowest at the intermediate 42 °C and highest at the cold and hot extremes (Datasets 1 and 2). PCI was sensitive both to peripheral sensitisation, as topical menthol and capsaicin selectively reduced PCI during cold stimulation (Dataset 1), and to changes in block-wise stimulus probability (Dataset 2). Across all analyses, classical ERP peak measures (N2–P2 amplitude/latency) failed to explain PCI variance. These findings demonstrate that sensory-evoked PCI reflects the brain's response to exogenous, sensory-driven perturbations, quantifying changes in neural complexity associated with both stimulus intensity, peripheral sensitisation and probabilistic manipulations. This supports its broader applicability as a measure of temporal and spatial differentiation in the domain of sensory and pain neuroscience.

Keywords

Perturbational Complexity Index; Sensory-evoked PCI; EEG; ERPs; Thermal-evoked responses; Temperature; Pain; TRP channels; Peripheral sensitisation

1 Introduction

Environmental perturbations evoke distributed patterns of neural activity constrained by the features of the underlying network, which can be leveraged to probe its spatial and temporal architecture. An established approach relies on the quantification of the dynamical richness of neurophysiological recordings by means of complexity measurements, a group of techniques based on frameworks operating under the premise that large-scale neuronal ensembles behave as non-linear dynamical systems (Khona & Fiete, 2022; Vignesh et al., 2025). When applied to electroencephalography (EEG), magnetoencephalography, or intracranial recordings, such approaches can characterise how information is processed across distributed brain networks (Sarasso et al., 2021).

Among these measures, the Perturbational Complexity Index (PCI) provides a single numerical estimate of the spatio-temporal richness of the brain's response to a brief, controlled perturbation. First introduced in the framework of Integrated Information Theory (IIT; (Tononi, 2004), the canonical protocol employs a focal transcranial magnetic stimulation (TMS) to generate a cortical perturbation and uses the Lempel-Ziv metric (Casali et al., 2013) or recurrence quantification techniques (Comolatti et al., 2019) to quantify the complexity of the ensuing multichannel EEG recording. This index reflects the complexity of the perturbed system, in terms of *temporal differentiation* (i.e., the variety of patterns that unfold over milliseconds) and *spatial/topological differentiation* (i.e., the number of networks/nodes generating a signal) (Sarasso et al., 2021). Higher PCI values indicate responses that are at the same time diverse and organised, reflecting a higher spatio-temporal richness of the EEG signal in response to a given perturbation, a profile that has been originally associated with conscious states in TMS–EEG studies when compared to sleep (Casali et al., 2013).

Crucially, PCI computation is independent of the mode of perturbation: provided that the stimulus is clearly identifiable to allow averaging across trials, sensory events or pharmacological challenges may theoretically be used in place of the TMS pulse. Here, we take advantage of this generality to compute PCI using thermosensory stimuli as perturbations. Sensory-evoked perturbational complexity is much less investigated than TMS-based PCI, and it has been usually assessed employing proxies for temporal differentiation (i.e. entropy), spatial differentiation (i.e. functional connectivity), or both at the same time (i.e. algorithmic complexity, like Lempel-Ziv measures).

The few EEG studies that have analysed responses to auditory, visual, or noxious electrical stimuli employing the Lempel-Ziv algorithm show that complexity is differentially modulated by the meaningfulness of visual and auditory stimuli information (Orłowski & Bola, 2023) and, in clinical cohorts, correlates with recovery in patients with disorders of consciousness (Wu et al., 2011). Complementary work with other complexity metrics has shown that functional connectivity differs for cold and hot non-painful stimuli (Cuevas et al., 2024), while painful thermal stimuli increase entropy-based measures (Nuñez-Ibero et al., 2021). Entropy-based indices have also been used to forecast nociceptive responses during anaesthetic sedation (Melia et al., 2015; Valencia et al., 2016), and shown sensitivity to stimulus frequency in healthy participants (Melia et al., 2018). Although these findings span different sensory modalities and analytical frameworks, they converge on the notion that complexity metrics can quantify the effects of both perceptual (e.g., non-painful vs. painful) and physical (e.g., temperature) features of thermal stimuli on the brain responses they elicit.

Beyond establishing thermal stimulation as a suitable perturbation for PCI, we investigated whether this index also tracks context-dependent modulations of pain. To this end, we analysed two independent EEG datasets in which pain perception was modulated at different processing stages. In Dataset 1 (Courtin & Mouraux, 2022), topical application of transient receptor potential (TRP) agonists altered peripheral transduction, enabling us to probe whether PCI registers the change in afferent gain produced by chemical

sensitisation. The agonists that were specifically considered were capsaicin for TRPV1, menthol for TRPM8 and cinnamic aldehyde for TRPA1. In Dataset 2 (Mulders et al., 2023), participants underwent a task that varied the block-wise transition probabilities of receiving noxious hot or non-noxious cold stimuli, allowing us to assess whether PCI reflects the influence of statistics of the stimulus sequence on cortical dynamics.

We formulated three linked hypotheses. First, we hypothesised that PCI values would differ across stimulus intensities, with complexity scaling monotonically with intensity in the non-noxious range. In contrast, when the participant experiences pain, this relationship between intensity and complexity may be disrupted, leading to either increased or decreased PCI. Second, we expected that chemical sensitisation would modulate this intensity-dependent effect: depending on whether afferent gain is amplified or reduced by TRP agonists, PCI differences between low and high intensity conditions may be enhanced or attenuated. Third, we hypothesised that the statistics of probabilistic stimulus sequences would shape cortical dynamics with PCI decreasing for more frequent stimuli due to habituation-related effects. By testing these predictions, we assessed PCI capacity to measure context-dependent changes in the spatial and temporal differentiation that underlies thermal and nociceptive processing.

2 Methods

2.1 Datasets description

Two publicly available datasets employing the same contact thermode (QST.Lab; Strasbourg, France) were re-analysed in this study.

Dataset 1 was originally collected by Courtin et al. (Courtin & Mouraux, 2022) and is available at https://dx.doi.org/10.17605/OSF.IO/VCK6S. The study investigated the effects of different TRP channel agonists on thermal event related potentials (ERP). It included 62 participants each assigned to one of four agonist groups: menthol (20%), cinnamaldehyde (10%), capsaicin (0.25%), or capsaicin (1%). Each participant was treated with an active patch (group-specific TRP agonist) on one forearm and a vehicle patch (only ethanol absolute) on the other one, in a randomised order. After the removal of each patch, the treated area was stimulated with three series of 30 thermal stimuli (target temperatures: 10°C, 42°C and 60°C; duration: 200 ms). EEG data was collected using actively shielded Ag-AgCl electrodes placed on the scalp according to the international 10/20 system (32 channels for the menthol, cinnamaldehyde and capsaicin 0.25% groups; 64 channels for the capsaicin 1% group; WaveGuard EEG cap, Advanced Neuro Technologies, Hengelo, The Netherlands).

