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ORIGINAL ARTICLE

Pain-free default mode network connectivity contributes to tonic experimental pain intensity beyond the role of negative mood and other pain-related factors

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Abstract

Background: Alterations in the default mode network (DMN) connectivity across pain stages suggest a possible DMN involvement in the transition to persistent pain.

Aim: This study examined whether pain-free DMN connectivity at lower alpha oscillations (8-10 Hz) accounts for a unique variation in experimental peak pain intensity beyond the contribution of factors known to influence pain intensity.

Methods: Pain-free DMN connectivity was measured with electroencephalography prior to 1 h of capsaicin-evoked pain using a topical capsaicin patch on the right forearm. Pain intensity was assessed on a (0–10) numerical rating scale and the association between peak pain intensity and baseline measurements was examined using hierarchical multiple regression in 52 healthy volunteers (26 women). The baseline measurements consisted of catastrophizing (helplessness, rumination, magnification), vigilance, depression, negative and positive affect, sex, age, sleep, fatigue, thermal and mechanical pain thresholds and DMN connectivity (medial prefrontal cortex [mPFC]-posterior cingulate cortex [PCC], mPFC-right angular gyrus [rAG], mPFC-left Angular gyrus [lAG], rAG-mPFC and rAG-PCC).

Results: Pain-free DMN connectivity increased the explained variance in peak pain intensity beyond the contribution of other factors ($\Delta R^2 = 0.10$, $p = 0.003$), with the final model explaining 66% of the variation ($R^2 = 0.66$, ANOVA: $p < 0.001$). In this model, negative affect ($\beta = 0.51$, $p < 0.001$), helplessness ($\beta = 0.49$, $p = 0.007$), pain-free mPFC-lAG connectivity ($\beta = 0.36$, $p = 0.003$) and depression ($\beta = -0.39$, $p = 0.009$) correlated significantly with peak pain intensity. Interestingly, negative affect and depression, albeit both being negative mood indices, showed opposing relationships with peak pain intensity.

Conclusions: This work suggests that pain-free mPFC-lAG connectivity (at lower alpha) may contribute to individual variations in pain-related vulnerability.

Significance: These findings could potentially lead the way for investigations in which DMN connectivity is used in identifying individuals more likely to develop chronic pain.

1 | INTRODUCTION

Identifying high-risk individuals for developing persistent pain could help create more focused pain-related interventions. At present, predicting those who transition to persistent pain remains difficult due to the multidimensionality of the pain experience. Only a few physiological measures have been shown to predict pain perception, such as peak alpha frequency (PAF) (Furman et al., 2020) and prefrontal-sensorimotor cortex activity (Curtin & Fossey, 2007). Additionally, resting-state functional connectivity between the nucleus accumbens and prefrontal cortex has been shown to predict the transition to chronic pain among subacute low back pain patients (Baliki et al., 2012), suggesting that resting-state connectivity may be a candidate for predicting chronic pain development.

The most researched resting-state network is the default mode network (DMN), which consists of the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC) and bilateral angular gyrus (AG) (Power et al., 2011). The connectivity between these regions is high at rest maintaining internal processes but decreases in response to attention-demanding tasks (Fox & Raichle, 2007). Alpha oscillations play a critical role within the DMN. At rest, increased alpha activity facilitates internal processing by blocking external sensory and motor responses, whereas reduced alpha activity during tasks can lead to less inhibitory effect and greater external attention to tackle these tasks (Mo et al., 2013; Van Diepen et al., 2019). The DMN is a key network in the dynamic pain connectome (Kucyi & Davis, 2015) that is altered during acute and chronic pain (Alhajri et al., 2022a; Alshelh et al., 2018; Baliki et al., 2014). The reliability of the DMN (Barkhof et al., 2014; Meindl et al., 2010) and its involvement across all stages of pain make its activity a potential marker for pain-related vulnerability.

However, abnormalities in the DMN have been linked to negative affect and depression, which are also linked to severe postoperative pain (Posner et al., 2016; Provenzano et al., 2021; Sheline et al., 2009). This suggests that the DMN's role in pain perception may be mediated by negative mood (Letzen & Robinson, 2017). It is unclear whether the role of pain-free DMN connectivity in pain perception is attributed solely to negative mood or whether it independently contributes to pain perception; if the latter, it could serve as a potential marker for pain-related vulnerability.

In addition to negative mood, catastrophizing (Papaioannou et al., 2009; Pavlin et al., 2005) vigilance (Lautenbacher et al., 2009), pain sensitivity (Georgopoulos et al., 2019; Gupta et al., 2007; Sharma et al., 2020), sleep quality (Campbell et al., 2013; Finan et al., 2013; Sivertsen et al., 2015), fatigue (Kaasa et al., 1999; Van Dartel et al., 2013), sex and age (Fillingim et al., 2009; Myers et al., 2006) are factors linked to both acute and chronic pain. This study aimed to assess whether pain-free electroencephalographic (EEG)-based DMN connectivity as measured by Granger causality could explain the variation in subsequent pain intensity (induced by 1 h of capsaicin) beyond the contribution of the above-mentioned factors. It was hypothesized that pain-free DMN connectivity would improve the model contributing to prolonged pain.

2 | METHODS

2.1 | Participants

Fifty-two healthy right-handed volunteers (26 women, age 26.2 ± 4.6 years, mean [M] ± standard deviation [SD]) were recruited online and through flyers posted at Aalborg University and participated in two studies where prospective data have already been published (Alhajri et al., 2022a, 2022b), and the present report represents a secondary analysis based on baseline data. The volunteers who were involved in the initial study did not participate in the subsequent study. Edinburgh Handedness Inventory (Oldfield, 1971) was used to determine handedness. There were no reports of neurological or psychiatric disorders, no pregnancy, no current or chronic pain, and no significant medical disorders. Participants were asked to avoid coffee or alcohol at least 6 h before the experiment. All subjects provided informed consent for study participation, and the procedures were carried out according to the Helsinki Declaration and approved by the local ethics committee (N-20190057). These data were collected at Aalborg University in Denmark between 31 January 2020 and 10 November 2021.

2.2 | Experimental design

In this crossover study participants experienced two conditions/sessions (control/capsaicin) separated by 24 h. As the capsaicin-patch may result in residual effects lasting

for a few days after patch removal (Lo et al., 2018), the control session always took place before the capsaicin session, although this was not revealed to the participants. Each session included measures of EEG acquisition and quantitative sensory testing (QST) assessing thermal and mechanical pain sensitivity. These measures were followed by 1 h of patch application (control or capsaicin). At the end of 1 h, EEG recordings and QST measures were repeated. The present analysis assessed the relationship between baseline measurements and pain intensity for the capsaicin condition only.

