



Review article

Gamma-band oscillations of pain and nociception: A systematic review and meta-analysis of human and rodent studies

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ABSTRACT

Pain-induced gamma-band oscillations (GBOs) are one of the most promising biomarkers of the pain experience. Although GBOs reliably encode pain perception across different individuals and species, considerable heterogeneity could be observed in the characteristics and functions of GBOs. However, such heterogeneity of GBOs and its underlying sources have rarely been detailed previously. Here, we conducted a systematic review and meta-analysis to characterize the temporal, frequential, and spatial characteristics of GBOs and summarize the functional significance of distinct GBOs. We found that GBO heterogeneity was mainly related to pain types, with a higher frequency (~66 Hz) GBOs at the sensorimotor cortex elicited by phasic pain and a lower frequency (~55 Hz) GBOs at the prefrontal cortex associated with tonic and chronic pains. Positive correlations between GBO magnitudes and pain intensity were observed in healthy participants. Notably, the characteristics and functions of GBOs seemed to be phylogenetically conserved across humans and rodents. Altogether, we provided a comprehensive description of heterogeneous GBOs in pain and nociception, laying the foundation for clinical applications of GBOs.

1. Introduction

The unpleasant sensory and emotional experience of pain warns us of harm and prevents us from actual or potential tissue damage (Raja et al., 2020). Due to its protective function, pain clearly has survival values. However, excruciating pain is a major kind of intense suffering. Chronic pain, which persists or recurs for more than three months, loses the risk warning and physical protection functions and is recognized as one of the most burdensome disabling diseases (Davis et al., 2020; Treede et al., 2019). It was estimated that 20–40% of the global adult population suffers from chronic pain (Dahlhamer et al., 2018; Fayaz et al., 2016; GBD 2019 Diseases and Injuries Collaborators., 2020), and the situation has become more severe during the COVID-19 pandemic (Clauw et al., 2020). To address the above issues, a deeper understanding of pain and its neural mechanisms is urgently required. In particular, exploring a mechanism-based biomarker of pain would benefit the objective assessment of pain, development of new pain therapeutics, and accurate prediction of therapeutic responses (Davis et al., 2020; Mouraux and Iannetti, 2018).

Over the past two decades, gamma-band oscillations (GBOs), also

known as gamma oscillations or gamma-band synchronization, have been proposed to be one of the most promising and selective biomarkers of pain perception (Gross et al., 2007; Hu and Iannetti, 2019; May et al., 2019; Ploner et al., 2017; Schulz et al., 2015; Yue et al., 2020; Zhang et al., 2012). GBOs, the synchronized neural network rhythms in the frequency ranging from 30 to 100 Hz (Bressler and Freeman, 1980; Buzsaki and Wang, 2012), are vital for the communications between different brain structures and networks (Bonnetfond et al., 2017; Fries, 2015). Therefore, GBOs have been suggested to subserve an integrative role of different functions for the generation of the conscious experience of pain (Naro et al., 2015; Schulz et al., 2011). Importantly, multiple lines of evidence supported the candidacy of GBOs as a promising pain biomarker. First, the correlation between GBOs and pain perception was consistently observed in different pain types (i.e., phasic, tonic, and chronic pains) and those elicited by different stimulation approaches (e.g., nociceptive laser, heat, and electrical stimulations) (De Pascalis and Cacace, 2005; Gross et al., 2007; Peng et al., 2014; Schulz et al., 2015; Zhou et al., 2018). Second, GBOs could not only encode pain variability from trial to trial (moment to moment) within individuals (Schulz et al., 2012b), but also predict pain sensitivity across different individuals (Hu

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and Iannetti, 2019), in both humans and rodents (Hu and Iannetti, 2019; Peng et al., 2018). Third, the correlation between GBOs and pain perception was independent of stimulus saliency (Zhang et al., 2012), even though saliency could strongly bias the relationship between most nociceptive-evoked brain responses and pain perception (Iannetti et al., 2008; Mouraux and Iannetti, 2009). Fourth, GBOs seemed to causally affect pain perception since modulating the GBO activity using the optogenetic technique could effectively affect pain sensitivity in mice (Tan et al., 2019).

Nevertheless, pain-related GBOs should not be considered as a single entity. There is substantial heterogeneity in GBO characteristics and functions reported by previous publications (Hauck et al., 2007; Kim et al., 2015; Liberati et al., 2018b; Nickel et al., 2017; Schulz et al., 2012a; Tiemann et al., 2015). For instance, GBOs elicited by different pain types were reported to originate from different brain regions, e.g., the primary sensorimotor cortex for phasic pain (Gross et al., 2007; Heid et al., 2020; Schulz et al., 2015; Tiemann et al., 2012; Zhang et al., 2012) and the prefrontal cortex for chronic pain (Lim et al., 2016; May et al., 2019; Zhou et al., 2018). Even for the same pain type (e.g., phasic pain), GBOs elicited by different stimulation approaches (e.g., nociceptive laser, electrical, and mechanical stimulations) demonstrated distinct time-frequency distributions (Chien et al., 2014; Fabrizio et al., 2016; Michail et al., 2016; Rossiter et al., 2013). Moreover, a consensus has not been reached regarding the functions of pain-related GBOs. For example, some researchers suggested that GBOs represented pain perception rather than other psychological processes (Croft et al., 2002; Gross et al., 2007; Michail et al., 2016; Naro et al., 2015; Zhang et al., 2012), whereas others considered GBOs to reflect the involuntary attention induced by painful stimuli (Chien et al., 2014; Hauck et al., 2007; Northon et al., 2021a; Tiemann et al., 2010). The aforementioned heterogeneity suggests that GBOs are unlikely to be a single entity and but should be classified into several distinct entities. However, the underlying sources of GBO heterogeneity and the classification of GBOs have rarely been explored empirically.

To address these issues, we conducted a systematic review and meta-analysis to summarize the characteristics and functional significance of GBOs. Briefly, the whole investigation consisted of two studies, which summarized human and rodent findings (i.e., Studies 1 and 2), respectively. In both studies, we focused on the effects of the group (i.e., healthy participants and chronic pain patients), pain type (i.e., phasic, tonic, and chronic pains), and stimulation approaches (e.g., nociceptive laser, electrical, and heat stimulations) on (1) the correlation between pain intensity and GBO magnitude, (2) the frequential, spatial, and temporal characteristics of GBOs, and (3) the functional significance of GBOs. These factors were consistently reported by most of the previous studies and were proposed to be associated with the heterogeneity of GBO characteristics and functions (Bassez et al., 2020; Gross et al., 2007; Li et al., 2016c; May et al., 2019; Rossiter et al., 2013; Schulz et al., 2015).

2. Methods

2.1. Protocol registration

This systematic review and meta-analysis has been preregistered on the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY202180072; DOI: 10.37766/inplasy2021.8.0072), according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (PRISMA) (Moher et al., 2015). Literature Search, Article Selection, and Data Coding were conducted by two researchers independently (ZJL and YXZ), and the final meta-analyses were performed and rechecked by two researchers (ZJL and QZ). Discrepancies between these researchers were brought to our team meeting and solved with an agreement from all team members.

2.2. Literature search

Articles were searched from four online databases: PubMed, Web of Science, Scopus, and EBSCO (Academic and Library). Only peer-reviewed articles written in English were considered. The search period was from the earliest date of each database to September 21st, 2021, and the search areas were the research topic, title, or abstract of each article. The searching keywords were:

- (1) **γ -related keywords:** [gamma-band event-related synchronization OR γ -band event-related synchronization OR gamma-ERS OR γ -ERS OR gamma-band oscillations OR gamma oscillations OR GBOs OR GBO];
- (2) **pain-related keywords:** [pain OR nociceptive stimul* OR *-evoked OR *-induced];
- (3) **technique-related keywords:** [electroencephalogram OR electroencephalography OR EEG OR magnetoencephalogram OR magnetoencephalography OR MEG OR local field potentials OR LFP OR electrocorticography OR electrocorticogram OR ECoG].

After duplicated articles were removed, 885 candidate articles were identified from the four databases (Fig. 1). These articles covered both human studies ($n = 730$) and animal studies ($n = 152$), as well as a few cross-species studies ($n = 3$). These candidate articles were further screened according to the inclusion criteria (see below).

2.3. Inclusion criteria

For **human studies**, articles were further scanned according to the following five inclusion criteria: (1) the research topic was pain elicited by noxious stimuli or spontaneous pain of chronic pain patients; (2) **signal features of GBOs were reported (e.g., time, frequency, or spatial distribution)**; (3) **only one type of noxious stimuli was applied in each trial**; (4) data had not been used by any other study of the candidate article pool; (5) **all participants were adults (i.e., minimal age ≥ 18)**.

The above inclusion criteria also applied to **animal studies** after a few modifications: (1) the research topic was nociception or pain, and the animals were subjected to noxious stimuli or were the chronic pain modeling; (2) **the study must be in vivo, rather than in vitro**; (3) **adult animals were used**.

2.4. Study 1: systematic review and meta-analysis of human GBO studies

2.4.1. Article selection

After the literature scanning according to the inclusion criteria, 74 candidate studies remained for the current systematic review and meta-analysis (see Fig. 1). The excluded articles were irrelevant, identified according to the study title (the 1st step, $n = 449$ excluded), abstract (the 2nd step, $n = 148$ excluded), and full-text (the 3rd step, $n = 61$ excluded). Meanwhile, one eligible study was recruited from the reference list of the remaining studies ($n = 1$ included). Finally, one human experiment of one cross-species investigation was identified ($n = 1$ included).

For conducting the meta-analysis, the remaining 74 articles were further scanned (Babiloni et al., 2002; Baroni et al., 2020; Bassez et al., 2020; Chen and Herrmann, 2001; Chien et al., 2014; Croft et al., 2002; De Pascalis and Cacece, 2005; De Pascalis et al., 2004, 2019; Dinh et al., 2019; Dowman et al., 2008; Ebrahimian et al., 2018; Fabrizio et al., 2016; Gross et al., 2007; Guo et al., 2020a; Hansen et al., 2017; Hauck et al., 2015, 2007, 2013, 2017; Heid et al., 2020; Hsiao et al., 2020; Hu and Iannetti, 2019; Huang et al., 2018; Kim et al., 2015; Levitt et al., 2020; Li et al., 2016b, 2016c; Liberati et al., 2018a, 2019, 2018b, 2020; Lim et al., 2016; Liu et al., 2015b, 2015a; Luo et al., 2020; May et al., 2019; Michail et al., 2016; Misra et al., 2017; Naro et al., 2015, 2016; Nickel et al., 2017; Nilsson et al., 2014; Northon et al., 2021a, 2019, 2021b; Papageorgiou et al., 2017; Parker et al., 2020; Peng et al., 2014; Ren et al., 2019; Rossiter et al., 2013; Rustamov et al., 2019, 2021, 2020;

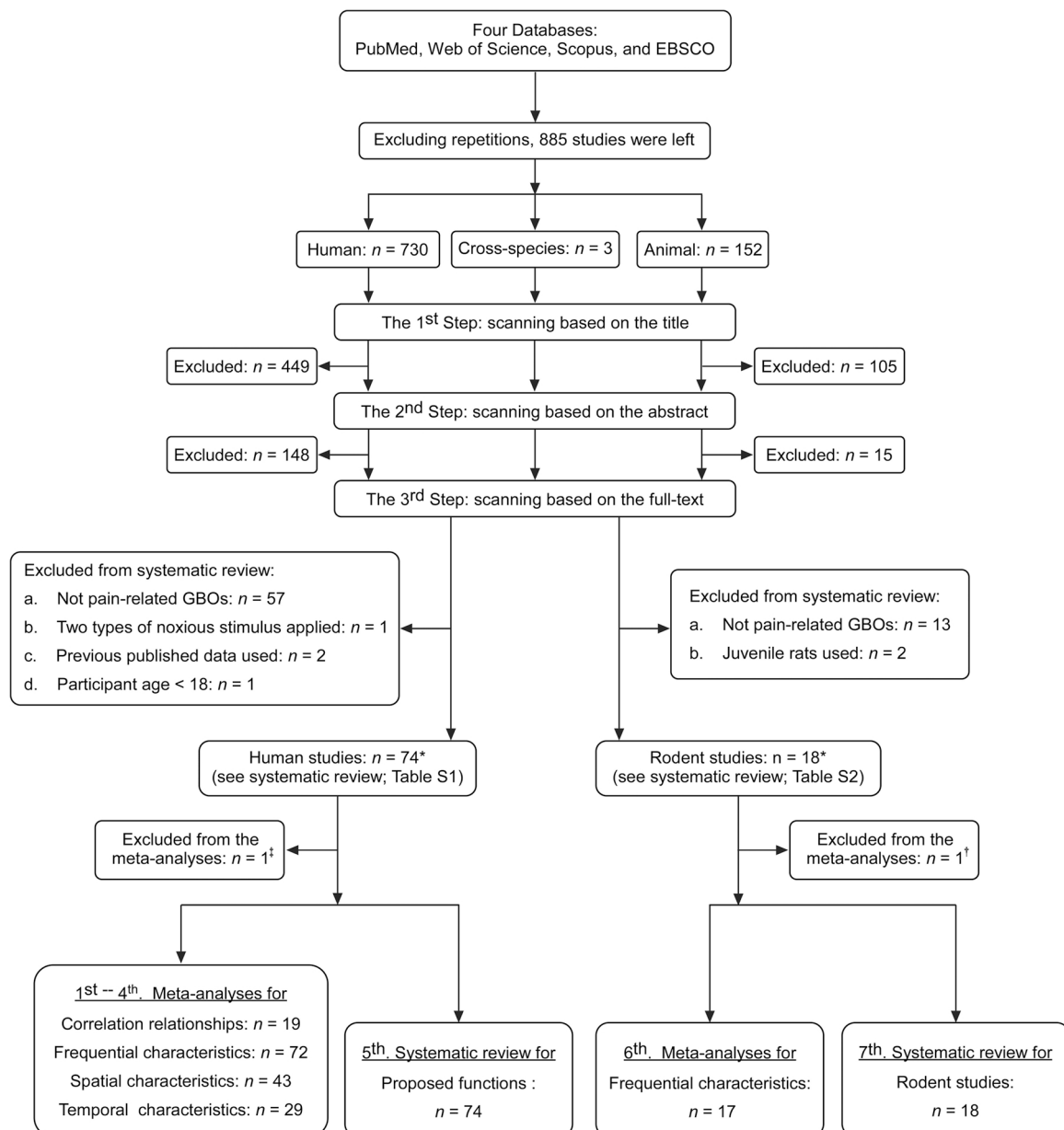


Fig. 1. Flowchart of the article selection. A total of 74 human studies and 18 rodent studies were included in the systematic reviews, and 73 human studies and 17 rodent studies were considered in the meta-analyses (n = number of studies). *A cross-species study (Hu and Iannetti, 2019) included both a human study and an animal study. One human study (Veerasarn and Stohler, 1992) was retrieved from the reference list and added to the meta-analyses. † One human study (Dowman et al., 2008) was excluded from the meta-analyses since it did not report the statistical results. † Since all animal studies were based on rodents, the subtitle of the meta-analyses was changed from animal studies to rodent studies. One rodent study was excluded from the meta-analyses in rodent studies since its sample size was not provided (Friesner et al., 2020).

