



Chronic pain – A maladaptive compensation to unbalanced hierarchical predictive processing

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ABSTRACT

The ability to perceive pain presents an interesting evolutionary advantage to adapt to an ever-changing environment. However, in the case of chronic pain (CP), pain perception hinders the capacity of the system to adapt to changing sensory environments. Similar to other chronic perceptual disorders, CP is also proposed to be a maladaptive compensation to aberrant sensory predictive processing. The local-global oddball paradigm relies on learning hierarchical rules and processing environmental irregularities at a local and global level. Prediction errors (PE) between actual and predicted input typically trigger an update of the forward model to limit the probability of encountering future PEs. It has been hypothesised that CP hinders forward model updating, reflected in increased local deviance and decreased global deviance. In the present study, we used the local-global paradigm to examine how CP influences hierarchical learning relative to healthy controls. As hypothesised, we observed that deviance in the stimulus characteristics evoked heightened local deviance and decreased global deviance of the stimulus-driven PE. This is also accompanied by respective changes in theta phase locking that is correlated with the subjective pain perception. Changes in the global deviant in the stimulus-driven-PE could also be explained by dampened attention-related responses. Changing the context of the auditory stimulus did not however show a difference in the context-driven PE. These findings suggest that CP is accompanied by maladaptive forward model updating where the constant presence of pain perception disrupts local deviance in non-nociceptive domains. Furthermore, we hypothesise that the auditory-processing based biomarker identified here could be a marker of domain-general dysfunction that could be confirmed by future research.

1. Introduction

Chronic pain (CP) is the primary source of worldwide suffering and disability affecting 20 % of the adult population (Breivik et al., 2006). It is defined as pain that persists or recurs for longer than 3 months (Treede et al., 2019). Persistent exposure to noxious stimuli results in hypersensitivity to nociceptive input, decreased pain threshold and cortical reorganisation (Baliki and Apkarian, 2015; Basbaum et al., 2009) different from that of prolonged acute pain (Apkarian et al., 2011; Ballantyne, 2018). CP affects several cognitive processes (De Ridder et al., 2021). Particularly, attentional resources are directed towards the interoceptive perception of pain depleting the brain from resources for

external tasks. Furthermore, perceptual decisions about any given input, including nociceptive signals, depend on the context in which the stimulus is presented (Wiech et al., 2010).

CP, like other chronic perceptual disorders (De Ridder et al., 2014; Mohan et al., 2022) and hallucinations in higher-level cognitive disorders (Powers et al., 2017), is explained through the predictive coding theory (Chen, 2023; Büchel et al., 2014). The theory states that the brain maintains an active model of the world that predicts the incoming input (Knill and Pouget, 2004; Friston and Kiebel, 2009). Discrepancies between bottom-up sensory input and top-down predictions generate prediction errors (PE) (Heilbron and Chait, 2018) which are then used to update the model, upon which the predictions are based (Bastos et al.,

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2012). Predictive coding operates in a hierarchical fashion where PEs from the lower level are used to update the predictions at the higher levels, and these predictions are cyclically used to minimise PEs at the lower levels (Wacongne et al., 2011). In CP, pain perception is hypothesised to be a maladaptive mechanism of the brain to minimise unresolved PEs at the lower level (Mohan and Vanneste, 2017).

To test this hypothesis, we use the local-global paradigm, a variation of the classic auditory oddball paradigm, designed to probe the hierarchical predictive coding system (Mohan et al., 2022; Wacongne et al., 2011; Bekinschtein et al., 2009). Unlike the classic oddball paradigm whose mechanism is argued to be possibly driven by neural adaptation, the local global-paradigm is repetitively shown to test the hierarchical predictive coding system (Wacongne et al., 2011; Uhrig et al., 2014). The paradigm consists of a standard (four tones and a noise burst), deviant (five tones) and omission (four tones) sequences which are presented in a 75 %–15 %–10 % oddball probability. The omission sequence is additionally presented by itself with 100 % probability. We define two prediction errors (i) the stimulus-driven PE (sPE) which measures the deviance in evoked response owing to the deviance of the 5th stimulus (noise burst) from the expectation of four tones and the deviance of the sequence of the five tones from the expectation of the four tones followed by the noise burst. This will be the primary outcome measure of the current project. (ii) context-driven PE (cPE) which measures the deviance to unexpected omission of the 5th stimulus. When compared to the expected omission of the 5th stimulus, it produces a response that is purely driven by the difference in probability of the same stimulus. Based on previous literature, we know that the context in which different stimuli are presented may alter the physiological response of the person with CP (Moseley, 2007; Moseley and Arntz, 2007; Arntz and Claassens, 2004). Although there is no potential threat posed by the auditory stimulus here, the examination of the change in context is the secondary outcome measure for the current project.

Each of the PEs has two components – (i) involuntary (exogenous or pre-attentive) component that reflects a deviation of stimulus characteristics from a predicted regularity or a short-term sensory memory trace. This is also known as the famous mismatch negativity (MMN) and may be considered the local deviance of the sPE and cPE (Näätänen and Picton, 1987) (ii) The second component is driven by changes in top-down attention (endogenous, attention-induced) (Wacongne et al., 2011) and is called the late positive potential or P300 and may be considered the global deviance of the sPE and cPE. The attentional disruption in CP has been reflected in decreased P300 amplitude in the classic auditory oddball paradigm (Gubler et al., 2022), although there is more ambiguity surrounding pre-attentive sensory processing in CP patients (Yao et al., 2011; Dick et al., 2003; Fan et al., 2018). However, no one has presented empirical evidence to CP being a maladaptive compensation to hierarchical predictive processing.

According to the original paper in healthy adults (Wacongne et al., 2011), the local deviance (MMN) is smaller, and the global deviance (P300) is bigger indicating the brain's hierarchical PE processing, where the global deviance at a higher level compensates for the local deviance. However, in CP, we would expect the opposite. If CP were a compensation of the system's lower-level deviance, we expect to see an increase in the local deviance (MMN) and decrease in the global deviance (P300) compared to controls.

Understanding the neural oscillatory signature of predictive coding and particularly of CP can further the identification of a biomarker for CP using the current paradigm. In the resting state, CP is associated with aberrant thalamocortical rhythms i.e. reduced alpha and increased theta the latter being correlated with the subjective pain perceptions (Llinás et al., 1999; Vanneste et al., 2018). However, increased theta activity in the prefrontal regions have also found been found to be associated with CP (Rustamov et al., 2022). In a mouse model of formalin-induced pain, the authors show a shift of the theta peak to lower frequencies during nociceptive phases and not during the pain-free phases (Iwamoto et al.,

2021), showing the involvement of theta waves in pain perception.

The rationale for using auditory stimuli to test the predictive hierarchy in CP is three-fold – (i) auditory and somatosensory afferents are known to interact at the level of the dorsal cochlear nucleus. This way we are able to use stimuli in another domain that interacts with the somatosensory domain. (ii) if CP was indeed a problem of predictive processing, this should be reflected in the domain-general predictive processing in other sensory domains as well. (iii) using non-somatosensory stimuli may also help in making the experiment more tolerable to patients with CP.

To summarise we hypothesise that CP patients will primarily demonstrate increased PEs at the lower level (local deviance of sPE, i.e. MMN) and decreased PE at the higher level of the hierarchy (global deviance of sPE, i.e. P300) owing to the brain's maladaptive compensation through the generation of a chronic phantom perception. We hypothesise that this component will be accompanied by increased theta activity which will be correlated with subjective pain perception. As a secondary outcome measure, we will look into effect of change in the context of a given auditory stimulus in CP. Since, from previous literature, we expect CP to have an effect on the context in which a stimulus is presented, we hypothesise that CP patients will differently process cPEs compared to controls. This way, we expect improper hierarchical updating, maladaptive responses to environmental deviance and maladaptive compensation to PEs to reflect an aberrant predictive coding system in CP perception. Furthermore, we expect to identify an appropriate neural oscillatory signature of CP that can also serve as a biomarker for aberrant predictive processing by correlating it with a subjective pain perception score. This will serve as an exploratory analysis which future studies can build on.

2. Methods

2.1. Ethical statement

Ethical approval was granted from the School of Psychology Research Ethics Committee and data management was in compliance with the EU General Data Protection Regulation 2016 (GDPR), Data Protection Acts 1988–2018 and Health Research Regulations. All participants gave their written, informed consent.

2.2. Data and code availability statement

The data and code are available with the corresponding author and will be shared on email request. The anonymised data after removing the identifying personal information will be provided.