2.3 | Experimental pain model

To evoke cutaneous pain, an 8% topical capsaicin patch (Transdermal patch, 'Qutenza', Astellas, 5 × 10 cm) was applied to the volar part of the dominant right forearm (about 5 cm from the wrist). Nitrile gloves were used to apply the capsaicin patch. To maintain blinding, two layers of medical tape were placed on the capsaicin patch (Fixomull stretch, BSN). Subjects rated their pain intensity on a numerical rating scale (NRS) anchoring from 0 'no pain' to 10 'the worst imaginable pain'. They reported NRS pain ratings every 5 min throughout the first hour of the capsaicin application. The peak pain NRS score (NRS-peak) showing the most intense pain reported throughout the 1-h application was used as a measure of pain intensity as peak pain seems most reflective of the negative impact of pain on individuals' lives (Harris et al., 2007).

2.4 | Questionnaires

Given the multidimensionality of pain, assessing only one aspect of this experience is unlikely to provide an accurate image of the vulnerability contributing to pain intensity. Therefore, in addition to mood and connectivity, simultaneous investigation of factors linked to pain perception may reveal the individual contribution of each including DMN connectivity.

Pain vigilance and awareness questionnaire (PVAQ): This questionnaire comprises 16 items assessing preoccupation and attention to one's pain over the past 2 weeks, rated between 0 = 'never' and 5 = 'always', with a maximum score of 80 (McCracken, 1997). Greater values signify greater preoccupation with pain.

Pain Catastrophizing Scale (PCS): This questionnaire includes 13 items assessed on a 5-point scale ranging from 0 = 'not at all' to 4 = 'all the time', with a maximum score of 52 (Sullivan, 1995). It evaluates three scales of catastrophizing: rumination, magnification and helplessness. Ratings reflect the extent to which particular thoughts and feelings are present when feeling pain over the last 3 months. Greater values indicate a greater level of pain catastrophizing.

Positive and Negative Affect Scale (PANAS): This scale comprises 20 items evaluating two groups of emotions: negative and positive (10 items each) (Watson et al., 1988). Subjects rated the intensity of a particular emotion they felt 'at the moment' on a scale (1 = 'very slightly or not at all' to 5 = 'Extremely'), with a maximum of 50 for each emotion group. Greater values suggest more intense emotions. The positive affect items were 'interested', 'excited', 'strong', 'enthusiastic', 'proud', 'alert', 'inspired', 'determined', 'attentive' and 'active'. The negative affect items were 'distressed', 'upset', 'guilty', 'scared', 'hostile', 'irritable', 'ashamed', 'nervous', 'jittery' and 'afraid'.

Beck Depression Inventory (BDI-II): The BDI measures the severity of depressive mood states (Richter et al., 1998) and comprises 21 questions evaluating hopelessness, guilt, fatigue and other physical symptoms, rated between 0 = 'no symptom impact' and 3 = 'maximum symptom impact' with a maximum score of 63. Greater values signify more severe depressive symptoms. To attain measures of trait depression, participants in this study were asked to rate the items based on how they generally feel.

Pittsburgh Sleep Quality Index (PSQI): PSQI evaluates sleep quality in seven dimensions: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction over the last month (Buysse et al., 1989). Each dimension was rated on a scale from 0 = 'no difficulty' to 3 = 'severe difficulty', with a maximum total score of 21. Greater scores signify poorer sleep quality.

Modified Fatigue Impact Scale (MFIS): The MFIS is a self-report tool assessing the impact of fatigue on overall functioning over the last 4 weeks (Fisk et al., 1994). It comprises three sub-measures: cognitive functioning (9 items), physical functioning (10 items) and psychosocial functioning (2 items). Subjects rated each item on a scale from 0 = 'no problem' to 4 = 'extreme problem', with a maximum total score of 84. Greater values indicate elevated levels of fatigue.

2.5 | Pain-free baseline electroencephalography

EEG signals were acquired for 5 min with eyes closed while participants were seated on a comfortable chair in a light- and sound-attenuated room. They were asked to relax, refrain from any movement and stay awake. An EEG cap consisting of 64 electrodes (g.GAMMA cap2) was used to acquire EEG signals. The cap was placed based on the 10–5 system with Cz on the vertex of the head and

an additional EEG electrode (Fp1) positioned above the left eye to monitor eye-related movement. EEG signals were acquired at a sampling rate of 1200 Hz and amplified (50,000x) using a g.HIamp biosignal amplifier with the impedances maintained below 5 kΩ. Data processing and analysis were carried out using Brain Electrical Source Analysis (BESA) (BESA Research 7.1, GmbH). A low-pass filter of 175 Hz and a high-pass filter of 0.53 Hz were used, and the data were notch-filtered at 50 Hz. The 5-min acquired EEG recordings were segmented into 2-s epochs, which were inspected visually for apparent artefacts. After cleaning the data manually, independent component analysis in BESA was used to remove eye movement and cardiac-related artefacts. The epochs were scanned further in BESA to exclude epochs having artefacts not related to cardiac or eye movement. If the epoch had amplitude jumps of >75 μV between two sampling points, or its amplitude was more than 120 μV or lower than 0.07 μV, it was regarded as bad. Connectivity analysis was run on the artefact-cleaned and accepted epochs.

2.6 | Default mode network connectivity

Using a discrete multiple source method (Scherg et al., 2019), EEG data were transformed in BESA to source space, and pre-defined resting-state source montages for the DMN were used focusing on four regions: mPFC, PCC, right and left angular gyrus (rAG and lAG) (Alhajri et al., 2022b). The locations of the DMN areas were determined by Montreal Neurological Institution based on the DMN system described by Power et al. (Power et al., 2011). Although some studies have not considered the AG a part of the DMN, other studies have listed this brain region as a DMN node (Bowman et al., 2017; Power et al., 2011; Samogin et al., 2019). DMN pain-free connectivity was investigated using BESA connectivity 1.0 (MEGIS Software GmbH). Using BESA connectivity, the artefact-cleaned data were transformed to the time-frequency domain by the way of complex demodulation. Complex demodulation is a time-frequency analysis method that defines the amplitude and phase of a given frequency component of a time series yielding a uniform frequency resolution across the examined bandwidth (Hao et al., 1992). Our previous work showed that five DMN connections (mPFC-rAG, mPFC-lAG, mPFC-PCC, rAG-mPFC, rAG-PCC) exhibited significant change following 1 h of capsaicin-induced pain (Alhajri et al., 2022a). As these five DMN connections are affected by pain and might be involved in pain processing, the present report focused on assessing whether baseline connectivity at these connections can contribute to pain intensity. A positive correlation between the activity of the DMN and the activity of alpha and beta bands has been revealed by various research techniques including fMRI-EEG (Bowman et al., 2017; Mantini et al., 2007; Samogin et al., 2019) and magnetoencephalography (Tang et al., 2017). Therefore, when examining the DMN, the focus was on these two bands. Machine learning approaches, however, have shown that when predicting subjective pain ratings, baseline alpha and gamma activity are the most accurate predictors (Kim & Davis, 2021). Therefore, this study investigated how the DMN connectivity at alpha (but not beta) contributes to peak pain intensity. Additionally, our previous work (Alhajri et al., 2022b) along with other findings (Klimesch et al., 2006; Nir et al., 2012) have also shown that lower alpha (8–10 Hz) may be more involved in pain perception than upper alpha (11–13 Hz) oscillations. Therefore, the contribution of pain-free DMN connectivity to pain intensity was examined at lower alpha (8–10 Hz).