Dataset 2 was collected by Mulders et al. (Mulders et al., 2023) and is available at https://osf.io/8xvtg/. It included 31 participants who completed 10 blocks of 100 interleaved thermal stimuli delivered on the forearm. Stimuli were 250 ms long and consisted of two temperatures: I1 was set to 15°C for most participants, but could range between 15°C and 20°C; I2 was 58°C for most participants, but could be decreased to 57°C. For additional details see (Mulders et al., 2023). Stimuli were presented with fixed transition probabilities within each block (i.e., $p(I_1|I_2)$ and $p(I_2|I_1)$). Five probability combinations were tested, each repeated twice. EEG data was recorded using 64 Ag-AgCl electrodes placed according to the international 10/10 system (WaveGuard 64-channel cap, Advanced Neuro Technologies).

2.2 Preprocessing

EEG recordings were pre-processed using the *mne* (Gramfort et al., 2013; Larson et al., 2024) and *mne_bids* (Appelhoff et al., 2019) packages for Python (version 3.12.3). Each recording was visually inspected to identify channels that were flat or excessively noisy. Recordings with more than 30% of bad channels were excluded. Noisy channels were interpolated using spline interpolation. The EEG signal was re-referenced to the average,

and ocular artifacts were identified and removed using independent component analysis (ICA). Data were filtered using a notch filter at 50Hz and a bandpass filter (0.1-45Hz, second-order Butterworth). Continuous EEG signal was then segmented into epochs from -500 ms to 1500 ms relative to stimulus onset, and baseline corrected using a window from -500 ms to -10 ms. Epochs exceeding a peak-to-peak amplitude of 200µV were excluded. For each dataset, if more than 30% of epochs were rejected within a given condition (defined as participant-patch-temperature combination for Dataset 1, or participant-block-temperature combination for Dataset 2), the entire condition was excluded from further analysis. If more than 30% of the conditions in a participant were rejected, the participant was excluded. Based on these criteria we excluded two participants in Dataset 1 and one participant in Dataset 2. Finally, we excluded one other participant in Dataset 1 who had been excluded in the original paper (Courtin & Mouraux, 2022). For all remaining participants, the EEG signal was averaged across the first 21 epochs within each condition, corresponding to the highest number of artifact-free epochs available for all conditions and participants. These condition-level averages were used in subsequent analyses.

2.3 Computation of perturbational complexity

The perturbational complexity index (PCI) was calculated for each condition following the state transition-based approach developed by Comolatti et al. (Comolatti et al., 2019). This method quantifies the spatio-temporal complexity of evoked EEG responses by computing state transitions (Fig 1). First, it computes the singular value decomposition of the signal matrix to select components that account for at least 99% of the response energy (*spatial differentiation* proxy). Among these, only components with a signal to noise ratio (SNR) above a minimum threshold (*min SNR*) were retained for further analysis. On these components, complexity is estimated in terms of recurrent quantification analysis by evaluating the number of *state transitions* (NST, *temporal differentiation* proxy). For each component, voltage-amplitude differences between all time points (distance matrices) were computed separately for pre-stimulus and post-stimulus windows. These matrices were then thresholded using several levels ε_n to obtain binary transition matrices indicating the number of times the signal crossed a threshold, capturing transitions between distinct states. Since the NST is quantified across several thresholds, the threshold ε_n* maximizing the difference in NST between the post- and pre-stimulus windows (ΔNST) was identified and retained, and the ΔNST values were summed across components to obtain the PCI for a given condition.

Several considerations were applied to ensure comparability with previous work. First, components with SNR below the *min SNR* threshold were excluded. Since it is possible to expect a lower SNR for thermal evoked potentials acquired over 30-100 epochs compared to the original signal for which this algorithm was designed (200 stimuli, TMS-EEG), the *min SNR* was set to 1.1, corresponding the lowest value previously investigated (Comolatti et al., 2019). Second, conditions with no surviving components (PCI = 0) were excluded. Third, to improve comparability across conditions, PCI was computed only on the first 21 epochs within each condition, corresponding to the highest number of retained trials across all conditions in both datasets. Fourth, while in Dataset 2 PCI was calculated using all the recording 64 channels, in Dataset 1 and in the models that grouped Dataset 1 and Dataset 2 together PCI was computed on a subsample of 32 common channels. Finally, the *k* parameter, which determines the relative weight of pre- and post-stimulus NST during thresholding, was fixed at 1.1 in accordance with the original implementation (Comolatti et al., 2019).