2.3. Participants

Sixteen participants with chronic pain (CP) were recruited (age = 40.69 ± 19.17 ; male:female = 6:10) through online study advertisements, J.C.'s physiotherapy practice, and/or internal flyers in Trinity College Dublin. The inclusion criterion of CP group was continuous pain perception for more than 3 months. Sixteen healthy controls (HC) were selected from an existing database of healthy controls recruited from Trinity College Dublin and the general public (age = 23.13 ± 3.86 ; male:female = 6:10). The CP and HC groups were matched for sex ($\chi^2 = 0$, $p = 1$) (Fig. 1a) but did not match for age ($t(30) = 3.59$, $p = .001$) (Fig. 1b).

All participants underwent an online hearing test (<https://hearing-screener.beyondhearing.org/hearingtest/SG3c0N/welcome>) where bilateral hearing thresholds at 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz were obtained. Participants with hearing thresholds at any frequency > 30 dB HL were excluded from the study. The CP and HC groups matched for hearing thresholds ($F(3,28) = 0.447$, $p = .772$) (Fig. 1c). All participants also completed a set of questionnaires including Beck's Depression Inventory (BDI), Beck's Anxiety Inventory (BAI) and subjective hallucination score (SHS), which were applied to

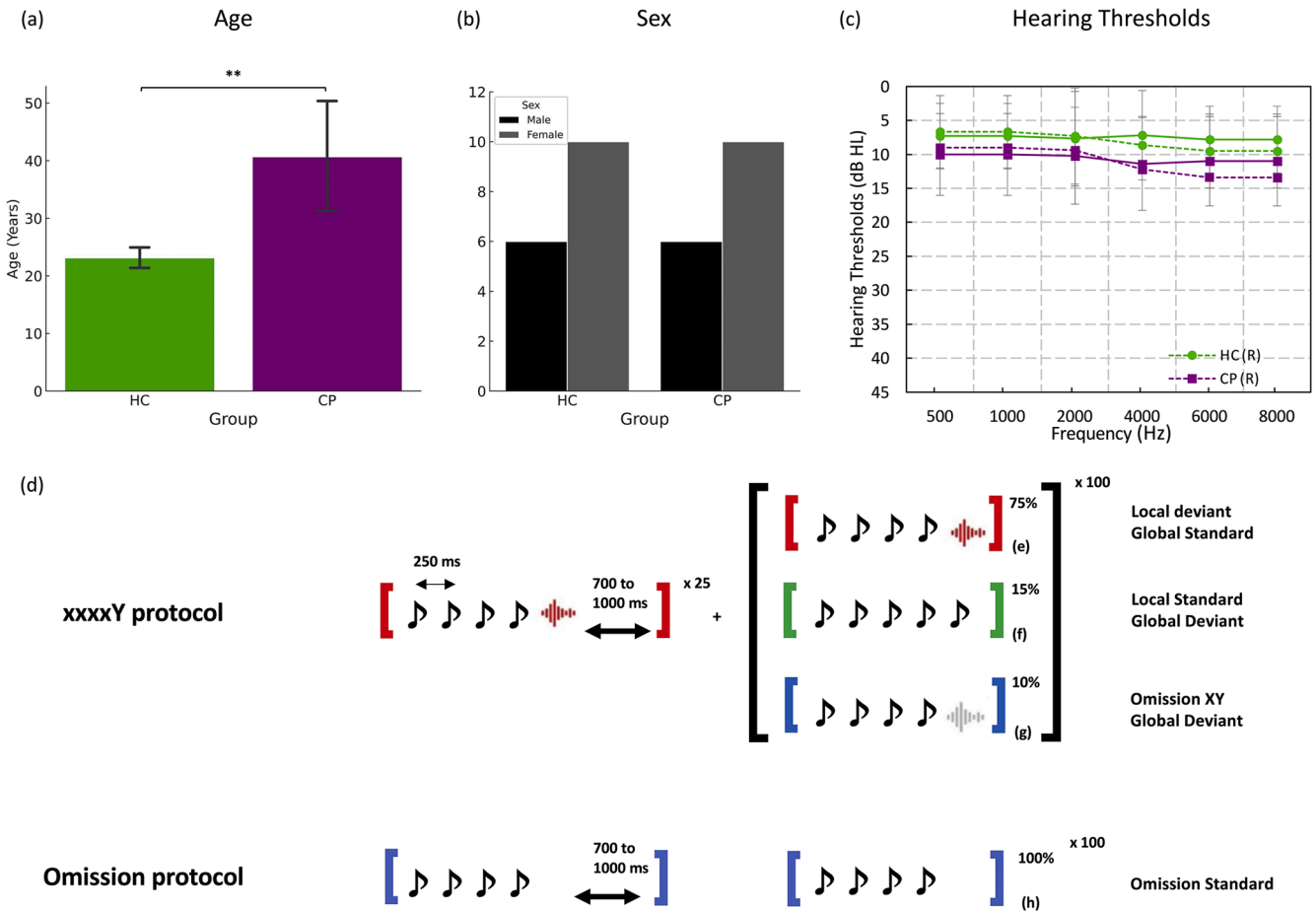


Fig. 1. Demographics and study design. The figure shows the distribution if (a) sex, (b) age and (c) hearing thresholds between the two groups. (d-f) shows a summary of the auditory oddball paradigm used in the study. Auditory stimuli consisted of 500 Hz tones (black notes), white noise bursts (red noise) and omitted stimuli (transparent noise burst; 1c). Sequences were comprised of 4 tones followed by a noise burst (d), tone (e), or omitted stimulus (f, g). The xxxxy protocol began with 100 % probability of the local deviant (global standard) sequence, followed by 75 % probability of the local deviant (d), 15 % probability of the local standard (global deviant; e), and 10 % probability of the omission XY (f) sequence. The omission protocol featured omission standard sequences with 100 % probability (g). cPEs were calculated by subtracting the two omission conditions, and sPEs were calculated by subtracting the global deviant and global standard conditions.

screen the mental health and the proneness to hallucinations. HC who scored higher than 13 or answered 1 or above to the question on suicidal thoughts in the BDI were excluded. The summary of these measures is given in Table 1. Exclusion criteria of the CP group consisted of other continuous phantom perception, chronic ear disorders (e.g., Menieres disease, ear infections, otosclerosis), and severe neurological disorders such as tumours, psychiatric disorders, or epilepsy. Exclusion criteria of the HC groups consisted of continuous phantom perception (tinnitus, verbal hallucination, phantom pain), chronic ear disorders (e.g., Menieres disease, ear infections, otosclerosis), and severe neurological disorders such as tumours, psychiatric disorders, chronic headaches.

Additionally, participants with CP reported their subjective level of pain on a Visual Analogue Scale on an interview performed within minutes of completion the data collection. The scale consisted of a line of

10 cm divided in 10 different sections of 1 cm where 0 = no pain 5 = moderate pain and 10= worst pain possible. Based on that interview and the diagnostic criteria proposed by the IASP, CP participants were classified as Chronic Primary Pain (N = 5), Chronic Secondary Musculoskeletal Pain (N = 6), Chronic Neuropathic Pain (N = 1) or Chronic Secondary Headache or Orofacial Pain (N = 4).

2.4. Study design

The local-global oddball paradigm was designed based on the original study (Wacongne et al., 2011) in Psychopy. The paradigm consisted of two auditory stimuli generated by MATLAB: a 500 Hz pure tone and a noise burst with broadband frequency. The duration of the two stimuli was 50 ms, with a rise-fall time of 7 ms. Three sound sequences that included either four or five auditory stimuli with an interstimulus interval of 250 ms were generated to probe the hierarchical PE processing. The standard sequence comprised four 500 Hz tones and one noise burst (Fig. 1e). The deviant sequence comprised five 500 Hz tones (Fig. 1f). The sequence with only four tones acted as the omission sequence (Fig. 1g & h).

The three sequences were presented to participants under two different protocols: xxxxy (7 blocks) and omission standard (1 block) protocols (Fig. 1d). The sequence of the two protocols were fully randomised for each participant. Each block consisted of 125 trials with the inter-trial jitter of 700–1000 ms. In the xxxxy protocol, each block

Table 1
Behavioural results.

	Chronic Pain		Controls	
	M	SD	M	SD
BAI	11.20	7.82	4.56	4.78
BDI	11.84	9.62	4.38	3.70
Age	39.96	16.73	21.26	3.34

Mean (M) and standard deviations (SD) are presented for the BAI, BDI, and age scores of the two groups.

started with 25 trials of global standard sequence to establish the global rule. For the following 100 trials, the global standard sequences were presented with 75 % probability, the global deviant sequences with 15 % probability, and the omission sequence with 10 % probability (omission XY). The sequences of the 100 trials were pseudo-randomised within each block, such that the global standard sequence would not be presented on 4 consecutive occasions. In the omission standard protocol, the 125 trials solely featured omission sequences. During the task, participants sat in a dark room and were instructed to direct their gaze at a fixation cross on a monitor in front of them and to pay close attention to the auditory stimuli.