2.7 | Pain sensitivity

Pain sensitivity was assessed through thermal and mechanical tests including warmth detection threshold (WDT), heat pain threshold (HPT) and mechanical pain threshold (MPT). These tests were performed on a predetermined area (5 × 2 cm) just above the to-be-applied capsaicin patch on the right dominant forearm. Before the actual tests, participants underwent familiarization sessions at the same location on the left forearm.

Thermal thresholds were assessed using an ascending method of limits paradigm with a thermal stimulator probe (3 × 3 cm, Pathway Medoc Ltd). With an initial temperature of 32°C, the probe temperature increased or decreased at a rate of 1°C/s until the subject pushes a stop button indicating the relevant threshold, which is followed by a return to the pain-free temperature. Subjects pressed a button as soon as warmth or an increase in temperature was detected, and this defined the WDT. This procedure was repeated four times and the final threshold was calculated as the average of these four repetitions. For HPT, subjects pressed a stop button as soon as the probe induced a painful sensation. This procedure was repeated three times and the final threshold was calculated as the average of these three trials.

The MPT was determined using a set of seven weighted pinprick stimulators consisting of steel tubes weighing 0.8, 1.6, 3.2, 6.4, 12.8, 25.6 and 51.2 g and ending with a tip contact diameter of 0.25 mm (MRC Systems GmbH). The stimulators were applied to the skin in an ascending order at a rate of 2 s on, 2 s off [77], starting with 0.8 g until the stimulator is perceived as sharp or stinging (first suprathreshold value). Once the first painful sensation was perceived, the stimulators where then applied in descending

order until the reported no pain or blunt sensation (first subthreshold value). This ascending/descending testing was performed five times and the final threshold was determined as the geometric mean of these five ascending/descending trials.

2.8 | Statistics

Data are presented as M and SD. Statistical analysis was carried out using IBM SPSS Statistics for Windows, version 27 (IBM Corp.). Significance was accepted at $p < 0.05$, unless stated otherwise. Normality was determined using Z scores of kurtosis and skewness statistics, and variables were considered normal when Z scores did not exceed ±1.96 (Field, 2018). To assess whether pain-free DMN connectivity uniquely explained the variation in capsaicin-induced peak pain NRS scores beyond the contribution of other factors, a hierarchal multiple regression analysis was performed. These factors were sex, age, sleep, fatigue, pain-related behaviour (vigilance, magnification, helplessness and rumination), mood (depression scores, positive and negative affect), baseline pain sensitivity (WDT, HPT, MPT) and pain-free DMN connectivity. Multiple connections were considered to reflect pain-free DMN connectivity including mPFC-PCC, mPFC-rAG, mPFC-lAG, rAG-mPFC and rAG-PCC, which were well-correlated. Therefore, to avoid multicollinearity between the five examined DMN connections, Pearson correlations were performed (Bonferroni correction for multiple correlations [i.e. $p < 0.01$]) to determine the DMN connections that could significantly contribute to NRS-peak pain and subsequently these connections were included in the regression analysis. In the regression analysis, variables were added in blocks using the inter method, with pain-free DMN connectivity representing the last block. Durbin—Watson tests and variation inflation factors (VIF)/tolerance coefficients were reported to assess the independence of errors and multicollinearity among the predictors, respectively.

3 | RESULTS

The baseline descriptive data of the criterion variable and all predictors are provided in Table 1.

Pearson's correlations between NRS-peak pain and connectivity among DMN connections (mPFC-PCC, mPFC-lAG, mPFC-rAG, rAG-PCC, rAG-mPFC) revealed that only pain-free mPFC-lAG connectivity correlated significantly with NRS-peak pain ($r = 0.42$, $p = 0.002$), with no significant correlation for the other four connections (mPFC-PCC: $r = 0.15$, $p = 0.279$; mPFC-rAG: $r = 0.13$, $p = 0.344$; rAG-PCC: $r = 0.13$, $p = 0.372$; rAG-mPFC: $r = 0.23$, $p = 0.104$). Therefore, pain-free mPFC-lAG connectivity (representing DMN connectivity) was included in the regression analysis.

TABLE 1 Descriptive statistics of baseline measurements.

Variable ($N = 52$)	Mean	SD
Age (years)	26.2	4.6
Sex (female)	$n = 26$ (50%)	
NRS-peak (0–10)	7.1	2.1
Sleep (PSQI)	4.9	2.2
Fatigue (MFSI)	20.8	13.4
Catastrophizing (PCS): rumination	5.8	3.9
Catastrophizing (PCS): magnification	3.6	2.1
Catastrophizing (PCS): helplessness	5.7	3.9
Vigilance (PVAQ)	35.2	13.7
Mood: depression (BDI-II)	4.4	3.1
Mood: positive affect (PANAS)	27.1	8.1
Mood: negative affect (PANAS)	12.7	2.4
Connectivity: mPFC-PCC (GC)	0.13	0.06
Connectivity: rAG-PCC (GC)	0.11	0.06
Connectivity: rAG-mPFC (GC)	0.13	0.07
Connectivity: mPFC-rAG (GC)	0.13	0.08
Connectivity: mPFC-lAG (GC)	0.14	0.07
Warmth detection threshold (°C)	34.1	0.6
Heat pain threshold (°C)	40.9	3.3
Mechanical pain threshold (g)	2.3	0.7

Note: Connectivity was measured by granger causality (GC).

Abbreviations: BDI-II, Beck Depression Inventory; lAG: left angular gyrus; MFIS, Modified Fatigue Impact Scale; mPFC: medial prefrontal cortex; PANAS, Positive and Negative Affect Scale; PCC: posterior cingulate cortex; PCS, Pain Catastrophizing Scale; PSQI, Pittsburgh Sleep Quality Index; PVAQ, Pain vigilance and awareness questionnaire; rAG: right angular gyrus.