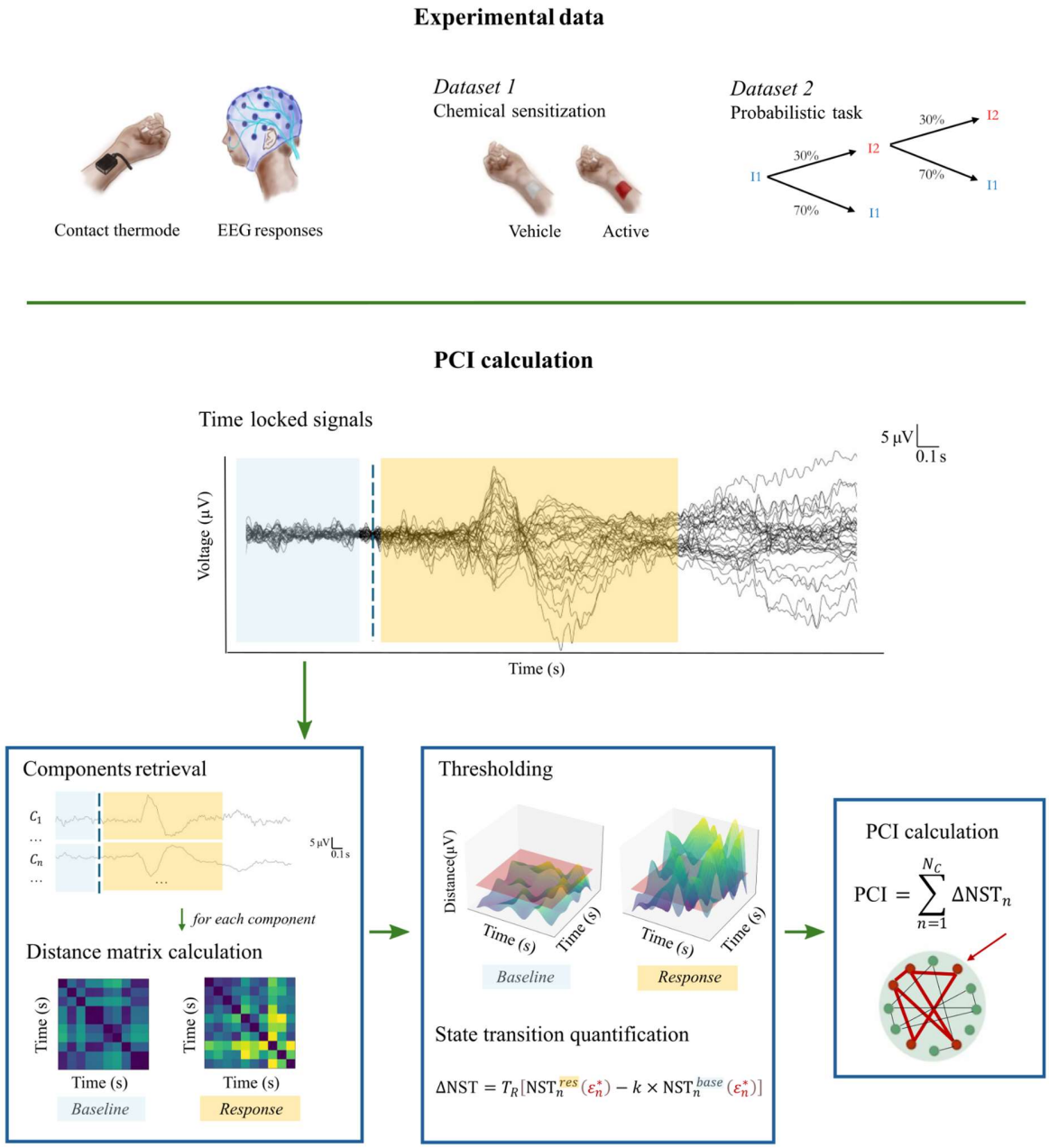

Fig 1. Workflow for estimating the Perturbational Complexity Index (PCI) from evoked EEG responses
PCI was estimated in two EEG datasets in which evoked responses were recorded following cold and hot stimulation delivered via a contact-thermode stimulator. Dataset 1 additionally involved the topical application of an agonist solution or vehicle (placebo-controlled), while in Dataset 2 participants completed a learning task and received sequences of cold (I1) and hot (I2) stimuli generated with five pairs of transition probabilities (here the probability of receiving a cold stimulus after a hot one p(I1|I2) = 0.7 and p(I2|I1) = 0.3). In both datasets, EEG data were identically preprocessed, and the stimulus-locked averaged signals were entered into the state-transition PCI algorithm of Comolatti et al. (Comolatti et al., 2019), that compared the state transitions of the baseline (blue) and response (yellow) time window (the dotted

vertical line indicates the stimulus onset). This yielded a single PCI value for each condition (participant- agonist - temperature in Dataset 1; participant - block - temperature in Dataset 2).

NST = number of state transitions; ε_n* = threshold that maximises the difference between baseline and response NST for the component n; T_R = number of samples in the response; k = weight parameter between pre- and post-stimulus transitions; N_c = number of total components C.

2.4 ERP peak parameters

To evaluate whether PCI reflects additional information compared to the amplitude or morphology of canonical evoked responses, we conducted a control analysis focused on the N2–P2 complex, a well-characterised biphasic deflection elicited by thermal stimulation, typically maximal at the vertex. This analysis aimed to determine whether PCI simply reflects the magnitude of evoked activity or instead indexes distinct aspects of spatio-temporal complexity.

Following established procedures in ERP research, the N2–P2 complex was identified in the averaged signal for each condition. Latencies and amplitudes of the N2 and P2 components were extracted using the *mne.preprocessing.peak_finder()* function, after visual inspection of both waveforms and topography to define an appropriate time window. If peaks could not be reliably identified or if the scalp distribution was ambiguous, the corresponding condition (defined as participant–agonist–temperature in Dataset 1 or participant–block–temperature in Dataset 2) was excluded from the analysis.

In Dataset 1, peak parameters were identified from the Cz electrode after averaging all valid epochs per condition. The EEG signal was re-referenced to the average of the mastoid electrodes (M1 and M2), to replicate the approach used in Courtin et al. (Courtin & Mouraux, 2022). In Dataset 2, peak extraction was also performed at Cz but on the average of the first 21 epochs per condition. Due to consistent artifact contamination at the mastoids, an average reference across all electrodes was applied to minimise condition-level exclusions. Because N2–P2 components were analysed only in relation to PCI within each dataset, and not compared across datasets, the use of different referencing schemes does not constitute a confound. This control analysis allowed us to directly compare classical ERP parameters with PCI estimates, testing whether PCI explains variance beyond canonical evoked responses.

2.5 Statistical analysis

All statistical analysis were performed in R (version 4.3.3, (*R: The R Project for Statistical Computing*, s.d.), using the *stats, car* and *emmeans* packages. To assess how PCI varied across conditions and datasets, we used linear regression models. The dependent variable was square-root-transformed PCI ($\sqrt{PCI}$) to preserve the normality assumption. Distribution of the residuals was assessed using quantile-quantile (QQ) plots to verify test assumptions. If a data point strongly violated normality, it was removed, and the model was re-estimated. When post-hoc comparisons were required, p-values were adjusted using the Holm-Bonferroni procedure to control for the family-wise error rate ($\alpha = .05$). We constructed four models to assess condition-specific effects and potential covariates.

2.5.1 Dataset 1: Effects of temperature and TRP agonists on PCI

To test the effect of different TRP channel agonists on PCI across three temperatures (10°C, 42°C, 60°C), we fitted the following model:

$\sqrt{PCI}$ ~ Temperature + Agonist + Temperature:Agonist + Temperature:Agonist:Patch (Model 1)

where Temperature, Agonist, and Patch were categorical predictors, with Patch indexing whether stimulation was preceded by an active or vehicle treatment. Since this model employs only categorical variables, we used a Type III ANOVA to investigate the significance of effects.