2.5. EEG data collection and pre-processing

The stimuli were presented through Psychopy which triggered the Biosemi ActiView software. The ERP data was collected using a 64-channel cap configured as per the International 10–20 placement system. The data collection was sampled at 4096 Hz and recorded by the BioSemi ActiveTwo system. Data was pre-processed using MATLAB, EEGLAB v2021.1 and ERPLAB v8.20. The pre-processing pipeline included removing disconnected and unused channels, decreasing the sampling rate to 500 Hz, re-referencing to an average reference, and filtering between 0.55 and 44 Hz. The data were epoched between -100 ms to $+1850$ ms relative to the onset of the first tone in all sound sequences. The epoched data was then subjected to temporal independent component analysis (ICA) to remove muscle artefacts, eye blinks, saccades, and other noise transients. Artefacts in all epochs were detected and deleted using a simple voltage threshold of $\pm 90 \mu\text{V}$ and manual inspection. The channels initially removed were finally interpolated using a spherical interpolation algorithm in EEGLAB.

2.6. Event related potential (ERP) analysis

2.6.1. Sensory-level analyses

The trial-level neural responses to the four sequence conditions (global standard, global deviant, omission XY and omission standard) were averaged for each participant in each group. The average subject-level ERPs were compared between the two groups for the four conditions using a cluster-based permutation test in the FieldTrip software in MATLAB (Oostenveld et al., 2011).

2.6.1.1. Cluster-based permutation test. For the non-parametric cluster-based permutation test, an independent samples *t*-test was calculated for each channel-time sample between the two groups with the alpha of 0.05 as the cluster-building threshold (two-tailed). The number of neighbouring channels were calculated using a standard template of the Biosemi 64 channel from FieldTrip. The minimum number of neighbouring channels to form a cluster was set to two. The resulting clusters were corrected for multiple comparisons using max-T, which takes the sum of the *t*-values within every cluster and compares them with the probability of clusters that were calculated by Monte-Carlo of 1000 permutations. Clusters that were larger than 95 % of the distribution of clusters were considered significant ($\alpha = 0.05$, two-tailed). All clusters that showed a significant condition difference were selected.

2.6.1.2. Mean amplitude of ERP and ERP AUC. Both the mean amplitude of the ERP and the area under the curve (AUC) were used as measures of different ERP components. While the mean amplitude can give us the average amplitude of a waveform between two time points, the AUC can help describe the morphology of the component. Both these measures have been shown by previous research to be stable components of ERP measures (Cassidy et al., 2012). Based on the significant differences obtained from the cluster-based analysis, mean amplitude of ERP was calculated for each participant for each sequence condition by averaging over the time-channel samples that showed a significant

difference in each cluster. All significant time-channel clusters from all the conditions were compared between the two groups using a Multivariate analysis of variance adding age as a covariate (MANCOVA). If the model was significant, post-hoc group comparisons were performed using a univariate ANCOVA which were then corrected for multiple comparisons using the Benjamini-Hochberg method (FDR rate of 10 %).

Furthermore, the area under the curve (AUC) in the averaged waveform for each participant and sequence condition was calculated as an index of the morphology of the waveform using ERPLAB. The rectified area (negative values become positive) was used. Interpolation factor was set as 1. The time windows were defined based on the classic latencies of the components in the oddball paradigm. As the averaged ERP waveforms induced by the events consisted of a sequence of positive and negative components, the time windows of P1 and N1-P2 components in the four sequence conditions were defined between 60–130 ms and 100–250 ms after the onset of the first or fifth auditory stimuli (Luck, 2014). Similar to the analysis of the mean ERP a MANCOVA was performed on the ERP AUC with group as between-subjects factor and the P1, N1-P2, AUC of the first and fifth stimulus as multivariate factors with age as a covariate. Post-hoc group comparisons were corrected for multiple comparisons using the Benjamini-Hochberg method (FDR rate of 10 %).

2.6.2. Hierarchical predictive coding analysis

To specify the neural correlates of hierarchical predictive coding system, sPE was defined as the difference in the neural responses to global deviant and global standard, whereas cPE was defined as the difference in the neural responses to omission XY and omission standard. Considering the unequal probability of sequence presentation, the four conditions showed an unequal number of trials: 70 trials for the global omission XY, 105 trials for the global deviant, 125 trials for the omission standard, and 700 trials for the global standard. (the conditions shown in Fig. 1d). Thus, a distribution of sample mean ERPs to the global standard and omission standard were calculated based on the by the concept of Central Limit Theorem. Fifty trials were randomly selected from the trial pool of the global standard and omission standard to compute the average ERP, and this was bootstrapped for 1000 times. Thus, the average sPE ERP was calculated for each participant as the ERP to global deviant – sample mean ERP to global standard, whereas the average cPE ERP was calculated as the ERP to omission XY – sample mean ERP to omission standard.

The average ERPs for the sPE and cPE were compared between the CP and HC group using the cluster-based permutation tests, with the same procedure mentioned above. Clusters that were larger than 95 % of the distribution of clusters were considered significant ($\alpha = 0.05$, two-tailed). All clusters that showed a significant condition difference were selected.

The mean amplitude of ERP was calculated for each participant and PE condition by averaging over the time-channel samples that showed significant difference in each cluster. Considering the age difference between the HC and CP group, and the influence of ageing on ERP amplitudes, a multivariate analysis of covariance (MANCOVA) was performed with the group as a fixed effect and age as a covariate. Post-hoc group comparisons were performed by the One-way ANCOVA with age as a covariate and were corrected for multiple comparisons using the Benjamini-Hochberg method (FDR rate of 10 %).

The sPE and cPE unlike the sensory-level responses produce a MMN (100 – 250 ms) in addition to the P300 (250 – 600 ms) after the onset of the fifth stimuli (Mohan et al., 2022). A MANCOVA to the ERP AUC within these timeframes was performed with the group as a fixed effect and age as a covariate. Post-hoc group comparisons were performed by the One-way ANCOVA with age as a covariate and corrected for multiple comparisons using the Benjamini-Hochberg method (FDR rate of 10 %).

2.7. Source localisation

Subject-average ERPs to 4 stimulus sequence conditions were source localized using Brainstorm toolbox (Tadel et al., 2011). Based on the ERP analysis, the time of interest (TOI) for the global standard was 134 to 194 ms and 404 to 514 ms after the onset of the fifth stimulus. The ERPs in the global deviant condition were averaged across 384 and 414 ms after the fifth stimulus, whereas in the omission standard condition, they were averaged across 244 and 354 ms after the onset of the third stimulus. The source activity of sPE condition was computed by subtracting the source activity between global deviant and global standard. The early and late potentials in the sPE condition were averaged across 145 and 204 ms, 254 and 312 ms and 498 and 542 ms after the onset of the fifth stimulus, respectively. The omission and cPE conditions were excluded for this analysis because no significant clusters were identified in the ERP analysis. ICBM-1522 template was selected for the head model and the forward model OpenMEEG BEM. The noise covariance matrix was calculated based on the 100 ms baseline before the first stimulus. Source reconstruction was performed using dynamic statistical parametric mapping (dSPM).

A whole-brain analysis was first performed. Localised source signals were compared between the two groups by the pixel-based permutation test for all conditions that showed group difference in the ERP analysis (see **supplementary Fig. 1**). The TOIs of each condition were specified as mentioned above. The null distribution of the group difference was calculated by the permutation of independent samples *t*-test for 5000 iterations. Only the observed difference (*t* values) that were larger than 95 % of the distribution were considered significant ($\alpha = 0.05$, two-tailed). Then, to specify the regions (ROIs) of interest that showed significant group difference in PE processing, ROI-based permutation test was performed with the same parameter setup. The ROIs were defined according to the Desikan-Killiany Atlas (Desikan et al., 2006).

The ROI-based permutation test identified the significant group difference in the global standard, global deviant, omission standard and sPE conditions (including MMN and P300). Then, post-hoc analysis was conducted to identify the ROIs that showed significant group difference controlling for the effect of age. For each subject, the activity of each ROI was first extracted and averaged across TOIs in each condition that showed significant group difference in the pixel-based permutation test. Then, a linear mixed-effect model (LME) was applied. Here, groups, conditions (global standard, global deviant, omission standard) and ROIs were used as the fixed factors, whereas subjects were used as the random factor. Age was used as the covariate. The post-hoc analysis of group differences for each ROI in each condition was conducted using Bonferroni test to correct for multiple comparisons ($\alpha = 0.05$, two-tailed).