Schulz et al., 2015, 2011, 2012a, 2012b; Senkowski et al., 2011; Shigihara et al., 2020; Strube et al., 2021; Taesler and Rose, 2016; Tiemann et al., 2018, 2015, 2010, 2012; Tripanpitak et al., 2021; Valentini et al., 2013; Veerasarn and Stohler, 1992; Vijayakumar et al., 2017; Wang et al., 2019; Zhang et al., 2012; Zhou et al., 2018, 2020) (Table S1). First, one study (Dowman et al., 2008) was excluded from all meta-analyses because it did not report statistical results of GBOs (n = 1 excluded). Second, studies were excluded from corresponding meta-analyses if (1) lacking statistical information about the correlation between pain intensity and pain-related GBOs (n = 54 excluded), (2) lacking information about the range of frequency of pain-related GBOs (n = 1 excluded), (3) lacking information about the spatial distribution of the electrodes containing pain-related GBOs (n = 30 excluded), or (4) lacking information about the range of latency of pain-related GBOs (n = 44

excluded). Eventually, four meta-analyses were conducted to explore (1) the correlation coefficient between pain intensity and GBOs (n = 19 remained studies), (2) the frequency range of GBOs (n = 72 remained studies), (3) the electrodes containing GBOs using a spatial activation likelihood estimation (ALE) (n = 43 remained studies), and (4) the latency range of GBOs (n = 29 remained studies).

2.4.2. Data coding

Both basic information and statistical information were coded for the current meta-analyses. Basic information was coded consistently for the four meta-analyses, covering (a) study name, (b) sample size and sex ratio of each study (i.e., female %), (c) participant group (i.e., healthy participants or patients), (d) pain type (i.e., phasic, tonic, or chronic pain), (e) stimulation type (e.g., laser, electrical, or heat stimulation), (f)

stimulation/pain side (e.g., left or right side of the body), and (g) recording technique (e.g., EEG, MEG, or LFP) (Table S1).

Statistical information was coded for the four meta-analyses separately:

(1) the correlational meta-analysis: the information coded was the correlation-related statistical information (e.g., Pearson's correlation coefficient and p -value). If any study presented Spearman's correlation coefficient r_s , we converted it to Pearson's correlation coefficient according to the conversion formula $r = 2\sin(r_s\pi/6)$ (Pearson, 1907; Rupinski and Dunlap, 1996). If a study reported the t -value or β coefficient (Peterson and Brown, 2005) of a univariate regression predicting pain intensity from the magnitude of GBOs, we directly transformed the t or β values to the r value in the meta-analysis (Table S2).

(2) the frequential meta-analysis: the information coded was the frequency range of GBOs (i.e., lower limit, upper limit, and mean) (Table S3).

(3) the spatial ALE of electrodes: the information coded was the labels of electrodes with the pain-related GBOs (e.g., Cz and Fcz, Table S4). In a few studies, the electrodes containing GBOs were reported, but the scalp distributions of GBOs were not presented. In these cases, the electrodes to extract pain-related GBOs could only be determined based on a hypothesis-driven approach, not a data-driven one. All labels of electrodes were projected to the Talairach space (x^{TAL} , y^{TAL} , z^{TAL}) through the following formula (Talairach and Tournoux, 1988): $x^{TAL} = -40 \times y^{EEG}$, $y^{TAL} = 40 \times x^{EEG}$, $z^{TAL} = 40 \times z^{EEG}$, where x^{EEG} , y^{EEG} , z^{EEG} are EEG electrode coordinates retrieved from the EEGLAB toolbox (i.e., the standard 10–20 Cap81.ced file) (Delorme and Makeig, 2004). The converted Talairach coordinates of the reported electrodes were used in the ALE analysis. A map of the 64-electrode cap with Talairach coordinates was used to decode the final ALE results.

(4) the temporal meta-analysis: the information coded was the latency range of GBOs (i.e., lower limit, upper limit, and mean) (Table S5).

2.5. Study 2: systematic review and meta-analysis of rodent GBO studies

2.5.1. Article selection

In total, 152 animal studies were identified from the four databases. These candidate articles were screened based on the study title (the 1st step, $n = 105$ excluded), abstract (the 2nd step, $n = 15$ excluded), and full-text (the 3rd step, $n = 15$ excluded) (Fig. 1). A systematic review was conducted based on the remaining studies ($n = 18$), which included 17 rodent studies and one rodent experiment presented in a cross-species study (Table S6). For the meta-analysis, one study had to be further excluded since the sample size was not given (Friesner et al., 2020). Therefore, a meta-analysis of the frequency range of GBOs was conducted based on the remaining 17 rodent studies (Fu et al., 2018; Guo et al., 2020b; Hu and Iannetti, 2019; Iwamoto et al., 2021; Li et al., 2016a, 2017; Liu et al., 2019; Neves et al., 2018; Peng et al., 2018; Ponsel et al., 2020; Shi et al., 2020; Tan et al., 2019; Wang et al., 2011, 2016; Xiao et al., 2019; Yue et al., 2020; Zhang et al., 2018) (Table S7).

2.5.2. Data coding

Information coded included from the animal studies were: (a) study name, (b) sample size, (c) animal group (i.e., mouse or rat), (d) pain type (i.e., phasic, tonic, or chronic pain), (e) stimulation type (e.g., laser or electrical stimulation), (f) frequency range of GBOs (i.e., lower limit, upper limit, and mean) (Table S7).

2.6. Methods of meta-analyses and systematic review

2.6.1. Traditional meta-analysis

The Comprehensive Meta-Analysis (CMA) V3 statistical software (Biostat. Inc., Englewood, NJ, USA) (Borenstein et al., 2014) was used to perform the traditional meta-analysis. Random-effects models were used to account for the within- and between-study variability (Lipsey and Wilson, 2001). In addition, we evaluated the moderation effects of

participant types (e.g., healthy participants vs. patients), pain types (e.g., phasic pain vs. tonic pain vs. chronic pain), and stimulation types (e.g., laser stimulation vs. electrical stimulation) on the meta-analysis results (Fig. 2). Furthermore, if any of the above comparisons among multiple subgroups (three or more subgroups) was significant, pairwise comparisons with Bonferroni correction (i.e., $P_{corrected} = P_{raw} \times n_{comparisons}$, to account for inflated Type I error) were conducted to identify the source of the group difference. For the foregoing meta-group comparisons, mixed-effects models (random-effects models to evaluate the mean effect size for each subgroup and fixed-effects models for group comparisons) were used. Importantly, meta-group comparisons were conducted only when there were sufficient number of effect sizes for each compared group ($k \geq 2$ per meta-group).

To gauge the risk of publication biases, we constructed the funnel plot with Duval and Tweedie's trim and fill correction (Duval and Tweedie, 2000) and performed the Begg and Mazumdar rank test with Kendall's tau with continuity correction (Begg and Mazumdar, 1994). If $p > 0.05$ for the Begg and Mazumdar rank test, we concluded that no evidence for significant publication bias existed. The heterogeneity of these analyses was assessed using Q and I^2 (Higgins and Thompson, 2002; Huedo-Medina et al., 2006). I^2 values of 25%, 50%, and 75% suggest low, moderate, and high heterogeneity, respectively (Higgins et al., 2003). Moreover, Cochrane Collaboration's tool (Higgins et al., 2011; Sterne et al., 2019) and SYRCLE's risk of bias tool (Hooijmans et al., 2014) were used to comprehensively evaluate other risks of biases (i.e., selection bias, performance bias, detection bias, attrition bias, and reporting bias) for individual human studies (Fig. S1) and rodent studies (Fig. S2), respectively. Finally, to evaluate the stability of these analyses, we conducted a sensitivity analysis using the 'one study removed method' (Borenstein et al., 2021).

2.6.2. Activation likelihood estimation

BrainMap GingerALE 3.0.2 was used for conducting the current ALE analyses (Eickhoff et al., 2012). In ALE, each coordinate (i.e., x^{TAL} , y^{TAL} , z^{TAL}) is treated as the center of an 'activation', spreading to adjoining areas following the Gaussian distribution. Each brain area's overall 'activation' is the combined 'activation' as per all inputs in the area. The final ALE results are the brain areas with 'activation' over a statistical threshold. In this study, the statistical threshold for the ALE was set to be $\alpha = 0.001$.

2.6.3. Systematic review

To supplement the meta-analysis results, a systematic review was conducted for human studies and rodent studies respectively. For human studies, we have synthesized and classified the main functions of GBOs proposed in previous studies. The GBO functions could be roughly divided into seven aspects: pain perception (reflecting subjective pain experience of individuals), pain attention (reflecting the involuntary attention attracted by noxious stimuli), general sensory processing (reflecting the general sensory processing of painful and non-painful stimuli), multidimensional processing of pain (reflecting the processing of multiple aspects of pain, such as active-avoidance control and pain emotion), motor responses (reflecting the transformation from pain sensory information to motor responses), pain relief (reflecting the reduction of pain experience after treatment), and pathophysiology of chronic pain (reflecting the abnormal brain activity in patients with chronic pain). For rodent studies, we summarized the information not revealed by the meta-analysis (e.g., correlation coefficient, latency range, and spatial distribution).

3. Results

3.1. Correlation between pain intensity and GBO magnitude in human studies

A total of 19 studies evaluated the correlation between pain intensity

Questions				Figures	
Human studies					
Q1: Are GBOs correlated with pain intensity in humans?				Figure 4	
Q2: What are the frequential features of GBOs in humans?				Figure 5	
Q3: How do GBOs distribute spatially in humans?				Figure 6	
Q4: When do GBOs occur temporally in humans?				Figure 7	
Q5: What are the functions of GBOs in humans?				Figure 8	
Animal studies					
Q6: What are the frequential features of GBOs in animals?				Figure 9	

	Human studies				Animal studies
Effects	Correlations with pain	Frequential characteristics	Spatial characteristics	Temporal characteristics	Frequential characteristics
Participant group/ Animal type	Fig. 4 (a-c)	Fig. 5 (a-e)	×	Fig. 7 (a-b)	Fig. 9 (a)
Pain type	Fig. 4 (d-e)	Fig. 5 (f-h)	Fig. 6 (a-b)	×	Fig. 9 (b)
Stimulation type	Fig. 4 (f-g)	Fig. 5 (i-k)	Fig. 6 (c)	Fig. 7 (c-d)	Fig. 9 (c)
Stimulation side	×	×	Fig. 6 (d)	×	×

Fig. 2. The summary of all meta-analyses performed on human studies and rodent studies. In human studies, a series of meta-analyses were performed to assess the correlation between GBO magnitude and pain intensity, and explore the frequential, spatial, and temporal characteristics of GBOs. Due to the limited number of animal studies, only one meta-analysis was performed to explore the frequential characteristic of GBOs of rodents.

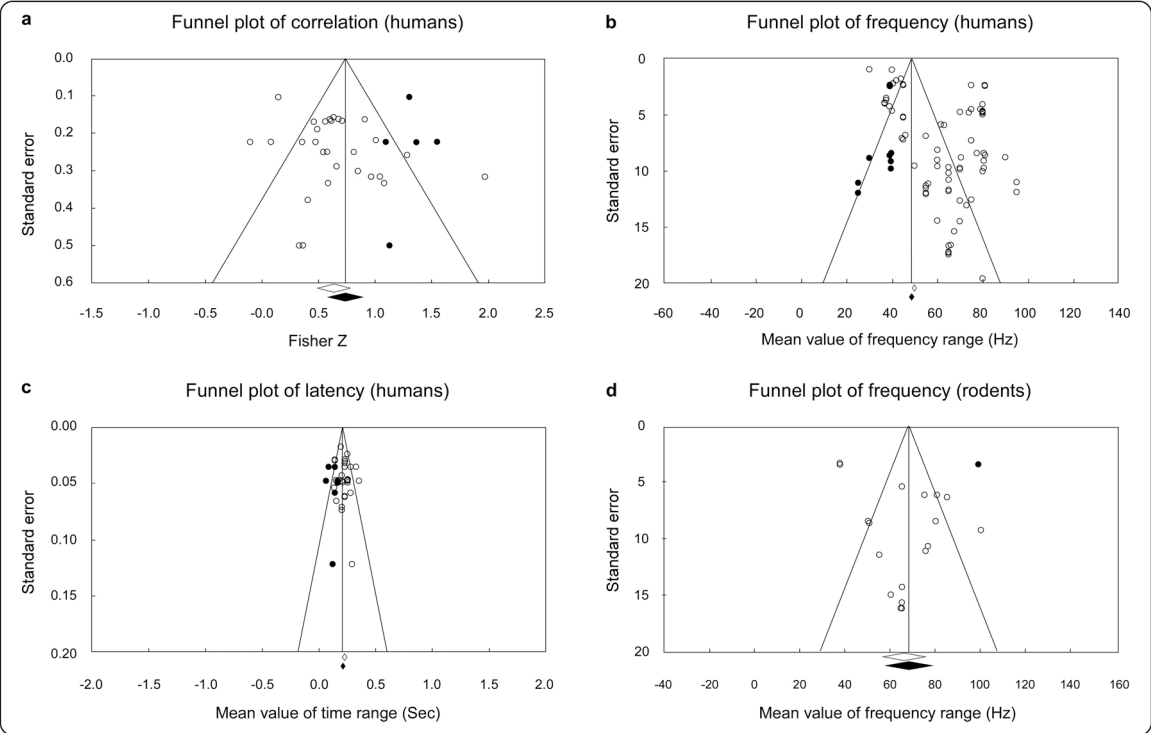


Fig. 3. Funnel plots of meta-analyses. Hollow circles indicate studies included in the meta-analysis, and solid black circles represents the missing studies indicated by Duval and Tweedie's trim and fill correction procedure. The horizontal axis represents the mean effect size, and the vertical axis represents the standard error. Hollow diamonds indicate the observed overall results, and solid black diamonds represent the adjusted overall results.

and GBO magnitude (participant $N = 561$, 30 experiments). The mean Pearson's correlation coefficient (r) of these studies was 0.57 (95% CI = [0.48, 0.65], $p < 0.001$) (Fig. S3). It is worth noting that this significant correlation mostly reflected within-individual correlations, although a recent study also found between-individual correlations between GBO magnitudes and pain intensity (Hu and Iannetti, 2019). In addition, moderate heterogeneity was observed among these studies ($Q = 78.04$, $df = 29$, $p < 0.001$; $I^2 = 62.84$). Kendall's S statistic (P-Q) was 26.00 for the Begg and Mazumdar rank test (Kendall's corrected $\tau = 0.06$, z for the $\tau = 0.45$, two-tailed $p = 0.66$). Duval and Tweedie's trim and fill procedure suggested that there could be five missing studies. Including these missing studies, a reanalysis suggested that the correlation coefficient increased to 0.64 (95% CI = [0.54, 0.72], $Q = 149.85$). Based on these results, there was no obvious evidence of publication bias (see Fig. 3a for the funnel plot).