In the multiple regression analysis, Durbin—Watson statistic for regression analysis was <3 and >1 (Table 2), indicating no violation of the independent of errors assumption (Field, 2018). Additionally, all the VIF and tolerance statistics are lower than 4 and higher than 0.2, respectively (Table 3), suggesting no sign of major multicollinearity between the predictors (Sarstedt et al., 2021; Shrestha, 2020). Moreover, the zero-order correlations among the predictors were less than 0.8 indicating no serious multicollinearity issues (Field, 2018; Shrestha, 2020).

Fifteen factors were assessed in the regression analysis (Tables 2 and 3). Sex, age, sleep and fatigue did not account for a significant variance in NRS-peak pain (Table 2). Adding mood (depression, positive and negative affect) increased the explained variance substantially

TABLE 2 Hierarchal multiple regression analysis for numerical rating scale-peak pain as the predicted variable and 15 predictors based on six models: including sex and age (model 1), model 1 as well as sleep and fatigue (model 2), model 1 and 2, as well as mood (depression, positive and negative affect) (model 3), model 1, 2 and 3, as well as pain-related behaviour including catastrophizing (rumination, magnification, helplessness) and vigilance (model 4), model 1, 2, 3 and 4, as well baseline pain sensitivity (warmth detection threshold, heat pain threshold, mechanical pain threshold) (model 5), model 1, 2, 3, 4 and 5 well as pain-free DMN connectivity (mPFC-lAG) (model 6). Significance has been set at $p < 0.05$. Predictors that accounted for a significant variation in peak pain intensity are shown in bold.

Model	Predictors	R^2	Adjusted R^2	ΔR^2	ΔF	p-Value	Durbin—Watson
1	Age and sex	0.04	0.00	0.04	1.06	0.354	
2	+Sleep and fatigue	0.07	−0.01	0.03	0.66	0.521	
3	**+Mood**	0.37	0.27	**0.30**	7.09	**0.001**	
4	**+Catastrophizing and vigilance**	0.53	0.41	**0.16**	3.48	**0.016**	
5	+Pain sensitivity	0.56	0.40	0.03	0.84	0.481	
6	**+Pain-free DMN connectivity**	0.66	0.52	**0.10**	10.35	**0.003**	2.3

Abbreviations: DMN, default mode network; lAG, left angular gyrus; mPFC, medial prefrontal cortex.

TABLE 3 Standardized coefficients from the hierarchal multiple linear regression analysis associated with 15 predictors of numerical rating scale-peak pain intensity based on model 6. Significance has been set at $p < 0.05$. Predictors that showed a significant relashionship with peak pain intensity are shown in bold.

	Unstandardized coefficients		Standardized coefficients			Collinearity diagnostics	
	B	SE	Beta	*t*	Sig.	Tolerance	VIF
(Constant)	−5.46	12.27		−0.45	0.659		
Age	0.03	0.05	0.06	0.49	0.626	0.73	1.37
Sex	−0.56	0.54	−0.14	−1.04	0.304	0.57	1.77
Sleep (PSQI)	0.04	0.13	0.04	0.28	0.783	0.52	1.92
Fatigue (MFIS)	0.03	0.02	0.19	1.47	0.152	0.55	1.81
Depression (BDI-II)	−0.27	0.10	**−0.39**	−2.75	**0.009**	0.48	2.10
Positive affect (PANAS)	−0.02	0.03	−0.07	−0.54	0.596	0.60	1.67
Negative affect (PANAS)	0.45	0.10	**0.51**	4.68	**<0.001**	0.81	1.24
Rumination (PCS)	−0.04	0.09	−0.08	−0.51	0.613	0.39	2.60
Magnification (PCS)	−0.24	0.13	−0.24	−1.88	0.068	0.58	1.72
Helplessness (PCS)	0.26	0.09	**0.49**	2.86	**0.007**	0.33	3.06
Vigilance	−0.02	0.02	−0.11	−0.85	0.403	0.55	1.82
Baseline WDT	0.35	0.38	0.11	0.94	0.354	0.75	1.34
Baseline HPT	−0.12	0.08	−0.19	−1.58	0.123	0.64	1.57
Baseline MPT	−0.18	0.32	−0.06	−0.55	0.585	0.74	1.35
Connectivity mPFC-lAG (GC)	10.95	3.40	**0.36**	3.22	**0.003**	0.76	1.31

Note: Connectivity was measured by granger causality (GC).

Abbreviations: BDI-II, Beck Depression Inventory; HPT, heat pain threshold; lAG, left angular gyrus; MFIS, Modified Fatigue Impact Scale; mPFC, medial prefrontal cortex; MPT, mechanical pain threshold; PANAS, Positive and Negative Affect Scale; PCS, Pain Catastrophizing Scale; PSQI, Pittsburgh Sleep Quality Index; WDT, warmth detection threshold.

to approximately 30% ($F(3,44) = 7.09$, $p = 0.001$). An additional 16% was accounted for by catastrophizing (helplessness, rumination and magnification) and vigilance ($F(4,40) = 3.48$, $p = 0.016$). Surprisingly, adding pain sensitivity did not account for an additional significant variance in peak pain intensity (Table 2). Interestingly, adding

pain-free mPFC-lAG connectivity increased the explained variance by 10% ($F(1,36)=10.35$, $p=0.003$). The final model (model 6) including all the factors explained 66% ($R^2=0.66$) of the total variance in pain NRS-peak pain (ANOVA: $F(15,36)=4.68$, $p<0.001$). In this model, only four variables significantly contributed to NRS-peak pain: Negative affect ($\beta=0.51$, $p<0.001$), pain-related helplessness ($\beta=0.49$, $p=0.007$), pain-free connectivity between mPFC and lAG ($\beta=0.36$, $p=0.003$) and depression ($\beta=-0.39$, $p=0.009$; Table 3).

4 | DISCUSSION

This study examined whether pain-free DMN connectivity at lower alpha oscillations accounts for a unique variation in experimental peak pain intensity beyond the contribution of sex, age, sleep, fatigue, pain catastrophizing (helplessness, rumination, magnification), vigilance, depression, negative and positive affect, as well as thermal and mechanical pain thresholds. The results revealed that pain-free mPFC-lAG connectivity accounted for a significant variation in peak pain beyond the contribution of other factors. Additionally, helplessness, depression and negative affect were also critical baseline characteristics contributing to peak pain intensity. Finally, sex, age, sleep, fatigue, positive affect, vigilance, rumination, magnification and thermal and mechanical thresholds were not associated with peak pain intensity.