2.8. Time-frequency analysis

Single-trial time-frequency decomposition was performed for each participant and sequence condition. This was done by convolving a family of Morlet wavelets with a logarithmically increasing number of cycles from 3 to 13 sampled at 500 Hz and frequencies from 1 to 44 Hz in steps of 1 Hz. The number of trials chosen for the analysis were described and justified below. Given the limited baseline time window (100 ms), 1500 ms of reflected data were concatenated to the beginning and end of the real signal before the single-trial data was first decomposed to minimise potential edge artifacts and subsequently discarded (Picton, 2010).

Then, we analysed inter-trial phase coherence (ITPC) to explore the phase-locked spectral power of the ERPs. ITPC provides a measure between 0 and 1 to indicate the consistency of phase-angle distribution at time-frequency points across trials from a single electrode (Cohen, 2014). A value of 0 would indicate random phases at a given time-frequency point, whereas a value of 1 would indicate identical phases at a time-frequency point. ITPC is calculated using the following

formula:

$$ITPC_{ij} = \text{abs}(\text{mean}(\exp(i * k))),$$

where *k* is a vector of phase angles at a single time-frequency point over trials

Give the phase-lag between electrodes, the FCz electrode was selected for ITPC analysis as it was consistently present in all significant clusters of cluster-based ERP analysis between the two groups. First, the trial-wise variance analysis of all 6 conditions (global standard, global deviant, omission standard, omission XY, sPE, cPE) was analysed. For each subject, each single-trial ERP activity was averaged across FCz and TOI that showed significant group difference in the cluster-based permutation test for each condition. Then, the variance of single-trial ERP activity was calculated for each subject and each condition. Finally, the variance of two groups was compared by the Levene's test (see **supplementary Fig. 2**).

Further, the ITPC analysis was performed. Given the uneven number of trials across conditions and sensitivity of ITPC to trial counts, wavelet decomposition for ITPC was performed on 1000 randomly permuted samples of 35 trials for each condition. 35 was the minimal number of trials present across all conditions and participants after EEG pre-processing (see **supplementary Table 1**). The permuted samples were then averaged to provide a more accurate representation of ITPC. The ITPC of the sPE and cPE for each participant was calculated as the difference of ITPC matrix between the global deviant condition global standard condition, and between the omission XY condition and the omission standard condition.

The group comparison of the ITPC for the 6 conditions were also computed based on pixel-based z-score analyses on the two groups with 1000 permutations (Swink and Stuart, 2012). For each condition, all participants were first pooled together and shuffled. Then, each ITPC matrix from a participant was randomly assigned into one group. Finally, the group difference was calculated. The second and third steps were repeated for 1000 times. Then a null distribution of group difference for each time-frequency sample was built and normalised by z-transformation. Observed values that were greater than 95 % of the distribution were considered significant ($\alpha = 0.05$, two-tailed). The average ITPC magnitude for the theta frequency band was calculated by averaging across all time-frequency samples that showed significant differences between the two groups in the same frequency band. We used the average ITPC magnitude of the theta frequency band in the global standard and deviant conditions to calculate the relative theta ITPC magnitude of the two by dividing the magnitude of the deviant by the magnitude of the standard.

2.9. Correlation with self-reported pain perception

To investigate the potential relationship between the altered PE processing and pain perception, partial correlation analysis was performed between the pain VAS scores and the mean amplitudes of ERP, the ERP AUC, and the corresponding theta ITPC magnitude after controlling for age. These correlations were corrected for multiple comparisons using the Benjamini-Hochberg method (FDR rate of 10 %).

3. Results

3.1. Sensory-level analysis

3.1.1. ERPs

We first investigated the group difference in the evoked ERP. For the global standard condition, compared to the HC group the CP group was identified with a significantly decreased ERP between 134 and 194 ms ($t_{\text{max}} = 2588.5$, $p = .022$) and between 404 and 514 ms ($t_{\text{max}} = -1975.2$, $p = .042$) after the onset of the fifth stimulus (Fig. 2a). The group difference was localised in the fronto-central channels. For the global

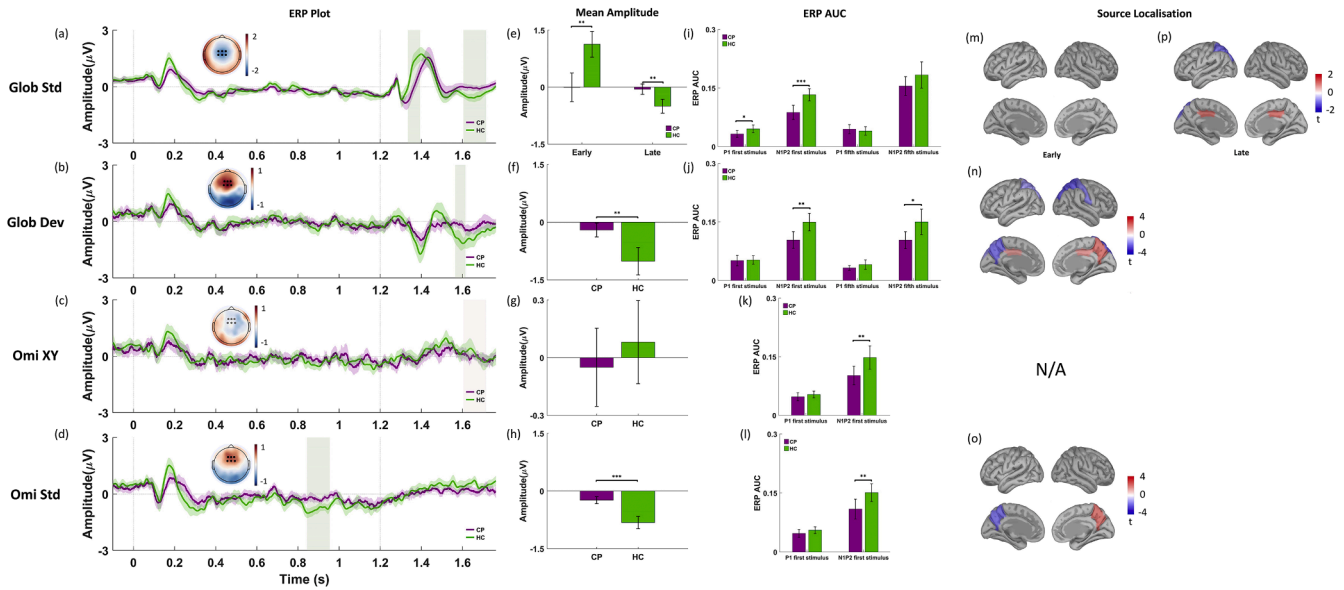


Fig. 2. Sensory-level analysis: ERP. Between-group differences of the ERPs, mean ERP amplitudes and ERP AUC for the four conditions (global standard, global deviant, omission XY and omission standard) are presented. (a–d) represent the group differences between the ERPs. The time-series averaged over significant channels (highlighted bold on scalp map) depicts the significantly different time range between the groups with green shading. The bar charts display age-corrected group differences for (e–h) averaged over the significant channel-time range and (i–l) for the AUC for standard tone-evoked responses. The HC group is represented in green, and the CP group is represented in purple.

deviant condition, we observed a significantly decreased ERP between 384 and 414 ms in the frontal region for the CP group relative to the HC group ($t_{max} = 1986.3$, $p = .004$) (Fig. 2b). By contrast, we did not observe any significant group difference of the ERP evoked by the omission XY sequence ($t_{max} = 387.4$, $p = .455$) (Fig. 2c). However, the evoked frontal ERP by the omission standard sequence showed significant group difference between 244 and 354 ms after the third stimulus ($t_{max} = 3009.4$, $p < .001$) (Fig. 2d).

3.1.2. Source localisation

The evoked ERP activities from the significant cluster in the global standard, global deviant and omission standard conditions were further source localised. For the early potential in the global standard condition, there was no significant group difference at the source level (Fig. 2m). By contrast, for the late potentials, we observed a significant increased activity for the CP group in the bilateral mid-posterior cingulate cortex (M-PCC), but a significant decreased activity in the left superior parietal lobule (SPL) (Fig. 2p). For the late potential in the global deviant condition, relative to the HC group, the CP group demonstrated a significant increase in the activity of the right precuneus, bilateral M-PCC but a significant decrease in the bilateral SPL, left precuneus and right post-central gyrus (i.e. primary somatosensory cortex S1) (Fig. 2n). For the omission standard condition, there was significantly increased activity of the right precuneus but significantly decreased one in the left precuneus for the CP group than the HC group (Fig. 2o).