3.1.1. Participant group effect

The correlation coefficient in healthy participants ($r = 0.60$, 95% CI = [0.51, 0.68], $p < 0.001$, $k = 26$) was marginally significantly ($Q = 3.62$, $p = 0.057$) larger than in patients ($r = 0.27$, 95% CI = [-0.13, 0.60], $p = 0.181$, $k = 4$) (Fig. 4a). For phasic pain, the correlation coefficient was significantly ($Q = 14.69$, $p < 0.001$) higher in healthy participants ($r = 0.63$, 95% CI = [0.50, 0.73], $p < 0.001$, $k = 19$) than in patients ($r = 0.07$, 95% CI = [-0.22, 0.34], $p = 0.644$, $k = 3$) (Fig. 4b). Moreover, for nociceptive laser stimulation, the correlation coefficient in healthy participants ($r = 0.63$, 95% CI = [0.44, 0.77], $p < 0.001$, $k = 13$) was significantly higher ($Q = 11.28$, $p < 0.01$) than in patients

($r = 0.07$, 95% CI = [-0.22, 0.34], $p = 0.644$, $k = 3$) (Fig. 4c). Due to insufficient studies on tonic pain and chronic pain in patients, no comparison was performed between the two participant groups. These results indicate that the correlation between pain intensity and GBOs in healthy participants is larger than in patients, especially for phasic pain induced by laser stimulation.

3.1.2. Pain type effect

Across participant groups, no significant differences of the correlation coefficient between phasic pain ($r = 0.58$, 95% CI = [0.44, 0.69], $p < 0.001$, $k = 22$) and tonic pain ($r = 0.55$, 95% CI = [0.45, 0.64], $p < 0.001$, $k = 7$) were observed ($Q = 0.087$, $p = 0.768$) (Fig. 4d). For studies with healthy participants, no significant pain type effects on the correlation ($Q = 0.966$, $p = 0.326$) were identified between phasic pain ($r = 0.63$, 95% CI = [0.50, 0.73], $p < 0.001$, $k = 19$) and tonic pain ($r = 0.55$, 95% CI = [0.45, 0.64], $p < 0.001$, $k = 7$) (Fig. 4e). The effect of pain types on the correlation in patients was not evaluated since there were only two studies of phasic pain ($r = 0.07$, 95% CI = [-0.22, 0.34], $p = 0.644$, $k = 3$) and one of chronic pain ($r = 0.70$, 95% CI = [0.27, 0.90], $p < 0.01$, $k = 1$). Taken together, these results show that the correlation between pain intensity and GBO magnitude persists regardless of pain types in healthy participants.

3.1.3. Stimulation type effect

Across participant groups, the correlation coefficients were not significantly different ($Q = 2.089$, $df = 2$, $p = 0.352$) among laser ($r = 0.55$, 95% CI = [0.36, 0.70], $p < 0.001$, $k = 16$), electrical

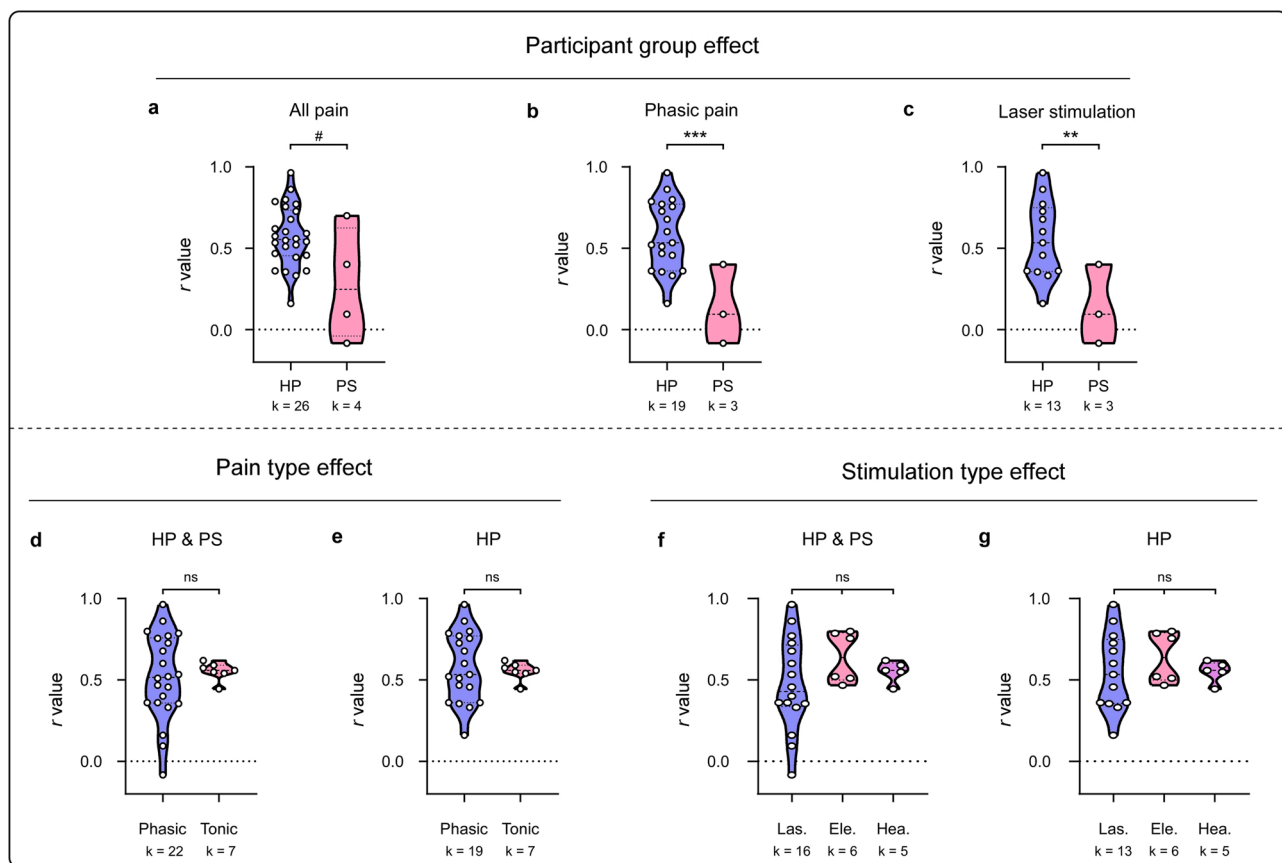


Fig. 4. The comparisons of correlation coefficients between pain intensity and GBO magnitude. The correlation between pain intensity and GBOs was larger in healthy participants (HP) than in patients (PS), especially under the condition of phasic pain evoked by laser stimulation (a: marginally significant; b-c: significant). In contrast, the correlation difference was not significant as per pain types (d-e) and stimulation types (f-g). The white circles indicate single studies, the labels for the x-axis include the number of studies in each condition, and the titles of the subplots indicate the category of studies included in the comparisons. Las. = Laser stimulation, Ele. = Electrical stimulation, Hea. = Heat stimulation. #, $p_{corrected} < 0.1$; *, $p_{corrected} < 0.05$; **, $p_{corrected} < 0.01$; ***, $p_{corrected} < 0.001$; ns, $p_{corrected} > 0.1$.

($r = 0.60$, 95% CI = [0.46, 0.71], $p < 0.001$, $k = 6$), and heat stimulations ($r = 0.55$, 95% CI = [0.43, 0.65], $p < 0.001$, $k = 5$) (Fig. 4f). For studies with healthy participants, no significant stimulation type effect on the correlation ($Q = 0.46$, $df = 2$, $k = 24$, $p = 0.794$) were identified among laser ($r = 0.63$, 95% CI = [0.44, 0.77], $p < 0.001$, $k = 13$), electrical ($r = 0.60$, 95% CI = [0.46, 0.71], $p < 0.001$, $k = 6$), and heat stimulations ($r = 0.55$, 95% CI = [0.43, 0.65], $p < 0.001$, $k = 5$) (Fig. 4g). These findings suggest that the stimulation type has little effect on the correlation coefficient between pain intensity and GBO magnitude.

Owing to inadequate number of publications, two studies using the other types of stimulations (chemical: $r = 0.57$, 95% CI = [0.33, 0.75], $p < 0.001$, $k = 1$; cold: ($r = 0.54$, 95% CI = [-0.05, 0.85], $p = 0.070$, $k = 1$) were excluded from the subgroup comparison of healthy participants. In addition, there were only two studies with laser stimulation in patients ($r = 0.07$, 95% CI = [-0.22, 0.34], $p = 0.644$, $k = 3$). Therefore, we did not meta-analyze the effect of stimulation types on the correlation between pain intensity and GBO magnitude in studies with patients.

3.2. Frequential characteristics of GBOs in human studies

In total, 72 studies (participant $N = 2029$, 83 experiments) presented the frequency range of GBOs. The mean of GBO frequency was 63.24 Hz (standard error = 2.31 Hz, 95% CI = [58.72, 67.76], $k = 83$) (Fig. S4). High heterogeneity among these studies was identified ($Q = 1881.97$, $df = 82$, $p < 0.001$; $I^2 = 95.64$). Kendall's S statistic (P-Q) in the Begg and Mazumdar rank test was -164.00 (Kendall's corrected tau = -0.05, z for the tau = 0.64, two-tailed $p = 0.52$). Meanwhile, Duval and Tweedie's trim and fill test indicated there could be ten missing studies. Adjusted with these missing studies, the mean value of GBO frequency was lowered to 60.17 Hz (standard error = 2.10 Hz, 95% CI = [56.06, 64.28], $Q = 1952.40$). Therefore, no apparent publication bias existed (see Fig. 3b for the funnel plot).

3.2.1. Participant group effect

The GBO frequency in healthy participants (63.59 ± 2.91 Hz, 95% CI = [57.88, 69.29], $k = 55$) and that in patients (62.33 ± 3.51 Hz, 95% CI = [55.45, 69.22], $k = 28$) were not significantly different ($Q = 0.076$, $p = 0.783$) (Fig. 5a). For phasic pain, no significant group differences of GBO frequency were found ($Q = 0.299$, $p = 0.585$) between healthy participants (66.22 ± 3.60 Hz, 95% CI = [59.16, 73.29], $k = 38$) and patients (69.35 ± 4.44 Hz, 95% CI = [60.64, 78.06], $k = 15$) (Fig. 5b). For tonic pain, no significant group differences were found ($Q = 0.163$, $p = 0.686$) between healthy participants (54.49 ± 3.56 Hz, 95% CI = [47.50, 61.48], $k = 17$) and patients (48.69 ± 13.93 Hz, 95% CI = [21.40, 75.98], $k = 2$) (Fig. 5c). More specifically, the GBO frequency was not significantly different between healthy participants and patients stimulated by either laser (73.09 ± 3.23 Hz, 95% CI = [66.76, 79.42], $k = 20$ [healthy] vs. 69.91 ± 4.90 Hz, 95% CI = [60.30, 79.51], $k = 11$ [patients]; $Q = 0.294$, $p = 0.588$, Fig. 5d) or electrical stimulations (57.55 ± 3.51 Hz, 95% CI = [50.67, 64.43], $k = 16$ [healthy] vs. 77.14 ± 10.52 Hz, 95% CI = [56.52, 97.78], $k = 3$ [patients]; $Q = 3.122$, $p = 0.077$, Fig. 5e). These results suggest no significant participant group effect on the GBO frequential characteristics.

3.2.2. Pain type effect

Across participant groups, there was a significant main effect of pain types on GBO frequency (phasic pain: 67.13 ± 3.09 Hz, 95% CI = [61.07, 73.20], $k = 53$; tonic pain: 53.21 ± 3.23 Hz, 95% CI = [46.87, 59.55], $k = 19$; chronic pain: 55.25 ± 4.10 Hz, 95% CI = [47.22, 63.28], $k = 11$; $Q = 25.774$, $df = 2$, $p < 0.001$). *Post hoc* comparisons showed that the frequency of GBOs elicited by phasic pain was significantly higher than that elicited by tonic pain ($Q = 9.671$, $p_{corrected} = 0.006$), and was marginally significantly higher than that elicited by chronic pain ($Q = 5.360$, $p_{corrected} = 0.063$) (Fig. 5f). In healthy

participants, there was significant difference of GBO frequency ($Q = 5.351$, $p = 0.021$) between phasic pain (66.23 ± 3.60 Hz, 95% CI = [59.16, 73.29], $k = 38$) and tonic pain (54.49 ± 3.57 Hz, 95% CI = [47.51, 61.49], $k = 17$) (Fig. 5g). In patients, there was a significant pain type effect (phasic pain: 69.35 ± 4.44 Hz, 95% CI = [60.64, 78.06], $k = 15$, tonic pain: 48.69 ± 13.93 Hz, 95% CI = [21.40, 75.98], $k = 2$, and chronic pain: 55.25 ± 4.10 Hz, 95% CI = [47.22, 63.28], $k = 11$; $Q = 7.66$, $df = 2$, $p = 0.022$). *Post hoc* comparisons showed that GBO frequency was marginally significantly higher for phasic pain than for chronic pain ($Q = 5.444$, $p_{corrected} = 0.060$) (Fig. 5h). These results indicate that phasic pain tends to induce higher GBO frequency than tonic and chronic pain do.

3.2.3. Stimulation type effect

There was a significant main effect of the stimulation type on GBO frequency ($Q = 1214.99$, $df = 5$, $p < 0.001$) among six stimulation types: laser (72.11 ± 2.65 Hz, 95% CI = [66.91, 77.31], $k = 31$), electrical (60.53 ± 3.45 Hz, 95% CI = [53.77, 67.28], $k = 19$), heat (64.29 ± 4.13 Hz, 95% CI = [56.20, 72.38], $k = 10$), cold (43.57 ± 3.82 Hz, 95% CI = [36.07, 51.07], $k = 6$), mechanical (43.15 ± 3.25 Hz, 95% CI = [36.79, 49.51], $k = 4$), and chemical stimulations (69.27 ± 8.35 Hz, 95% CI = [52.92, 85.63], $k = 2$). *Post hoc* comparisons revealed the following results. First, the frequencies of GBOs induced by laser, electrical, and heat stimulations were significantly higher than those induced by cold and mechanical stimulations (electrical vs. cold: $p_{corrected} < 0.05$; others: $p_{corrected} < 0.01$). Secondly, GBO frequencies induced by cold and mechanical stimulations were marginally significantly lower than that induced by chemical stimulation (cold vs. chemical: $p_{corrected} = 0.075$; mechanical vs. chemical: $p_{corrected} = 0.06$) (Fig. 5i).

We then examined the stimulation type effect in different participant groups. In healthy participants, a significant main effect of stimulation types on GBO frequency was identified ($Q = 28.26$, $df = 5$, $p < 0.001$) among laser (73.09 ± 3.23 Hz, 95% CI = [66.76, 79.42], $k = 20$), electrical (57.55 ± 3.51 Hz, 95% CI = [50.67, 64.43], $k = 16$), heat (64.19 ± 4.40 Hz, 95% CI = [55.56, 72.82], $k = 9$), cold (45.56 ± 4.70 Hz, 95% CI = [36.34, 54.77], $k = 5$), mechanical (42.69 ± 3.63 Hz, 95% CI = [35.57, 49.80], $k = 3$), and chemical stimulations (69.27 ± 8.35 Hz, 95% CI = [52.92, 85.63], $k = 2$). *Post hoc* analysis revealed the following results. First, the frequency of GBOs induced by laser stimulation was significantly higher than those induced by electrical, cold, and mechanical stimulations (laser vs. electrical: $p_{corrected} < 0.05$; others: $p_{corrected} < 0.01$). Second, the frequencies of GBOs induced by heat, electrical and chemical stimulations were significantly higher than that induced by mechanical stimulation (heat vs. mechanical: $p_{corrected} < 0.01$; electrical/chemical vs. mechanical: $p_{corrected} < 0.05$). In addition, the GBO frequency induced by heat stimulation was marginally significantly higher than that induced by cold stimulation ($p_{corrected} = 0.060$) (Fig. 5j).