4.1 | Pain-free default mode network connectivity contributes uniquely to peak pain intensity

Both acute and chronic pain have been shown to alter DMN connectivity (Alhajri et al., 2022b; Alshelh et al., 2018). These alterations across both pain stages suggest a possible DMN involvement in the transition from acute to persistent pain. However, due to the established link between negative mood and DMN connectivity among both healthy individuals (Alhajri et al., 2022b; Provenzano et al., 2021) and those with mood disorders (Marchetti et al., 2012; Sheline et al., 2009), it was argued that the role of the DMN in pain perception may be attributed to negative mood (Letzen & Robinson, 2017). In the present study, pain-free mPFC-lAG connectivity at lower alpha accounted for a significant variance in peak pain intensity beyond the contribution of negative mood and other examined factors. Specifically, pain-free mPFC-lAG was positively correlated with peak pain intensity. This finding could be explained by the involvement of mPFC and lAG in self-related processing. Specifically, high mPFC activity is associated with an increased focus on self-referential thoughts and emotions (Smith et al., 2014). For the lAG, increased activity in this area has been shown when subjects attribute their emotions or actions to themselves rather than to others (Decety & Grèzes, 2006; Ganesh et al., 2012). Considering these studies, our findings suggest that individuals who can identify with and monitor their internal emotions are more likely to report more pain intensity. The activity of lower alpha may help facilitate this internal monitoring by suppressing irrelevant external information (Mo et al., 2013; Van Diepen et al., 2019).

Previous studies have also shown the involvement of alpha oscillations in pain perception. For example, slower PAF over the sensory regions has been linked to higher pain intensity and proposed as a biomarker for prolonged pain sensitivity (Furman et al., 2018, 2020). Additionally, there is evidence that the increased power of slower alpha rhythms (8–9.5 Hz), which is almost the frequency range examined here, has been shown to contribute to the development of pathological pain (Llinás et al., 2005).

The unique contribution of high mPFC-lAG connectivity at lower alpha qualifies it, with further validation, as a potential objective marker for identifying vulnerability to high pain intensity. It is noteworthy, however, that replicating these findings in patients may be challenging due to potential differences in the impact of catastrophizing, depression, anxiety and sleep disorders between healthy individuals and patients. Nonetheless, mPFC-lAG connectivity can be employed as a preventative measure. Research has shown that immediate post-operative pain can accurately predict chronic pain development (Yarnitsky et al., 2008). Although speculative, measuring mPFC-lAG connectivity before surgery may help in predicting post-operative pain and hence identifying those at risk of developing persistent pain. This may allow for appropriate immediate pre- and post-operative pain interventions to reduce that risk.

4.2 | Positive/negative affect and capsaicin-induced pain intensity

In line with previous pain studies (Geisser et al., 2000; van Wijk & Hoogstraten, 2009), the present study revealed a strong positive correlation between negative affect and pain intensity. In contrast, positive affect was not associated with pain intensity. These two affective states reflect distinct, but not opposite, constructs and typically show low correlations with one another in non-painful (Cacioppo & Berntson, 1999) and painful (Danhauer et al., 2013; Finan & Garland, 2015) contexts. This difference in impact between positive and negative affect may be partially evolutionary

in nature. 'Survival requires urgent attention to possible bad outcomes, but it is less urgent with regard to good ones' (Baumeister et al., 2001). Generally, negative emotions have a more powerful lingering effect, are processed more thoroughly and are more resistant to disconfirmation than positive emotions (Baumeister et al., 2001). As such, negative emotions may trigger avoidance of stimuli causing them (e.g. pain), aiding survival. Linking negativity to pain intensity can help avoid painful situations that may pose a threat to survival. However, there is accumulating evidence linking induced positive affect to reduced pain perception in experimental settings (Hanssen et al., 2017). Future research should examine whether spontaneously experienced positive affect, as investigated in this study, and deliberately induced positive affect, as studied in prior research, have different predictive values for pain perception.

4.3 | Depression and capsaicin-induced pain intensity

Interestingly, negative affect and depression showed opposite relationships with peak pain intensity although both are mood-related disturbances. Higher depression scores were associated with lower pain intensity, whereas higher negative affect scores indicated higher pain intensity. There is evidence describing depression as a risk factor for chronic (Carroll et al., 2004) and post-operative pain (Etcheson et al., 2018; Pérez-Prieto et al., 2014). However, depression is also linked to increased pain thresholds and decreased pain sensitivity (Bär et al., 2005). The association between depression and pain perception is highly dependent on the pain modality where depression is associated with increased pain threshold/tolerance during exteroceptive pain (e.g. cutaneous) and decreased thresholds during interoceptive pain (e.g. ischemic) (Thompson et al., 2016). This may be because interoceptive pain is more emotionally salient than cutaneous pain due to its involvement of deep structures such as muscles and joints (Thompson et al., 2016). As capsaicin-induced pain is cutaneous and thermal in nature, the negative depression-pain intensity association reported here is not surprising (Bär et al., 2005). It is noteworthy, however, that none of our subjects were clinically depressed (all BDI score < 30). Yet, it is interesting to still see this distinction between depression and negative affect among healthy individuals.

4.4 | Pain-related helplessness and pain intensity

Although pain catastrophizing is a robust predictor of pain-related outcomes (Papaioannou et al., 2009; Sullivan et al., 2011), less is known about the unique contribution of catastrophizing subscales (i.e. rumination, magnification, helplessness) to pain perception. Among these, rumination is found to characterize healthy individuals who report more pain during experimentally induced tonic pain (e.g. for 20 min) (Alshelh et al., 2018). However, in the present study, helplessness uniquely contributed to pain intensity, which is in line with previous research among chronic pain patients (Craner et al., 2016). The relevance of helplessness for chronic pain and long-lasting experimental pain, as used in this study, but not for short-lasting experimental pain suggests that long-lasting pain models may be more closely related to chronic pain conditions.

4.5 | Prediction model

The current model explained about 66% of the variation in peak pain intensity. Several models were proposed for predicting pain intensity. For example, in a study assessing the effect of psychological factors on postoperative pain outcomes, gender and catastrophizing explained 81% of the variance in pain intensity (Papaioannou et al., 2009). Physiologically, using the capsaicin-heat pain model, Furman and colleagues found that 50% of the variation in pain intensity could be explained by PAF (Furman et al., 2018). Although informative, these studies solely examined the predictive value of certain measures, without accounting for other pain-related factors that may also impact these measures. In contrast, the present study included additional measures, which allowed for taking various factors contributing to the pain experience into account. A model that includes both subjective and objective measures, encompassing various components of the pain experience, would be more informative for identifying vulnerability to chronic pain development.