2.5.2 Dataset 2: Effects of temperature and probabilistic context on PCI

To assess the effect of the absolute probability of receiving a cold stimulus (p(I1) = 1 - p(I2)) on PCI values across different blocks, we tested the following model:

$\sqrt{PCI}$ ~Temperature*p(I1) (Model 2)

where Temperature was a categorical predictor, (reference = I1), and p(I1) a metric variable, mean-centered prior to the regression. Regression coefficients and marginal effects were employed to evaluate the significance of effects.

2.5.3 Comparison across datasets

To assess the effect of Temperature across the 2 datasets, we tested the following model:

$\sqrt{PCI}$ ~Temperature*Type (Model 3)

where Temperature was a metric variable encompassing all the temperatures in the two datasets, and Type represents the categorical variable encoding the stimulus type (cold vs hot). Regression coefficients and marginal effects were employed to evaluate the significance of effects.

2.5.4 ERP control analysis

To test whether PCI could be explained by canonical evoked responses, we modelled PCI as a function of N2 and P2 latency and amplitude:

$\sqrt{PCI}$ ~ N2P2_Amplitude*N2_Latency*P2_Latency (Model 4)

Predictor variables were mean-centred and scaled to reduce multicollinearity. Regression coefficients and marginal effects were employed to evaluate the significance of effects. The 95% confidence interval for the model's R^2 was estimated using the *Ci.rsq()* function from the *psychometric* package in R.

3 Results

3.1 PCI varies as a function of temperature

To assess whether PCI reflects differences in stimulus intensity, we first examined the effect of temperature on PCI for each dataset separately. In Dataset 1, participants received three temperature stimuli (10°C, 42°C, and 60°C). Model 1 revealed a significant main effect of temperature on $\sqrt{PCI}$ ($F(2,321) = 16.72$, $p < .001$). Pairwise comparisons within the vehicle condition indicated that $\sqrt{PCI}$ at 42°C was significantly lower than at both 10°C and 60°C (difference $\Delta_{42\text{-}10} = -1.50$, $SE_{42\text{-}10} = 0.13$, $p < .001$; $\Delta_{42\text{-}60} = -1.24$, $SE_{42\text{-}60} = 0.13$, $p < .001$). Additionally, $\sqrt{PCI}$ at 10°C was slightly higher than at 60°C ($\Delta_{10\text{-}60} = 0.25$, $SE_{42\text{-}10} = 0.13$, $p = .048$).

In Dataset 2, participants received two temperature stimuli (I1≈15°C, I2≈58°C). Model 2 revealed a significant effect of Temperature, with lower values associated with hot stimuli (average marginal effect AME of Temperature I2: = -0.35, SE = 0.09, $p < .001$), a finding in line with Dataset 1.

Model 3 assessed the main effect of Temperature on both datasets, allowing us to control for stimulus type (Type = hot or cold) and to investigate how PCI varies across all the considered temperatures. The results of the regression showed significant effects of both Temperature (regression coefficient β = -0.10, SE = 0.04 p = .014), Type (β_{hot} = -5.68, SE = 0.72, p < .001) and the interaction term Type × Temperature (β = 0.17, SE = 0.04, p < .001), indicating that stimulus type influences the Temperature slope. Indeed, the marginal effect of temperature varied for the cold and hot stimuli (Marginal Effect ME_{cold} = -0.10, SE = 0.04, p =.014; ME_{hot} = 0.07, SE = 0.01, p < .001), suggesting a U-shaped relationship: the more the stimulus temperature departs from the baseline, the more the complexity increases.

Together, these findings indicate that PCI is modulated by stimulus temperature, with increased complexity observed at temperatures further from baseline (Fig 2), and a slightly more pronounced effect within the cold temperature range. This effect may be due to the limited range of temperatures tested, their asymmetry in their physical distance from baseline, differences in perceived intensity, or by distinct neural processing engaged by cold and hot stimuli.

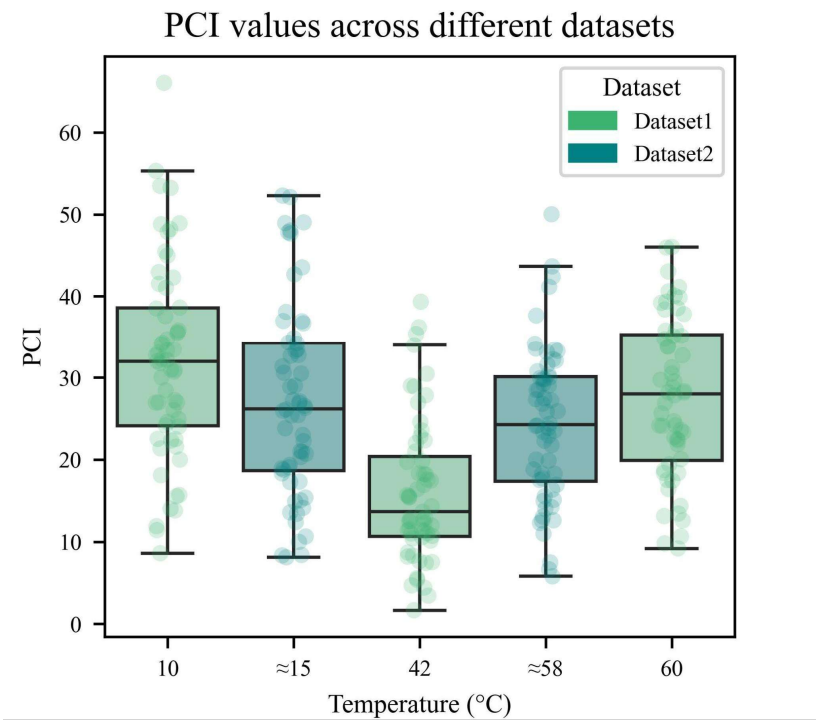

Fig 2. PCI values across temperature conditions in both datasets.
Box-and-whisker plots summarise PCI values computed on the 32-channel montage for each temperature in Dataset 1 (Courtin & Mouraux, 2022; 10 °C, 42 °C, 60 °C, patch="vehicle") and Dataset 2 (Mulders et al., 2023; I1≈15 °C and I2≈58 °C, transition probabilities = 0.5). The single PCI estimate for each condition is shown as a semi-transparent dot. Boxes denote the median and inter-quartile range (IQR), whiskers extend to 1.5 × IQR. The PCI varied non-linearly with temperature across both datasets, reaching highest values at the temperature extremes (10 °C and 60 °C, Dataset 1) and a minimum at the intermediate 42 °C.