In patients, there was only one study for each of the three stimulation types (i.e., heat, cold, and mechanical stimulations, each $k = 1$). Therefore, the stimulation type effect was only evaluated based on the laser and electrical stimulations. No significant difference in GBO frequency ($p = 0.533$) was identified between laser (69.91 ± 4.90 Hz, 95% CI = [60.30, 79.51], $k = 11$) and electrical stimulations (77.15 ± 10.52 Hz, 95% CI = [56.52, 97.78], $k = 3$) (Fig. 5k).

Overall, stimulation types have a significant effect on GBO frequency. Laser, electrical, heat, and chemical stimulations induce GBOs with a higher frequency than cold and mechanical stimulations do. Notably, laser stimulation elicits significantly higher GBO frequency than electrical stimulation in healthy individuals but not in patients.

3.3. Spatial characteristics of GBOs in human studies

Based on 43 human studies (participant $N = 1331$, 57 experiments, 111 foci), ALE yielded the following thirteen foci related to GBO

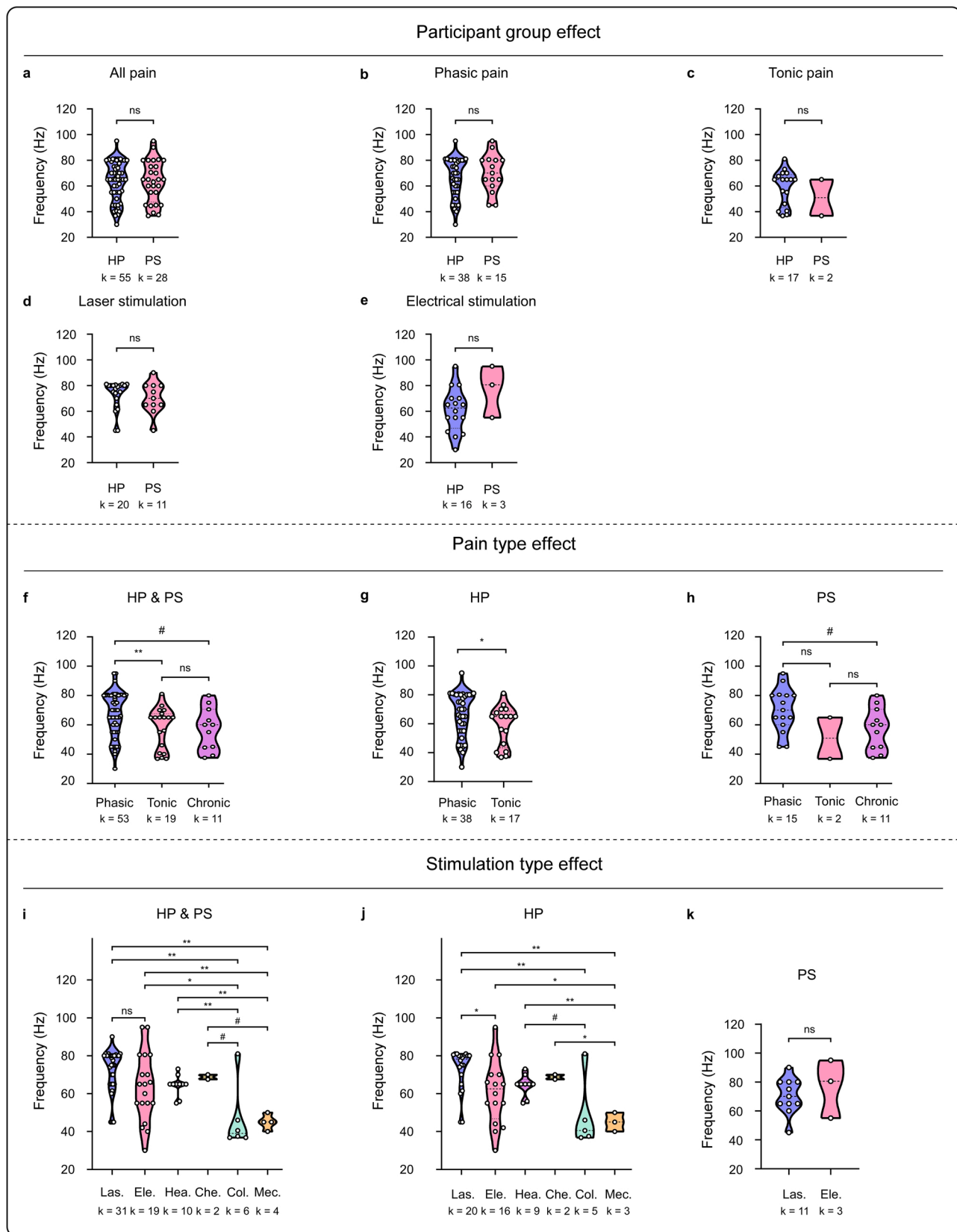


Fig. 5. The comparisons of GBO frequency. Whereas no participant group effect on GBO frequency was observed (a-e), GBO frequency tended to be higher for phasic pain than tonic and chronic pain (f-h). For phasic pain, GBO frequency evoked by different stimulation types was quite different, e.g., GBOs elicited by cold and mechanical stimulations had a lower frequency than those elicited by other types of stimulation (i-k). The white circles indicate single studies, the labels for the x-axis include the number of studies in each condition, and the titles of the subplots indicate the category of studies included in the comparisons. HP: healthy participants, PS: patients. Las. = Laser stimulation, Ele. = Electrical stimulation, Hea. = Heat stimulation, Che. = Chemical stimulation, Col. = Cold stimulation, Mec. = Mechanical stimulation. #, $p_{corrected} < 0.1$; *, $p_{corrected} < 0.05$; **, $p_{corrected} < 0.01$; ***, $p_{corrected} < 0.001$; ns, $p_{corrected} > 0.1$.

responses (sorted by the *ALE*-value): Cz (*ALE* = 0.215), FCz (*ALE* = 0.090), Fz (*ALE* = 0.083), C2 (*ALE* = 0.067), C4 (*ALE* = 0.065), C3 (*ALE* = 0.064), AF3 (*ALE* = 0.047), AF4 (*ALE* = 0.032), FP2 (*ALE* = 0.027), FC1 (*ALE* = 0.026), FC2 (*ALE* = 0.025), FP1 (*ALE* = 0.019), and F3 (*ALE* = 0.018).

3.3.1. Pain type effect

In healthy participants, GBOs elicited by phasic pain ($N = 926$, 35

experiments, 58 foci) were mainly located at seven central-frontally distributed foci: Cz (*ALE* = 0.167), FCz (*ALE* = 0.074), C2 (*ALE* = 0.051), C4 (*ALE* = 0.048), Fz (*ALE* = 0.035), F1 (*ALE* = 0.009), and C3 (*ALE* = 0.034) (Fig. 6a). In contrast, five frontally distributed foci was identified based on studies of GBOs elicited by tonic pain ($N = 298$, 10 experiments, 28 foci): AF3 (*ALE* = 0.040), FP1 (*ALE* = 0.010), Fz (*ALE* = 0.041), AF4 (*ALE* = 0.032), and FP2 (*ALE* = 0.010) (Fig. 6a). In patients, GBOs elicited by phasic pain ($N = 157$, 9 experiments, 19 foci) were

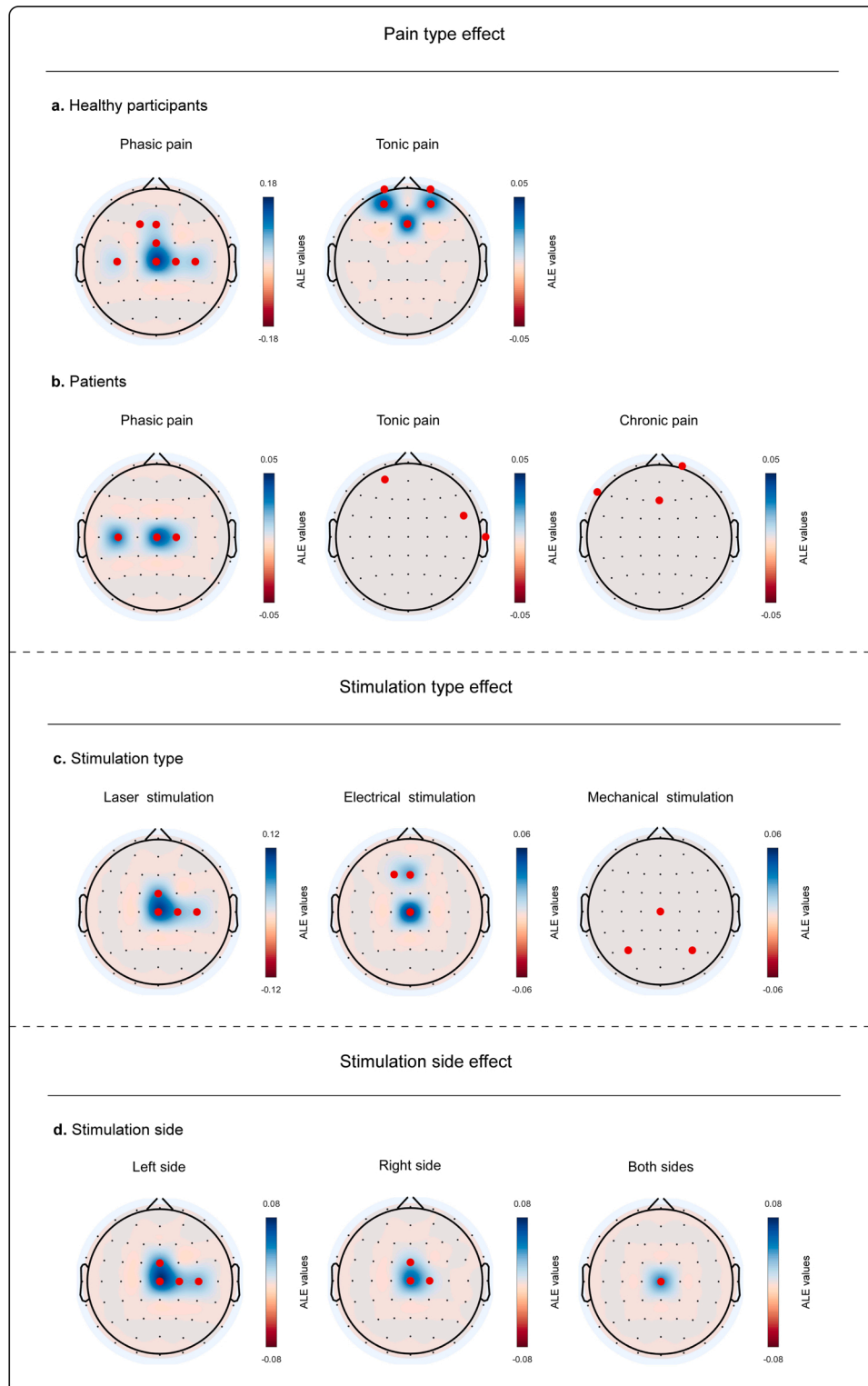


Fig. 6. Spatial distributions of GBOs in different subgroups. GBOs elicited by phasic pain were more centrally distributed, while those elicited by tonic and chronic pain showed a more frontal distribution (a-b). For phasic pain, different types of stimulation consistently elicited GBOs around the central electrodes (c), with a stronger activation contralateral to the left side stimulation (d). Electrodes with significant GBOs were marked in red. For patient studies with tonic and chronic pain (b) as well as studies with mechanical stimulation (c), the available studies were insufficient to conduct the ALE analyses ($k \leq 2$ contrasts). In these cases, the electrodes (i.e., red dots) are displayed according to the original reports without ALE values.

mainly located at three central electrodes: Cz ($ALE = 0.041$), C2 ($ALE = 0.016$), and C3 ($ALE = 0.030$) (Fig. 6b). No convergent ALE results were identified based on two studies with chronic pain patients (the two studies provided only three candidate electrodes, i.e., Fz, F7, and FP2) (Fig. 6b). No ALE analysis was conducted for tonic pain since there was only one patient study (providing three electrodes, i.e., T8, AF3, and FC6). Although limited by small sample sizes, these results indicate that phasic and tonic pain induce different activation patterns of GBOs in healthy individuals and patients, and there is no clear evidence for and against different spatial characteristics of GBOs for tonic pain and chronic pain in patients.

3.3.2. Stimulation type effect

In healthy participants, GBOs elicited by laser stimulation ($N = 550$, 21 experiments, 35 foci) appeared at four central electrodes: Cz ($ALE = 0.107$), FCz ($ALE = 0.066$), C2 ($ALE = 0.051$), and C4 ($ALE = 0.027$) (Fig. 5c). GBOs elicited by electrical stimulation ($N = 331$, 12 experiments, 20 foci) were distributed at three centro-frontal foci: Cz ($ALE = 0.059$), Fz ($ALE = 0.027$), and F1 ($ALE = 0.008$) (Fig. 6c). For mechanical stimulation ($N = 45$, 2 experiments, 3 foci), no significant ALE results were found, although two original studies provided three distinct peak electrodes of GBOs: Cz, P3, and P4 (Fig. 6c). Taken together, these results show that different types of transient stimulation consistently elicit GBOs around Cz in healthy individuals, suggesting a sensorimotor origin of GBOs associated with phasic pain.

3.3.3. Stimulation side effect

For studies with left-side pain stimulation ($N = 426$, 16 experiments, 29 foci), GBOs were distributed at central electrodes with some extension to the right hemisphere: Cz ($ALE = 0.076$), FCz ($ALE = 0.050$), C2 ($ALE = 0.035$), and C4 ($ALE = 0.030$) (Fig. 6d). For studies with right-side pain stimulation ($N = 271$, 12 experiments, 20 foci), GBOs were more centrally distributed: Cz ($ALE = 0.056$), FCz ($ALE = 0.024$), and C2 ($ALE = 0.017$) (Fig. 6d). Moreover, for studies with bilateral stimulations ($N = 229$, 7 experiments, 9 foci), significant GBOs were only identified at Cz ($ALE = 0.045$) (Fig. 6d). These results indicate that the spatial distribution of GBOs is partially lateralized, which may be explained by three possible reasons, i.e., (1) the bias in the hypothesis-driven approach in electrode selection, (2) the low signal-to-noise ratio of GBOs (Ray and Maunsell, 2015), and (3) the strong emotional process of the right brain hemisphere (Borod et al., 1998; Duerden and Albanese, 2013).