4.6 | Limitations

This study did not examine the effect of other factors shown to influence pain perception such as pain expectations (Lorenz et al., 2005), temporal summation of pain, conditioned pain modulation (Lavand'Homme, 2011) and anxiety (Hinrichs-Rocker et al., 2009). Moreover, examining mPFC connectivity with other networks that are shown to be involved in pain perception (e.g. salience network Baliki et al., 2014) or modulatory pain system (Li et al., 2016; Meeker et al., 2022) would shed more light on the role of pain-free DMN connectivity in contributing to pain intensity. Furthermore, while a pain-related contralateral effect has been observed in the somatosensory cortex, there are mixed results for this effect in other

regions involved in pain processing (Bingel et al., 2003; Youell et al., 2004). To explore a possible hemispheric effect on pain-related DMN connectivity, it would be interesting to examine both right and left forearms.

4.7 | Conclusion

This study presents a comprehensive model explaining 66% of the variation in peak pain intensity considering different aspects of the pain experience by encompassing both subjective and objective physiological measures. In this model, pain-free mPFC-lAG connectivity appears to be a potential biomarker explaining individual differences in pain-related vulnerability. However, future studies should assess the validity of the proposed measure.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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REFERENCES

Alhajri, N., Boudreau, S. A., & Graven-Nielsen, T. (2022a). Decreased default mode network connectivity following 24 hours of capsaicin-induced pain persists during immediate pain relief and facilitation. *The Journal of Pain*, *24*(5), 796–811.

Alhajri, N., Boudreau, S. A., & Graven-Nielsen, T. (2022b). Angular gyrus connectivity at alpha and beta oscillations is reduced during tonic pain – Differential effect of eye state. *NeuroImage Clinical*, *33*, 102907.

Alshelh, Z., Marciszewski, K. K., Akhter, R., Di Pietro, F., Mills, E. P., Vickers, E. R., Peck, C. C., Murray, G. M., & Henderson, L. A. (2018). Disruption of default mode network dynamics in acute and chronic pain states. *NeuroImage Clinical*, *17*, 222–231.

Baliki, M. N., Mansour, A. R., Baria, A. T., & Apkarian, A. V. (2014). Functional reorganization of the default mode network across chronic pain conditions. *PLoS One*, *9*, e10633.

Baliki, M. N., Petre, B., Torbey, S., Herrmann, K. M., Huang, L., Schnitzer, T. J., Fields, H. L., & Apkarian, A. V. (2012). Corticostriatal functional connectivity predicts transition to chronic back pain. *Nature Neuroscience*, *15*, 1117–1119.

Bär, K. J., Brehm, S., Boettger, M. K., Boettger, S., Wagner, G., & Sauer, H. (2005). Pain perception in major depression depends on pain modality. *Pain*, *117*, 97–103.

Barkhof, F., Haller, S., & Rombouts, S. A. R. B. (2014). Resting-state functional MR imaging: A new window to the brain. *Radiology*, *272*, 29–49.

Baumeister, R. F., Bratslavsky, E., Finkenauer, C., & Vohs, K. D. (2001). Bad is stronger than good. *Review of General Psychology*, *5*, 323–370.

Bingel, U., Quante, M., Knab, R., Bromm, B., Weiller, C., & Büchel, C. (2003). Single trial fMRI reveals significant contralateral bias in responses to laser pain within thalamus and somatosensory cortices. *NeuroImage*, *18*, 740–748.

Bowman, A. D., Griffis, J. C., Visscher, K. M., Dobbins, A. C., Gawne, T. J., DiFrancesco, M. W., & Szaflarski, J. P. (2017). Relationship between alpha rhythm and the default mode network: An EEG-fMRI study. *Journal of Clinical Neurophysiology*, *34*, 527–533.

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*, 193–213.

Cacioppo, J. T., & Berntson, G. G. (1999). The affect system: Architecture and operating characteristics. *Current Directions in Psychological Science*, *8*, 133–137.

Campbell, C. M., Bounds, S. C., Kuwabara, H., Edwards, R. R., Campbell, J. N., Haythornthwaite, J. A., & Smith, M. T. (2013). Individual variation in sleep quality and duration is related to cerebral mu opioid receptor binding potential during tonic laboratory pain in healthy subjects. *Pain Medicine*, *14*, 1882–1892.

Carroll, L. J., Cassidy, J. D., & Côté, P. (2004). Depression as a risk factor for onset of an episode of troublesome neck and low back pain. *Pain*, *107*, 134–139.

Craner, J. R., Gilliam, W. P., & Sperry, J. A. (2016). Rumination, magnification, and helplessness how do different aspects of pain catastrophizing relate to pain severity and functioning? *The Clinical Journal of Pain*, *32*, 1028–1035.

Curtin, M., & Fossey, E. (2007). Appraising the trustworthiness of qualitative studies: Guidelines for occupational therapists. *Australian Occupational Therapy Journal*, *54*, 88–94.

Danhauer, S. C., Legault, C., Bandos, H., Kidwell, K., Costantino, J., Vaughan, L., Avis, N. E., Rapp, S., Coker, L. H., Naughton, M., Naylor, C., Terracciano, A., & Shumaker, S. (2013). Positive and negative affect, depression, and cognitive processes in the cognition in the study of tamoxifen and raloxifene (Co-STAR) trial. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *20*, 532–552.

Decety, J., & Grèzes, J. (2006). The power of simulation: Imagining one's own and other's behavior. *Brain Research*, *1079*, 4–14.

Etcheson, J. I., Gwam, C. U., George, N. E., Virani, S., Mont, M. A., & Delanois, R. E. (2018). Patients with major depressive disorder experience increased perception of pain and opioid consumption following total joint arthroplasty. *The Journal of Arthroplasty*, *33*, 997–1002.

Field, A. (2018). *Discovering statistics using IBN SPSS statistics*. Sage.

Fillingim, R. B., King, C. D., Ribeiro-Dasilva, M. C., Rahim-Williams, B., & Riley, J. L. (2009). Sex, gender, and pain: A review of recent clinical and experimental findings. *The Journal of Pain*, *10*, 447–485.

Finan, P. H., & Garland, E. L. (2015). The role of positive affect in pain and its treatment. *The Clinical Journal of Pain*, *31*, 177–187.

Finan, P. H., Goodin, B. R., & Smith, M. T. (2013). The association of sleep and pain: An update and a path forward. *The Journal of Pain*, *14*, 1539–1552.