The LME analysis was conducted to control for age. The results showed that there was a significant main group effect on the evoked activity at the source level ($F(1344.094) = 46.003$, $p < .001$). Further, there was a significant two-way interaction effect between group and condition ($F(2344.042) = 21.422$, $p < .001$) and between group and ROI ($F(6344.121) = 23.706$, $p < .001$), as well as three-way interaction effect between group, condition, and ROI ($F(3344.042) = 6.100$, $p < .001$). The post-hoc pairwise comparisons were further performed. No significant group difference was observed after corrected for multiple comparisons in the global standard condition. By contrast, in the global deviant condition, the evoked activity in the bilateral M-PCC significantly increased for the CP group. In the omission standard condition, the CP group demonstrated significantly increased activity of the right

precuneus but significantly decreased activity in the left precuneus for the CP group (Table 2).

3.1.3. Time frequency analysis

Compared to the HC group, the CP group showed a significant decrease in low frequency (primarily alpha) ITPC magnitude after the onset of the first stimulus in the global standard (Fig. 3c), global deviant (Fig. 3f) and omission standard conditions (Fig. 3i). Following the 5th stimulus, we observed a significantly decreased alpha power of the CP group between 0 and 224 ms post-stimulus and increased delta power during 374 ms to 450 ms post-stimulus in the global standard condition (Fig. 3c), whereas a significant decrease in the theta ITPC magnitude was observed across the post-stimulus time for the global deviant (Fig. 3f). The ratio of theta ITPC magnitude between the global deviant and global standard condition was calculated for each subject as a measure of the balance between local and global deviance. The one-sample t -test with the value 1 (perfect balance) showed no significant difference between the ITPC ratio in the HC group and 1 (mean = 1.115, SD = 0.488) ($t(15) = 0.946$, $p = .359$), suggesting a balance between

Table 2

The results of pairwise comparisons for evoked scout activity.

Condition	Scout	df	t value	P value
std_P3	Superior parietal L	30	−3.117	.746
	Middle- Posterior cingulate L	30	3.669	.139
	Middle-Posterior cingulate R	30	3.673	.110
dev_P3	Superior parietal L	30	−2.867	.544
	Superior parietal R	30	−5.068	.344
	Precuneus L	30	−4.667	.162
	Precuneus R	30	5.395	.068
	Middle-Posterior cingulate L	30	3.370	.035*
omistd	Middle-Posterior cingulate R	30	3.761	.022*
	Postcentral R	30	−4.073	.282
	Precuneus L	30	−2.843	.007**
	Precuneus R	30	3.094	<0.001***

Results were corrected for multiple comparisons by Bonferroni.

* : $p < .05$.

** : $p < .01$.

*** : $p < 0.001$.

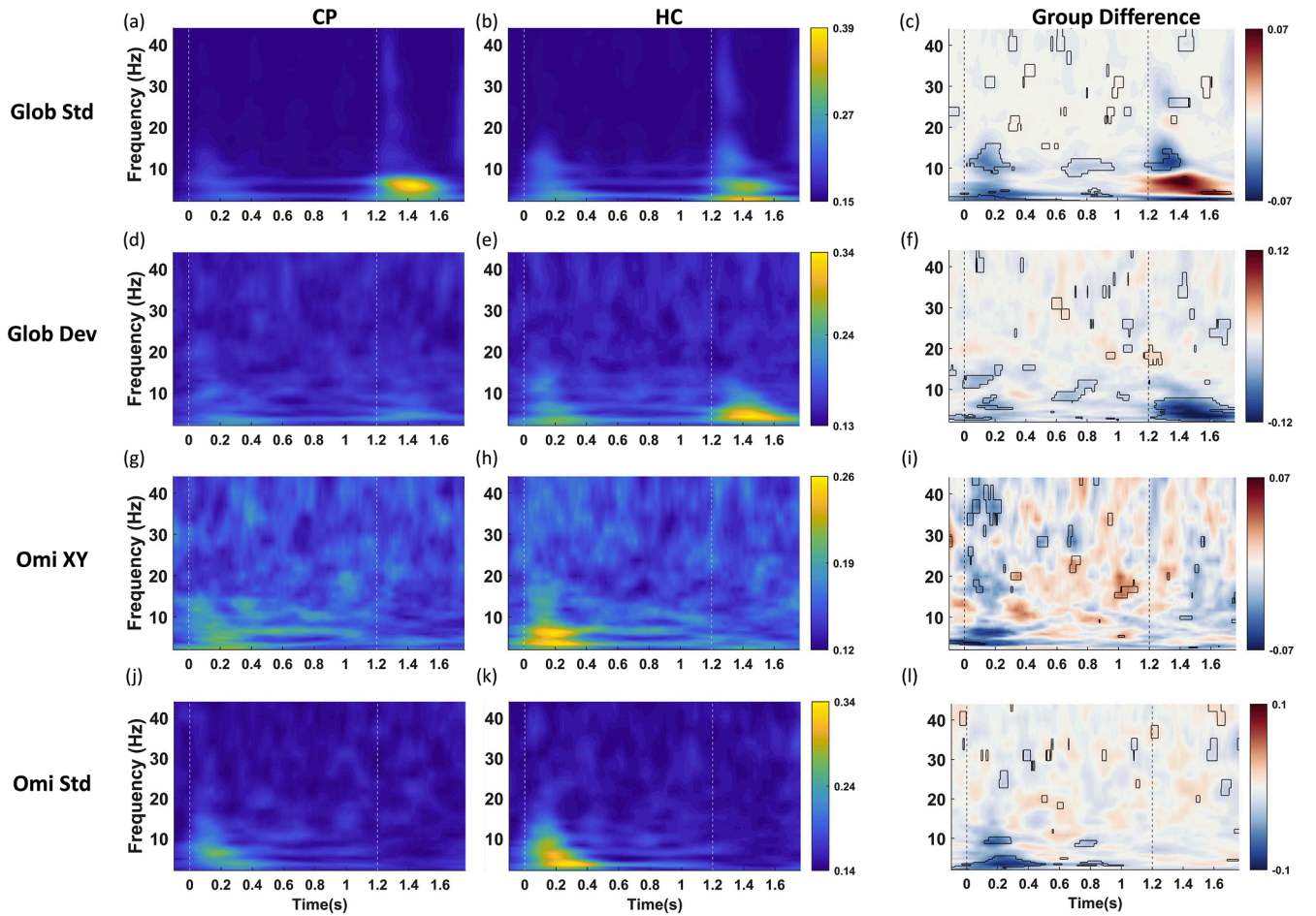


Fig. 3. Sensory level analysis: ITPC magnitude. The figure depicts the ITPC magnitude for the two groups and the group difference for four conditions: (a – c) global standard, (d – f) global deviant, (g – i) omission XY and (j – l) omission standard. The regions that are outlined in black are those time-frequency points that are significantly different between the two groups.

local and global deviance in the HC group. By contrast, the ITPC ratio of the CP group (mean = 0.606, SD = 0.277) was significantly lower than the HC group ($t(30) = -3.633$, $p = .001$), which is consistent with hypothesis that CP patients possibly show an imbalanced local-global

deviance processing where the balance is shifted towards increased local deviance.

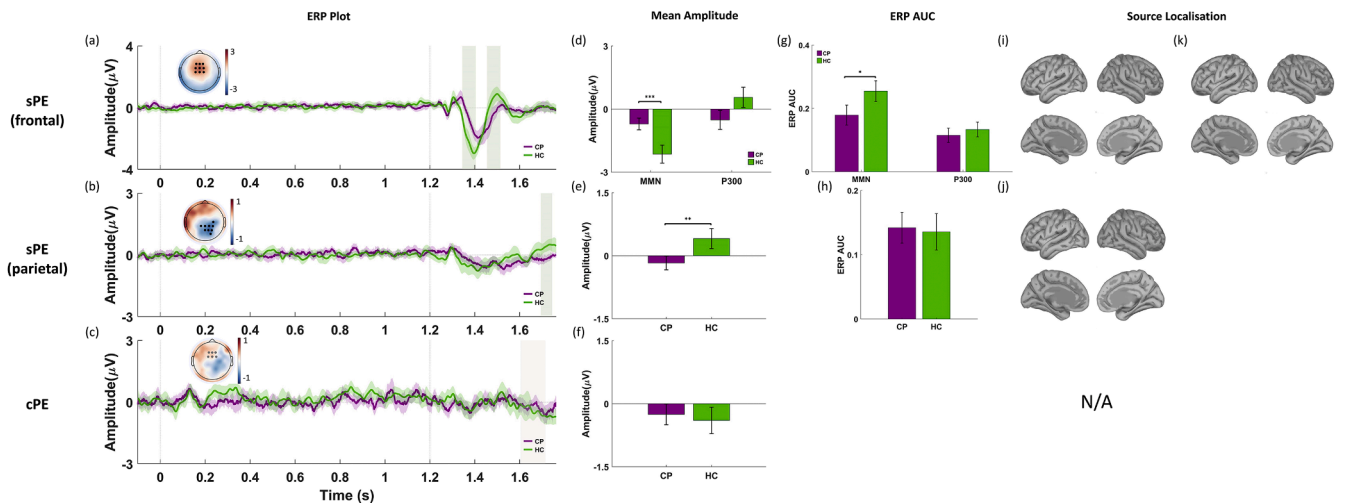


Fig. 4. Hierarchical analysis: ERPs. Between-group differences of the ERPs, mean ERP amplitudes and ERP AUC for the two PE conditions (sPE, cPE) are presented. (a – c) represent the group differences between the ERPs. The time-series averaged over significant channels (highlighted bold on scalp map) depicts the significantly different time range between the groups with green shading. The bar charts display age-corrected group differences for (d – f) averaged over the significant channel-time range and (g, h) for the AUC for MMN and P300 components. The HC group is represented in green, and the CP group is represented in purple.