3.4. Temporal characteristics of GBOs elicited by phasic pain in human studies

In total, 29 phasic pain studies reported the latency range of GBOs (participant $N = 771$, 35 experiments). The mean of GBO latency range was 220.09 ms (standard error = 8.71 ms, 95% CI = [203.02, 237.16]). These studies exhibited low heterogeneity ($Q = 49.89$, $df = 34$, $p < 0.05$; $I^2 = 31.86$) (Fig. S5). As for the Begg and Mazumdar rank test, the Kendall's S statistic (P-Q) was -18.00 (Kendall's corrected tau = -0.03 , z for the tau = 0.24, two-tailed $p = 0.81$). Additionally, there could be seven missing studies indicated by Duval and Tweedie's trim and fill test. The adjusted mean with the missing studies included was 205.74 ms (standard error = 9.47 ms, 95% CI = [187.17, 224.31], $Q = 81.04$). As a result, there was no obvious evidence of publication bias (see Fig. 3c for the funnel plot).

3.4.1. Participant group effect

The mean latency of GBOs was not significantly different ($Q = 1.721$, $p = 0.190$) between healthy participants (226.51 ± 10.65 ms, 95% CI = [205.63, 247.39], $k = 27$) and patients (203.44 ± 13.99 ms, 95% CI = [176.01, 230.87], $k = 8$) (Fig. 7a). In studies with laser stimulation, no significant differences of GBO mean latency were found ($Q = 2.873$, $p = 0.090$) between healthy participants (238.37 ± 12.46 ms, 95% CI = [213.94, 262.80], $k = 19$) and patients (203.92 ± 16.05 ms, 95% CI = [172.47, 235.38], $k = 7$) (Fig. 7b). There were eight studies with healthy participants that used electrical stimulation (181.04 ± 20.23 ms, 95% CI = [141.39, 220.68], $k = 8$) but only one with patients (200 ± 43.37 ms, 95% CI = [115.01, 284.99], $k = 1$). Therefore, we did not assess the participant group effect in studies with electrical stimulation. These results show that the temporal characteristics of GBOs are unlikely to be affected by the participant group.

3.4.2. Stimulation type effect

Across participant groups, the mean latency of GBOs was significantly later ($Q = 4.337$, $p = 0.037$) for laser stimulation (228.06 ± 10.15 ms, 95% CI = [208.17, 247.96], $k = 26$) than electrical stimulation (184.43 ± 18.33 ms, 95% CI = [148.50, 220.35], $k = 9$) (Fig. 7c). This observation was replicated when only studies with healthy participants were considered: Compared to laser stimulation (238.37 ± 12.46 ms, 95% CI = [213.94, 262.80], $k = 19$), the mean latency of GBOs induced by electrical stimulation (181.04 ± 20.23 ms, 95% CI = [141.39, 220.68], $k = 8$) was significantly earlier ($Q = 5.823$,

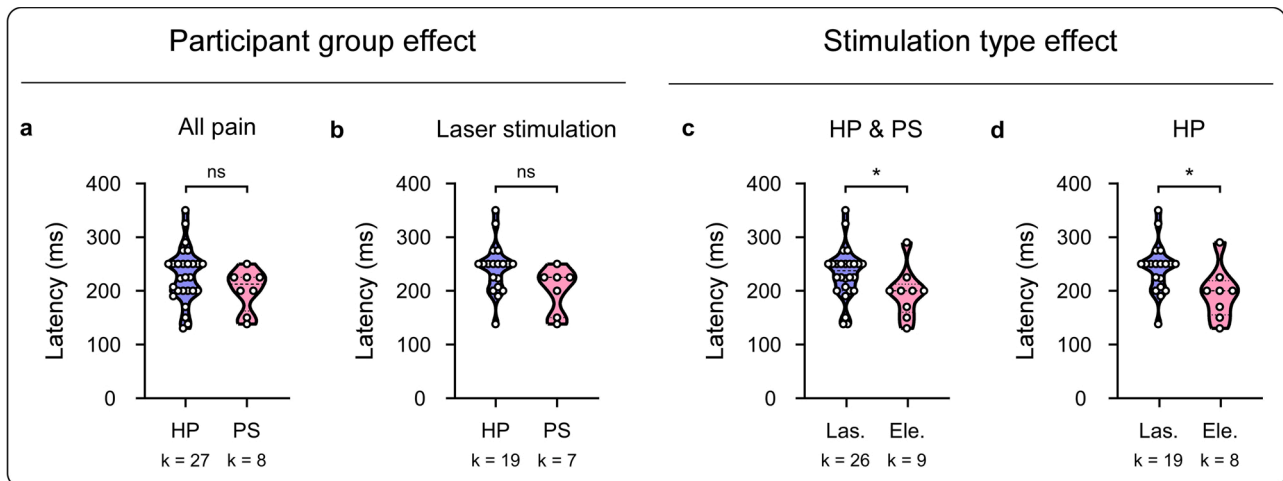


Fig. 7. The comparisons of GBO latency. No significant GBO latency differences were observed between healthy participants and patients across stimulation types (a), as well as the pain elicited by laser stimulation (b). However, GBO latency was significantly earlier for electrical stimulation than laser stimulation (c-d). The white circles indicate single studies, the labels for the x-axis include the number of studies in each condition, and the titles of the subplots indicate the category of studies included in the comparisons. HP: healthy participants, PS: patients. Las. = Laser stimulation, Ele. = Electrical stimulation. *, $p_{corrected} < 0.05$; ns, $p_{corrected} > 0.1$.

$p = 0.016$) (Fig. 7d). There were six studies in patients with laser stimulation (203.92 ± 16.05 ms, 95% CI = [172.47, 235.38], $k = 7$) but only one with electrical stimulation (200 ± 43.37 ms, 95% CI = [115.01, 284.99], $k = 1$). Therefore, the stimulation type effect on GBOs' temporal characteristics was not assessed for studies with patients.

3.5. Narrative description of the proposed functions of GBOs

Several distinct functions of human GBOs were proposed in previous studies. These proposed functions mainly consist of seven categories, namely, pain perception ($n = 31$), pain attention ($n = 10$), general sensory processing ($n = 2$), multidimensional processing of pain ($n = 12$), motor responses ($n = 4$), pain relief ($n = 5$), and pathophysiology of chronic pain ($n = 10$). Crucially, different functions were proposed for GBOs induced by different types of pain (Fig. 8, Table S8). Among studies recruiting healthy participants and using phasic pain ($n = 31$), the majority (55.8%) interpreted pain-related GBOs as reflecting pain perception, followed by smaller percentages of them attributing pain attention (16.1%) and multidimensional processing of pain (16.1%) to GBOs. Only a few studies claimed GBOs to represent motor responses (6.5%), general sensory processing (3.2%), and pain relief (3.2%). In tonic pain studies with healthy participants ($n = 16$), less than half (43.8%) attributed pain perception to GBOs, while a quarter (i.e., 25.0%) supported a multidimensional processing role of GBOs. Motor responses (12.5%), pain attention (6.3%), sensory processing (6.3%), and pain relief (6.3%) were less often attributed to tonic pain-induced GBOs in healthy participants. Among patient studies using phasic pain stimulation ($n = 14$), pain perception (42.9%) was also the most frequent function proposed, followed by pain attention (28.6%), pathophysiology of chronic pain (14.3%), and multidimensional processing of pain (14.3%). On the other hand, the three studies using tonic pain stimulation attributed pain perception (33.3%), the pathophysiology of chronic pain (33.3%), and multidimensional processing of pain (33.3%) to GBOs. In studies focusing on chronic pain of patients ($n = 10$), the assumed functions of GBOs were the pathophysiology of chronic pain (70.0%) and pain relief (30.0%). In summary, phasic pain-induced GBOs were more likely to be associated with pain perception; tonic pain-induced GBOs were more related to multidimensional processing of pain compared with phasic pain-induced GBOs; and chronic pain-induced GBOs were more frequently claimed to reflect the pathophysiology of chronic pain.

3.6. Frequential characteristics of GBOs in rodent studies

Based on the overall 17 rodent studies (22 experiments), the mean frequency of GBOs was 66.41 Hz (standard error = 4.71 Hz, 95% CI = [57.18, 75.64], $p < 0.001$). Nevertheless, the high heterogeneity of these studies could be a concerning issue ($Q = 164.13$, $df = 21$, $p < 0.001$; $I^2 = 87.21$) (Fig. S6). Kendall's S statistic (P-Q) of the Begg and Mazumdar rank test was -33.00 (Kendall's corrected tau = -0.14 , z for the tau = 0.90, two-tailed $p = 0.37$). Duval and Tweedie's trim and fill test suggested one missing study. If the meta-analysis was re-conducted with the missing study, the frequency of GBOs would increase to 68.10 Hz (95% CI = [57.48, 78.72], $Q = 281.02$). There was no noticeable evidence of publication bias based on the results of the Begg and Mazumdar rank test ($p > 0.05$; see Fig. 3d for the funnel plot).

3.6.1. Animal type effect

The frequency of GBOs was not significantly different between rats and mice ($Q = 2.264$, $p = 0.132$), although mice (78.52 ± 8.22 , 95% CI = [62.42, 94.62], $k = 4$) tended to have a higher GBO frequency than rats (rats: 64.01 ± 5.05 , 95% CI = [54.12, 73.91], $k = 18$) (Fig. 9a).

3.6.2. Pain type effect

For phasic and tonic pain, significant group differences of GBO frequency were identified in rats ($Q = 36.263$, $p < 0.001$; phasic pain: 69.66 ± 3.52 , 95% CI = [62.77, 76.56], $k = 14$; tonic pain: 39.15 ± 3.65 , 95% CI = [32.00, 46.29], $k = 3$) (Fig. 9b). This effect is reminiscent of the pain type effect on GBO frequency in human studies. The only one study of chronic pain with rodents were excluded from the relevant meta-group comparisons (64.50 ± 16.19 , 95% CI = [32.78, 96.22], $k = 1$).

3.6.3. Stimulation type effect

A significant main effect was observed ($Q = 44.573$, $df = 3$, $p < 0.001$) for the stimulation type in rats: laser (69.25 ± 4.62 , 95% CI = [60.20, 78.31], $k = 9$), electrical (62.31 ± 11.00 , 95% CI = [40.74, 83.87], $k = 2$), mechanical (75.45 ± 5.05 , 95% CI = [65.54, 85.35], $k = 4$), and chemical stimulations (39.15 ± 3.65 , 95% CI = [32.00, 46.29], $k = 3$). *Post hoc* comparisons showed that the frequency of GBOs induced by chemical stimulation was significantly lower than both laser and mechanical stimulations (both $p_{corrected} < 0.001$) (Fig. 9c).

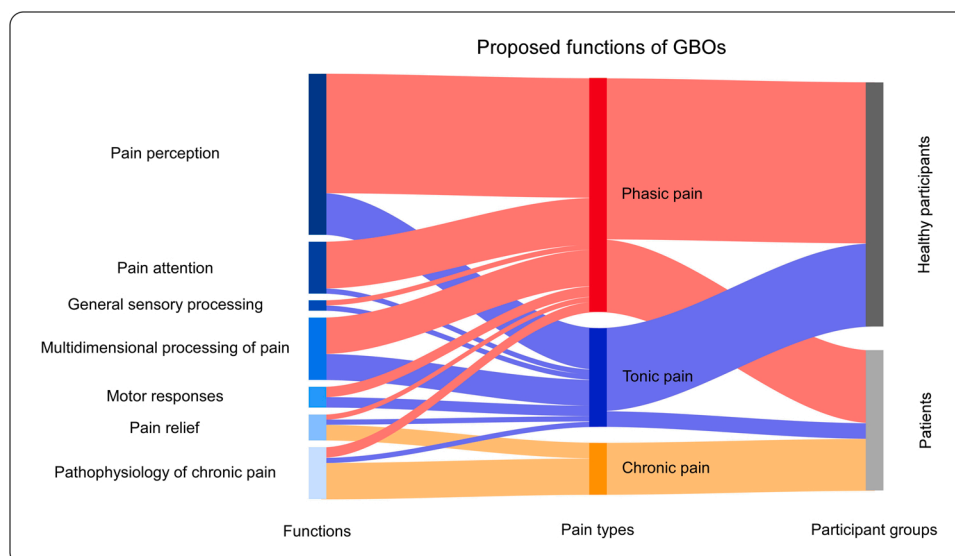


Fig. 8. Proposed functions of human GBOs. The proposed functions of GBOs in human studies are described using the Sankey plot, in which the functions, pain types, and participant groups are displayed from left to right. Different columns of categorization and branches between different layers represent proportions. GBOs induced by phasic pain were more likely to reflect pain perception (55.8%). In contrast, GBOs elicited by tonic pain were more likely to reflect multidimensional processing of pain in addition to pain perception. For patients, GBOs induced by chronic pain were more frequently claimed to reflect the pathophysiology of chronic pain (70%).

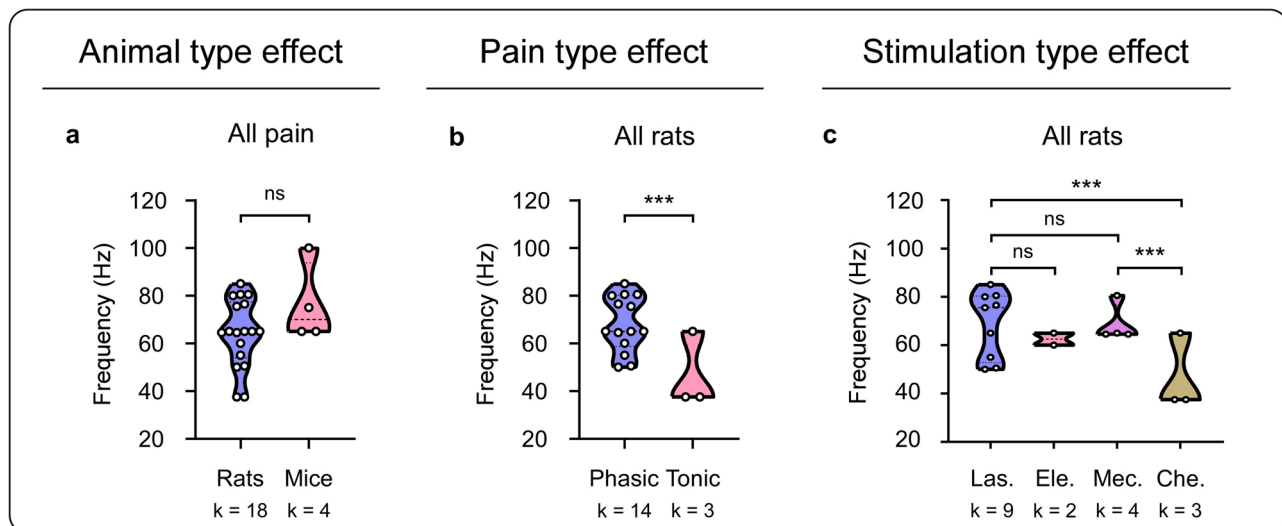


Fig. 9. The comparisons of rodent GBO frequency. No significant differences in GBO frequency were observed between rats and mice (a). However, the GBO frequency was significantly modulated by pain type (b) and stimulation type (c). The white circles indicate single studies, the labels for the x-axis include the number of studies in each condition, and the titles of the subplots indicate the category of studies included in the comparisons. Las. = Laser stimulation, Ele. = Electrical stimulation, Mec. = Mechanical stimulation, Che. = Chemical stimulation. ***, $p_{corrected} < 0.001$; ns, $p_{corrected} > 0.1$.