Fisk, J. D., Ritvo, P. G., Ross, L., Haase, D. A., Marrie, T. J., & Schlech, W. F. (1994). Measuring the functional impact of fatigue: Initial validation of the fatigue impact scale. *Clinical Infectious Diseases*, *18*, S79–S83.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews. Neuroscience*, *8*, 700–711.

Furman, A. J., Meeker, T. J., Rietschel, J. C., Yoo, S., Muthulingam, J., Prokhorenko, M., Keaser, M. L., Goodman, R. N., Mazaheri, A., & Seminowicz, D. A. (2018). NeuroImage cerebral peak alpha frequency predicts individual differences in pain sensitivity. *NeuroImage*, *167*, 203–210.

Furman, A. J., Prokhorenko, M., Keaser, M. L., Zhang, J., Chen, S., Mazaheri, A., & Seminowicz, D. A. (2020). Sensorimotor peak alpha frequency is a reliable biomarker of prolonged pain sensitivity. *Cerebral Cortex*, *30*, 6069–6082.

Ganesh, S., Van Schie, H. T., De Lange, F. P., Thompson, E., & Wigboldus, D. H. J. (2012). How the human brain goes virtual: Distinct cortical regions of the person-processing network are involved in self-identification with virtual agents. *Cerebral Cortex*, *22*, 1577–1585.

Geisser, M. E., Roth, R. S., Theisen, M. E., Robinson, M. E., & Riley, J. L. I. I. I. (2000). Negative affect, self-report of depressive symptoms, and clinical depression: Relation to the experience of chronic pain. *The Clinical Journal of Pain*, *16*, 110–120.

Georgopoulos, V., Akin-Akinyosoye, K., Zhang, W., McWilliams, D. F., Hendrick, P., & Walsh, D. A. (2019). Quantitative sensory testing and predicting outcomes for musculoskeletal pain, disability, and negative affect: A systematic review and meta-analysis. *Pain*, *160*, 1920–1932.

Gupta, A., McBeth, J., Macfarlane, G. J., Morriss, R., Dickens, C., Ray, D., Chiu, Y. H., & Silman, A. J. (2007). Pressure pain thresholds and tender point counts as predictors of new chronic widespread pain in somatising subjects. *Annals of the Rheumatic Diseases*, *66*, 517–521.

Hanssen, M. M., Peters, M. L., Boselie, J. J., & Meulders, A. (2017). Can positive affect attenuate (persistent) pain? State of the art and clinical implications. *Current Rheumatology Reports*, *19*, 1–9.

Hao, Y. L., Ueda, Y., & Ishii, N. (1992). Improved procedure of complex demodulation and an application to frequency analysis of sleep spindles in EEG. *Medical & Biological Engineering & Computing*, *30*, 406–412.

Harris, K., Li, K., Flynn, C., & Chow, E. (2007). Worst, average or current pain in the brief pain inventory: Which should be used to calculate the response to palliative radiotherapy in patients with bone metastases? *Clinical Oncology*, *19*, 523–527.

Hinrichs-Rocker, A., Schulz, K., Järvinen, I., Lefering, R., Simanski, C., & Neugebauer, E. A. M. (2009). Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) – A systematic review. *European Journal of Pain*, *13*, 719–730.

Kaasa, S., Loge, J. H., Knobel, H., Jordhøy, M. S., & Brenne, E. (1999). Fatigue. Measures and relation to pain. *Acta Anaesthesiologica Scandinavica*, *43*, 939–947.

Kim, J. A., & Davis, K. D. (2021). Neural oscillations: Understanding a neural code of pain. *The Neuroscientist*, *27*, 544–570.

Klimesch, W., Doppelmayr, M., & Hanslmayr, S. (2006). Upper alpha ERD and absolute power: Their meaning for memory performance. *Progress in Brain Research*, *159*, 151–165.

Kucyi, A., & Davis, K. D. (2015). The dynamic pain connectome. *Trends in Neurosciences*, *38*, 86–95.

Lautenbacher, S., Huber, C., Kunz, M., Parthum, A., Weber, P. G., Griessinger, N., & Sittl, R. (2009). Hypervigilance as predictor of postoperative acute pain: Its predictive potency compared with experimental pain sensitivity, cortisol reactivity, and affective state. *The Clinical Journal of Pain*, *25*, 92–100.

Lavand'Homme, P. (2011). The progression from acute to chronic pain. *Current Opinion in Anaesthesiology*, *24*, 545–550.

Letzen, J. E., & Robinson, M. E. (2017). Negative mood influences default mode network functional connectivity in patients with chronic low back pain: Implications for functional neuroimaging biomarkers. *Pain*, *158*, 48–57.

Li, Z., Liu, M., Lan, L., Zeng, F., Makris, N., Liang, Y., Guo, T., Wu, F., Gao, Y., Dong, M., Yang, J., Li, Y., Gong, Q., Liang, F., & Kong, J. (2016). Altered periaqueductal gray resting state functional connectivity in migraine and the modulation effect of treatment. *Scientific Reports*, *6*, 1–11.

Llinás, R., Urbano, F. J., Leznik, E., Ramírez, R. R., & Van Marle, H. J. F. (2005). Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. *Trends in Neurosciences*, *28*, 325–333.

Lo, V. S., Andersen, H. H., & Arendt-Nielsen, L. (2018). The time course of brief and prolonged topical 8% capsaicin-induced desensitization in healthy volunteers evaluated by quantitative sensory testing and vasomotor imaging. *Experimental Brain Research*, *236*, 2231–2244.

Lorenz, J., Hauck, M., Paur, R. C., Nakamura, Y., Zimmermann, R., Bromm, B., & Engel, A. K. (2005). Cortical correlates of false expectations during pain intensity judgments – A possible manifestation of placebo/nocebo cognitions. *Brain, Behavior, and Immunity*, *19*, 283–295.

Mantini, D., Perrucci, M. G., Del Gratta, C., Romani, G. L., & Corbetta, M. (2007). Electrophysiological signatures of resting state networks in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 13170–13175.

Marchetti, I., Koster, E. H. W., Sonuga-Barke, E. J., & De Raedt, R. (2012). The default mode network and recurrent depression: A neurobiological model of cognitive risk factors. *Neuropsychology Review*, *22*, 229–251.

McCracken, L. M. (1997). "Attention" to pain in persons with chronic pain: A behavioral approach. *Behavior Therapy*, *28*, 271–284.

Meeker, T. J., Schmid, A. C., Keaser, M. L., Khan, S. A., Gullapalli, R. P., Dorsey, S. G., Greenspan, J. D., & Seminowicz, D. A. (2022). Tonic pain alters functional connectivity of the descending pain modulatory network involving amygdala, periaqueductal gray, parabrachial nucleus and anterior cingulate cortex. *NeuroImage*, *256*, 119278.