3.2 PCI varies as a function of TRP agonist application

Dataset 1 included within-subject comparisons of electrophysiological responses following application of either a TRP agonist or vehicle patch to the forearm. Using Model 1, we found that the Temperature × Agonist × Patch interaction was significant ($F(12,321)$ = 2.01, p = .023), prompting further analysis within each patch

condition. Notably, Agonist and Temperature x Agonist effects were not significant ($F(3,321) = 2.54$, $p = .057$; $F(6,321) = 1.27$, $p = .27$, respectively), suggesting that the effect is specific to the three-way interaction.

Significant decreases in $\sqrt{PCI}$ were observed under cold stimulation (10°C) for both capsaicin 1% ($\Delta_{vehicle\text{-}agonist} = 0.91$, $SE_{42\text{-}10} = 0.37$, $p = .039$) and menthol 20% ($\Delta_{vehicle\text{-}agonist} = 1.08$, $SE_{42\text{-}10} = 0.36$, $p = .012$). Agonist manipulation did not lead to significant differences at 42 °C or 60 °C (Fig 3), and no effects were observed on any temperature under capsaicin .25% or Cinnamic aldehyde 10%.

Overall, topical capsaicin and menthol selectively reduced complexity during cold stimulation, with no detectable influence at warmer temperatures.

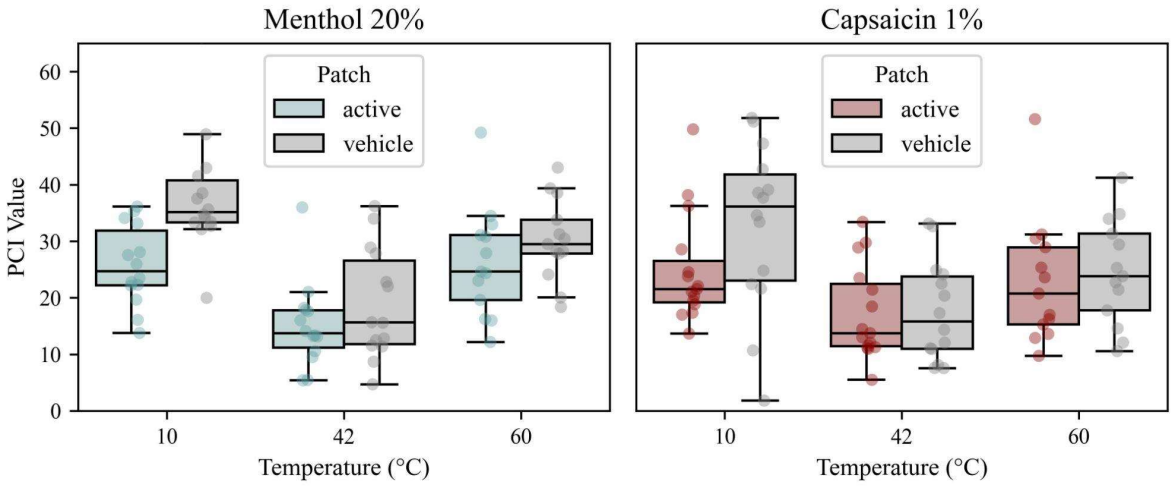

Fig 3. PCI values as a function of temperature and topical patch in Dataset 1.
Box-and-whisker plots show raw PCI scores (32-channel montage) for menthol 20 % (left) and capsaicin 1 % (right). For each agonist, participants received a vehicle patch and an active patch before stimulation at 10 °C, 42 °C, and 60 °C; the patch order was counter-balanced within subjects. Semi-transparent dots represent the single PCI estimate for every participant-temperature-patch combination, boxes mark the median and IQR, and whiskers extend to 1.5 × IQR. Both agonists selectively lowered complexity at 10 °C, whereas no consistent patch effect emerged at 42 °C or 60 °C.

3.3 PCI is affected by probabilistic manipulations

Dataset 2 allowed us to examine whether cortical complexity is modulated by expectation as, across successive blocks, the absolute probability of receiving a cold ($I_1 \approx 15$°C) stimulus was set to $p(I_1) = 0.3$, 0.5, or 0.7. Notably, the probability of receiving a hot (I_2) stimulus varied accordingly but in the opposite fashion, being $p(I_2) = 1 - p(I_1)$. Thus, three different combinations of absolute stimulus probabilities were present in the dataset.

Model 2 assessed the main effect of this stimulus probability change and its interaction with stimulus temperature on $\sqrt{PCI}$ (Fig 4). The regression coefficients associated with $p(I_1)$ ($\beta = 0.14$, $SE = 0.07$, $p = .034$) and the interaction term $p(I_1)$ x Temperature ($\beta = -0.24$, $SE = 0.09$, $p = .011$) were significantly different from zero. When fixing the Temperature to I_1 (cold), $p(I_1)$ at I_1 temperature marginal effect was significant and positive ($ME_{cold} = 0.14$, $SE = 0.07$, $p = .034$), indicating that complexity increased with the absolute probability of cold stimuli. In contrast, for I_2 (hot) stimuli, the effect was negative and not significant ($ME_{hot} = -0.10$, $SE = 0.07$, $p = .140$). Since $p(I_2) = 1 - p(I_1)$, this implies that complexity tended to increase with the absolute probability of a given stimulus, more reliably so for cold temperatures.