3.2. Hierarchical predictive coding analysis

3.2.1. ERPs

Furthermore, the hierarchical PE responses were compared between the two groups. In the sPE condition, we observed significant and decreased fronto-central ERP between 145 and 204 ms ($t_{max} = 2337.2$, $p = .002$), which corresponded to the MMN timeframe, and 254 and 312 ms ($t_{max} = -1608.8$, $p = .005$), which corresponded to the P300 timeframe, for the CP group (Fig. 4a). The similar group difference was also localised in the right parietal region from 498 to 542 ms ($t_{max} = -950.9$, $p = .040$) (Fig. 4b). Nevertheless, no significant group difference was found in the cPE condition ($t_{max} = 449.1$, $p = .267$) (Fig. 4c).

3.2.2. Source localisation

The evoked activity in the sPE condition was further analysed at the source level. The results of ROI-based permutation test were plotted in the Fig 4i-k. No significant group difference was observed in neither condition.

3.2.3. Time frequency analysis

A significant decrease in the delta-theta ITPC magnitude across the post 5th stimulus time was observed for the sPE condition (Fig. 5c), whereas distributed increase in alpha ITPC magnitude was observed for the cPE condition (Fig. 5f).

3.3. Mean ERP and ERP AUC for the sensory-level and hierarchical analysis

The mean amplitudes of ERPs of six conditions (4 sequences and 2 PEs) were calculated over the significant clusters and compared between the two groups using the MANCOVA controlling for age. In general, we observed a significant main group effect on the mean amplitude with the smaller ERP amplitudes in the CP group ($F(9,21) = 5.482$, $p = .001$). The post-hoc analyses showed significantly decreased ERP amplitude for the CP group in the global standard (early: $F(1,29) = 9.372$, $p = .005$; late: $F(1,29) = 13.741$, $p = .001$) (Fig. 2e), global deviant ($F(1,29) = 8.684$, $p = .006$) (Fig. 2f), omission standard ($F(1,29) = 22.671$, $p < .001$) (Fig. 2g), sPE conditions (frontal MMN: $F(1,29) = 15.698$, $p < .001$; parietal late: $F(1,29) = 7.974$, $p = .008$) (Fig. 4d & e) after controlling for age. No significant group difference was observed in the other conditions (supplementary Table 2).

Further, the ERP AUC was computed and compared between the two groups by the MANCOVA controlling for age. Although the model did not show a main group effect on the ERP AUC ($F(19,11) = 2.234$, $p = .087$), the post-hoc comparisons between the two groups showed significant difference in the AUC of N1P2 component after the first and/or fifth stimulus (Fig. 2c-I). For the N1P2 component after the first stimulus, relative to the HC group, the CP group showed a significant decrease in the ERP AUC for all four sequence conditions (global std: $F(1,29) = 26.457$, $p < .001$; global dev: $F(1,29) = 8.457$, $p = .007$; omission XY: $F(1,29) = 11.091$, $p = .002$; omission std: $F(1,29) = 11.393$, $p = .002$). For the N1P2 component after the fifth stimulus, there was also a significant decrease in the ERP AUC for the CP group than the HC group in the global deviant ($F(1,29) = 4.596$, $p = .041$) (Fig. 2j). In the sPE condition, the ERP AUCs of MMN, P300 (Fig. 4g) and late potential (Fig. 4h) were also compared between the two groups but the CP group only showed significant decrease in the AUC of MMN than the HC group ($F(1,29) = 7.387$, $p = .011$) (Fig. 4g). The P1 components after the first tone was significantly decreased in the CP group ($F(1,29) = 6.011$, $p = .020$). No significant group difference was observed in the other conditions (supplementary Table 3).

3.4. Correlation between ERP results and pain perception

Given the reduced neural activities to the sPE in the CP group, we investigated the potential relationship between maladaptive PE processing and the pain perception. The mean amplitudes of ERP, ERP AUC, and theta ITPC magnitude of the MMN and P300 in the sPE condition were correlated with the pain VAS scores in the CP group controlling for age. In particular, although there was no significant correlation between pain perception and the mean amplitude of MMN ($r = 0.107$, $p = .705$) (Fig. 6a), mean amplitude of P300 ($r = -0.441$, $p = .100$) (Fig. 6b) and ERP AUC of P300 ($r = -0.357$, $p = .191$) (Fig. 6d), we observed a significant and negative correlation between the pain perception and ERP AUC of MMN ($r = -0.583$, $p = .023$) (Fig. 6c). The similar correlation was observed with the theta phase locking of the MMN ($r = -0.583$, $p = .021$) and P300 ($r = -0.648$, $p = .009$) of the sPE condition (Fig. 6e, f).

4. Discussion

In the current study, we empirically tested the hypothesis that CP was associated with maladaptive changes in the hierarchical predictive

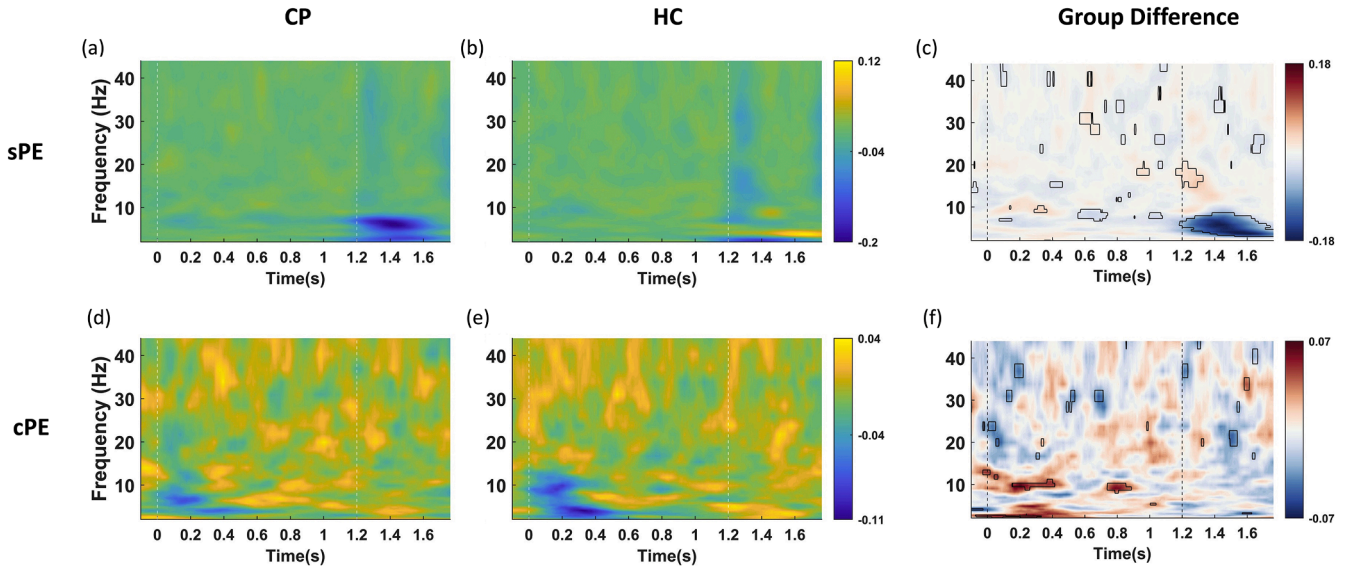


Fig. 5. Hierarchical analysis: ITPC magnitude. The figure depicts the ITPC magnitude for the two groups and the group difference for two PE conditions: (a – c) sPE, (d – f) cPE, (g – i). The regions that are outlined in black are those time-frequency points that are significantly different between the two groups.