3.7. A systematic review of rodent studies

Whereas all 18 rodent studies reported the frequency range of GBOs, only four studies reported the time characteristics of GBOs: mean latency = 151 ms (Hu and Iannetti, 2019), latency range = 119 ~ 313 ms (Peng et al., 2018), latency range = 100 ~ 250 ms (Yue et al., 2020), and latency range = 200 ~ 1000 ms (Wang et al., 2011). Most studies reported that the magnitude of GBOs increased with the physical intensity of nociceptive inputs ($n = 14$). In particular, a study on electrocorticography (ECoG) recorded in rats reported a strong correlation between pain behavioral scores and GBOs (between-subjects: mean $r = 0.74$; within-subjects: mean $r = 0.46$) (Peng et al., 2018). However, another four studies reported inconsistent results of their relationship ($n = 4$) (Table S6). Specifically, by recording the field potential from the medial frontal cortex (mPFC), one study reported that GBO magnitude was decreased by noxious electrical stimulation, and there were no significant changes in GBOs following noxious mechanical and chemical stimulations (Li et al., 2016a). Another study with the same recording area showed decreased GBO magnitude following mechanical stimulation and a complex pattern of GBO magnitude changes (first increase, then decrease) in nerve injury-induced chronic neuropathic pain (Fu et al., 2018). The remaining two studies recorded the electrophysiological signals from the anterior cingulate cortex (ACC) and primary somatosensory cortex (S1), respectively, and both studies reported decreased GBO magnitude following tonic pain induced by chemical stimulation (Ponsel et al., 2020; Shi et al., 2020) (Table S6).

4. Discussion

We conducted two sets of systematic reviews and meta-analyses to characterize the temporal, frequential, and spatial characteristics of GBOs and summarize the functional significance of GBOs. These analyses yielded six major findings: (1) GBO magnitudes significantly correlated with pain intensity in healthy participants, regardless of the pain type. (2) GBO frequency varied significantly with different pain types, and phasic pain tended to induce higher GBO frequency than tonic and chronic pain. (3) Whereas GBOs induced by phasic pain were more centrally distributed, suggesting a sensorimotor origin, GBOs induced by tonic and chronic pain were more frontally distributed over the prefrontal cortex. (4) The latency of GBOs induced by phasic pain was significantly modulated by stimulation types: electrical stimulation

induced an earlier GBOs than laser stimulation. (5) Some characteristics and functions of GBOs (e.g., frequential characteristics and correlations with pain intensity) seemed to be phylogenetically conserved across humans and rodents. (6) Previous studies proposed seven major functions of GBOs, the pattern of which differed among different pain types. Altogether, these results provide a comprehensive characterization of the heterogeneous GBOs in pain and nociception and deepen our understanding of the sources of GBO heterogeneity.

4.1. The heterogeneity of GBOs associated with pain and nociception

Although rarely discussed explicitly, a considerable amount of GBO heterogeneity can be observed in previous studies (Table S1). Due to such heterogeneity, it is difficult to ascertain what GBOs really represent, which may lead to conceptual confusion and ineffective clinical applications. For example, some studies suggest that GBOs could selectively encode subjective pain experience (Gross et al., 2007; Michail et al., 2016; Schulz et al., 2015, 2011; Zhang et al., 2012), but others suggest otherwise (Hauck et al., 2007; Northon et al., 2021a; Rossiter et al., 2013; Tiemann et al., 2015, 2010). One simple explanation could be that they are talking about different GBOs; thus, no real disagreements exist. To avoid conceptual confusion and promote potential clinical applications, it is imperative to examine the heterogeneity of GBOs in a systematic and unbiased way.

Following the standard steps of preregistered systematic reviews and meta-analyses, we summarized the existent studies on pain-related GBOs and examined the effect of participant groups, pain types, stimulation types, and species on the characteristics of GBOs. These efforts revealed the sources of heterogeneity of pain-related GBOs. First, phasic pain elicited GBOs with a higher frequency than tonic pain in both human and animal studies. Second, GBOs elicited by phasic pain were more centrally distributed in human studies than those elicited by tonic pain and chronic pain, which had a more frontal scalp distribution. Third, the proposed functions of GBOs elicited by different pain types were quite different: GBOs elicited by phasic, tonic, and chronic pain are more likely to be associated with pain perception, multidimensional processing of pain, and the pathophysiology of chronic pain, respectively. These findings provide empirical evidence that phasic pain-induced GBOs may be a distinct electrophysiological entity from GBOs elicited by tonic pain and chronic pain. This conclusion is consistent with the experiential differences between phasic and tonic/chronic pain.

Phasic pain is transient, lasting a few seconds at best; tonic pain is more enduring, lasting up to several minutes or even longer; chronic pain is long-lasting for a few months or years (Ploner et al., 2017). Phasic pain is more likely to reflect the nociceptive information processing of the nociceptive system, while tonic pain and chronic pain are more associated with the emotional information processing of pain (Hashmi et al., 2013; May et al., 2019; Ploner et al., 2017; Schulz et al., 2015). This functional difference is also supported by distinct neural sources of GBOs: the sensorimotor cortex for phasic pain and the prefrontal cortex for tonic pain (Schulz et al., 2015) and chronic pain (May et al., 2019).

It should be noted that GBOs induced by tonic pain and chronic pain had similar frequential and spatial characteristics in human studies, although they were proposed to have different functions. Therefore, it would be difficult to conclude that GBOs induced by tonic and chronic pain are distinct entities based on the current evidence, which supports the notion that tonic pain is a better model for chronic pain than phasic pain from this point of view (Ploner et al., 2017).

Moreover, GBOs elicited by phasic pain of different stimulation types (e.g., laser, electrical, mechanical stimuli) also exhibited distinct frequential characteristics. For instance, GBO frequency induced by laser stimulation was significantly higher than cold and mechanical stimulations in humans and chemical stimulation in rodents. Nevertheless, inconsistent results of frequency differences were observed across species (i.e., humans and rodents), which may be due to the unequal number of studies adopting each type of stimulation and the limited number of rodent studies. With all the present evidence, dividing phasic pain-induced GBOs into further subtypes seems necessary, but more studies are needed in the future to test this hypothesis.

Taken together, our systematic reviews and meta-analyses support the separation of phasic pain-induced GBOs from those induced by tonic pain and chronic pain. Meanwhile, tonic pain-induced GBOs phenomenologically resemble chronic pain-induced GBOs, although they may have different functions. The general term of “pain-related GBOs” should thus be used with care to avoid conceptual misunderstandings. Caution should also be taken when directly comparing studies with different pain types (i.e., phasic, tonic, and chronic pains) and studies with phasic pain elicited by different stimulation types (e.g., laser, electrical, and chemical stimulations).

4.2. Participant group difference in the correlation between pain intensity and GBO magnitude

The meta-analysis results suggested that the correlation between pain intensity and GBO magnitude in healthy participants is larger than in patients, especially for phasic pain induced by laser stimulation. This discrepancy could be explained by three factors at least. First, chronic pain patients are in a pathological state, which may interfere the generation of GBOs and thus disrupt the relationship between GBOs and pain perception (Bassez et al., 2020; Kuner and Kuner, 2021; Ye et al., 2019). Second, the considerable variability of chronic pain pathology may result in inconsistent correlation results in previous patient studies, e.g., a high correlation of 0.7 in post-herpetic neuralgia patients (Zhou et al., 2018) and no correlation of 0.09 in migraine patients (Bassez et al., 2020) (see Table S2). Third, the available study numbers were uneven between the two groups ($k_{\text{healthy}}=26$ vs. $k_{\text{patients}}=4$), leading to poor statistical power of the patient studies.

4.3. Stimulation type difference in the latency of phasic pain-induced GBOs

For phasic pain, we found a significant stimulation type effect on the temporal characteristics of GBOs, with electrical stimulation inducing earlier GBOs than laser stimulation, a finding that could be explained by different peripheral neural transduction mechanisms (Abraira and Ginty, 2013; Hird et al., 2018; Iannetti et al., 2004). Specifically, electrical stimulation unavoidably activates non-nociceptive A β fibers

conveying vibrotactile sensations. Because of their large diameter, A β fibers have a faster transduction velocity and a lower electrical impedance, and thus a lower electrical activation threshold than small-myelinated A δ and unmyelinated C fibers (Abraira and Ginty, 2013). It would thus be expected that electrical stimulation induces earlier GBOs than laser stimulation. Importantly, even if electrical stimulation of higher intensity can also activate A δ and C fibers, these nociceptive afferents are never activated by electrical stimulation in a selective fashion. When a nociceptive stimulus is not selective and coactivates A β afferents, it becomes very difficult to determine whether the elicited brain responses (including GBOs) are triggered by the nociceptive input or by the concomitant non-nociceptive input. The neurophysiological investigation of the nociceptive system requires the use of stimuli that selectively activate cutaneous A δ - and C-fibers, without concomitant activations of large myelinated A β fibers (Crucce et al., 2008). Such selective activation of nociceptive fibers can be optimally achieved using laser radiant heat pulses, a stimulation technique widely used to investigate the peripheral and central processing of nociceptive input in healthy participants and patients (Iannetti et al., 2003; Treede et al., 2003). For these reasons, GBOs elicited by different stimulation types may represent distinct entities, and caution should be taken when investigating the functional significance of pain-related GBOs not using pain selective stimulation.

4.4. Phylogenetically conserved GBO characteristics across humans and rodents

Brain oscillations, including GBOs, have been remarkably preserved in evolution among different species (Buzsaki et al., 2013). Indeed, our meta-analyses showed similar GBO characteristics between humans and rodents. First, the frequency of GBOs induced by phasic pain was higher than that induced by tonic pain in both humans (Fig. 4i) and rodents (Fig. 8b). Second, strong correlations were observed between GBO magnitude and subjective pain intensity in humans (Fig. 3) and between GBO magnitude and pain behavioral scores in rodents (see the systematic review of rodent studies). Note that these correlations were evident both within and across individuals (Hu and Iannetti, 2019; Peng et al., 2018). Third, the neural sources of pain-related GBOs could be the same for both humans and rodents, at least for phasic pain. For instance, our recent rodent paper showed that GBOs reflect neural activity in the primary somatosensory cortex contralateral to the stimulation side (Yue et al., 2020), a finding in line with a series of previous human GBO studies (Gross et al., 2007; Hauck et al., 2015; Schulz et al., 2015; Tiemann et al., 2010, 2012; Zhang et al., 2012). Altogether, the characteristics and functions of GBOs, especially for those elicited by phasic pain, are probably phylogenetically conserved, at least across humans and rodents. The finding of this shared neural response is important as it could make translational pain research between humans and rodents more effective (Mao, 2012; Tan et al., 2021).

4.5. Neuronal basis of pain-related GBOs

GBOs (30–100 Hz) exist in a wide range of brain structures and are supposedly driven by GABAergic interneurons with local and long-range projections (Buzsaki and Wang, 2012; Cardin, 2018; Melzer and Monyer, 2020). Among all interneurons, fast-spiking parvalbumin (PV)-expressing interneurons and somatostatin (SOM)-expressing interneurons are the main types of neurons driving GBOs (Antonoudiou et al., 2020; Hu et al., 2014). Our recent study showed that pain-related GBOs reflect neural activity coupled with the spike firing of interneurons in the superficial layers of the S1 contralateral to the stimulation side (Yue et al., 2020). Furthermore, inducing GBOs via optogenetic activation of PV-expressing interneurons in the S1 of mice could enhance nociceptive sensitivity and induce aversive avoidance behavior (Tan et al., 2019). Together with others, these studies suggest that fast-spiking PV-expressing interneurons are the main neuronal basis of pain-related GBOs.

However, due to the limited number of studies in this research direction at the current stage, more investigations, especially those performed on different pain types, should be carried out to further reveal the detailed neuronal basis of pain-related GBOs in the future.

4.6. Limitations and future directions

There are several limitations in the present study. First, the number of studies included was limited, especially for patient studies and rodent studies. This limitation restricted the statistical power of our analyses and made certain analyses inappropriate or even impossible. For instance, the results obtained from the few patient studies in the meta-analyses yielded weak evidence to support some of our statements. New meta-analyses including more studies are required to provide more solid evidence in the future. Second, the potential heterogeneity, publication bias, and other types of biases were unlikely to be entirely controlled by the current meta-analysis procedure. Therefore, the nature of the GBOs waits to be confirmed by future researchers based on more publications on this topic. Third, due to the low signal-to-noise ratio of GBO signals, many studies adopted hypothesis-driven strategies to define the temporal, frequential, and spatial ranges of GBOs, which may not accurately reflect the actual characteristics of GBOs. This bias also potentially affected our meta-analyses which built on these original empirical studies. Advanced data analysis methods with standard procedures are needed to improve the signal-to-noise ratio of GBOs and more accurately define the temporal, frequential, and spatial ranges of GBOs in future studies. Fourth, in addition to the factors that have been investigated in this study, there are many other factors associated with GBO characteristics (e.g., attention and anticipation). Due to the limited number of available studies, this meta-analysis did not investigate the above characteristics. Future systematic reviews and meta-analyses are required to provide a more comprehensive description of the nature of GBOs if more relevant studies are available.

Declaration of Competing Interest

The authors declare no commercial or financial conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neubiorev.2023.105062](https://doi.org/10.1016/j.neubiorev.2023.105062).