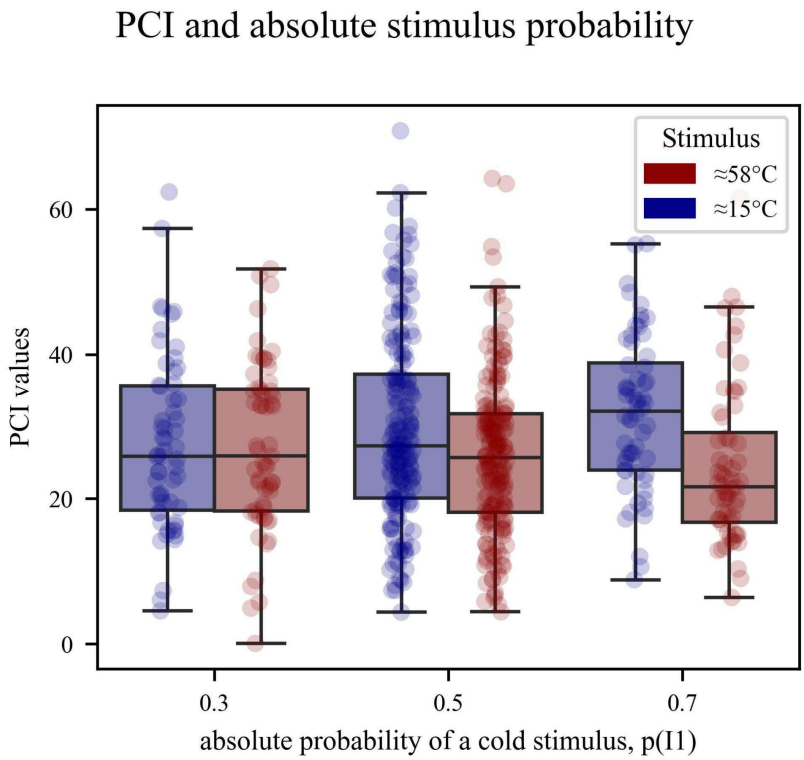

Fig 4. PCI as a function of p(I1).
Box-and-whisker plots show raw PCI scores calculated from the full 64-channel montage, grouped by the block-wise probability of receiving a cold stimulus I1≈ 15 °C (0.3, 0.5, 0.7). Colours distinguish the two temperatures: hot I2≈ 58 °C (red) and cold I1≈ 15 °C (blue). Each semi-transparent dot represents the single PCI estimate for one participant in a given probability × temperature block; boxes mark the median and IQR and whiskers extend to 1.5 × IQR. Consistent with the statistical analysis (Sections 3.1 and 3.3), it is possible to observe a Temperature effect on PCI, being it lower for hot stimuli (AME = -0.35, p < .001). Furthermore, complexity increases when p(I1) increases for cold stimuli (ME_{cold} = 0.140, p = .034).

3.4 PCI is largely independent of conventional N2–P2 peak metrics

To determine whether PCI merely tracks the latency or amplitude of the N2–P2 complex, we fitted Model 4 separately for each dataset and temperature. In Dataset 1 (Fig 5), for cold stimuli, the marginal effect of N2-P2 amplitude on $\sqrt{PCI}$ was significant (AME = 0.23, SE = 0.10, p = .024), but no significant effect was found for N2 and P2 latency (AME = -0.17, SE = 0.11, p = .124; AME = 0.09, SE = 0.12, p = .448, respectively). For hot stimuli, no marginal effect proved significant, even though a negative trend was present for N2 latency (N2 latency: AME -0.25, SE = 0.13, p = .052; P2 Latency: AME = -0.14, SE = 0.11, p = .188; N2-P2 Amplitude: AME = 0.02, SE = 0.11, p = .835).

In Dataset 2 (Fig 6), no significant marginal effects were found for all the regressors for cold stimuli (N2 latency: AME 0.03, SE = 0.05, p = .504; P2 Latency: AME = -0.02, SE = 0.05, p = .753; N2-P2 Amplitude: AME = 0.03, SE = 0.06, p = .570). For hot stimuli, only N2 latency had a significant effect on complexity (N2 Latency: AME = 0.20, SE = 0.05, p < .001, P2 Latency: AME = -0.03, SE = 0.05, p = .523; N2-P2 Amplitude: AME = 0.04, SE = 0.05, p = .496).

To summarise, these results, while showing some sporadic association between peak parameters and complexity, do not point towards a consistent effect, suggesting that PCI may explain other features associated with EEG responses to thermal stimuli. Furthermore, the models explained little variance: R^2 never

exceeded .10 and every 95 % confidence interval included zero for both cold (Dataset 1: $R^2 = .10$, CI [-.22, .42]; Dataset 2: $R^2 = .02$, CI [-.20, .25]) and hot stimuli (Dataset 1, $R^2 = .10$, CI [-.27;.48]; Dataset 2, $R^2 = .05$, CI [-.23;.34]).

These results suggest that classical ERP peak parameters account for only a small fraction of PCI variability, reinforcing the idea that PCI quantifies aspects of spatio-temporal complexity beyond traditional amplitude-latency measures.

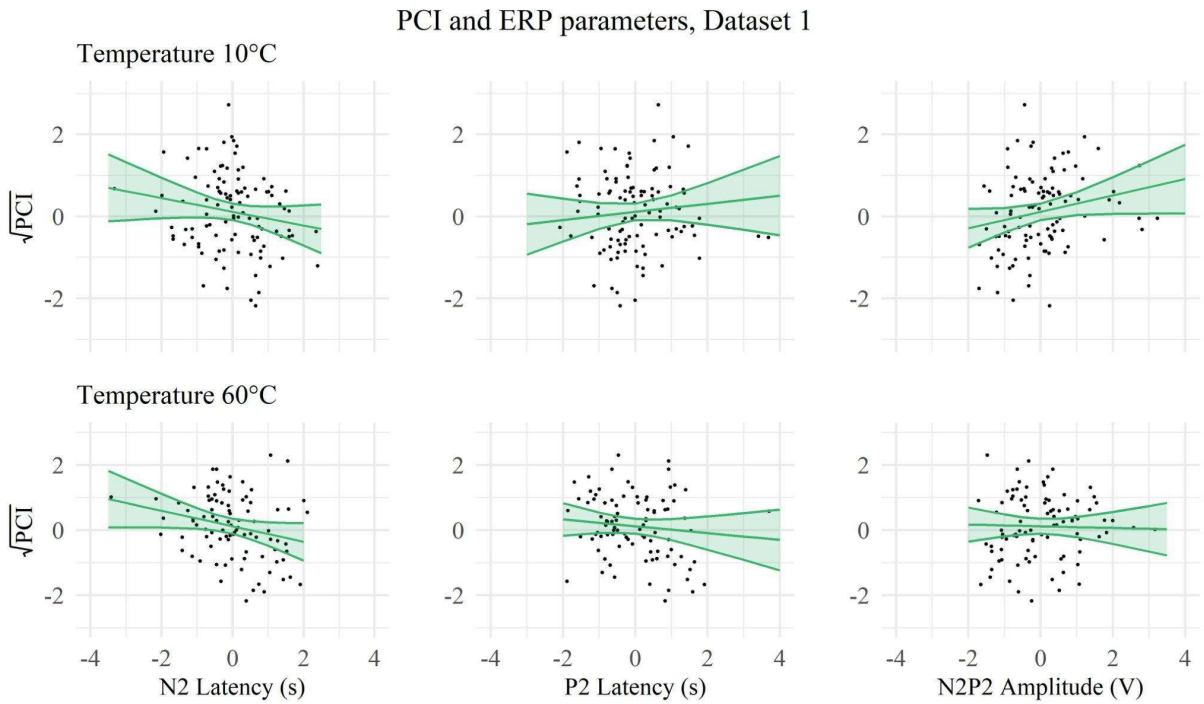

Fig 5. Relationship between PCI and N2–P2 peak parameters in Dataset 1. Each panel shows z-scored PCI plotted against N2 latency, P2 latency, or N2–P2 amplitude; the upper row corresponds to 10 °C, the lower row to 60 °C. Solid lines are least-squares fits with 95 % confidence bands. For cold temperature, N2-P2 Amplitude had a significant effect on PCI (AME = .23, p = .024), while no other significant effect was found between peak parameters and complexity. All the variables in the plot have been mean-scaled and centered.