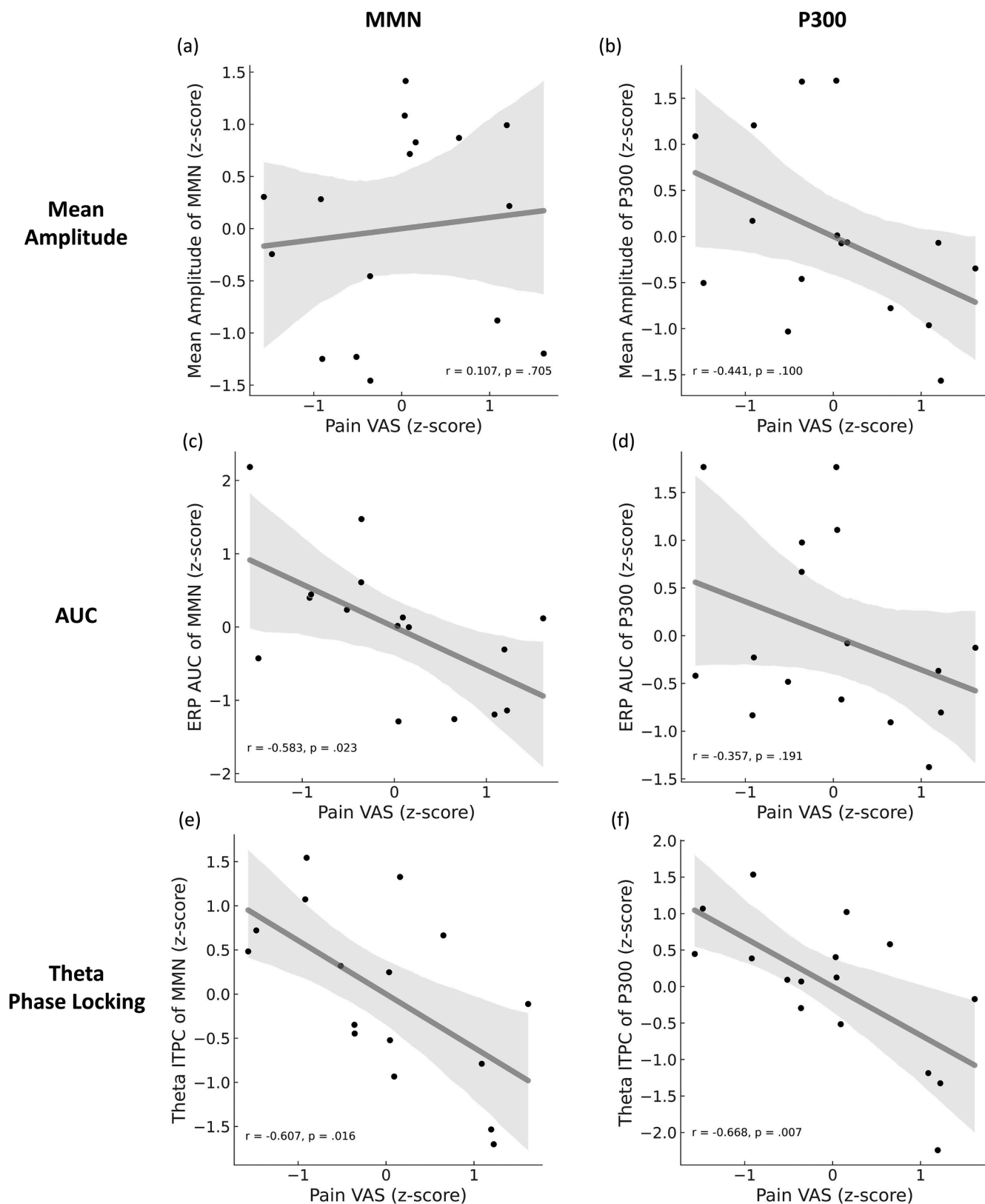


Fig. 6. Correlation with pain scores. The figure depicts the correlation between the mean ERP, ERP AUC, and theta ITPC magnitude for the MMN and P300 of the sPE from the pain group with the VAS score of subjective pain perception.

coding system. Similar to other chronic perceptual disorders such as tinnitus (De Ridder et al., 2014; Mohan et al., 2022) we provide evidence that CP may be explained under the same framework reflected by an abnormal increase in PEs in the lower and decrease in PEs at the higher levels of the predictive coding hierarchy. These changes reflect improper updating of the internal model, attention deficits towards external stimuli and a maladaptive compensation of increased lower-level PEs that, as we propose, might be influenced by consistent exposure to pain perception in the somatosensory domain.

4.1. Sensory and attentional processing deficits in CP patients

At a sensory level, we observe that patients with CP fundamentally process auditory stimuli differently from HC participants. Although there were no differences in the instantaneous amplitude, we observed that the AUC of the N1-P2 complex to the first stimulus in the sequence is consistently reduced for every sequence in CP patients, even after controlling for age as a covariate. This change in the pre-attentive auditory ERP to a tone indicates a dysfunction in the sensory processing of simple auditory tones in CP patients compared to HC (Lightfoot, 2016). This is accompanied by increased theta and reduced alpha phase locking in the FCz electrode as seen in the time-frequency plots which could suggest an effect of age. However, considering that the effect at the ERP-level was present after controlling for age, it is possible that this pattern is indicative of a thalamocortical dysrhythmia in CP patients as indicated by resting state literature (Llinás et al., 1999).

Following the 5th stimulus, we observe a change in the amplitude of the N1-P2 response in the CP group compared to the HC group, both in the global standard and deviant. In the global standard, we observe no change in the AUC of the P1 or N1-P2 components of the ERP to the 5th stimulus. In the global deviant, we observe a decrease in the AUC of the N1-P2 complex. This shows that CP patients and controls have similar morphology of the pre-attentive ERPs to the global standard (or local deviance of the 5th stimulus) and have different pre-attentive ERPs to the global deviance of the sequence. This pattern suggests the first level of evidence of impaired hierarchical processing in CP patients. These pre-attentive changes are not observed in the omission XY or the omission standard condition.

Investigating the spectral content of these sensory-level ERPs, we observe: i) *increased* theta phase locking to the local deviance of the 5th stimulus in the CP group compared to that of the HC group and ii) a *decreased* theta phase locking to the global deviance of the sequence compared to the HC. It is important to note that the relative global/local deviance in the HC group is not significantly different from 1 (perfect balance) suggesting the local and global deviance of the HC system is balanced. However, relative global/local deviance in the CP group is significantly lower than that observed in the control group. This is a particularly important finding. Although at the ERP-level we observed no significant changes in local processing, we find that there is relatively decreased theta phase locking to the relative global/local deviance suggesting a shift of the balance in deviance processing to increased local processing in CP patients. This pattern not only provides further confirmation to impaired hierarchical processing in CP but also suggests increased sensitivity to local deviations at the stimulus level.

This increase in sensitivity of sensory processing at a local level may reflect a domain-specific increase in sensitivity to auditory stimuli as suggested by previous literature (Staud et al., 2021). Additionally, the increase in theta phase locking magnitude together with a decrease in alpha phase locking magnitude observed following the local deviance, in the FCz electrodes supports a domain-general decrease in top-down suppression of non-novel input (Rauschecker et al., 2015). The top-down inhibitory system is known to “gatekeep” noisy information from reaching consciousness (Leaver et al., 2011; Leaver et al., 2016). Together with the striatal limbic system, it evaluates the “affective value” of salient stimuli (Rauschecker et al., 2015). Chronic perceptual disorders such as tinnitus and CP are shown to be accompanied by

dysregulation of top-down inhibition (Vanneste et al., 2019; Vanneste and De Ridder, 2021). Furthermore, changes in theta amplitude are shown to be a correlate of maladaptive sensory gatekeeping in the auditory phantom perception (Vanneste et al., 2019; Vanneste et al., 2018; Hong et al., 2012) literature.

Changes in involuntary and attention-driven ERP components may also reflect a change in attention-related processing. Comparing the sensory-level responses of the different sequences, we observed a consistent decrease in instantaneous amplitude of the attention-related P300 components in the CP group compared to the HC in the global standard, global deviant, and omission standard conditions. The attention-related change in global standard and deviant is localised to the mid-posterior cingulate cortex and the precuneus, which are both key regions in monitoring deviance from an expected stimulus and are key regions activated during a conscious experience. Attention-related deficits in CP patients have been consistently reported in previous studies using auditory oddball paradigms (Gubler et al., 2022) and through different attention-orientated tasks (Moore et al., 2012). An increase in attentional resources towards the internally orientated CP may impair attention to external stimuli thereby reducing attention-related ERP components. Particularly in the global deviant condition, this is accompanied by decreased theta-alpha phase locking during the P300 timeframe, a component well established to be driven by attention.