References

- Abraira, V.E., Ginty, D.D., 2013. The sensory neurons of touch. *Neuron* 79, 618–639.
- Antonoudiou, P., Tan, Y.L., Kontou, G., Upton, A.L., Mann, E.O., 2020. Parvalbumin and somatostatin interneurons contribute to the generation of hippocampal gamma oscillations. *J. Neurosci.* 40, 7668–7687.
- Babiloni, C., Babiloni, F., Carducci, F., Cincotti, F., Rosciarelli, F., Arendt-Nielsen, L., Chen, A.C., Rossini, P.M., 2002. Human brain oscillatory activity phase-locked to painful electrical stimulations: a multi-channel EEG study. *Hum. Brain Mapp.* 15, 112–123.
- Baroni, A., Severini, G., Straudi, S., Buja, S., Borsato, S., Basaglia, N., 2020. Hyperalgesia and central sensitization in subjects with chronic orofacial pain: analysis of pain thresholds and EEG biomarkers. *Front. Neurosci.* 14, 552650.
- Bassez, I., Ricci, K., Vecchio, E., Delussi, M., Gentile, E., Marinazzo, D., de Tommaso, M., 2020. The effect of painful laser stimuli on EEG gamma-band activity in migraine patients and healthy controls. *Clin. Neurophysiol.* 131, 1755–1766.
- Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 50, 1088–1101.
- Bonnefond, M., Kastner, S., Jensen, O., 2017. Communication between brain areas based on nested oscillations. *eNeuro* 4, e0153–0116.
- Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2014. Comprehensive meta-analysis (Version 3) [Computer software]. Biostat. (<https://www.meta-analysis.com/>).
- Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R., 2021. Introduction to meta-analysis. Wiley.
- Bressler, S.L., Freeman, W.J., 1980. Frequency analysis of olfactory system EEG in cat, rabbit and rat. *Electroencephalogr. Clin. Neurophysiol.* 50, 19–24.
- Buzsaki, G., Wang, X.J., 2012. Mechanisms of gamma oscillations. *Annu. Rev. Neurosci.* 35, 203–225.
- Buzsaki, G., Logothetis, N., Singer, W., 2013. Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. *Neuron* 80, 751–764.
- Cardin, J.A., 2018. Inhibitory interneurons regulate temporal precision and correlations in cortical circuits. *Trends Neurosci.* 41, 689–700.
- Chen, A.C.N., Herrmann, C.S., 2001. Perception of pain coincides with the spatial expansion of electroencephalographic dynamics in human subjects. *Neurosci. Lett.* 297, 183–186.
- Chien, J.H., Liu, C.C., Kim, J.H., Markman, T.M., Lenz, F.A., 2014. Painful cutaneous laser stimuli induce event-related oscillatory EEG activities that are different from those induced by nonpainful electrical stimuli. *J. Neurophysiol.* 112, 824–833.
- Clauw, D.J., Hauser, W., Cohen, S.P., Fitzcharles, M.A., 2020. Considering the potential for an increase in chronic pain after the COVID-19 pandemic. *Pain* 161, 1694–1697.
- Croft, R.J., Williams, J.D., Haenschel, C., Gruzelier, J.H., 2002. Pain perception, hypnosis and 40 Hz oscillations. *Int. J. Psychophysiol.* 46, 101–108.
- Crucchi, G., Aminoff, M.J., Curio, G., Guerit, J.M., Kakigi, R., Mauguire, F., Rossini, P.M., Treede, R.D., Garcia-Larrea, L., 2008. Recommendations for the clinical use of somatosensory-evoked potentials. *Clin. Neurophysiol.* 119, 1705–1719.
- Dahlhamer, J., Lucas, J., Zelaya, C., Nahin, R., Mackey, S., DeBar, L., Kerns, R., Von Korff, M., Porter, L., Helmick, C., 2018. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. *MMWR Morb. Mortal. Wkly Rep.* 67, 1001–1006.
- Davis, K.D., Aghaeepour, N., Ahn, A.H., Angst, M.S., Borsook, D., Brenton, A., Burczynski, M.E., Crean, C., Edwards, R., Gaudilliere, B., Hergenroeder, G.W., Iadarola, M.J., Iyengar, S., Jiang, Y., Kong, J.T., Mackey, S., Saab, C.Y., Sang, C.N., Scholz, J., Segerdahl, M., Tracey, I., Veasley, C., Wang, J., Wager, T.D., Wasan, A.D., Pellemounter, M.A., 2020. Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities. *Nat. Rev. Neurol.* 16, 381–400.
- De Pascalis, V., Cacace, I., 2005. Pain perception, obstructive imagery and phase-ordered gamma oscillations. *Int. J. Psychophysiol.* 56, 157–169.
- De Pascalis, V., Cacace, I., Massicotte, F., 2004. Perception and modulation of pain in waking and hypnosis: functional significance of phase-ordered gamma oscillations. *Pain* 112, 27–36.
- De Pascalis, V., Scacchia, P., Papi, B., Corr, P.J., 2019. Changes of EEG band oscillations to tonic cold pain and the behavioral inhibition and fight-flight-freeze systems. *Pers. Neurosci.* 2, e12.
- Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21.
- Dinh, S.T., Nickel, M.M., Tiemann, L., May, E.S., Heitmann, H., Hohn, V.D., Edenharter, G., Utpadel-Fischler, D., Tolle, T.R., Sauseng, P., Gross, J., Ploner, M., 2019. Brain dysfunction in chronic pain patients assessed by resting-state electroencephalography. *Pain* 160, 2751–2765.
- Dowman, R., Rissacher, D., Schuckers, S., 2008. EEG indices of tonic pain-related activity in the somatosensory cortices. *Clin. Neurophysiol.* 119, 1201–1212.
- Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 56, 455–463.
- Ebrahimi, M., Razeghi, M., Zamani, A., Bagheri, Z., Rastegar, K., Motealleh, A., 2018. Does High Frequency Transcutaneous Electrical Nerve Stimulation (TENS) Affect EEG Gamma Band Activity? *J. Biomed. Phys. Eng.* 8, 271–280.
- Eickhoff, S.B., Bzdok, D., Laird, A.R., Kurth, F., Fox, P.T., 2012. Activation likelihood estimation meta-analysis revisited. *Neuroimage* 59, 2349–2361.
- Fabrizi, L., Verriotti, M., Williams, G., Lee, A., Meek, J., Olhede, S., Fitzgerald, M., 2016. Encoding of mechanical nociception differs in the adult and infant brain. *Sci. Rep.* 6, 28642.
- Fayaz, A., Croft, P., Langford, R.M., Donaldson, L.J., Jones, G.T., 2016. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open* 6, e010364.
- Fries, P., 2015. Rhythms for cognition: communication through coherence. *Neuron* 88, 220–235.
- Friesner, I.D., Martinez, E., Zhou, H.C., Gould, J.D., Li, A.N., Chen, Z.S., Zhang, Q.S., Wang, J., 2020. Ketamine normalizes high-gamma power in the anterior cingulate cortex in a rat chronic pain model. *Mol. Brain* 13, 129.
- Fu, B., Wen, S.N., Wang, B., Wang, K., Zhang, J.Y., Liu, S.J., 2018. Acute and chronic pain affects local field potential of the medial prefrontal cortex in different band neural oscillations. *Mol. Pain* 14.
- GBD 2019 Diseases and Injuries Collaborators., 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 396, 1204–1222.
- Gross, J., Schnitzler, A., Timmermann, L., Ploner, M., 2007. Gamma oscillations in human primary somatosensory cortex reflect pain perception. *PLoS Biol.* 5, e133.
- Guo, S., Lu, J., Wang, Y., Li, Y., Huang, B., Zhang, Y., Gong, W., Yao, D., Yuan, Y., Xia, Y., 2020a. Sad music modulates pain perception: an EEG study. *J. Pain. Res.* 13, 2003–2012.
- Guo, X., Zhang, Q., Singh, A., Wang, J., Chen, Z.S., 2020b. Granger causality analysis of rat cortical functional connectivity in pain. *J. Neural Eng.* 17, 016050.

- Hansen, T.M., Mark, E.B., Olesen, S.S., Gram, M., Frøkjær, J.B., Drewes, A.M., 2017. Characterization of cortical source generators based on electroencephalography during tonic pain. *J. Pain Res.* 10, 1401–1409.
- Hashmi, J.A., Baliki, M.N., Huang, L., Baria, A.T., Torbey, S., Hermann, K.M., Schnitzer, T.J., Apkarian, A.V., 2013. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain* 136, 2751–2768.
- Hauck, M., Lorenz, J., Engel, A.K., 2007. Attention to painful stimulation enhances gamma-band activity and synchronization in human sensorimotor cortex. *J. Neurosci.* 27, 9270–9277.
- Hauck, M., Metzner, S., Rohlfis, F., Lorenz, J., Engel, A.K., 2013. The influence of music and music therapy on pain-induced neuronal oscillations measured by magnetoencephalography. *Pain* 154, 539–547.
- Hauck, M., Domnick, C., Lorenz, J., Gerloff, C., Engel, A.K., 2015. Top-down and bottom-up modulation of pain-induced oscillations. *Front Hum. Neurosci.* 9, 375.
- Hauck, M., Schroder, S., Meyer-Hamme, G., Lorenz, J., Friedrichs, S., Nolte, G., Gerloff, C., Engel, A.K., 2017. Acupuncture analgesia involves modulation of pain-induced gamma oscillations and cortical network connectivity. *Sci. Rep.* 7, 16307.
- Heid, C., Mouraux, A., Treede, R.D., Schuh-Hofer, S., Rupp, A., Baumgartner, U., 2020. Early gamma-oscillations as correlate of localized nociceptive processing in primary sensorimotor cortex. *J. Neurophysiol.* 123, 1711–1726.
- Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* 21, 1539–1558.
- Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. *BMJ* 327, 557–560.
- Higgins, J.P., Altman, D.G., Gotzsche, P.C., Juni, P., Moher, D., Oxman, A.D., Savovic, J., Schulz, K.F., Weeks, L., Sterne, J.A., Cochrane Bias Methods, G., Cochrane Statistical Methods, G., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clin. Res. Ed.)* 343, d5928.
- Hird, E.J., Jones, A.K.P., Talmi, D., El-Deredy, W., 2018. A comparison between the neural correlates of laser and electric pain stimulation and their modulation by expectation. *J. Neurosci. Methods* 293, 117–127.
- Hooijmans, C.R., Rovers, M.M., de Vries, R.B., Leenaars, M., Ritskes-Hoitinga, M., Langendam, M.W., 2014. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Method.* 14, 43.
- Hsiao, F.J., Chen, W.T., Liu, H.Y., Wang, Y.F., Chen, S.P., Lai, K.L., Pan, L.L.H., Wang, S. J., 2020. Individual pain sensitivity is associated with resting-state cortical activities in healthy individuals but not in patients with migraine: a magnetoencephalography study. *J. Headache Pain.* 21, 133.
- Hu, H., Gan, J., Jonas, P., 2014. Interneurons. Fast-spiking, parvalbumin⁺ GABAergic interneurons: from cellular design to microcircuit function. *Science* 345, 1255263.
- Hu, L., Iannetti, G.D., 2019. Neural indicators of perceptual variability of pain across species. *Proc. Natl. Acad. Sci. USA* 116, 1782–1791.
- Huang, Y., Green, A.L., Hyam, J., Fitzgerald, J., Aziz, T.Z., Wang, S., 2018. Oscillatory neural representations in the sensory thalamus predict neuropathic pain relief by deep brain stimulation. *Neurobiol. Dis.* 109, 117–126.
- Huedo-Medina, T.B., Sánchez-Meca, J., Marín-Martínez, F., Botella, J., 2006. Assessing heterogeneity in meta-analysis: Q statistic or I² index? *Psychol. Methods* 11, 193–206.
- Iannetti, G.D., Truini, A., Romaniello, A., Galeotti, F., Rizzo, C., Manfredi, M., Cruccu, G., 2003. Evidence of a specific spinal pathway for the sense of warmth in humans. *J. Neurophysiol.* 89, 562–570.
- Iannetti, G.D., Leandri, M., Truini, A., Zambreau, L., Cruccu, G., Tracey, I., 2004. Adelta nociceptor response to laser stimuli: selective effect of stimulus duration on skin temperature, brain potentials and pain perception. *Clin. Neurophysiol.* 115, 2629–2637.
- Iannetti, G.D., Hughes, N.P., Lee, M.C., Mouraux, A., 2008. Determinants of laser-evoked EEG responses: pain perception or stimulus saliency? *J. Neurophysiol.* 100, 815–828.
- Iwamoto, S., Tamura, M., Sasaki, A., Nawano, M., 2021. Dynamics of neuronal oscillations underlying nociceptive response in the mouse primary somatosensory cortex. *Sci. Rep.* 11, 1667.
- Kim, J.H., Chien, J.H., Liu, C.C., Lenz, F.A., 2015. Painful cutaneous laser stimuli induce event-related gamma-band activity in the lateral thalamus of humans. *J. Neurophysiol.* 113, 1564–1573.
- Kuner, R., Kuner, T., 2021. Cellular circuits in the brain and their modulation in acute and chronic pain. *Physiol. Rev.* 101, 213–258.
- Levitt, J., Edhi, M.M., Thorpe, R.V., Leung, J.W., Michishita, M., Koyama, S., Yoshikawa, S., Scarfo, K.A., Carayannopoulos, A.G., Gu, W., Srivastava, K.H., Clark, B.A., Esteller, R., Borton, D.A., Jones, S.R., Saab, C.Y., 2020. Pain phenotypes classified by machine learning using electroencephalography features. *Neuroimage* 223, 117256.
- Li, A.-L., Yang, X., Chiao, J.-C., Peng, Y.B., 2016a. Reduced local field potential power in the medial prefrontal cortex by noxious stimuli. *Brain Res Bull.* 127, 92–99.
- Li, F., Xiang, J., Wu, T., Zhu, D., Shi, J., 2016b. Abnormal resting-state brain activity in headache-free migraine patients: a magnetoencephalography study. *Clin. Neurophysiol.* 127, 2855–2861.
- Li, L.L., Liu, X.W., Cai, C., Yang, Y., Li, D.S., Xiao, L.Z., Xiong, D.L., Hu, L., Qiu, Y.H., 2016c. Changes of gamma-band oscillatory activity to tonic muscle pain. *Neurosci. Lett.* 627, 126–131.
- Li, X., Zhao, Z., Ma, J., Cui, S., Yi, M., Guo, H., Wan, Y., 2017. Extracting neural oscillation signatures of laser-induced nociception in pain-related regions in rats. *Front Neural Circuits* 11, 71.
- Liberati, G., Algoet, M., Klocker, A., Ferrao Santos, S., Ribeiro-Vaz, J.G., Raftopoulos, C., Mouraux, A., 2018a. Habituation of phase-locked local field potentials and gamma-band oscillations recorded from the human insula. *Sci. Rep.* 8, 8265.
- Liberati, G., Klocker, A., Algoet, M., Mulders, D., Maia Safronova, M., Ferrao Santos, S., Ribeiro Vaz, J.G., Raftopoulos, C., Mouraux, A., 2018b. Gamma-band oscillations preferential for nociception can be recorded in the human insula. *Cereb. Cortex* 28, 3650–3664.
- Liberati, G., Algoet, M., Santos, S.F., Ribeiro-Vaz, J.G., Raftopoulos, C., Mouraux, A., 2019. Tonic thermosensory stimulation selectively modulates ongoing neural oscillations in the human posterior insula: Evidence from intracerebral EEG. *Neuroimage* 188, 70–83.
- Liberati, G., Mulders, D., Algoet, M., van den Broeke, E.N., Santos, S.F., Ribeiro Vaz, J.G., Raftopoulos, C., Mouraux, A., 2020. Insular responses to transient painful and non-painful thermal and mechanical spinothalamic stimuli recorded using intracerebral EEG. *Sci. Rep.* 10, 22319.
- Lim, M., Kim, J.S., Kim, D.J., Chung, C.K., 2016. Increased low- and high-frequency oscillatory activity in the prefrontal cortex of fibromyalgia patients. *Front Hum. Neurosci.* 10, 111.
- Lipsey, M.W., Wilson, D.B., 2001. Practical meta-analysis. Sage Publications, Inc.,
- Liu, C.C., Chien, J.H., Kim, J.H., Chuang, Y.F., Cheng, D.T., Anderson, W.S., Lenz, F.A., 2015a. Cross-frequency coupling in deep brain structures upon processing the painful sensory inputs. *Neuroscience* 303, 412–421.
- Liu, C.C., Chien, J.H., Chang, Y.W., Kim, J.H., Anderson, W.S., Lenz, F.A., 2015b. Functional role of induced gamma oscillatory responses in processing noxious and innocuous sensory events in humans. *Neuroscience* 310, 389–400.
- Liu, L.Y., Zhang, R.L., Chen, L., Zhao, H.Y., Cai, J., Wang, J.K., Guo, D.Q., Cui, Y.J., Xing, G.G., 2019. Chronic stress increases pain sensitivity via activation of the rACC-BLA pathway in rats. *Exp. Neurol.* 313, 109–123.
- Luo, H., Huang, Y., Xiao, X., Dai, W., Nie, Y., Geng, X., Green, A.L., Aziz, T.Z., Wang, S., 2020. Functional dynamics of thalamic local field potentials correlate with modulation of neuropathic pain. *Eur. J. Neurosci.* 51, 628–640.
- Mao, J., 2012. Current challenges in translational pain research. *Trends Pharm. Sci.* 33, 568–573.
- May, E.S., Nickel, M.M., Ta Dinh, S., Tiemann, L., Heitmann, H., Voth, I., Tolle, T.R., Gross, J., Ploner, M., 2019. Prefrontal gamma oscillations reflect ongoing pain intensity in chronic back pain patients. *Hum. Brain Mapp.* 40, 293–305.
- Melzer, S., Monyer, H., 2020. Diversity and function of corticopetal and corticofugal GABAergic projection neurons. *Nat. Rev. Neurosci.* 21, 499–515.
- Michail, G., Dresel, C., Witkovsky, V., Stankewitz, A., Schulz, E., 2016. Neuronal oscillations in various frequency bands differ between pain and touch. *Front Hum. Neurosci.* 10, 182.
- Misra, G., Wang, W.E., Archer, D.B., Roy, A., Coombes, S.A., 2017. Automated classification of pain perception using high-density electroencephalography data. *J. Neurophysiol.* 117, 786–795.
- Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* 4, 1.
- Mouraux, A., Iannetti, G.D., 2009. Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. *J. Neurophysiol.* 101, 3258–3269.
- Mouraux, A., Iannetti, G.D., 2018. The search for pain biomarkers in the human brain. *Brain* 141, 3290–3307.
- Naro, A., Leo, A., Bramanti, P., Calabro, R.S., 2015. Moving toward conscious pain processing detection in chronic disorders of consciousness: anterior cingulate cortex neuromodulation. *J. Pain.* 16, 1022–1031.
- Naro, A., Leo, A., Cannavo, A., Buda, A., Bramanti, P., Calabro, R.S., 2016. Do unresponsive wakefulness syndrome patients feel pain? Role of laser-evoked potential-induced gamma-band oscillations in detecting cortical pain processing. *Neuroscience* 317, 141–148.
- Neves, R.M., van Keulen, S., Yang, M., Logothetis, N.K., Eschenko, O., 2018. Locus coeruleus phasic discharge is essential for stimulus-induced gamma oscillations in the prefrontal cortex. *J. Neurophysiol.* 119, 904–920.
- Nickel, M.M., May, E.S., Tiemann, L., Schmidt, P., Postorino, M., Ta Dinh, S., Gross, J., Ploner, M., 2017. Brain oscillations differentially encode noxious stimulus intensity and pain intensity. *Neuroimage* 148, 141–147.
- Nilsson, M., Piasco, A., Nissen, T.D., Graversen, C., Gazerani, P., Lucas, M.F., Dahan, A., Drewes, A.M., Brock, C., 2014. Reproducibility of psychophysical and electroencephalography during offset analgesia. *Eur. J. Pain.* 18, 824–834.
- Northon, S., Rustamov, N., Piché, M., 2019. Cortical integration of bilateral nociceptive signals: when more is less. *Pain* 160, 724–733.
- Northon, S., Deldar, Z., Piche, M., 2021a. Cortical interaction of bilateral inputs is similar for noxious and innocuous stimuli but leads to different perceptual effects. *Exp. Brain Res.* 239, 2803–2819.
- Northon, S., Deldar, Z., Piche, M., 2021b. Spinal and cerebral integration of noxious inputs in left-handed individuals. *Brain Topogr.* 34, 568–586.
- Papageorgiou, C., Manios, E., Tsaltas, E., Koroboki, E., Alevizaki, M., Angelopoulos, E., Dimopoulos, M.A., Papageorgiou, C., Zakopoulos, N., 2017. Brain Oscillations Elicited by the Cold Pressor Test: A Putative Index of Untreated Essential Hypertension. *Int. J. Hypertens.* 2017, 7247514.
- Parker, T., Huang, Y., Raghu, A.L.B., Fitzgerald, J.J., Green, A.L., Aziz, T.Z., 2020. Dorsal root ganglion stimulation modulates cortical gamma activity in the cognitive dimension of chronic pain. *Brain Sci.* 10, 95.
- Pearson, K., 1907. Mathematical Contributions to the Theory of Evolution. XVI. On Further Methods of Determining Correlation. *Drapers Company of Research Memoirs.* Cambridge University Press, Cambridge.
- Peng, W., Hu, L., Zhang, Z., Hu, Y., 2014. Changes of spontaneous oscillatory activity to tonic heat pain. *PLoS ONE* 9, e91052.
- Peng, W., Xia, X., Yi, M., Huang, G., Zhang, Z., Iannetti, G., Hu, L., 2018. Brain oscillations reflecting pain-related behavior in freely moving rats. *Pain* 159, 106–118.