Meindl, T., Teipel, S., Elmouden, R., Mueller, S., Koch, W., Dietrich, O., Coates, U., Reiser, M., & Glaser, C. (2010). Test-retest reproducibility of the default-mode network in healthy individuals. *Human Brain Mapping*, *31*, 237–246.

Mo, J., Liu, Y., Huang, H., & Ding, M. (2013). Coupling between visual alpha oscillations and default mode activity. *NeuroImage*, *68*, 112–118.

Myers, C. D., Tsao, J. C. I., Glover, D. A., Kim, S. C., Turk, N., & Zeltzer, L. K. (2006). Sex, gender, and age: Contributions to laboratory pain responding in children and adolescents. *The Journal of Pain*, *7*, 556–564.

Nir, R. R., Sinai, A., Moont, R., Harari, E., & Yarnitsky, D. (2012). Tonic pain and continuous EEG: Prediction of subjective pain perception by alpha-1 power during stimulation and at rest. *Clinical Neurophysiology*, *123*, 605–612.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*, 97–113.

Papaioannou, M., Skapinakis, P., Damigos, D., Mavreas, V., Broumas, G., & Palgimesi, A. (2009). The role of catastrophizing in the prediction of postoperative pain. *Pain Medicine*, *10*, 1452–1459.

Pavlin, D. J., Sullivan, M. J. L., Freund, P. R., & Roesen, K. (2005). Catastrophizing: A risk factor for postsurgical pain. *The Clinical Journal of Pain*, *21*, 83–90.

Pérez-Prieto, D., Gil-González, S., Pelfort, X., Leal-Blanquet, J., Puig-Verdié, L., & Hinarejos, P. (2014). Influence of depression on total knee arthroplasty outcomes. *The Journal of Arthroplasty*, *29*, 44–47.

Posner, J., Cha, J., Wang, Z., Talati, A., Warner, V., Gerber, A., Peterson, B. S., & Weissman, M. (2016). Increased default mode network connectivity in individuals at high familial risk for depression. *Neuropsychopharmacology*, *41*, 1759–1767.

Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., Vogel, A. C., Laumann, T. O., Miezin, F. M., Schlaggar, B. L., & Petersen, S. E. (2011). Functional network organization of the human brain. *Neuron*, *72*, 665–678.

Provenzano, J., Fossati, P., Dejonckheere, E., Verduyn, P., & Kuppens, P. (2021). Inflexibly sustained negative affect and rumination independently link default mode network efficiency to subclinical depressive symptoms. *Journal of Affective Disorders*, *293*, 347–354.

Richter, P., Werner, J., Heerlein, A., Kraus, A., & Sauer, H. (1998). On the validity of the Beck depression inventory. A review. *Psychopathology*, *31*, 160–168.

Samogin, J., Liu, Q., Marino, M., Wenderoth, N., & Mantini, D. (2019). Shared and connection-specific intrinsic interactions in the default mode network. *NeuroImage*, *200*, 474–481.

Sarstedt, M., Ringle, C. M., & Hair, J. F. (2021). Partial least squares structural equation modeling. In *Handbook of market research* (pp. 587–632). Springer.

Scherg, M., Berg, P., Nakasato, N., & Beniczky, S. (2019). Taking the EEG back into the brain: The power of multiple discrete sources. *Frontiers in Neurology*, *10*, 1–23.

Sharma, S., Ohrbach, R., Fillingim, R. B., Greenspan, J. D., & Slade, G. (2020). Pain sensitivity modifies risk of injury-related temporomandibular disorder. *Journal of Dental Research*, *99*, 530–536.

Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., Mintun, M. A., Wang, S., Coalson, R. S., & Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 1942–1947.

Shrestha, N. (2020). Detecting multicollinearity in regression analysis. *American Journal of Applied Mathematics and Statistics*, *8*, 39–42.

Sivertsen, B., Lallukka, T., Petrie, K. J., Steingrimsdottir, O. A., Stubhaug, A., & Nielsen, C. S. (2015). Sleep and pain sensitivity in adults. *Pain*, *156*, 1433–1439.

Smith, R., Fass, H., & Lane, R. D. (2014). Role of medial prefrontal cortex in representing one's own subjective emotional responses: A preliminary study. *Consciousness and Cognition*, *29*, 117–130.

Sullivan, M. J. (1995). *The Pain Catastrophizing Scale: clinical applications*.

Sullivan, M. J. L., Adams, H., Martel, M. O., Scott, W., & Wideman, T. (2011). Catastrophizing and perceived injustice: Risk factors for the transition to chronicity after whiplash injury. *Spine*, *36*, S244–S249.

Tang, W., Liu, H., Douw, L., Kramer, M. A., Eden, U. T., Hämäläinen, M. S., & Stufflebeam, S. M. (2017). Dynamic connectivity modulates local activity in the core regions of the default-mode network. *Proceedings of the National Academy of Sciences of the United States of America*, *114*, 9713–9718.

Thompson, T., Correll, C. U., Gallop, K., Vancampfort, D., & Stubbs, B. (2016). Is pain perception altered in people with depression? A systematic review and meta-analysis of experimental pain research. *The Journal of Pain*, *17*, 1257–1272.

Van Dartel, S. A. A., Repping-Wuts, J. W. J., Van Hoogmoed, D., Bleijenberg, G., Van Riel, P. L. C. M., & Fransen, J. (2013). Association between fatigue and pain in rheumatoid arthritis: Does pain precede fatigue or does fatigue precede pain? *Arthritis Care and Research*, *65*, 862–869.

Van Diepen, R. M., Foxe, J. J., & Mazaheri, A. (2019). The functional role of alpha-band activity in attentional processing: The current zeitgeist and future outlook. *Current Opinion in Psychology*, *29*, 229–238.

van Wijk, A. J., & Hoogstraten, J. (2009). Anxiety and pain during dental injections. *Journal of Dentistry*, *37*, 700–704.

Watson, D., Clark, L. A., & Carey, G. (1988). Positive and negative affectivity and their relation to anxiety and depressive disorders. *Journal of Abnormal Psychology*, *97*, 346–353.

Yarnitsky, D., Crispel, Y., Eisenberg, E., Granovsky, Y., Ben-Nun, A., Sprecher, E., Best, L. A., & Granot, M. (2008). Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain*, *138*, 22–28.

Youell, P. D., Wise, R. G., Bentley, D. E., Dickinson, M. R., King, T. A., Tracey, I., & Jones, A. K. P. (2004). Lateralisation of nociceptive processing in the human brain: A functional magnetic resonance imaging study. *NeuroImage*, *23*, 1068–1077.

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