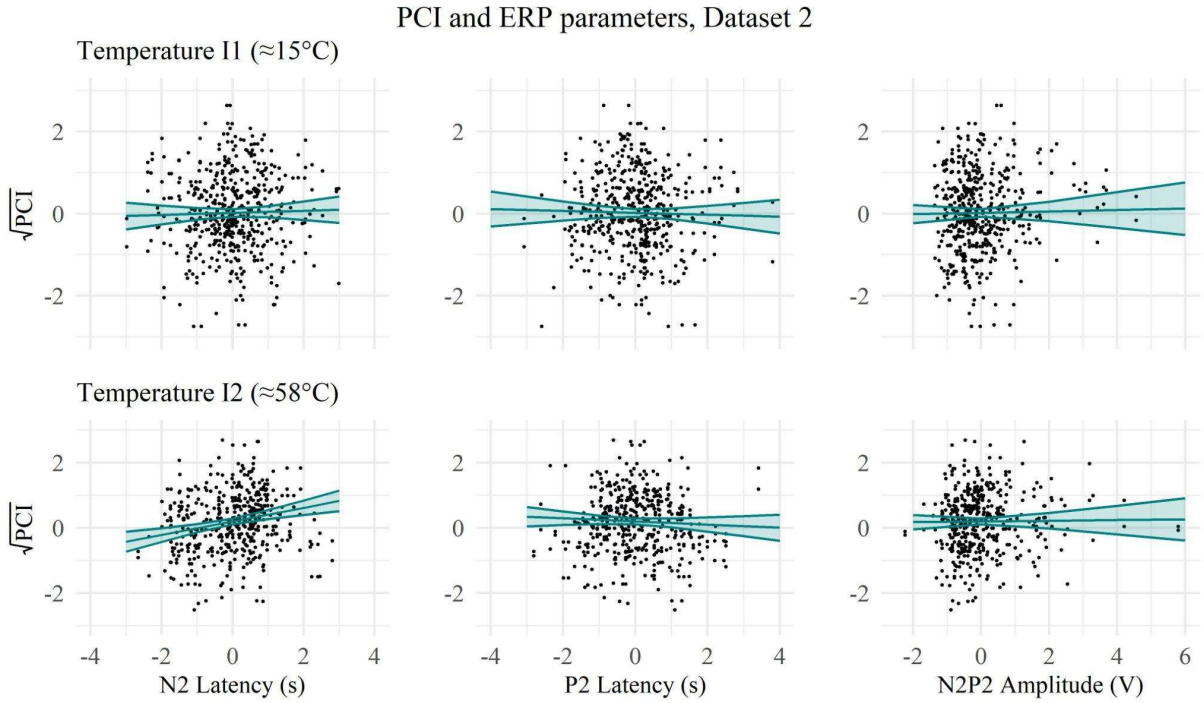

Fig 6. Relationship between PCI and N2–P2 peak parameters in Dataset 2. Each panel shows z-scored PCI plotted against N2 latency, P2 latency, or N2–P2 amplitude; the upper row corresponds to I1≈ 15 °C, the lower row to I2≈ 58°C. Solid lines are least-squares fits with 95 % confidence bands. For hot stimuli, there was a significant marginal effect of N2 Latency (AME = .20, $p < .001$). All the variables have been mean-scaled and centered.

4 Discussion

The present study used sensory-evoked perturbational complexity to characterise how the human cortex integrates and differentiates information under graded thermal input, peripheral sensitisation, and probabilistic manipulation. Four key findings emerged: (1) cortical complexity scaled with stimulus intensity in a non-linear manner; (2) peripheral sensitisation reduced PCI during cold perception; (3) probabilistic manipulations have a detectable impact on PCI; and (4) PCI captured aspects of the evoked response beyond those reflected in conventional ERP measures of latency and amplitude.

In response to graded thermal input, PCI systematically varied with the stimulus distance from baseline skin temperature. In Dataset 1, PCI exhibited a U-shaped pattern, reaching its minimum at 42 °C and increasing significantly at both 10 °C and 60 °C. Notably, 10 °C elicited slightly higher PCI values than 60 °C, suggesting that intense cold may recruit a more diverse or distributed set of cortical states than intense hot, a finding confirmed also in Dataset 2 (≈15°C vs ≈58°C). This non-linear profile aligns with previous findings, which show that thermal extremes yield a decrease in EEG alpha power, likely reducing low-frequency synchronisation (Courtin & Mouraux, 2024; Tayeb et al., 2022). The differential effects of cold and hot stimulation may emerge from differences in information processing, as suggested by the difference in spatio-temporal and spectral characteristics of brain activity elicited by cold and hot stimuli (Watanabe et al., 2025). However, such effects may also stem from imperfect matching of stimuli across modalities, for example in terms of perceived intensity or painfulness. Another key finding is that PCI was sensitive to peripheral sensitisation induced by TRP agonists. In Dataset 1, topical application of menthol (20%) and capsaicin (1%) significantly reduced PCI in response to cold stimulation (10 °C), relative to vehicle patches. This reduction in PCI may suggest that complexity is dependent on the state of the system prior to the stimulus, perhaps more than on the differences in afferent gain. Indeed, menthol may reduce perceived intensity of cold in some contexts (Andersen et al., 2015) but capsaicin typically does not (Courtin & Mouraux, 2022), despite both increasing spontaneous sensations during patch application. PCI may thus reflect not only the properties of the stimulus, but also the brain's readiness to process it in a flexible, integrative manner, highlighting that spatio-temporal complexity may exhibit some degree of state dependency (Battaglia, 2014).