- Peterson, R.A., Brown, S.P., 2005. On the use of beta coefficients in meta-analysis. *J. Appl. Psychol.* 90, 175–181.
- Ploner, M., Sorg, C., Gross, J., 2017. Brain rhythms of pain. *Trends Cogn. Sci.* 21, 100–110.
- Ponsel, S., Zhang, J., Pilz, M., Yanovsky, Y., Brankač, J., Draguhn, A., 2020. Alterations of distributed neuronal network oscillations during acute pain in freely-moving mice. *IBRO Rep.* 9, 195–206.
- Raja, S.N., Carr, D.B., Cohen, M., Finnerup, N.B., Flor, H., Gibson, S., Keefe, F.J., Mogil, J. S., Ringkamp, M., Sluka, K.A., Song, X.J., Stevens, B., Sullivan, M.D., Tutelman, P.R., Ushida, T., Vader, K., 2020. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain* 161, 1976–1982.
- Ren, J., Xiang, J., Chen, Y., Li, F., Wu, T., Shi, J., 2019. Abnormal functional connectivity under somatosensory stimulation in migraine: a multi-frequency magnetoencephalography study. *J. Headache Pain.* 20, 3.
- Rossiter, H.E., Worthen, S.F., Witton, C., Hall, S.D., Furlong, P.L., 2013. Gamma oscillatory amplitude encodes stimulus intensity in primary somatosensory cortex. *Front Hum. Neurosci.* 7, 362.
- Rupinski, M.T., Dunlap, W.P., 1996. Approximating Pearson product-moment correlations from Kendall's Tau and Spearman's Rho. *Educ. Psychol. Meas.* 56, 419–429.
- Rustamov, N., Northon, S., Tessier, J., Leblond, H., Piche, M., 2019. Integration of bilateral nociceptive inputs tunes spinal and cerebral responses. *Sci. Rep.* 9, 7143.
- Rustamov, N., Wagenaar-Tison, A., Doyer, E., Piche, M., 2020. Electrophysiological investigation of the contribution of attention to altered pain inhibition processes in patients with irritable bowel syndrome. *J. Physiol. Sci.* 70, 46.
- Rustamov, N., Sharma, L., Chiang, S.N., Burk, C., Haroutounian, S., Leuthardt, E.C., 2021. Spatial and frequency-specific electrophysiological signatures of tonic pain recovery in humans. *Neuroscience* 465, 23–37.
- Schulz, E., Tiemann, L., Schuster, T., Gross, J., Ploner, M., 2011. Neurophysiological coding of traits and states in the perception of pain. *Cereb. Cortex* 21, 2408–2414.
- Schulz, E., Tiemann, L., Witkovsky, V., Schmidt, P., Ploner, M., 2012a. gamma Oscillations are involved in the sensorimotor transformation of pain. *J. Neurophysiol.* 108, 1025–1031.
- Schulz, E., Zherdin, A., Tiemann, L., Plant, C., Ploner, M., 2012b. Decoding an individual's sensitivity to pain from the multivariate analysis of EEG data. *Cereb. Cortex* 22, 1118–1123.
- Schulz, E., May, E.S., Postorino, M., Tiemann, L., Nickel, M.M., Witkovsky, V., Schmidt, P., Gross, J., Ploner, M., 2015. Prefrontal gamma oscillations encode tonic pain in humans. *Cereb. Cortex* 25, 4407–4414.
- Senkowski, D., Kautz, J., Hauck, M., Zimmermann, R., Engel, A.K., 2011. Emotional facial expressions modulate pain-induced beta and gamma oscillations in sensorimotor cortex. *J. Neurosci.* 31, 14542–14550.
- Shi, Y., Yao, S., Shen, Z., She, L., Xu, Y., Liu, B., Liang, Y., Jiang, Y., Sun, J., Wu, Y., Du, J., Zhu, Y., Wu, Z., Fang, J., Shao, X., 2020. Effect of electroacupuncture on pain perception and pain-related affection: dissociation or interaction based on the anterior cingulate cortex and S1. *Neural Plast.* 2020, 8865096.
- Shigihara, Y., Hoshi, H., Fukasawa, K., Ichikawa, S., Kobayashi, M., Sakamoto, Y., Negishi, K., Haraguchi, R., Konno, S., 2020. Resting-state magnetoencephalography reveals neurobiological bridges between pain and cognitive impairment. *Pain. Ther.* 10, 349–361.
- Sterne, J.A.C., Savovic, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., Cates, C. J., Cheng, H.Y., Corbett, M.S., Eldridge, S.M., Emberson, J.R., Hernan, M.A., Hopewell, S., Hrobjartsson, A., Junqueira, D.R., Juni, P., Kirkham, J.J., Lasserson, T., Li, T., McAleenan, A., Reeves, B.C., Shepperd, S., Shrier, I., Stewart, L.A., Tilling, K., White, I.R., Whiting, P.F., Higgins, J.P.T., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clin. Res. Ed.)* 366, 14898.
- Strube, A., Rose, M., Fazeli, S., Büchel, C., 2021. The temporal and spectral characteristics of expectations and prediction errors in pain and thermoception. *eLife* 10, 1–41.
- Taessler, P., Rose, M., 2016. Prestimulus Theta Oscillations and Connectivity Modulate Pain Perception. *J. Neurosci.* 36, 5026–5033.
- Tan, L.L., Oswald, M.J., Heintz, C., Retana Romero, O.A., Kaushalya, S.K., Monyer, H., Kuner, R., 2019. Gamma oscillations in somatosensory cortex recruit prefrontal and descending serotonergic pathways in aversion and nociception. *Nat. Commun.* 10, 983.
- Tan, L.L., Oswald, M.J., Kuner, R., 2021. Neurobiology of brain oscillations in acute and chronic pain. *Trends Neurosci.* 44, 629–642.
- Tiemann, L., Schulz, E., Gross, J., Ploner, M., 2010. Gamma oscillations as a neuronal correlate of the attentional effects of pain. *Pain* 150, 302–308.
- Tiemann, L., Schulz, E., Winkelmann, A., Ronel, J., Henningsen, P., Ploner, M., 2012. Behavioral and neuronal investigations of hypervigilance in patients with fibromyalgia syndrome. *PLoS One* 7, e35068.
- Tiemann, L., May, E.S., Postorino, M., Schulz, E., Nickel, M.M., Bingel, U., Ploner, M., 2015. Differential neurophysiological correlates of bottom-up and top-down modulations of pain. *Pain* 156, 289–296.
- Tiemann, L., Hohn, V.D., Ta Dinh, S., May, E.S., Nickel, M.M., Gross, J., Ploner, M., 2018. Distinct patterns of brain activity mediate perceptual and motor and autonomic responses to noxious stimuli. *Nat. Commun.* 9, 4487.
- Treede, R.D., Lorenz, J., Baumgartner, A., 2003. Clinical usefulness of laser-evoked potentials. *Neurophysiol. Clin.* 33, 303–314.
- Treede, R.D., Rief, W., Barke, A., Aziz, Q., Bennett, M.I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N.B., First, M.B., Giambardino, M.A., Kaasa, S., Korwisi, B., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B. H., Svensson, P., Vlaeyen, J.W.S., Wang, S.J., 2019. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain* 160, 19–27.
- Tripanpitak, K., He, S., Sonmezisik, I., Morant, T., Huang, S.Y., Yu, W., 2021. Granger causality-based pain classification using EEG evoked by electrical stimulation targeting nociceptive Aδ and C Fibers. *IEEE Access* 9, 10089–10106.
- Valentini, E., Betti, V., Hu, L., Aglioti, S.M., 2013. Hypnotic modulation of pain perception and of brain activity triggered by nociceptive laser stimuli. *Cortex* 49, 446–462.
- Veerasarn, P., Stohler, C.S., 1992. The effect of experimental muscle pain on the background electrical brain activity. *Pain* 49, 349–360.
- Vijayakumar, V., Case, M., Shirinpour, S., He, B., 2017. Quantifying and characterizing tonic thermal pain across subjects from EEG data using random forest models. *IEEE Trans. Biomed. Eng.* 64, 2988–2996.
- Wang, J., Li, D., Li, X., Liu, F.Y., Xing, G.G., Cai, J., Wan, Y., 2011. Phase-amplitude coupling between theta and gamma oscillations during nociception in rat electroencephalography. *Neurosci. Lett.* 499, 84–87.
- Wang, J., Wang, J., Xing, G.G., Li, X., Wan, Y., 2016. Enhanced gamma oscillatory activity in rats with chronic inflammatory pain. *Front Neurosci.* 10, 489.
- Wang, W.E., Roy, A., Misra, G., Ho, R.L.M., Ribeiro-Dasilva, M.C., Fillingim, R.B., Coombes, S.A., 2019. Altered neural oscillations within and between sensorimotor cortex and parietal cortex in chronic jaw pain. *Neuroimage Clin.* 24, 101964.
- Xiao, Z.D., Martinez, E., Kulkarni, P.M., Zhang, Q.S., Hou, Q.N., Rosenberg, D., Talay, R., Shalot, L., Zhou, H.C., Wang, J., Chen, Z.S., 2019. Cortical pain processing in the rat anterior cingulate cortex and primary somatosensory cortex. *Front Cell Neurosci.* 13, 165.
- Ye, Q., Yan, D., Yao, M., Lou, W., Peng, W., 2019. Hyperexcitability of cortical oscillations in patients with somatoform pain disorder: a resting-state EEG study. *Neural Plast.* 2019, 2687150.
- Yue, L., Iannetti, G.D., Hu, L., 2020. The neural origin of nociceptive-induced gamma-band oscillations. *J. Neurosci.* 40, 3478–3490.
- Zhang, Q., Xiao, Z., Huang, C., Hu, S., Kulkarni, P., Martinez, E., Tong, A.P., Garg, A., Zhou, H., Chen, Z., Wang, J., 2018. Local field potential decoding of the onset and intensity of acute pain in rats. *Sci. Rep.* 8, 8299.
- Zhang, Z.G., Hu, L., Hung, Y.S., Mouraux, A., Iannetti, G.D., 2012. Gamma-band oscillations in the primary somatosensory cortex—a direct and obligatory correlate of subjective pain intensity. *J. Neurosci.* 32, 7429–7438.
- Zhou, R., Wang, J., Qi, W., Liu, F.Y., Yi, M., Guo, H., Wan, Y., 2018. Elevated resting state gamma oscillatory activities in electroencephalogram of patients with post-herpetic neuralgia. *Front Neurosci.* 12, 750.
- Zhou, S., Lithfous, S., Despres, O., Pebayle, T., Bi, X., Dufour, A., 2020. Involvement of frontal functions in pain tolerance in aging: evidence from neuropsychological assessments and gamma-band oscillations. *Front Aging Neurosci.* 12, 131.