4.2. Maladaptive hierarchical predictive coding system in CP patients

From a predictive coding perspective, we can account for the changes in local deviance observed in the above results as changes in the lower level of the predictive hierarchy (Wacongne et al., 2011). From this perspective, we observed that CP patients present increased deviance at the lower level of the hierarchy. To further delve into changes in global deviance we calculated the higher-level PE sensitivity to stimulus and contextual changes by subtracting the ERPs to the global deviant – global standard and omission XY – omission standard, respectively.

We observed a decrease in the mean amplitude of the local (MMN) and global (P300) deviance components in CP patients in the sPE condition and not cPE condition. Furthermore, we observed that the morphology of the MMN is different in CP patients as observed from the reduction in AUC of the MMN in CP patients when compared to HC. From a neural oscillatory perspective, we observed increased theta phase locking during both MMN and decreased phase locking during the P300 timeframes for the sPE and not the cPE. These changes reflected in the sPE and not the cPE condition suggest that CP patients have increased local deviance and decreased global deviance.

A reduction in MMN in CP patients has been observed in several classic oddball studies (Yao et al., 2011; Dick et al., 2003; Fan et al., 2018). Since the MMN is regarded as a pre-attentive automatic detection of a change in stimulus characteristics and switching attention from an ongoing standard to a deviant (Ungan et al., 2019; Näätänen, 2018) a reduction in the MMN in CP patients may be regarded as a lack of attention switching. This may also be attributed to the inability of the CP group to produce a strong memory trace and update the model at the second level of the predictive hierarchy (Fitzgerald and Todd, 2020; Garrido et al., 2009). Although more sensitive to local deviations in stimulus (MMN), CP patients are less sensitive to global deviations in the sequence (P300) as observed in this study. According to the original study (Wacongne et al., 2011), local deviations in stimuli are compensated by encoding the global deviations to the sequence at the higher level in the hierarchy displaying features of hierarchical learning and model updating. However, in the current study, we observe that the increase in local deviations is not compensated by the global deviations in CP.

According to the predictive coding hypothesis, CP is a maladaptive compensation to resolve increased lower-level PEs (De Ridder et al., 2014; Mohan and Vanneste, 2017; Eckert et al., 2022). This is observed

from the correlation of both the AUC of the MMN and amplitude of theta phase locking both during the MMN and P300 timeframes of the sPE with the subjective pain perception scores. The negative correlation between the AUC and self-reported pain perception using VAS suggests the amount of pain is inversely related to the size of the PE. However, the theta phase locking is calculated as the difference in phase locking between the global deviance and local deviance. Therefore, the more negative the difference (i.e. greater the phase locking to the local deviance or the lesser the phase locking to the global deviance) the greater the subjective pain perception. This suggests that CP may be a maladaptive inference of the brain to (i) increased PE at the lower level of the hierarchy owing to hypersensitivity to sensory stimuli as explained above and/or (ii) inefficient updating of the prediction at a higher level of the hierarchy.

To summarise the results, this study revealed predictive coding differences in varying parts of the hierarchy between CP patients and HC when presented with changing stimulus characteristics. Patients with CP demonstrated an increase in sensitivity to local deviance of stimuli (MMN) and decrease in sensitivity to global deviance of sequences (P300). The relative balance of global/local deviance seems to have shifted towards local deviance. The changes in P300 could also suggest decreased top-down attention to stimulus-related changes and/or maladaptive updating of their PEs at the higher level of the predictive hierarchy and reduction of PEs at this level. Changes in phase-locking of PE at the local and global level are correlated with the self-reported subjective pain perception suggesting that the CP may be maladaptively compensating these PEs, as predicted with other phantom perceptions, thereby presenting a biomarker for CP (9,10).

4.3. Clinical significance and future directions

It is important to highlight that CP patients usually suffer from a wide range of physical and cognitive comorbidities. By studying neural changes in a CP population to an uncertain auditory environment, we have demonstrated the complex intricate domain-general neuroplastic changes that occur across the dysfunctional CP brain, in regions beyond the somatosensory domain. The ability to perceive pain presents an interesting evolutionary advantage to adapt to an ever-changing environment (Walters and Williams, 2019). It is considered a “homeostatic emotion” that drives both perceptual and behavioural systems to maintain an internal balance (Craig, 2003). However, in the case of CP, pain hinders the capacity of the system to adapt to change and increases the total allostatic load (the burden of sustained chronic stress) (Lunde and Sieberg, 2020) allocating physiological and mental resources to resolve a potential threat for survival. Therefore, the CP brain could be seen as a system in a constant and unsuccessful attempt to reach balance that impairs its ability to process local and global changes across different domains.

The correlation of the MMN morphology and the theta phase locking with the subjective pain perception presents an elegant and novel auditory biomarker for CP indicating a dysfunctional self-regulatory system (Quadt et al., 2022) with effects that go beyond somatosensory processing. The increase in theta phase locking at the lower levels and decrease in the higher level of the hierarchy provide initial evidence of sensitisation across domains. We propose that, under specific circumstances, the constant exposure to pain perception in the somatosensory domain, triggers the enhanced local responses we observed in auditory domain in the CP population. The neuroanatomical and physiological pathways for this somatosensory-auditory interaction have been described by Wu and colleagues (Wu et al., 2015). Future studies can confirm the reproducibility and robustness of this neural marker, identify the limitations and disadvantages of a domain-general biomarker, and explore the potential different sensitivity and specificity amongst different subtypes of CP.

An alternative explanation to increase local deviance is dysfunction of the autonomic nervous system. Given the prolonged experience of

pain, patients with CP demonstrate a shift in homeostatic balance. This increased physiological stress is called allostatic load. Although the current study cannot confirm if this is a marker of domain-general autonomic dysfunction, future studies will be able to confirm this by looking at markers of allostatic load using heart rate monitoring, pupil dilation, salivary alpha amylase concentration, cortisol concentration, galvanic skin conductance etc. Furthermore, the use of auditory signals to study neural markers of autonomic dysfunction in CP patients presents an experimental advantage. Given that patients with chronic pain may be more tolerable to auditory stimuli than they will be to nociceptive stimuli, the current study is a proof of concept of clinical implementation of this experimental design.

Future studies could also implement the local-global paradigm using nociceptive and non-nociceptive somatosensory stimuli to study the changes in predictive processing in patients with CP. This combined with domain-general markers of predictive processing (such as the one presented in this study) and autonomic system activity (as proposed above) in an age and gender matched population, could provide a more holistic extension of understanding the mechanism of CP. Furthermore, this could be implemented with ease in a multi-site study to generate a large dataset to then be trained using a machine learning algorithm to extract the neural and biological markers that best predict CP pathology. This set up can also be downsized robustly in a clinical setting with 19-channel EEG. This way, it becomes a handy and attractive measure to be further used in regular clinical practice.

4.4. Limitations

The current study comes with a few limitations. (i) Although age has been added as a covariate, future studies could have an age-matched control group to confirm the results of the current study. (ii) The current study excluded people with hearing loss > 30 dB to limit the effect of hearing loss on auditory predictive processing. However, this may not be the reality in people with CP. Hence, future studies should include people with hearing loss to further understand the changes in auditory predictive processing in CP. (iii) Although having a biomarker outside the sensory domain of interest has its advantages, it is also important to discuss its limitations. The prevalence of CP increases with age and is much higher in people > 45 years of age. This is also the time when hearing loss increases in the population which could introduce confounding changes in neurophysiology. Some people who are poly-symptomatic i.e. have other disorders such as tinnitus (the continuous ringing in the ear) along with CP, may show changes in hierarchical predictive processing that may not be related to CP. Therefore, it is important to replicate the current paradigm in the somatosensory domain as well to see then understand the holistic view of domain-specific and domain-general changes in hierarchical predictive processing in CP.

5. Conclusion

This study was the first to use the local-global oddball paradigm to examine predictive coding differences between CP patients and HC. Previous literature has noted that patients with chronic perception disorders employ compensatory predictive coding mechanisms to address the uncertainty of their sensory input. The results of this study provide compelling evidence that CP patients implement similar strategies to compensate for an aberrant predictive coding system by amplifying responsiveness to local stimulus-level irregularities, and maladaptively overcompensating to higher-level environmental irregularities. It provides a novel biomarker of pain perception that can be further examined in the clinic. This framework could hence open new ways to investigate pain processing in clinical populations.

CRedit authorship contribution statement

Jorge Castejón: Writing – original draft, Methodology, Data curation, Conceptualization. **Feifan Chen:** Writing – original draft, Formal analysis. **Anusha Yasoda-Mohan:** Writing – review & editing, Writing – original draft. **Colum Ó Sé:** Formal analysis, Data curation. **Sven Vanneste:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest to disclose concerning the research paper.

Data availability

Data will be made available on request.

Data

Data and coding is available on request in agreement with ethics approval.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2024.120711](https://doi.org/10.1016/j.neuroimage.2024.120711).

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