These results are consistent with prior ERP findings from the same dataset, where menthol application led to reduced N2–P2 amplitudes and prolonged latencies, and capsaicin similarly reduced amplitude without significantly affecting latency (Courtin & Mouraux, 2022). Critically, even though in the original paper significant variations in amplitude and latencies could be observed also for hot-evoked responses in response to menthol 20%, capsaicin 1% and cinnamic aldehyde 10% patches, such effects were not significant for PCI. Yet, while classical ERPs capture signal magnitude and timing at specific scalp locations and may be correlated to some extent to spatio-temporal complexity, PCI offers a global, state-based account of how stimulus-evoked activity unfolds across time and space, possibly providing different information, thus accounting for this discrepancy. PCI reductions cannot indeed be fully explained by changes in conventional ERP features. While decreases in N2–P2 amplitude or shifts in latency could hypothetically lower the number of high-SNR components retained during the PCI calculation leading to a PCI decrease, regression analyses showed that ERP parameters explained only a small fraction of PCI variance ($R^2 \leq .10$ across conditions).

Finally, when assessing PCI sensitivity to probabilistic manipulations (i.e., sequence statistics) we found evidence of modulation of PCI by the probability of receiving a cold stimulus in Dataset 2. Concurrently, existing evidence points towards an effect of sequence statistic on complexity, as studies using laser-evoked potentials have shown that the N2-P2 waveform can be modulated by stimulus novelty in combination with saliency, unpredictability, and behavioural relevance (Ronga et al., 2013; Torta et al., 2012). However, whether our findings genuinely reflect changes in cognitive processing related to the probabilistic

manipulation is not certain. Because stimulus probabilities were asymmetrical in some blocks and we analysed the first 21 artefact-free epochs for each temperature-probability combination, stimuli with a low probability were on average delivered later in the sequence than stimuli with a high probability. Thus, we could not control for the effect of habituation across trials, which is known to influence brain responses to thermal stimuli and may have lowered the complexity associated with low-probability conditions (Greffrath et al., 2007).

Theoretical implications: PCI beyond consciousness research

PCI was originally developed within the framework of Integrated Information Theory to quantify the brain's capacity for consciousness based on the complexity of cortical responses to direct perturbation, typically via transcranial magnetic stimulation (TMS) (Casali et al., 2013; Comolatti et al., 2019; Tononi, 2004). It reflects the degree to which neural activity is both *differentiated* (i.e., rich in diverse, time-varying components) and *integrated* (i.e., distributed across interconnected sources).

In this framework, *differentiation* corresponds to the number and diversity of unique neural responses: the more diverse the unique neural responses, the more complex and unpredictable the signal will be over time (Marshall et al., 2016). This notion is closely linked to *temporal differentiation*, as the recorded signal reflects the composition of multiple irreducible time series. In contrast, *integration* reflects the coherent propagation of activity across brain regions, enabling distant neural populations not directly affected by the perturbation to respond in a coordinated manner (Marshall et al., 2016). This is conceptually related to *spatial differentiation,* since functional integration requires interconnections among spatially distributed sources. Notably, there is an overlap between IIT constructs of *differentiation* and *integration* and the measurable signal properties of *temporal* and *spatial differentiation*. For example, the diversity of unique neural responses (*IIT differentiation*) depends in part on the variety of contributing brain regions (*spatial differentiation*), while the coordinated propagation of activity (*IIT integration*) shapes the structure of the temporal signal (*temporal differentiation*) (Sarasso et al., 2021). PCI concurrently captures both dimensions simultaneously (Casali et al., 2013). Indeed, TMS-evoked PCI has been shown to clearly distinguish between states of consciousness, suggesting that this combined approach more accurately reflects the richness of brain dynamics (Casarotto et al., 2016; Sinitsyn et al., 2020; Wang et al., 2022).

Extending this framework to sensory-evoked PCI introduces a new interpretive domain. In contrast to TMS, sensory stimulation is already embedded within conscious perceptual experience. Yet, the same principles apply: high PCI may indicate that the stimulus engages brain-wide, temporally rich processing that supports adaptive, flexible responses; low PCI may signal reduced integration or differentiation, consistent with less flexible or stereotyped neural responses.

Within predictive coding frameworks (Friston, 2005), a low complexity could correspond to failures in hierarchical inference, such as maladaptive precision weighting or impaired model updating, both of which have been implicated in chronic pain pathophysiology (Chen & Wang, 2023). Notably, this interpretation aligns with evidence from chronic pain research, where states of increased sensitivity or persistent pain are associated with less variable, more spatially and temporally constrained cortical dynamics (Apkarian et al., 2011; Baliki et al., 2008; Wei et al., 2022). Therefore, future research may investigate PCI in response to thermal stimuli delivered to individuals with chronic pain.

These findings open new avenues for applying complexity-based metrics in sensory neuroscience, particularly in understanding how endogenous state changes and exogenous manipulations jointly shape the brain's capacity to process, integrate, and interpret nociceptive input. Further research should systematically investigate how PCI varies within a single individual over time, in response to different stimulation modalities, recording techniques (e.g., magnetoencephalography), and contextual modulation to fully characterise its utility as a systems-level marker of adaptive or maladaptive brain states.

5 Conclusion

Perturbational complexity has primarily been applied as a global index of consciousness, showing that reduced complexity reflects loss of integration and differentiation of the information carried on by a TMS perturbation. Here, we extended the use of PCI to sensory-evoked perturbations, applying it to characterise the network states underlying thermal and nociceptive processing. Across two independent datasets, we found that PCI was sensitive to both stimulus intensity, peripheral sensitisation via TRP agonists, and probabilistic manipulations. The negligible association between PCI values and conventional ERP parameters highlights PCI capacity to quantify large-scale changes in the spatio-temporal organisation of evoked cortical responses.

By assessing PCI sensitivity to stimulus features and contextual modulation, our findings support the use of perturbational complexity-based metrics as a sensitive tool for probing the large-scale neural dynamics associated with thermosensation and pain perception.

Data and Code Availability

All data are publicly available via the Open Science Framework
(Dataset 1: https://dx.doi.org/10.17605/OSF.IO/VCK6S; Dataset 2: https://osf.io/8xvtg/).
The analysis code used in this study is available at: https://github.com/Body-Pain-Perception-Lab/pain-PCI_pipeline/tree/main/publication.

Authors contributions

KTM: Conceptualisation, data curation, formal analysis, funding acquisition, methodology, project administration, software, validation, visualisation, original draft, writing – review & editing.
ASC: Investigation, methodology, resources, supervision, validation, original draft, writing – review & editing.
DM: Investigation, methodology, resources, writing – review & editing.
FF: Funding acquisition, methodology, project administration, supervision, original draft, writing – review & editing.

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Declaration of Competing Interest

Authors report no conflicts of interest

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